FUMJ

Foundation University Medical Journal

Vol. 1, No. 2, Jul – Dec 2014
ISSN: 2312-6531

Online issue available at: **www.fui.edu.pk**
E mail (for electronic submission of articles):
fumj@fui.edu.pk

Publication Office: Department of Pharmacology, Foundation University Medical College, DHA Phase-I, Islamabad, Pakistan 46000

FOUNDATION UNIVERSITY MEDICAL JOURNAL

Vol-1 No.2, Jul - Dec 2014

Contents

EDITORIAL

PROBLEMS CONFRONTING THE ETHICAL PRACTICE OF MEDICINE

As Apollo 11 neared the moon in July 1969, one nervous NASA executive wondered if the mission would go according to plan. After all, they had awarded the contract of each major component of the Saturn-V rocket to the lowest bidder. Would everything hold? Remember that only a fine line existed between a miracle of engineering and a colossal disaster.

The same rule applies to purchases by the government and many autonomous organisations. To the lowest bidder go the spoils of war. While it may not be a problem in the acquisition of stationery or linen for a hospital, the same cannot be said regarding the purchase of medicine, especially the life-saving ones. Raw material for their manufacture is usually imported from the cheapest source, then left to languish in hot and humid conditions of warehouses for many months, awaiting clearance from the customs department. Many purported factories of manufacturing firms turn out to be dilapidated houses in seedy localities. The quantity of a drug stuffed inside a tablet in no way reflects the bio-availability of the same. One can only watch in disdain as unheard of pharmaceutical firms bag the contract to supply anti-tuberculous drugs. Even though the 'brand-leader' is yelling himself hoarse, he will bridge the difference from the lowest bid by providing sufficient tablets free of cost. Such offers are rejected because they do not conform to the laid-down regulations, yet another reason for the increasing resistance in tuberculosis.

Where an enterprising administrator takes the initiative and purchases a better antibiotic worth a few pennies more, the Department gets taken to court by the 'aggrieved' party. And the 'offending' doctor ends up apologizing to his employers. The end-user would rather live with locally produced insulin of questionable efficacy than face the corporate alligators lurking in the murky waters of the pharmaceutical world, itching to punch legal holes in the scientific proof provided - ready to sue for umpteen million, give or take a million or two.

Not long ago, a WHO/UNICEF sponsored multi-center trial was conducted in one premier teaching hospital of each major city of the country. It was to study the efficacy of "Oral Ampicillin versus Injection Ampicillin for treatment of Pneumonia in infants aged less than one year." No country except Somalia had previously permitted this trial, yet it was eagerly lapped up here and allowed to proceed in perhaps all the chosen centers. Why do we let others use our children as guinea pigs and cannon fodder? Simply because they are children of the poor and death pays in dollars. For a few dollars more, oral ampicillin might even be found superior to the injectable form. One has only to sweeten the pill or capsule in this instance. Of course this particular trial was nipped in the bud by the ethics committee of our institution, on which I served.

Why is an Ethics Committee often called an Ethical Committee, thereby implying all the remaining committees are unethical? Why is it not unusual in this country for the most unethical person within a forty mile radius to be proposed for chairing such a committee?

A new drug for Hepatitis C is undergoing extensive trials the world over. Details of our prospective recipients are sent to those conducting the study, with the local physician out of the loop in the ultimate selection of patients and provision of drug. Any trial worth the name has to be a randomized, double-blind, controlled trial. One sincerely hopes most of our patients have not ended up being 'randomized' into the group receiving placebo. There are enough anecdotal concoctions floating around in this country as it is, many cheaper ones, at that.

How does a muscle relaxant not recommended for prolonged use get approved by the Drug Regulatory Authority of Pakistan? Especially when its rare but serious side effects include syncope, arrhythmias, myocardial infarction, seizures and stroke. Surely, safer substitutes have been available for decades. The commercially enticing name it is allocated conveys the comfortable feeling one gets sitting on a double-padded sofa. How the concerned marketing firm locates the expert to whom it has been sent for evaluation is another matter.

Why are we, platter in hand, flocking around the dinner tables of pharmaceutical firms celebrating their

achieving some 'exalted' award or higher rating? Why do we grin from ear to ear on winning a paid trip to Dubai in a 'lucky draw'? And why does the luck of the draw always benefit someone in a position to return the favour? One could go on and on.

This write-up is primarily meant to pose pointed questions. Do some individual soul-searching. It cannot be expected to provide all the answers. That remains the domain of the sages of our medical community, those in a position of influence, those with the power to legislate and above all, those with conscience. Let all of them come forward and show the way.

References:

- Anwar M MD, Sherman KE MD. HCV treatment of special populations: HIV coinfected, liver transplant and renal failure, 2014. Clinical liver disease: 4(4); 80 – 83.
- American Geriatrics Society. Updated Beers Criteria for Potentially Inappropriate Medcation use in older adults. The American Geriatrics Society 2012 Beers Criteria update expert panel. J Am Geriatr Soc 2012; 60(4): 616 – 631.
- Web site: www.drap.gov.pk

Syed Irfan Ahmed
Professor of Medicine
Rawalpindi Medical College, Rawalpindi

PROTECTIVE EFFECT OF GREEN TEA ON LIVER FROM DELETERIOUS EFFECT OF CYPERMETHRIN IN MICE

Saima Manzoor, Khadija Mehboob[1], Abdul Khaliq Naveed[1]

Deparment of Biochemistry, Foundation University Medical College, Islamabad
[1]Deparment of Biochemistry, Army Medical College, Rawalpindi

ABSTRACT

Objective:

The objective of this study was to monitor antioxidant effect of green tea on hepatic parameters of mice exposed to insecticide Cypermethrin.

Design:

Randomized control trial.

Place of study:

Army Medical College, Rawalpindi Biochemistry and Pathology Department in collaboration with National Institute of Health Islamabad from May to June 2013.

Material and Methods:

30 Balb/C mice divided into 3 groups. Group a was taken as a control which received normal diet. Group b* was given Cypermethrin and Group c* was given Cypermethrin and green tea. All other experimental groups received normal diet and supplements. These substances were given by oral route for 1 month. After this period liver parameters were evaluated by measuring serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The data were analyzed with SPSS version 15. Anova was applied, followed by post hoc Tukey test.*

Results:

The result demonstrated that liver parameters were significantly (p-value<0.001) increased in group b as compared to control group a*. Treatment with green tea in group c* illustrated significant (p-value<0.001) decrease in these parameters as compared to group b* and these were nearly equal to the control group.*

Conclusion:

Green tea like countless bounties of nature produced solace against Cypermethrin induced oxidative stress.

Keywords:

Cypermethrin, oxidative stress, antioxidant, green tea

Introduction:

There is continuous creation of free radicals in our body. There is an unpaired electron in free radicals so these are extremely reactive substances and perish in seconds. Before this happens these strike with other molecules and remove an electron to become stable. In this manner collision give rise to another radical formation. So the only way to get rid of free radicals is to stop this chain reaction. It happens when two free radicals react with one another, so that the pairing of electron occurs. It occurs rarely due to ability of radical to perish rapidly and due to extremely less amount of these harmful substances in tissues. In living organisms oxygen radicals are extremely dangerous which includes hydroxyl, super oxide and perhydroxyl ions. These harmful substances produce injury to cells, which is called oxidative damage. Their formation is enhanced by various harmful substances like insecticides. Nature is generous to produce substances which can neutralize these harmful mediators which are called antioxidants[1].

Correspondence:
Dr. Saima Manzoor
Deparment of Biochemistry
Foundation University Medical College, Islamabad.
E.mail: saimasheheryar@gmail.com

Free radicals can damage lipids, nucleic acids and proteins which are not only essential constituents of the cell but also maintain its basic fabulous architecture. Smash up with this arrangement by free radicals can cause cancer, premature aging and plaque formation in humans[2].Nature has been generous to bestow a variety of protective arrangements in our body as well as in the surroundings which sustain a strong equilibrium. These consist of indigenous enzymes as well as other substances like α tocopherol, catechin, vitamin C and carotene. Their preparations are also available, but vegetable and fruit are the best form of these micronutrients for optimum health[3]. According to World Health Organization (WHO) 1989 Cypermethrin is type 2 pyrethroid which is a synthetic form of pyrethrin (acquired from chrysanthemum plant). It has a prolonged duration of action with ability to excrete rapidly from human body[4] Its frequent use has opened a new Pandora box of hazards. Cypermethrin was linked with many biochemical and hematological pathologies in male dwarf goats[5]. Pyrethroid remains have been found in water, soft drinks, milk and even in animal tissue[6]. As Cypermethrin influences acetylcholine, phosphatases and glutamate receptors so it is a main perpetrator to create oxidative stress[7].

Oxidative stress is a detrimental course that can produce harm to cell organization in the liver and other organs. The increase in levels of serum alkaline phosphatase (ALP), serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) are good indicators of hepatic injury[6]. The tea (camellia sinensis) is most commonly used drink after water in whole world. Most of the people consume black tea. Only 20 percent use green tea and less than 2 percent use oolong tea[8].

Tea is an essential herbal resource of catechins. These catechin have antioxidant ability to decrease pathologies related to heart and blood vessels. These also decreases incidence of cancer[9]. These scavenge free radical and chelate metallic ions . This function is due to their unique tri hydroxl structure as well as amount and position of hydroxyl groups. Catechin show different antioxidant effect. Epi gallocatechin- 3 -gallate is the best in scavenging ability.

Epicatechin-3-gallate is better while epicatechin is a good scavenger of free radicals.

Epigallocatechin has least antioxidant activity[10]. Green tea polyphenols hinder free radical provoked damage in cells so improving skin smoothness. There is evidence of prolong moisturizing activity as well[11].

The liver, the chemical factory of the body, has a diversity of functions. Many metabolic pathways depend on its normal status. It is also responsible for removal of injurious substances so changes in its biochemical parameter are a clue to observe oxidative stress[5]. So this study was designed to monitor antioxidant effect of green tea on hepatic parameters of mice exposed to Cypermethrin.

Materials & Methods:

The study was conducted in National Institute of Health (NIH) Islamabad in collaboration with Pathology Laboratories Army Medical College Rawalpindi. The period of this study was 4 weeks. All chemicals are purchased from the local pharmacy and are of analytical grade.

In this study 30 adult Balb\c mice of 30-40 g were used. The mice were obtained from National Institute of Health Islamabad. They were kept under standard conditions in animal house of the National Institute of Health at temperature 23 ± 5°C. The day and night cycle of 12 hours was maintained. The mice were indiscriminately divided into 3 categories. Each group comprised of 10 mice placed in iron cages (5/cage).

Group a* was control which had free access to water and standard food. Group b* was Cypermethrin group which was given Cypermethrin (15mg/kg body weight) by gastric gavage method[12]. This group also had free access to water and standard food. Group c* was the green tea group which had received both Cypermethrin and green tea. The green tea extract was prepared by adding 15 g powdered green tea in 1 liter boiling water for 5 minutes[13]. The solution was sieved to get green tea extract which was provided to mice as their solitary supply of drinking water. This group got the normal standard diet. All these drugs were orally administered for 4 weeks. After 1month mice were anesthetized in a chloroform chamber in groups and intra-cardiac sampling was done. The samples were placed in labeled gel separator tubes, centrifuged and stored at -4 ° in Pathology Laboratory of Army Medical College Rawalpindi till biochemical tests were performed. ALT UV kit, ALP UV diagnostic

Kit and AST diagnostic kit procured from Global, Gulf and Medico companies respectively, were used while sample were run in an auto analyzer in the pathology laboratory in Army Medical College Rawalpindi. Data was presented as the mean ±standard error by means. Statistical analysis was done by SPSS version 15. Statistical analysis was performed by using one way analysis of variance (ANOVA) and post hoc Tukey test. The p value <0.001 was selected as a criteria for statistically significant value.

Results:

To compare different liver parameters, one way ANOVA was applied as documented in table no. I. The groups a*, b* and c* were significantly different ($p<0.001$) in biochemical tests.

The results showed that Cypermethrin group had raised liver parameters due to its toxic effect while green tea significantly averted the amplification of ALT, AST, and ALP levels.

In table no. II there is documentation of the post hock Tukey test. Assessment of control and the

Cypermethrin levels divulged that liver parameters significantly increased in Cypermethrin group as compared to control group ($p<0.001$). Assessment in the antioxidant groups divulged that liver parameters were significantly decreased in mice which received green tea ($p<0.001$).

Table No. I: Comparison of serum ALT, AST and ALP levels between different groups by one way ANOVA .Values are represented as mean ±SD

PARAMETER	GROUP a*	GROUP b*	GROUP c*	p-VALUE
ALT	_	161.6±18.50 U/L	73.80±10.06 U/L	<0.001
AST	99.60±12.04 U/L	138.8±2.93 U/L	96.60±15.84 U/L	<0.001
ALP	223.2±26.00 U/L	368.4±39.90 U/L	225.2±15.92 U/L	<0.001

Table No. II : Comparison of groups (ANOVA followed by Tukey HSD) ALP, ALT and AST

PAIRED ON POST HOCK	p VALUE	p VALUE	p VALUE
GROUP a* VS GROUP b*	<0.001	<0.001	<0.001
GROUP a* VS GROUP c*	0.998	0.713	0.9190
GROUP b* VS GROUP c*	<0.001	<0.001	<0.001

Discussion:

Nowadays pyrethroids are widely used as insecticide and pesticide. There is limited work published on hepatotoxicity relieved by green tea. In this study, we measured liver enzymes ALT, AST and ALP involved in the transfer of amino groups and phosphate groups in biochemical reactions. Chlorpyrifos (CPF) induced deleterious effects include increasing formation of free radicals which reduce the activity of several enzymes belonging to male reproductive system14. Our results showed a significant ($P<0.05$) increase in serum ALT, AST and ALP of mice treated with Cypermethrin. It correlates well with research work in which 20mg Carbendazim, 10mg Cypermethrin and 10mg Imazalil alone and in combination were used[15]. The result demonstrated that mishmash of these three substances generated more DNA harm to hepatic cells. The results of our study correlate well with other studies that document rise in ALT, ALP and AST due to Cypermethrin toxicity[16].The activities of ALT, AST and ALP enzymes are the most commonly used parameters which show the severity of hepatocyte injury and toxicity[17]. There are marked rise in plasma levels of AST, ALT and ALP with the introduction of Cypermethrin in mice diet which shows oxidative stress induced by Cypermethrin [18]. This increase is due to injury to the cell membrane of liver cells, which cause these enzymes to leak in the circulatory system so it is an indicator of inflammation [19]. Alkaline phosphatase is an enzyme which is present in the bile ducts and it is the most significant factor to be aware of when considering liver excretory function[20]. The alkaline phosphatase levels increase tremendously in conditions associated with bile stasis. The green tea antioxidant effect protects bile ducts from toxic effect of free radicals and prevents stasis of bile in an efficient manner. It is according to information published earlier in literature[21, 22] and its antioxidant effect also showed by our results.

Free radicals are formed either due to a variety of hazardous pollutants in our surroundings or due to various metabolic pathways operating in the body[23] .In a healthy person effect of oxygen free radicals is counteracted by antioxidants and there is a balance in the production of free radicals and neutralization of anti-oxidant system[24]. Drastic effect like formation of plaque in arterial vessels, cancer and premature aging develops in our body due to disturbance in this equilibrium state. All these injurious effects are the outcome of free radical injury which produced oxidative stress in cells[25].

Oxidative stress is the main culprit to produce a hostile environment in the cell which leads to abnormal consequences[26]. It correlates well with previous research in which rats were divided into four groups. One was a control with normal diet. Group 2 was given sesame oil, group 3 was given Cypermethrin and group 4 was given both Cypermethrin and sesame oil by gavage method. Results showed increase in ALT, AST, ALP, serum urea and serum creatinine with a decrease in glutathione and other antioxidant enzymes in Cypermethrin group. Sesame oil produced marked protection against Cypermethrin induced oxidative stress[27]. Oxidative stress involves in alteration of many events in the cell by a variety of processes. As it changes the way in which gene is going to express for this event and activates factors involved in the process of transcription. It can change the permeability of mitochondrial membrane which is extremely harmful for the cell[28].

The use of antioxidants to counteract the formed free radicals is the bedrock to minimize their deleterious effect. So, the main beneficial substances in green teas are tea catechins that have the most superior antioxidant action. Tea catechins are strong free radical deactivators as these can trim down one electron. [29,30] Antioxidant effect of green tea increased too many folds due to vitamins and mineral contents. Research on human subjects advocates its contribution in the prevention of carcinogenesis and diseases related to the cardiovascular system. Green tea antiviral and antibacterial activities are also reported in the literature. It protects nervous system and reduces damage produced by ultraviolet radiation. So there is a long list of miracles due to its antioxidant effects[31]. The decrease in plasma levels of ALT, AST and ALP to near normal in comparison to control reveals that green tea can shield hepatocellular membrane from free radical injury and also revitalizes the damage tissue. It is a well established information that transaminases recover to normal values with healing from oxidative stress induce injury[32].

Conclusion:

Green tea is an efficient pacifier of Cypermethrin toxicity as it improved liver biochemical parameter of mice affected by Cypermethrin.

References:

1. Halliwell, B, Gutteridge. Free radicals, antioxidants and human disease: where are we now? J Lab Clin Med.1992; 119-598.[PMID: 1593209]
2. Asplund K. Antioxidant vitamins in prevention of cardiovascular disease :a systematic review. J Intern Med.2002;251(5):372-392.
3. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomised trials of antioxidant supplements for primary and secondary prevention. JAMA . 2007; 297(8):842 -57.
4. World Health Organization. Environmental Health Criteria. Cypermethrin. Geneva: United Nations Environmental Programme, the International Labour Organization, and the World Health Organization.1989;82.
5. Khan A, Faridi HA, Ali M, Khan MZ, Siddique M and Hussain I . Effects of Cypermethrin on some clinico-hemato -biochemical and pathological parameters in male dwarf goats (Capra hircus).Exp Toxicol Pathol.2009; 61(2) : 151–160.
6. Grewal G, Verma PK, Dhar V,Srivastava AK.Toxicity of subacute oral administration of cypermethrin in rats with special refrence to histopathological changes.Int J Green Pharmacy 2009;3:293-9.
7. Singh AK, Tiwari MN, Upadhyay G, Patel DK, Singh D and Prakash O. Long term exposure to cypermethrin induces nigrostriatal dopaminergic neurodegeneration in adult rats. Postnatal exposure enhances the susceptibility during adulthood. Neurobiology of Aging.2012;33(2):404-15.
8. Katiyar SK, Mukhtar H. Tea in chemoprevention of cancer. epidemiologic and experimental studies. Int J Oncology. 1996;8:221-238.
9. McKay DL, Blumberg JB.The role of tea in human health. An update .J. Am .Coll. Nutr.2002;21(1) 1-13
10. Hu JX, Li YF, Li J, Pan C, He Z and Dong HY.Toxic effect of cypermethrin on the male reproductive system:With emphasis on the

androgen receptor.Journal Of Applied Toxicology.2013;33(7):576-585.

11. Gianeti, MD and Mercurio, DG. Campos, PM.The use of green tea extract in cosmetic formulations:not only an antioxidant active ingredient .Dermatologic Therapy.2013;26(3):267-271
12. Nishal Kumar P, Manjusha C, Itishri Sahu,Sirisha D.Protective effect of leucoverin on Cypermethrin-induced toxicity in mice. J Bio, Innov.2012;1(2):33-40.
13. Kumar V,Bicey A, Kumar S.Antioxidant effect of green tea extract in Cadmium chloride intoxicated rats.Advances In Applied Science Research.2010;1(2):9-13.
14. Afaf AE, Hanan AT .Chlorpyrifos effect on testicular biochemistry of male albino rats. Journal of American Science. 2010;6(7):252-261.
15. Dickic D, Mojsovic-Cuic A,Cupor A, Benkovic V,Horvat-Knezevic A and Lisicic D. Carbendazim combined with imazalil or cypermethrin potentiate DNA damage in hepatocyte of mice.Hum Exp Toxicol.2012.;31(5):492-505.
16. El-Demerdash FM.Antioxidant effect of vitamin E and selenium on lipid peroxidation,enzyme activities and biochemical parameters in rats exposed to aluminium .J Trace Elem Med Biol.2004;18(1):113-21.
17. Stockham SL, Scott MA.Fundamentals of Veterinary clinical pathology. Iowa State: University Press Ames. 2002; 434–459.
18. Kalender S,Uzun FG, Durak D, Demir F, Kalender Y.Malathion-induce hepatotoxicity in rats:the effect of vitamin C and E.Food Chem Toxicol.2010;48:633-638.
19. Toor HK, Sangha GK, Khera KS.Imidacloprid induced histological and biochemical alterations in liver of female albino rats.Pesticide Biochemistry and Physiology.2013;105(1):1-4
20. Skrzydlewsja E, Augustyniak A, Ostrowska J, Luczaj W, Tarasiuk E.Green tea protection against aging induced oxidative stress.Free Radic Biol Med.2002;555-557.
21. David C, Twedt DM. Liver diseases: Lecture notes. Academic Veterinary Medicine Inc. Med Biol 2001; 18 : 113–121.
22. Zhang Q, Kelly AP, Wang L, French W,Tang X and Duong HS .Green tea extract and epigallocatechin-3-gallate inhibit mast cell stimulated type 1 collagen expression in fibroblasts.J Invest Dermatol.2006;7-13
23. Hussein HK, Elnaggar MH, Al Dailamy. JM. Protective role of vitamin C against hepatorenal toxicity of fenvalerate in male rats. GARJEST .2012; 1(4) : 60-65.
24. Sun Y. Free radicals, antioxidant enzymes and carcinogenesis. Free Radic Biol Med.1990;8:583-599.
25. Hogg N.Free radicals in disease.Semin Reprod Endocrinol.1998;16:241-288.
26. Kaplowitz N, Tsukamoto H.Oxidative stress and liver disease.Prog Liver Dis.1996;14:131-59.
27. Abdou HM,Hussein HM,Yousef MI. Deleterious effects of cypermethrin on rat liver and kidney.Protective role of sesame oil.J Environ Sci Health B.2012;47(4):306-14.
28. Halliwell B, Gutteridge,JMC. Free Radicals in Biology and Medicine.3rd edn.Oxford: University press Inc.2002;105-245.
29. Higdon JV, Frei B.Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions.Crit Rev Food Sci Nutr.2003;43(1):89-143.
30. Dubick MA, Omaye ST.Grape wine and tea polyphenols in the modulation of atherosclerosis and heart disease.Handbook of nutraceuticals and functional foods.2nd edn.:CRC Press.2007;2:101-130.
31. Carbera C, Artacho R, Gimenez R.Beneficial effects of green tea-a review.J AM Coll Nutr.2006;25(2)79-99.
32. Frei B, Higdon JV.Antioxidant activity of tea polyphenols in vivo:evidence from animal studies.J Nutr.2003;133(10):3275S-3284S.

SAFETY AND TOLERABILITY PROFILE OF AN EXPANDED SIX-DRUG REGIMEN FOR TREATMENT OF MODERATELY ADVANCED PULMONARY TUBERCULOSIS WITH CAVITARY LESIONS

Madiha Malik, Bushra Tayyaba Khan, Muzammil Hasan Najmi[1]

Department of Pharmacology and Therapeutics, Army Medical College, Rawalpindi
[1]Department of Pharmacology and Therapeutics, Foundation University Medical College, Islamabad

ABSTRACT

Objective:

The study was designed to evaluate the safety and tolerability of adding second line anti tuberculosis drugs, Amikacin and Levofloxacin, to the first line anti-tuberculosis drugs in the treatment of moderately advanced pulmonary tuberculosis with cavitary lesions.

Materials and Methods:

Sixty patients were included in the study and were equally randomized into two groups. First or control group received six months course of first line anti tuberculosis drugs according to the World Health Organization guidelines, while the second (Experimental group) received amikacin and levofloxacin in addition to the first line drugs for six months duration. The safety and tolerability of these drugs was compared by observing adverse drug reactions for first 100 days in the clinical and laboratory parameters. Serum uric acid, Serum urea, Craetinine, ALT, Alkaline phosphatase and serum total bilirubin were estimated at 60 and 100 days and compared with the control values.

Results:

Some clinical symptoms like tinnitus, paraesthesia, visual dysfunction, GI abnormalities, headache, fever, rash and myalgia were observed in both the groups with no statistically significant difference. The changes in laboratory parameters were also found to be insignificant in the two groups. Based on the results, it is inferred that addition of the second line drugs to the regimen did not produce significant additional adverse effects as compared to the conventional first line regimen.

Conclusion:

The results of this study suggest that addition of amikacin and levofloxacin to the standard first-line drug regimen in moderately advanced pulmonary tuberculosis with cavitary lesion is well tolerated and does not lead to significant additional adverse effects.

Introduction:

Tuberculosis (TB) retains its foothold among human populations despite increasing implementation of highly effective control measures around the world. High burden countries would benefit from interventions that decrease the disease transmission. As majority of new cases of multidrug-resistant (MDR) TB arise from patients with cavitary pulmonary disease, strategies targeting this group of patients could significantly influence the disease transmission, as well as improve cure rates and decrease antimicrobial resistance[1].

Fluoroquinolones are currently recommended by WHO as second line agents for the treatment of MDR TB and for patients showing intolerance to the first line agents[2]. In addition, consensus guidelines from the American Thoracic Society, United States Center for Disease Control and Prevention and Infectious Disease Society of America have suggested incorporating fluoroquinolones for prophylaxis of those exposed to MDR TB[3].

Amikacin is indicated for treatment of TB caused by streptomycin-resistant or MDR strains. It should be used in combination with at least one and

Correspondence:
Bushra Tayyaba Khan
Associate Professor,
Department of Pharmacology & Therapeutics
Army Medical College, Abid Majeed Road, Rawalpindi
E.mail: bushrakhan1@hotmail.com

preferably two or three other drugs to which the strain is susceptible for treatment of drug resistant cases[4]. Innovative alternate regimens have been used to treat selected cases of tuberculosis. However, these may not be well tolerated by the patients. An intermittent regimen of Rifampicin, Pyrazinamide and ethambutol resulted in hepatoxicity and other adverse effects in patients of INH resistant cavitary pulmonary tuberculosis[5]. The present study was planned to evaluate the safety and tolerability of adding levofloxacin and amikacin to the standard first-line regimen in patients suffering from cavitary pulmonary TB.

Materials & Methods:

The study was carried out in collaboration with Department of Pulmonology, Military Hospital Rawalpindi and Department of Pathology, Army Medical College Rawalpindi. It was a prospective phase-2 randomized clinical trial. Sixty four patients of newly diagnosed pulmonary TB were included in the study. Four patients were later on excluded; one due to poor follow up and three due to being MDR on drug susceptibility testing. Sixty patients were then equally randomized into two groups. The Group 1(Control group) which was treated with first line anti-TB drugs only and Group 2 (Experimental group) which was treated with first line anti TB drugs and additional two drugs i.e. amikacin and levofloxacin. Each patient was given six months course of treatment. The study protocol was approved by the Institutional Ethical Committee and written informed consent was obtained from all subjects prior to enrollment.

Inclusion Criteria:

1. Patients of either gender aged 20 – 50 years.
2. Chest cavitary lesions on radiological examination.
3. Moderately advanced pulmonary TB present in one or both lungs. Total extent not exceeding the following limits.
   a) Disseminated lesions of slight to moderate density that may extend throughout the volume of one lung or equivalent in both lungs.
   b) Dense and confluent lesions limited in extent to one third of the volume of both lungs.
   c) Total diameter of cavitation less than 4 cm[6].
4. Erythrocyte sedimentation rate (ESR) more than 10 mm[7].

Exclusion Criteria:

1. Age below 20 and above 50 years.
2. Body weight below 33 kg.
3. Pregnancy and lactation.
4. MDR TB on culture / sensitivity testing.
5. Patient with any evidence of heart, hepatic, renal disease or gastrointestinal problems.
6. Patients taking concomitant medication reported to increase the QTc interval.
7. Known allergy to the study drugs.
8. Serious mental illness or limited mental capacity to the extent that the subject was unable to provide legal consent and information regarding the side effects or tolerance of the study drugs.
9. Use of any over-the-counter medication within two weeks preceding the study, but patients could take the other drugs prescribed by the physician during the study.
10. Previous use of antiTB drugs.
11. Patients receiving antiretroviral therapy.
12. Patient showing any abnormality of routine blood and urine analysis.

Study groups:

Group 1(Control)

Thirty patients were given following drugs.

Isoniazid 5 milligram per kilogram of body weight per day (mg/kg/d).

Rifampicin 10 mg/kg/d.

Pyrazinamide 20 mg/kg/d.

Ethambutol 15 mg/kg/d.

All these drugs were given for two months to cover the initial phase while isoniazid, rifampicin and ethambutol were continued in the continuation phase for the remaining four months.

Group 2 (experimental)

Thirty patients were given following drugs Isoniazid, rifampicin, pyrazinamide, ethambutol in

the doses mentioned earlier with addition of the following newer drugs:

Amikacin 15 mg/kg/d.

Levofloxacin 500 mg/d.

All these drugs were given for two months in the initial phase while isoniazid, rifampicin, ethambutol, amikacin and levofloxacin were continued for the remaining four months. Doses of all drugs were worked out according to the WHO guidelines.

Parameters:

It has been reported in the literature that most adverse effects of anti TB agents occur in the first 100 days of therapy[8]. Adverse drug reactions (ADRs) monitoring/evaluation for first 100 days was therefore, planned. The patients who showed any abnormality regarding the ADRs in the first 100 days were planned for further investigations and follow up which was not found to be needed.

Clinical examination of Central Nervous System, Musculoskeletal System, Gastrointestinal System, skin, visual functions and auditory functions was carried out.

Laboratory investigations included the following;

Renal Functioin Tests:

Serum urea, serum creatinine

Liver Function Tests:

Alanine transaminase (ALT), Alkaline phosphatase (ALP)

Total bilirubin (Tbil).

Complete Blood Count.

Serum uric acid level.

ECG particularly for QTc interval.

The changes in the laboratory investigations were compared with the baseline data at 60 days and 100 days of therapy.

Statistical Analysis:

Data was analyzed using SPSS version 15. Descriptive statistics were used to describe the data. Independent samples "t test" was used to compare numeric variables between the groups. Categoric variables were compared using "chi test". p value of less than 0.05 was considered significant.

Results:

Change in serum hemoglobin level

Average decrease in Hb level from the start to 60 days in Group 1 was 0.66g/dl (SD= 2.02). The decrease in Hb level was slightly more in Group 2 as compared to Group 1, but this difference was insignificant (p=0.883).

Change in serum uric acid level

Average increase in serum uric acid level from the start to 60 days in group 1 was 153.60 µmol/1 (SD= 79.10). The increase in serum uric acid level was slightly more in Group 1 as compared to Group 2 but the difference was insignificant (p=0.846).

Average increase in serum uric acid level from start to 100 days in Group 1 was 107.23 µmol/1(SD= 87.49) whereas in Group 2 it was 117.13 µmol/1(SD=73.27). The increase in serum uric acid level was slightly more in Group 2 as compared to Group 1 but this difference was insignificant (p = 0.636).

Change in serum urea level

Average increase in serum urea level from the start to 60 days in Group 1 was 0.42 mmol/1 (SD=1.06) whereas in Group 2 it was 1.26 mmol/1(sd=1.69). The increase in serum urea level was significantly more in Group 2 as compared to Group 1 (p = 0.024).

Average increase in serum urea level from start to 100 days in Group 1was 0.35 mmol/1 (SD=0.88) whereas in Group 2 it was 2.19 mmol/1 (SD=1.95). The increase in serum urea level was significantly more in Group-2 as compared to Group-1 (p<0.001).

Change in serum creatinine level

Average increase in serum creatinine level from start to 60 days in Group 1 was 19.67µmol/1(SD=21.61) whereas in Group 2 it was 28.53 µmol/1 (SD=22.62). The increase in serum creatinine level was slightly more in Group 1 as compared to Group 2 but the difference was insignificant (p = 0.126).

Average increase in serum creatinine level from the start to 100 days in Group 1 was 28.13 µmol/1 (SD=20.22) whereas in Group 2 it was 42.20

µmol/1(SD=21.61). The increase in serum creatinine level was more in Group 2 as compared to Group 1 and this difference was significant (p = 0.012).

Change in serum total bilirubin level

Average increase in serum Tbil level from start to 60 days in group 1 was 4.28 µmol/1(SD = 4.40) whereas in group 2 it was 5.62 µmol/1 (SD = 4.10). The increase in serum Tbil level was slightly more in group 2 as compared to group 1 but the difference was insignificant (p = 0.229).

Average increase in serum Tbil from start to 100 days in group-1 was 5.75 µmol/ (SD=4.98) whereas in group 2 it was 4.94 µmol/ (SD=4.56). The increase in serum Tbil level was more in group 1 as compared to group 2 but this difference was insignificant (p = 0.512).

Change in serum alanine transaminase level

Average increase in serum ALT level from start to 60 days in group 1 was 32U/1 (SD = 21.64) where as in group 2 it was 25.30 U/1 (SD = 20.93). The increase in serum ALT level was slightly more in group 2 as compared to group 1 but the difference was insignificant (p = 0.228).

Average increase in serum ALT level from start to 100 days in group 1 was 46.57U/ (SD = 28.06). Whereas in group-2 it was 40U/1 (SD=59.29). The increase in serum ALT level was slightly more in group 1 as compared to group 2 but this difference was insignificant (p = 0.586).

Change in serum alkaline Phosphatase level

Average increase in serum ALP level from start to 60 days in group 1 was 63.37 U/1 (SD = 65.69). Whereas in group 2 it was 68.60U/1 (SD = 75.18). The increase in serum ALP was slightly more in group 2 as compared to group 1 but the difference was insignificant (p = 0.775)

Average increase in serum ALP level from start to 100 days in group 1 was 103.63 U/1 (SD = 78.18).Whereas in group-2 it was 102.50 U/1 (SD = 68.23). The increase in serum ALP level was slightly more in group 1 as compared to group 2 but this difference was insignificant (p = 0.953).

Corrected QT interval in ECG

All patients had their ECGs done at the designated time intervals. No patient had abnormal QTc interval.

Some clinical symptoms were observed in both the groups which are shown in Table-1

Table I: Change in Biochemical Parameters at 60 and 100 Days of Study

Parameter Studied	Group – 1 (Control)			Group – 2 (Experimental)		
	Day 0	Day 60 (*p* Value)	Day 100 (*p* Value)	Day 0	Day 60 (*p* Value)	Day 100 (*p* Value)
Haemoglobin (g/dl)	11.12 ± 1.52	10.46 ± 1.05 (p = 0.009)	9.98 ± 1.00 (p < 0.001)	11.19 ± 1.45	10.46 ± 0.84 (p = 0.003)	10.11 ± 0.98 (p = 0.001)
Serum Uric Acid (µ mol / l)	214.5 ± 12.44	368.10 ± 103.39 (p < 0.001)	321.73 ± 89.58 (p < 0.001)	219.23 ±	368.23 ± 76.19 (p < 0.001)	336.37 ± 64.10 (p < 0.001)
Serum Urea (mg/dl)	3.53 ± 0.63	3.95 ± 0.68 (p = 0.04)	3.88 ± 0.66 (p = 0.037)	3.83 ± 0.98	5.09 ± 1.5 (p < 0.001)	6.02 ± 1.92 (p < 0.001)
Serum Creatinine (µ mol / l)	70.20 ± 15.77	89.87 ± 15.02 (p < 0.001)	98.33 ± 18.36 (p < 0.001)	72.33 ± 13.57	100.87 ± 26.20 (p < 0.001)	114.53 ± 22.05 (p < 0.001)
Serum Total Bilirubin (µ mol / l)	8.91 ± 2.20	13.19 ± 3.40 (p < 0.001)	14.67 ± 4.28 (p < 0.001)	8.86 ± 2.43	14.48 ± 3.55 (p < 0.001)	13.80 ± 3.25 (p < 0.001)
ALT (units / l)	28.43 ± 7.07	60.43 ± 20.95 (p < 0.001)	75.0 ± 27.98 (p < 0.001)	30.03 ± 6.90	55.33 ± 21.24 (p < 0.001)	70.03 ± 59.82 (p < 0.001)
Alkaline Phosph – (units / l)	188.60 ± 59.53	251.97 ± 64.49 (p < 0.001)	292.23 ± 77.85 (p < 0.001)	209.03 ± 60.02	277.63 ± 110.32 (p < 0.001)	311.53 ± 91.79 (p < 0.001)

Table II: Comparison of Clinical Symptoms in Both the Groups

Complications	Group-1 Frequency(%)	Group-2 Frequency(%)	*p*-value
Seizures	0(0)	0(0)	1.00
Tinnitus	0(0)	2(6.7)	0.150
Paresthesia	2(6.7)	2(6.7)	1.00
Visual function problem	4(13.3)	1(3.3)	0.161
Auditory function problem	0(0)	1(3.3)	0.313
Headache	8(26.7)	3(10)	0.095
Tachycardia	0(0)	1(3.3)	0.313
Chest pain	0(0)	1(3.3)	0.313
Nausea	5(16.7)	4(13.3)	0.718
Vomiting	2(6.7)	2(6.7)	1.00
Abdominal pain	5 (16.7)	4 (13.3)	0.718
Fever	2 (6.7)	2 (6.7)	1.000
Rash	2 (6.7)	1 (3.3)	0.554
Myalgia	1 (3.3)	2(6.7)	0.554

Discussion:

Patients diagnosed to have pulmonary TB are customarily treated by the standard four drugs regimen, but moderately advanced pulmonary TB with cavitary lesions appears to have a higher failure and relapse-rate with this conventional treatment[9]. In humans almost all MDR tubercle bacilli develop in pulmonary cavity formation, is one such fact that has been almost completely neglected[10]. Recent studies (USPHS-22, BMRC trials) also lend support to these observations that the presence of cavities at the time of diagnosis and sputum smear positivity after two months, were responsible for relapse in up to 21% cases at two years. Treatment of such cases according to WHO standard guidelines leaves residual structural changes (in up to 40%) in spite of patients having apparently been "cured" (sputum culture negativity)[11]. The use of amikacin and levofloxacin in moderately advanced pulmonary TB with cavitary lesions needs to be explored and a proactive approach may be considered to prevent the development of MDR or extensive drug resistant (XDR) TB. The aim of treatment should be to provide the safest and most effective therapy in the shortest period of time. Despite considerably different price situation from time to time and place to place, short course regimens rely heavily on generally expensive drugs. However, these regimens are probably more cost effective than the cheaper regimens, and drug cost should not preclude access to effective and appropriate treatment[12]. The question arises that whether regimens containing amikacin and levofloxacin have more toxicity than the standard anti TB regimens or not. In the present study, we evaluated the incidence of major adverse events of anti TB regimens containing amikacin and levofloxacin as additional drugs and compared it with matched control subjects receiving standard anti TB regimens in moderately advanced pulmonary TB with cavitary lesions. It was observed that the adverse effect profile of the six-drug regimen is not much different from the four-drug regimen and the safety and tolerability of the modified therapy can be further ensured by close monitoring of ADRs. Our observations are supported by a study showing that the six-drug regimen when used in pulmonary TB patients in retreatment category resulted in no significant side effects[13]. However, further evaluation is required to determine the safety in extreme age groups who are prone to develop the adverse effects. Drugs other than anti TB which have potentially similar adverse effects should not be prescribed to the patients receiving the extended drug therapy. As poor adherence linked with adverse treatment outcomes is not unexpected and emphasizes the importance of directly observed therapy (DOTS) in the treatment of TB, therefore the patients in group 2 (experimental) were the admitted patients in the wards where nursing assistants were assigned to monitor them. The drugs were given under direct supervision of the consultant pulmonologist and patients were well counseled about the clinical manifestations of the ADRs. The results showed that Tbil, ALT, ALP, uric acid and Hb were insignificantly changed in both the groups from baseline levels and also there was insignificant difference between the control and the experimental groups. The increase in serum creatinine level was slightly more in group 1 as compared to group 2 but the difference was insignificant ($p = 0.126$). This may possibly be due to transient derangement of renal function tests usually seen during first two months of rifampicin therapy[4]. Serum urea was significantly deranged from the baseline levels and also between the two groups. However, these changes in serum urea and creatinine levels were in the upper limits of the normal values.

Conclusion:

It is concluded from the study that for moderately advanced pulmonary TB with cavitary lesions, the six-drug regimen containing additional amikacin and levofloxacin, is well tolerated. The adverse effect profile of six drugs regimen is not much

different from the four drugs regimen. The safety and tolerability of the modified therapy can be ensured if close monitoring of ADRs is carried out.

References:

1. Mark AY, Gyanu L, William RB. Cavitary pulmonary tuberculosis: The Holey: Grail of disease transmission. Current Science, 2004; 86(1):55 – 59. transmission. Current science 2004.86(1).
2. Crofton J, Choculet P, Maher D. World Health Organization. (WHO) Report 1997 : Guidelines for the management of drug resistant tuberculosis.
3. American Thoracic Society/ Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of tuberculosis. Am J Respir Crit Care Med 2003.167:603=662.
4. Henry FC. Anti mycobacterial drugs. Basic and Clinical Pharmacology. Lange Medical Publications 2007; 47(11): 823 – 834.
5. Reeves R, Hamilton, cb, TapyJ Narita M, Kyle RP et al. Evaluating the efficacy and safety of intermittent tuberculosis treatment when Isoniazid cannot be used. Am J Respir Crit Care Med, 183; 2011: A4040
6. National Tuberculosis Association of the USA. (NTA) 1961.
7. Robert L, Yeager JR. The behavior of moderately advanced tuberculosis with cavity. Preliminary report 1938.
8. Fawziah M, Carlo A Marra, Susanne M, Peilin SH, Kevin ER, Greg SRN, Mark FJ. Levofloxacin Treatment of Active Tuberculosis and Risk of Adverse Events. Chest 2005.128(3):1406-1413.
9. Benator D, Bhattacharya M, Bozeman L, Burman W, Gordin F, Horsburgh CR, Horton J, Khan A, Villarino ME, Wang YC, Weiner M Weis S. Rifapentine and isoniazed twice a week for treatment of drug susceptible pulmonary tuberculosis in HIV negative patients: a randomized clinical trial. Lacent 2002. 360:528-534.
10. Dannenberg AM. Liquefaction and cavity formation in pulmonary TB. Tuberculosis 2009.89(4):243-7.
11. Perez-Stable EJ. Hopewell PC. Chemotherapy of Tuberculosis. Semin Respir Med 1988.9:459.
12. John B, Laurence SF, Philip CH, Richard B, Richard FJ, Fredrick R, Dixie ES, George, T. Treatment of Tuberculosis and Tuberculosis Infection in Adult s and Children. American Journal of Respiratory and Critical Care Medicine 1994.149.
13. Saeed W, Naseem A, Ahmed J. Retrospective audit of patients treated for MDR TB in Retreatment category. J Ayub Med Coll Abbottabad 2009.21(2).

HISTOPATHOLOGICAL FINDINGS OF ENDOMETRIAL CURETTES IN PATIENTS WITH ABNORMAL UTERINE BLEEDING

Shahida Akhtar, Maria Ashraf, Alia Noureen, Mehwish Malik, Waqar Ahmed

Department of Gynaecology & Obstetrics, Fauji Foundation Hospital, Rawalpindi

ABSTRACT

Objective:

To demonstrate the frequency of different histopathological findings in endometrial samples of patients presenting with abnormal uterine bleeding.

Study Design:

Cross-sectional study

Setting:

This study was carried out in the Gynaecology Department of Fauji Foundation Hospital Rawalpindi from Nov 2013 to April 2014.

Materials and methods:

The endometrial samples were obtained by using endocurettes from 190 patients presenting to the OPD with abnormal uterine bleeding. They were sent to the Pathology laboratory of FFH for histopathological analysis. The results were analysed, tables and charts made using the Microsoft Excel software. Inclusion criteria was heavy menstrual bleeding, post coital bleeding, intermenstrual bleeding and post-menopausal bleeding. Our exclusion criteria included the endometrial samples obtained for complaints other than abnormal uterine bleeding.

Results:

The mean age of our sample population was 46 years whereas the age ranged from 27 years to 80 years. Among the 190 patients who went endometrial sampling, 55 (29 %) had secretory endometrium, 47 (24.7 %) had proliferative endometrium, 23 (12.1 %) had disordered proliferative, 10 (5.2 %) had complex hyperplasia with atypia, 6 (3.1 %) had simple cystic hyperplasia, 6 (3.1 %) had pill pattern, 4 (2.1 %) had benign endometrial polyp whereas 32 (16.8 %) samples were scanty. Only 1 % of the samples were adenocarcinomas.

Conclusion:

Our study concluded that most of the endometrial samples were normal or benign whereas only 1 % of the samples were found to be adenocarcinomas.

Keywords:

Endometrial sampling, Endocurette, HMB, AUB, Endometrial biopsy

Introduction:

Abnormal Uterine Bleeding (AUB) which comprises of heavy menstrual bleeding, inter-menstrual bleeding, post-coital bleeding and post-menopausal bleeding, is one of the commonest problems dealt with by the Gynaecologists. It is important that all women with abnormal uterine bleeding particularly those who are >40 yrs of age undergo endometrial biopsy to exclude endometrial cancer and confirm the benign nature of the disease, so that they can be offered medical or conservative treatment and radical surgery can be avoided[1]. Majority of such patients undergo office hysteroscopy and endometrial sampling as part of their evaluation [2].

With the evolution of medicine and the increasing focus on lesser invasive techniques, traditional

Correspondence:

Dr. Shahida Akhtar
Department of Gynaecology & Obstetrics
Fauji Foundation Hospital, Rawalpindi
E.mail: drshahidaakhtar@yahoo.com

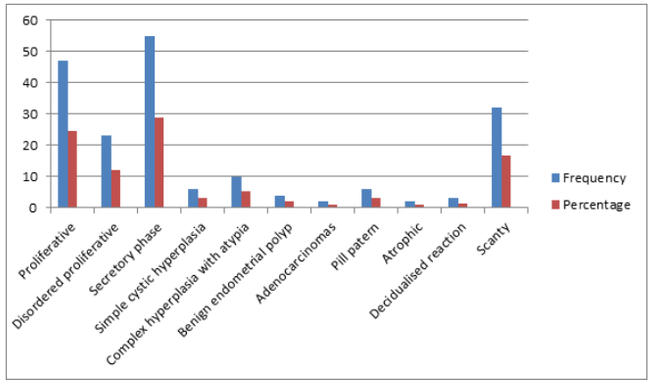
endometrial sampling procedures like Dilatation & Curettage are rapidly being replaced by modern office-based endometrial sampling methods[3]. Examples of devices used for these procedures include Pipelle sampler, Novak's curette, Explora sampler, manual vacuum aspirator and Vabra aspirator[4]. These minimally invasive options are increasingly being used for the diagnosis of endometrial cancer, hyperplasia and other endometrial pathologies. Moreover, endometrial biopsy can also identify other hormonally induced changes in the endometrial lining[5,6]. Endometrial sampling is an effective and acceptable way of obtaining endometrial samples for histopathological analysis in the OPD setting[7] as it is less costly, is an outdoor procedure which can be done in few minutes and does not require general anaesthesia. Contraindications to endometrial biopsy include pregnancy, presence of acute cervicitis or endometritis, coagulation disorders and febrile illness[8].

Materials and Methods:

Prior to initiating our study permission was taken from the ethical committee of FFH for our research. A total of 190 patients who came to the Gynae OPD with the complaints of heavy menstrual bleeding, inter-menstrual bleeding, post coital bleeding and post-menopausal bleeding were included in our study. After proper counselling and obtaining written informed consent, endometrial biopsy samples were obtained from these patients using the endocurettes endometrial sampling device in the Gynae OPD. These endometrial samples were labelled, stored in formalin and sent to the Histopathology department of Fauji Foundation Hospital Rawalpindi for evaluation. The results obtained were recorded in a data base. Microsoft Excel software was used to analyse the data and generate tables and charts for our study.

Results :

The mean age of our sample population was 46 years whereas the age ranged from 27 to 80 years. Among the 190 patients who went endometrial sampling, 55 (29 %) had secretory endometrium, 47 (24.7 %) had proliferative endometrium, 23 (12.1 %) had disordered proliferative, 10 (5.2 %) had complex hyperplasia with atypia, 6 (3.1 %) had simple cystic hyperplasia, 6 (3.1 %) had pill pattern, 4 (2.1 %) had benign endometrial polyp whereas 32 (16.8 %) samples were scanty. An important finding was that only 2 out of 190 samples i.e. only 1 % had adenocarcinoma. These results have been depicted in figure 1.



Graph 1: Frequency and percentages of histopathological findings of endometrial sampling using endometrial curettes.

Discussion:

Endometrial sampling is an important step in the evaluation of the patients with menorrhagia, inter-menstrual bleeding, post-coital bleeding and post-menopausal bleeding. By using these minimally invasive office based sampling techniques, endometrial cancer can be ruled out and benign conditions confirmed so that patients can be treated conservatively and radical surgery like hysterectomy can be avoided. Almost all of the pathologies revealed in our results can be managed medically and conservatively. Only 1 % of the patients had adenocarcinomas and only these patients may require radical surgery. In another study done by Yasmin Jaffar et al [9], hysterectomy samples were analysed by histopathology and it was found that all 222 hysterectomies were done for benign conditions like leiomyomas, endometrial hyperplasia etc. If endometrial sampling techniques were used in the evaluation of these patients, many hysterectomies could have been prevented.

Conclusion:

Office based endometrial sampling techniques constitute an important and convenient method of excluding endometrial cancer in women with abnormal uterine bleeding[10] and thus help to prevent radical surgery in these women who could be managed medically or conservatively.

References:

1. Goldenstein SR. Modern evaluation of endometrium. Obstet Gynecol 2010; 116:168-76.
2. Nagele F., H. O'Connor, A. Davies, A. Badawy, H. Mohamed, and A. Magos, "2500 Outpatient diagnostic hysteroscopies," Obstetrics and Gynecology, vol. 88, no. 1, pp. 87–92, 1996.
3. Grimes DA. Diagnostic dilation and curettage: a reappraisal. Am J Obstet Gynecol 1982; 142:1.
4. Elsandabesee D1, Greenwood P. The performance of Pipelle endometrial sampling in a dedicated postmenopausal bleeding clinic. J Obstet Gynaecol. 2005 Jan;25(1):32-4.
5. Apgar BS, Newkick GR, Endometrial biopsy. Primary care 1997;24:303-26.
6. Apgar BS. Dysmenorrhoea and dysfunctional uterine bleeding. primary care 1997;24:161-78
7. Batool T., Reginald P. W., and Hughes J. H., "Outpatient pipelle endometrial biopsy in the investigation of postmenopausal bleeding," British Journal of Obstetrics and Gynaecology, vol. 101, no. 6, pp. 545–546, 1994.
8. Yang GC, Wang L S, Del Priore G.Factors influencing the detection of uterine cancer by suction curettage and endometrial brushing Reprod Med .2002,47:1005- 10.
9. Yasmin Jaffar, Naila Ehsan, Nosheen "Histopathological findings of abdominal hysterectomies in patients presenting with Heavy Menstrual Bleeding (HMB)" Med. Forum. Vol 24. No.2 Feb 2003.
10. Choby BA. Endometrial biopsy. In: Pfenninger JL, Fowler GC, eds. Pfenninger & Fowler's Procedures for Primary Care. 3rd ed. Philadelphia, Pa: Elsevier Mosby; 2010:chap 143.

A COMPARATIVE STUDY TO EVALUATE CHRONOTROPIC AND INOTROPIC EFFECTS OF NIMODIPINE AND VERAPAMIL ON INTACT FROG'S HEART

Javaria Arshad, Naila Abrar, Munir Ahmad Khan

Department of Pharmacology & Therapeutics, Yusra Medical and Dental College, Islamabad

ABSTRACT

Background:

Nimodipine and verapamil are calcium channel blocking drugs. These drugs differ chemically hence their pharmacological actions are also different. Verapamil has predominant action on myocardial calcium channels while nimodipine acts more on Ca++ channels of vascular smooth muscle. Nimodipine has established use in subarachnoid haemorrhage. In this study effect of nimodipine on cardiac muscle has been compared with verapamil. Both the inotropic and chronotropic effects are compared.

Method:

After stunning and pithing of frog, its heart was exposed and the apex was attached to force transducer of Power Lab. Frog's Ringer solution was used as the nutrient medium. Drug solutions were applied directly on the heart and effects were observed and recorded on power lab monitor.

Result:

Verapamil produced characteristic negative inotropic and chronotropic effect on intact frog's heart ($p<0.05$). Nimodipine produced positive inotropic and negative chronotropic effect on intact frog's heart. As 't' test show value of 0.01 regarding force of contraction and 0.007 regarding heart rate as compared to normal baseline reading. On comparison between nimodipine and verapamil regarding force of contraction and heart rate the P values are 0.01 and 0.16.

Conclusion:

In conclusion, nimodipine produced positive inotropic and negative chronotropic effect on intact frog's heart. On comparison with verapamil, nimodipine has increased force of contraction of heart while verapamil has significantly reduced force of contraction of heart. Regarding heart rate both drugs decrease the rate of heart contraction. Clinically, after this observation nimodipine will be helpful for patients with subarachnoid haemorrhage along with cardiac failure.

Keywords:

Nimodipine, Verapamil, Inotropic, Chronotropic, Frog heart, comparison

Introduction:

The incidence of ischemic heart diseases is increasing day by day all over the world especially in urban population1. Calcium channel blockers are used for treatment of heart diseases which include angina, hypertension and arrhythmia.[2] Verapamil has predominant action on myocardial calcium channels while nimodipine is vascular smooth muscle selective, while diltiazem exhibit intermediate selectivity[3]. Regarding nimodipine major interest to date, has focused on its use in the prevention and treatment of the delayed ischaemic neurological deficits that frequently occur in patients with subarachnoid haemorrhages as a result of sustained cerebral vasospasm. It has been said that nimodipine work by relaxing narrowed blood vessels in the brain near the area of bleeding so blood can flow more easily and brain tissue in the vicinity is not effected by hypoxia. This effect reduces brain damage. Intra-arterial nimodipine is effective and safe for the management of symptomatic vasospasm after subarachnoid haemorrhage[4]. Insufficient data is available for

Correspondence:
Dr Javaria Arshad
Department of Pharmacology & Therapeutics,
Yusra Medical and Dental College, Islamabad
E.mail: drjavaria@yahoo.com

effects of nimodipine on cardiac tissue in comparison with the verapamil.

Verapamil belong to chemical class of phenylalkylamine which is a less potent vasodilator than are the dihydropyridines. At the doses of verapamil which are sufficient to produce peripheral dilatation of arterial blood vessel, there are more direct negative chronotropic, dromotropic and inotropic effects than with the dihydropyridines.[5]

Important differences seen among the available calcium channel blockers arise from the details of their interactions with cardiac ion channels and differences in their relative smooth muscle against cardiac effects. Verapamil and diltiazem interact with the calcium channel receptor in a different manner than the dihydropyridines. The dihydropyridines seem to block smooth muscle calcium channels at concentrations below those needed for significant cardiac effects,so they are less depressant on the heart than verapamil.[6]

Based on the existing knowledge of nimodipine and verapamil we have observed the effect of nimodipine on the force and rate of contraction of frog's heart in comparison with the verapamil.

Aims & Objectives:

The aim of the present study was to compare cardiac effects of two type of calcium channel blockers, verapamil & nimodipine on intact frog (Rana tigrina) heart preparation.

Materials & Methods:

Animals: 24 Frogs weighing approx. 500-750 g were used. The nutrient medium used was Ringers solution. The force of contraction and heart rate was recorded on power lab Model ML 856, Serial-T26-2412 through the force transducer. Approval for using frogs for the research study was taken from Institutional Ethical Committee.

Drugs used were Nimodipine $C_{21}H_{26}N_2O_7$ (1,4-dihydropyridine) and Verapamil. Solutions were prepared in distilled water to deliver a dose of 10 µg/kg of nimodipine7 and 8 µg/kg of verapamil. [8]

After stunning and pithing of frog, it was fixed on the frog board with the help of pins. The heart was exposed by cutting the sternum. One end of heart clip was fixed on the apex of the heart and the thread tied to other end was attached to the force transducer (0-500g) MLT-500/A. The transducer transmitted impulses to power lab and the recordings were displayed on the monitor. Three parameters were visualized simultaneously, force of contraction, heart rate and ECG. First the baseline readings were observed. Solutions of drugs were applied directly on the heart through dropper and then the effect of nimodipine was recorded. Then the effect produced by verapamil was recorded. The readings were compared and statistically analysed. The experiment was performed on three groups each comprising of six animals. In group I (Base line) normal heart rate and force of contraction was recorded. In group II effect of nimodipine on heart rate and force of contraction was recorded. In group III (Control) effect of verapamil on these parameters was recorded.

Statistical analysis:

The results were expressed as Means + Standard Error of Means. The arithmetic means of amplitudes of contractions and SEMs were calculated using SPSS version 15. In order to find the significance of the difference between two observations 'student t test' was used.

Results:

Verapamil at dose of 8 µg/kg produced a decrease in force of contraction of heart muscle from 0.15 (mean value) to 0.02 N (mean value) Table (I) and significant decrease in heart rate from 47.9 to 24.4 beats per min Table (II). T-test show P value of 0.03 and 0.004 respectively which is highly significant as values are < 0.05.

Table I: Effect of verapamil on force (N) of contraction of frog's heart.

Force of Contraction (N)		
	Base Line	**Effect of Verapamil**
	0.263	0.021
	0.304	0.054
	0.258	0.015
	0.028	0.012
	0.046	0.01
	0.017	0.065
Mean	0.152	0.029
S.D	0.135	0.0237
SEM	0.051	0.0089

Nimodipine at dose of 10 µg/kg produced increase in force of contraction from 0.15 to 0.20 N Table (III) and decrease in heart rate from 47.9 (mean value) to 30.3 beats per min Table (IV). T-test show P value of 0.01 and 0.007 respectively which is highly significant as values are < 0.05.

Table II: Effect of verapamil on frog's heart rate (beats/min)

Frog's heart rate (beats /min)		
	Base Line	**Effect of Verapamil**
	35.3	17.9
	62.3	21
	49.5	27.6
	46.5	22.6
	39.3	37.2
	54.7	20.5
Mean	47.9	24.4
S.D	9.90	7.01
SEM	3.74	2.65
P value	0.004	

On comparison between verapamil and nimodipine regarding force of contraction of heart muscle figure (I), t test show P value of 0.01 which is significant as P < 0.05.

On comparison between verapamil and nimodipine regarding heart rate, t test show P value of 0.16. Both drugs cause decrease in heart rate figure (II)

Table III: Effect of nimodipine on force (N) of contraction of frog's heart.

Force of Contraction (N)		
	Base Line	**Effect of nimodipine**
	0.263	0.283
	0.304	0.405
	0.258	0.27
	0.028	0.152
	0.046	0.064
	0.017	0.075
Mean	0.152	0.208
S.D	0.135	0.134
SEM	0.051	0.050
P value	0.017	

Table IV: Effect of Nimodipine on frog's heart rate (beats/min)

Rate of Contraction (beats/min)		
	Base Line	**Effect of nimodipine**
	35.3	22.8
	62.3	45.8
	49.5	15.2
	46.5	20.5
	39.3	40
	54.7	38
Mean	47.9	30.3
S.D	9.90	12.4
SEM	3.74	4.702
P value	0.007	

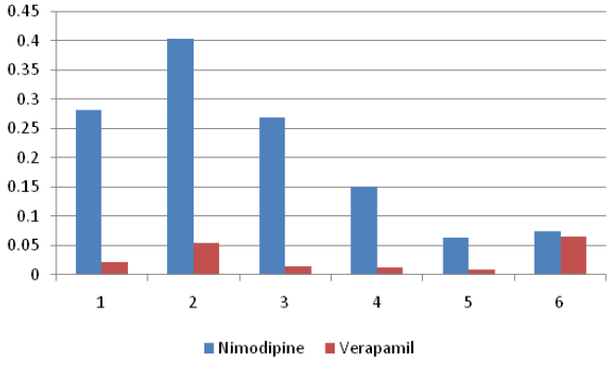


Figure I: Comparison between nimodipine and verapamil regarding force of contraction of heart

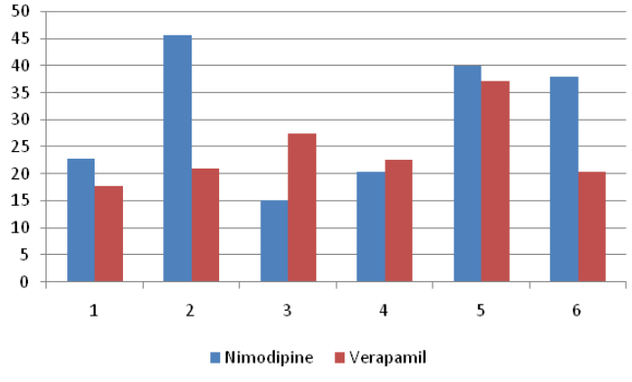


Figure II: Comparison between Nimodipine and Verapamil regarding heart rate

Discussion::

Based on the results shown by the experiment it is evident that verapamil produced characteristic negative inotropic and chronotropic effect on intact frog's heart. As 't' test show value of 0.03 and 0.004 respectively as compared to normal baseline readings, both the values are significant as they are < 0.05. This is in consistent with study conducted by Ponce and his colleagues[9].

Nimodipine produced positive inotropic and negative chronotropic effect on intact frog's heart. As 't' test show value of 0.01 and 0.007 respectively. The values are highly significant as P < 0.05. These values show that nimodipine produced a slight increase in force of contraction of frog's heart this result is in consistent with a study performed by Kazanova GV and his colleagues in Russia in 1990. They performed experiment on anesthetized cats and dogs and found that nimodipine enhances the contractile function of the myocardium 10. In another study conducted by Millard and his colleagues in dogs showed that nifedipine produces increase in left ventricular pressure in comparison to verapamil and diltiazem11 .As both nifedipine and nimodipine are dihydropyridines, they can have similar effect of increasing force of contraction of heart muscle.

Amsterdam et al. (1987) reported that nifedipine and nitrendipine cause a positive inotropic effect in guinea pig hearts, suggesting that calcium antagonists have partial agonistic properties[12]. Positive inotropic effect caused by vasodilator nimodipine can be explained by the 'garden-hose-effect'.[13] This effect explains that many biological tissues exhibit increased stiffness when perfusion pressure is increased. So, nimodipine by causing vasodilatation of coronary vessels results in increase perfusion pressure leading to increase in force of contraction of heart muscle.[14]

The dominant type of calcium channel in cardiac and smooth muscle is L-type and it contain several drug receptors. Nifedipine and other dihydropyridines have been demonstrated to bind to one site on the α1 subunit whereas verapamil and diltiazem appear to bind to closely related but not identical receptors in another region of the same subunit. Binding of a drug to the verapamil or diltiazem receptors allosterically affects dihydropyridine binding. These receptor regions are stereoselective, because marked differences in both stereoisomer-binding affinity and pharmacologic potency are observed for enantiomers of verapamil, diltiazem and optically active nifedipine congeners. In the vascular system, arterioles appear to be more sensitive than veins. The ratio of vascular smooth muscle effects of dihydropyridines is greater relative to cardiac effects than do diltiazem and verapamil. The dihydropyridines may differ in their potency in different vascular beds. For example nimodipine is claimed to be particularly selective for cerebral blood vessels. These differences appears to be due to splice varriants in the structure of the α1 channel subunit.[15]

Nimodipine is a dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. There are at least five different types of calcium channels in Homo sapiens: L-, N-, P/Q-, R- and T-type. CCBs target L-type calcium channels, the major channel in muscle cells that mediates contraction. Similar to other dihydropyridines CCBs, nimodipine binds directly to inactive calcium channels stabilizing their inactive conformation. Since arterial smooth muscle depolarizations are longer in duration than cardiac muscle depolarizations, inactive channels are more prevalent in smooth muscle cells. Alternative splicing of the alpha-1 subunit of the channel gives nimodipine additional arterial selectivity. Compared to other DHP CCBs, nimodipine is more active in the cerebral vasculature than in the periphery. This may be due to its high lipophilicity and ability to penetrate the blood brain barrier. This unique property of nimodipine led to clinical studies for its use to improve neurological outcomes in patients after subarachnoid hemorrhage due to ruptured intracranial aneurysms. While it has been approved as adjunct treatment for this indication, the exact mechanism by which it exerts these effects is unclear. Nimodipine has little effect on cardiac myocytes and conduction cells at therapeutic sub-toxic concentrations.[16,17]

Thus our study has revealed that nimodipine produced positive inotropic and negative chronotropic effect on intact frog's heart. On comparison with verapamil, nimodipine has increased force of contraction of heart while verapamil has significantly reduced force of contraction of heart. Regarding heart rate both drugs decrease the rate of heart contraction.

Clinically, as nimodipine has well established role in subarachnoid haemorrhage, after this study we can say it will be more beneficial in patients of subarachnoid haemorrhage with cardiac failure. Nimodipine will improve cardiac contraction and also decrease after load. Further clinical evaluation is required to establish its use in specific cardiac conditions.

References::

1. Fuster V, Kelly BB. Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health. Washington (DC): National Academic Press (US): 2010;2
2. Sharma HL. Drugs Therapy of Hypertension, Angina Pectoris, Arrhythmias. In Principles of Pharmacology. 2011: 3:279-307.
3. Sharma HL. Drugs Therapy of Angina Pectoris. In Principles of Pharmacology. 2011; 3:284.
4. Alessandra B, Giuseppe KR, Louis P, Lamine A M, Jacques C and Rémy V E. Intra-Arterial Nimodipine for the Treatment of Symptomatic Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage: Preliminary Results. AJNR: 2004; 25: 1067-1076.
5. Nielsen-Kudsk F, Askholt J, Jensen PH. A comparative study of the pharmacodynamic effects of nimodipine and nifedipine in the isolated spontaneously beating rabbit heart. Acta Pharmacol Toxicol (Copenh):1983 ;52(2):105-11
6. Millard RW, Grupp G, Grupp IL, DiSalvo J, DePover A , Schwartz A. Chronotropic, inotropic, and vasodilator actions of diltiazem, nifedipine, and verapamil. A comparative study of physiological responses and membrane receptor activity. Circ Res:1983; 52 (2):129-37.
7. Schindler l, Weindlmayr-Goettel M, Susani M, Gilly H, Steinberethner K. Anesth Analq. 1994; 78 (1): 87-93.
8. Sudhakar L. The effect of verapamil and diltiazem on cardiac stimulant effect of adrenaline and calcium chloride on isolated frog heart. IJMRHS. 2013; 2(2): 143-146.
9. Ponce-Hornos JE, Effects of verapamil. Am J Phsiol : 1990; 258 (1): 64-72
10. Kazanova GV, Kirsanova G, Tsarin IB and Chichkanov GG. A comparative study of the effects of nimodipine and flunarizine on the intact and ischemic myocardium. Farmakot Toksikot:1990 ; 53 (3): 13-5.
11. Millard RW, Grupp G, Grupp IL, DiSalvo J, DePover A , Schwartz A. Chronotropic, inotropic, and vasodilator actions of diltiazem, nifedipine, and verapamil. A comparative study of physiological responses and membrane receptor activity. Circ Res:1983; 52 (2): 129-39.
12. Amsterdam M, Has M, Zaagsma J. Dynamic and kinetic differences of the vascular and Myocardial effects of Ca++ Antagonists in the Rat heart. J Cardiovasc Pharm. 1987; 9 (5) 570-577.
13. Yukihiro K, Mary C, Corretti, Hideo, Kusuoka, Eduardo M. Mechanism of early ischemic contractile failure. Inexcitability , metabolite accumulation or vascular collapse. Circ. Res: 1991; 68:255-262.
14. Punt N C, Amsterdam M Van, Goldjin M M, Hass M, Zaagsma J. Positive inotropic effects of calcium channel antagonists are not necessarily caused by partial calcium agonism. Arch Pharmacol.1988; 338:211-214.
15. Hachisu M , Pappano AJ. A comparative study of the blockade of calcium-dependent action potentials by verapamil, nifedipine and nimodipine in ventricular muscle. JPET: April 1983; 225 (1) 112-120.
16. Nimotop tablets. [Electronic version]. e-CPS. Retrieved August 13, 2009.
17. Striessnig, J. Ca2+ channel blockers. In S. Offermanns, & W. Rosenthal (Eds.). Encyclopedic reference of molecular pharmacology. 2004 (pp. 201-207). Berlin, Germany: Springer

BURDEN AND INDICATIONS FOR OCULAR ULTRASONOGRAPHY IN OUTDOOR PATIENTS

Sarah Amber Samuel, Tahira Ayub[1], Ayesha Amin[2]

Department of Ophthalmology, Christian Hospital, Taxilla
[1]Foundation University Medical College, Islamabad
[2]Al-Shifa Trust Eye Hospital, Rawalpindi

ABSTRACT

Purpose:

To assess the burden and indications for ocular ultrasonography in outdoor patients.

Material and Methods:

A retrospective observational study written after reviewing the records of 3010 patients from a period of 15th March 2014 to 05th April 2014 presenting at the general, subsidized and private OPD of ASTEH. After ethical approval structured performa were filled and the results were analyzed using SPSS.

Results:

107 (3%) patients were advised B Scan. The patients were in the age range 17-80 years. There were 60 males and 47 females requiring B Scan among which 06 were bilateral cases. 44 patients were advised B scans for right eye and 57 were advised B Scan for left eye. All of the patients had their B Scan done the same day.81 cases had cataract as the reason for which B Scan was advised and 26 had other pathologies as the reason for B Scan which included Retinal detachment, Endophthalmitis, Vitreous hemorrhage, Corneal abscess, Anterior uveitis, PDR and intra ocular foreign body.

Conclusion:

B Scan is not offering a major burden to ASTEH and provision of service is 100% to all patients on the same day as advised.

Keywords:

Ultrasonography, Endophthalmitis, Corneal abscess, Retinal detachment

Introduction:

B-scan ultrasonography is an important adjuvant for the clinical assessment of various ocular and orbital diseases. With understanding of the indications for ultrasonography and proper examination technique, a vast amount of information can be gathered which is not possible with clinical examination alone[1,2].

The rationale of this study is to measure the burden of B Scan being faced by ASTEH in the outdoor patient department alone on daily basis. It measures the frequency or volume of service provided in terms of number of B Scans advised and effectiveness of delivery. The report also helped to find out the indications for B Scan in those patients which can add up valuable information to the future research studies focusing on B scan. It is a daily procedure contributing to the major burden as most commonly prescribed diagnostic and therapeutic procedure for outdoor and admitted patients irrespective of the speciality and clinic.

Correspondence:
Dr. Sarah Amber Samuel
Department of Ophthalmology, Christian Hospital Taxilla.
E.mail: sarahsamuels1@hotmail.com

Methodology:

Study Design: Retrospective observational study. The study was done after reviewing the records of 3010 patients from a period of 15th March 2014 to 05th April 2014 presenting at the general, subsidized and private OPD of ASTEH. After ethical approval structured performa were filled and the results were analyzed using SPSS.

Restults:

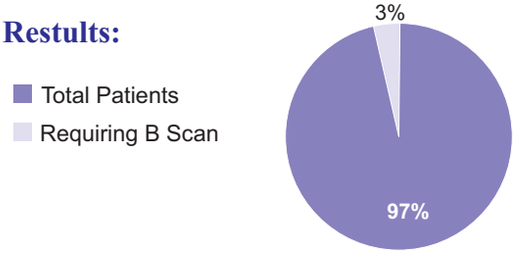


Fig. 1: Proportion of Patients Presenting to OPD and Requiring B Scan

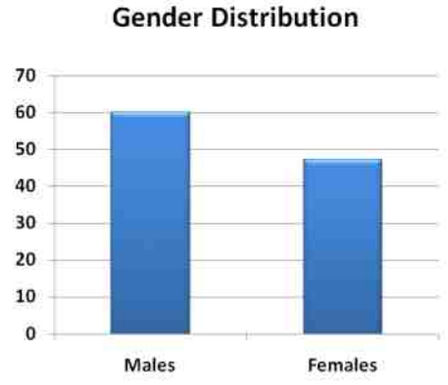


Fig 2: Gender distribution among cases requiring B Scan

The main reasons/indications for B Scan were divided into two categories:

- Cataract
- Poor retinal view

The patients with cataract were further subdivided into those who had a normal B scan and those with an abnormal B Scan. Poor retinal view was subdivided according to the diagnosis. The figures are summarized in table I.

Table I: Indications for Ultrasonography

Sr.#	Causes for Ultrasonography	Number of cases (%)
1.	Cataract • Normal B Scan • Abnormal B Scan	**81** 70 11
2.	Poor Retinal View • Retinal detachment • Endophthalmitis • Vitreous hemorrhage • Corneal abscess • Anterior uveitis • PDR • Intra ocular foreign body	**26** 12 05 04 02 01 01 01
	Total	**107**

Discussion:

B-scan ultrasound is most useful when direct visualization of intraocular structures is difficult or impossible. Situations that prevent normal examination include lid problems (eg, severe edema, partial or total tarsorrhaphy), keratoprosthesis, corneal opacities (eg, scars, severe edema), hyphema, hypopyon, miosis, pupillary membranes, dense cataracts, or vitreous opacities (eg, hemorrhage, inflammatory debris)[2,3].

In such cases, diagnostic B-scan ultrasound can accurately image intraocular structures and give valuable information on the status of the lens, vitreous, retina, choroid, and sclera. However, in many instances, ultrasound is used for diagnostic purposes even though pathology is clinically visible. Such instances include differentiating iris or ciliary body lesions; ruling out ciliary body detachments; and differentiating intraocular tumors, serous versus hemorrhagic choroidal detachments, rhegmatogenous versus exudative retinal detachments, and disc drusen versus papilledema[4].

A study was done at ASTEH to estimate the burden of B Scan. Out of the 3010 patients only 3% required further investigation in the form of B Scan. Rest was diagnosed by clinical examination alone. This low rate of the requirement of investigation can be attributed to the skills and expertise of the examining/treating Ophthalmologists.

The most remarkable finding was the provision of the test on same day as it was advised to all the patients making it 100% effective. Also comprising only 3% of the total patients, it is not offering a significant burden to the hospital. The demand is met effectively and no additional resources and finances are required to be allocated in this regard.

This audit helped to gather additional information which included that the maximum number of cases being advised this procedure were cataract. B Scan was advised to confirm the status of the posterior segment of the eye. The remaining cases were those having poor retinal view which was further subdivided according to the cause giving a prevalence of the specific cases in a limited data. Among them the highest cases were of retinal detachment followed by endophthalmitis, VH, corneal abscess, anterior uveitis, PDR and IOFB. It is to be kept in mind that the data was collected for adult patients with age range of 17-80 years.

It was also observed that more number of male patients required B Scan which can be due to the nature of life style with the male being more exposed to trauma and job related exposure.

This additional data can be used for future research and audit projects as not much relevant data about the indications of B Scan is present internationally. It is the first study of Asia considering these aspects of B Scan. Only one more study from Moorfields Hospital is present in which 100 consecutive patients referred to orbital clinic were considered and the results were[5]:

· 62/100 diagnosed by clinical examination and

routine X-rays alone

- 38/100 required further investigations
- 24/38 received ultrasonic investigation
- 13/24 correctly diagnosed by ultrasound 19/24 ultrasound 'valuable'
- 6/24 ultrasonic abnormality was noted
- 5/24 no ultrasonic abnormality noted

Conclusion:

B Scan is not offering a major burden to outdoor OPD at ASTEH and provision of service is 100% to all patients on the same day as advised.

Limitations

- Limited time period for which data is collected.
- Most patients of Zakat/free category and a few of subsidized category present late because of non-affordability therefore increasing the prevalence of complications found on Ultrasonography as compared to the private category patients.

Recommendations

- Such studies should be repeated annually to know about the burden a hospital has to bear for B Scan, its effective provision and changing trends in indications for B Scan.
- There should be improved record keeping preferably electronic data storage.
- A separate room for B Scan.

References:

1. Qureshi MA, Laghari K. Role of B-scan ultrasonography in pre-operative cataract patients. Int J Health Sci (Qassim). Jan 2010;4(1):31-7. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3068804/
2. Byrne SF, Green RL. Ultrasound of the Eye and Orbit. 2nd ed. St. Louis, Mo: Mosby Year Book; 2002
3. Coleman DJ, Silverman RH, Lizzi FL, Rondeau MJ. Ultrasonography of the Eye and Orbit. 2nd ed. Lippincott Williams & Wilkins; 2006
4. DiBernardo C, Schachat AP, Fekrat S. Ophthalmic Ultrasound: A Diagnostic Atlas. New York: Thiemes Medical Publishers, Inc; 1998
5. Marie Restori,David McLeod,John E Wright. Diagnostic ultrasound in ophthalmology. Journal ofthe Royal Society of Medicine Volume 73 April 1980

CAN CLINICAL EXAMINATION OBVIATE THE NEED FOR BIOCHEMICAL EVALUATION BY THYROID FUNCTION TESTS IN PATIENTS WITH GOITRE?

Muhammad Atique Sadiq, Eitezaz Ahmed Basher, Kokab Shah, Inamullah Shah, Khalil ur Rehman, Gul Naseeb

Deparment of Surgery, Fauji Foundation Hospital, Rawalpnidi

ABSTRACT

Objective:

To assess validity of clinical examination and thyroid function tests in patients with goitre.

Design:

Cross sectional study.

Place & Duration of Study:

This study was carried out in the Department of Surgery, Fauji Foundation Hospital, and Rawalpindi from 1st July 2010 to 30th June 2012.

Design:

A total of 100 patients were included in this study. All of them were females who were clinically euthyroid. Mode of presentation was the outdoor patient department of Fauji Foundation hospital. Presenting complaint was swelling in front of neck. All patients were evaluated clinically and impression about thyroid status was drawn which was later compared with thyroid function tests. Sixty eight patients were clinically found to have simple goitre and 62 out of these were confirmed to be so by thyroid function tests whereas remaining 6 patients were found toxic biochemically. Clinical diagnosis of euthyroid goitre was accurate in 91.17 % of cases.

Thirty-two patients were having clinical features of toxicity which was confirmed to be so by biochemical assessment. So accuracy of clinical assessment of toxicity was 100 %.

Conclusions:

Thyroid status of a patient with goitre can promptly be assessed clinically. Thyroid function tests are only required when one or more of clinical features of toxicity make clinical judgment confusing.

Keywords:

Goitre, thyroid function test, Hyperthyroidism, hypothyroidism

Introduction:

Goitre is the cardinal symptom of most thyroid diseases. It develops as a result of stimulation of thyroid gland by TSH in response to a low level of circulating thyroid hormones[1].

The prevalence of goitre in iodine-deficient regions is up to 25%-54%. The mountainous regions in north-west of Pakistan & Kashmir are probably the worst affected areas in the World[2-3]. These areas are labeled as 'goiter belt' due to high incidence of the disease in the area[4].

Correspondence:

Dr. Muhammad Attique Sadiq
Department of Surgery, Fauji Foundation Hospital, Rwp.
E.mail: dratiqsadiq@yahoo.com

The development of goitre is more common among females due to increased requirement of iodine at the age of puberty. In addition females require extra iodine during pregnancy making them prone to develop goitre[15,6].

Thyroid gland synthesize thyroxine or T4 (80%) and triiodothyronine or T3 (20%)[7,8,11]. In circulation, all T4 is secreted by thyroid gland but most of T3 (80%) is produced from conversion of T4 to T3 in peripheral organs. In serum most of T4 and T3 is bound to binding proteins and only 0.02% of T4 and 0.3% of T3 is free. Because of their higher

diagnostic value, free T4 and free T3 measurement is preferred to total (free + bound) hormone determination[9].

The patients with goitre can be euthyroid, hyperthyroid or hypothyroid.

To evaluate the thyroid status of a patient with goitre, the most cost-effective tools are the hands, ears and mouth of the thyroid clinician10.

However, this technique of clinical assessment of thyroid status is frequently underestimated and its accuracy is not valued since the clinicians depend largely on laboratory armamentarium to tests thyroid functions.

Therefore, we examined the question whether precise history and thorough clinical examination of thyroid gland can obviate the need of biochemical evaluation by thyroid function tests.

Materials & Methods:

After taking permission from the ethical committee of the hospital and written consent from the patients, study was carried out in the Department of Surgery, Fauji Foundation Hospital, Rawalpindi from 1st July 2010 to 30th June 2012. Information was collected on a designed proforma.

As this hospital provides health care services to the families of ex-servicemen, therefore all the patients included in study were females. After precise history and clinical examination of 100 patients with goitre, findings were recorded on the proforma and diagnoses were established that whether the patient is clinically euthyroid, hyperthyroid or hypothyroid. After that, blood samples were taken for biochemical evaluation so that a comparison of clinical finding with thyroid function tests could be made. The consecutive sampling technique was employed and 100 female patients with enlarge thyroid gland were included in the study. Recurrent goitre and patients with proven malignancy of thyroid gland were excluded from the study.

The data was analyzed by using SPSS version 16. The spearman correlation coefficient was calculated to determine the correlation between various attributes of the patient with goiter. A multivariate regression analysis was used to establish the neutrality between the clinical assessment and bio chemical examination (two alternate tests) employed for the evaluation of the status of thyroid in patients with goitre.

Results:

Sixty-eight patients were clinically found to have simple goitre and 62 out of these were confirmed to be so by thyroid function tests whereas remaining 6 patients were found toxic biochemically.so clinical diagnosis was accurate in 91.17 % of cases.

Thirty-two patients were having clinical features of toxicity which was confirmed to be so by biochemical assessment. So accuracy of clinical assessment of toxicity was 100 %.

Around 72 percent of the total females were up to the age of 47 years indicating that problem was dominant in mostly young or middle-aged women. The emotional lability was found to have very significant effect so as the Pearson correlation coefficient for clinical diagnosis and bio chemical diagnoses was found 0.70 hence indicating quite high correlation between the two tests.

The correlation coefficient was found relatively high -.23 between age and goiter with negative sign that re-confirmed the enormity of the problem particularly in young and middle aged women. The correlation coefficient of the other observed attributes of the patients like sex, emotional liability, age, pulse, palpitation, tiredness with goitre etc. were found to be comparatively low. The F-value was also found to be highly significant for two models that indicates that predictors jointly affect the clinical and bio chemical diagnosis significantly.

The results from multivariate regression analysis showed that there was neutrality between two models based on clinical versus bio-chemical diagnoses as the R-square value was found statistically significant for both models as well as very small difference was found between two competing tests. This indicates the efficacy of clinical assessment. The two models were found to have similar adjusted R-square value that was .82 that confirmed the neutrality of the two tests.

In clinical diagnoses model, palmar sweating, emotional lability and tremors were found statistically significant as the p value of each was found to be less than 0.05 (p value less than 0.05 was considered significant).

Table-1: Multivariate Regression Analysis; Clinical Diagnostic Variables

	Co- efficient	p-value
constant	3.032	.000
Pulse	-.058	.109
Weather preference	-.007	.847
Weight change	.016	.671
Palmar sweating	-.489	.000
Tremors	-.485	.000
Bruit	-.036	.819
Emotional liability	.232	.017
Tiredness	.007	.896

In bio-chemical diagnoses,the values taken as reference were TSH (0.3–3.3 mU/L) T4 (10–30 nmol/L) and T3 (3.5–7.5 µmol/L).The values of TSH was found statistically significant(p value less than .05) as shown in table below:

Table-2: Multivariate Regression Analysis; Bio-chemical Diagnostic Test of Thyroid Status

	coefficient	p-value
T3	-0.94	.442
T4	-0.44	.408
TSH	-.438	.000

Discussion:

Persistent stimulation of thyroid gland causes diffuse hyperplasia. Later as a result of fluctuating stimulations a mixed pattern develops with areas of active and inactive nodularity. Active nodules become more vascular and hyperplastic until haemorrhage results in necrosis. Continual repetition of this process leads to nodular goiter. Toxicity results in early tiredness, emotional liability, heat intolerance, weight loss, excessive appetite, palpitations, tachycardia, hot moist palms myopathy and thyroid bruit.

Presently there are a sufficient number of sensitive and specific tests of thyroid function to establish a diagnosis of thyroid status with a high degree of precision. A variety of clinical situations like thyroid hormone resistance states, alterations in thyroid-binding proteins and nonthyroidal illness, however, challenge the clinician to evaluate the thyroid status of the patient. Clinical assessment remains superior in this situation to help in deciding the diagnosis and further management.

Conclusion:

Despite the sophistication of today's thyroid function tests, a good, careful, detailed clinical examination suffices the diagnosis of thyroid status in most of the patients with goitre. Thyroid function tests are, however, required in certain cases posing diagnostic dilemma. The prudent use of Thyroid function tests only in such cases saves the institution from unnecessary financial burden.

References:

1. Sooch SS, Deo MG, Karmarker MG. Prevalence of endemic goiter with iodized salt. Bull WHO 1973. 49:307
2. Zafar A, Survey of school going children in Murree for prevalence of goiter. J Surg PIMS 1993;(3):62-65
3. Delang F. The disorders induced by iodine deficiency thyroid 1994;4(1): 107-28
4. Zahid MA. Role of thyroid scan in the management of thyroid disorders. Annal of PIMS 2006;2(1):92-94
5. Tariq Saeed, ShahidMahmood, Muhammad Taimur, Sadaf Faisal Bhopal. Co relation of thyroid function test with clinical presentation. Medical Forum,2011;22(9):33-35
6. Küpper FC, Carpenter LJ, McFiggans GB. Iodide accumulation provides an inorganic antioxidant impacting atmospheric chemistry: Proceedings of the National Academy of Sciences of the United States of America 2008. 105(19): 6954–8.
7. Venturi, S; Bégin ME.Thyroid Hormone, Iodine and Human Brain Evolution". Environmental Influences on Human Brain Evolution: John Wiley & Sons. 2010:105–124.
8. Sapin R, Schlienger JL. Thyroxine (T4) and tri-iodothyronine (T3) determinations: techniques and value in the assessment of thyroid function.Ann BiolClin, 2003;61(4):411-20.
9. Biersack HJ, Hotze A. The clinician and the thyroid.Eur J Nucl Med,1991;18(9):761-78.
10. Wong ET, Steffes MW. A fundamental approach to the diagnosis of diseases of the thyroid gland:Clin Lab Med,1984;4(4):655-70.
11. Khandelwal D, Tandon N.Overt and subclinical hypothyroidism: who to treat and how. Drugs. 2012 Jan 1;72(1):17-33.

Foundation University Med J 2014; 1(2):28-33 Review Article

NANOTECHNOLOGY AND EXPLOSION IN NANO-MEDICINE DEVELOPMENT

N. M. Butt

Preston Institute of Nano Science and Technology (PINSAT), Preston University, Islamabad

ABSTRACT

Nanotechnology is the emerging and fast growing technology in the world.The idea of nanotechnology was first derived from the lecture given by the Nobel Prize Winner in Physics, Richard P. Feynman in December 1959 on the topic "There's Plenty of Room at the Bottom"[1] and the term "Nanotechnology" was first introduced in the scientific literature by the Japanese solid state Physicist Norio Taniguchi in 1974[2]. He was engaged in semiconductor physics looking at the effect of electronic properties of a material when a single atom is deposited on atomic layers of another substrate. Norio was thus controlling the use of single atoms in an attempt to make better semiconducting devices like transistors. Thus he named this technology as nanotechnology as the atoms and molecules he was controlling are of sizes of nanometers. Independently the term "nanotechnology" (which paralleled Taniguchi's "nano-technology") was applied by Drexler in his 1986 book Engines of Creation: The Coming Era of Nanotechnology which popularized Drexler's ideas and the concept of nanotechnology to a wide audience[3].The size of a single atom of Helium for example is about o.1 nanometer[4]. Scientists using and controlling atoms and molecules for making devices started using the term nanotechnology.

The term "Nanotechnology" is defined as the study, manipulation, control and use of nanomaterials and their structures at nano sizes i-e sizes between 0.1 nanometer (nm) and100 nanometers. "To give an idea of how small 1 nm is, the thickness of a human hair or a sheet of paper is some 80,000 nm (1nm is one billionth of a meter. The sizes of atoms and molecules are thus in nanometers or what we may call "at nanoscale"). Looking in another way nanotechnology (the word "nano" is derived from Greek word which means "dwarf".) is the creation of devices like nanosensors[5]. By using nanomaterials (nanoparticles of silver, gold, iron, zinc and carbon nanotubes, quantum dots etc.) and by controlling the matter at the nanometer scale (between 0.1-100 nm). It is important that nanomaterials should have atleast one dimension at the nanoscale. Some nanomaterials are three dimensional (nanoashells,quantum dots, nanoparticles), some are two dimensional (single walled carbon nanotubes, nanowires, fibers) and some are one dimensional (anti-adhesive anti-coating layers, coatings).

Since the study and control of atoms concerns with all types of materials whether biological, chemical or engineering materials, the nanotechnology is therefore inherently multidisciplinary and it gives the concept of joint and interrelated sciences in which all the fields merge. It is the most interdisciplinary science and technologyinvolving Physics, Biology ,Chemistry, Engineering etc., Nanotechnology is further divided into different fields depending upon its applications like nanobiotechnology, nanoengineering or nano medicine etc., depending upon which field of science and engineering is under consideration[6]. Similarly, nanoelectronics is the combination of electronics and nanotechnology.

Keywords:

Nanotechnology, nanometers, nanoscale, nanoshells, nanoparticles

Importance of Nanotechnology:

This technology is applied to almost all kinds of industries,like for example, health care, medicine, energy, clean drinking water, environment, defense, pharmaceuticals and drugs, solar cells, oil and gas exploration, communication, information technology, construction industry and what not. The reason is that it is based on the control and the use of very small size materials (the nanoscale sizes, as small as the atoms and molecules, the size of nanometers) in the industrial products and by doing so the performance of the product is greatly enhanced and as well as the value is added.

The scientific reason for improvement in performance of industrial products is that smaller the particle size of the material used, the surface to volume ratio increases and therefore the bulk properties (mechanical, chemical, electrical etc.) are greatly different than the properties of these

Correspondence:
Professor N. M. Butt
Preston Institute of Nano Science and Technology (PINSAT)
Preston University, Islamabad.
E.mail: nmbutt36@gmail.com

materials at the nanoscale.The other important scientific reason of different properties at nanoscale (the atomic scale) is that the laws governing the behavior of atoms and molecules are the quantum laws and the classical laws (of physics or chemistry) do not hold at the atomic sizes. Consequently the experience of atomic science and technology greatly helps the nanotechnology.

Since nanotechnology is being used in products of all types of industries therefore Nanotechnology is rightly being referred to as another Industrial Revolution. Advanced countries have invested and are investing to the tune of annually billions of dollars from mainly two points of view; first to excel in socio economic and strategic matters as compared to the competing countries and second, to lead in defense to become the most powerful country among bigger nations. Thirdly also to have strong economic and strategic influence on the developing countries to keep their hegemony.

Socio-economic Importance Of Nanotechnology:

Nanotechnology is such an important socio-economic force that it is going to influence our socio-economic structure for the next 40-50 years.It is estimated that the global marketing of nanotechnology based products will be to the tune of over 2-3 trillion by 2015 and that there would be job creation of about 2 million with 1 million jobs only for USA[7]. This is huge job requirement.

According to November, 2011 survey of a German Company[8] already some 2586 nano based industrial products are on the global market.

Nanotechnology and The Advanced Countries:

Advanced countries are in a serious race to lay hands on nanotechnology for the reasons that they want to acquire the economic and strategic hegemony over the poor and developing nations as early as possible. The result is that countries like USA, Japan, China, EU countries are investing billions of dollars annually and all of them are pursing nanotechnology as their top national level programs with of course full support of the top political and bueurocratic leaders .Taking the case of USA the budget of National Nanotechnology Initiative(NNI) has been increasing every year and from 2001- 2014 USA has spent about $ 21 billion (with about $1.5b for the year 2015) since the inception of the NNI in 2001 ,including the 2015 request[9]. Russia was a little behind and President Putin allocated on priority $5.5b in the year 2007 to be spent on urgent basis during the next 5 years.EU is spending a similar amount on Nanotechnology. China is going very fast as of 2013 the research publications in Nanotechnology by China has surpassed those of USA[10].

Apart from government investments in Nanotechnology lot of companies have invested heavily in Nanotechnology business. At the latest count, over 2100 companies from 48 countries are involved in nanotechnology research, manufacturing or applications - a number that keeps growing at a considerable pace.

With more than 1100 companies, the U.S. is home to roughly half of all nanotechnology firms. 670 companies are in Europe, 230 in Asia and 210 elsewhere in the world. Within Europe, Germany is represented with 211 companies, followed by the U.K. with 146 companies.

Such is the rapid world economic shakeup nanotechnology has caused just in the last 10 years.

Nanotechnology & Neighboring Countries:

Neighboring countries like India and Iran are also following national level programs of Nanotechnology. Due to the importance given to nanotechnology development on national level by the President of Iran Mahmoud Ahmadinejad, Iran now claims to be the 8th country of the world and first in the region in terms of research publications of nanotechnology and claims several important patents for industrial use[11]. The former President of India said that one of the two technologies that will take India by 2015 to the level of advanced countries is Nanotechnology. Some 30 Indian private companies are involved in the business of nanotechnology[12].

Nanotechnology in Pakistan:

As early as 2003 Professor Atta ur Rahman, as Minister of S&T, with the initiative of the author, set up a National Commission on Nano Science and Technology (NCNST) of which the author worked as Chairman (on honorary basis) from 2003 -2008 and then with the funds of about Rs 900 million from HEC and MoST , nanotechnology projects were funded at Q.A. Univ, PCSIR, CIIT, PIEAS, PINSTECH and NIBGE.

These laboratories are now equipped with state of the art nanotechnology instruments and are publishing research papers in reputed Impact Factor journals abroad. A recent paper published by PINSAT ,Preston University , it was found that the number of research papers from Pakistan in nanotechnology has increased 10 times during the last 8 years[13] This is quite encouraging.

Awareness of Nanotechnology in Pakistan:

Due to the nanotechnology activities at laboratories in Pakistan some awareness has been created but much more is needed to be done as nanotechnology has acquired a fast growing status across the world and we cannot afford to stay behind.

It is important to note that the Present Government of Muslim League (N) as manifesto has included Nanotechnology in the S&T chapter of this manifesto[14]. It is hoped that the Ministry of Science and Technology will take advantage of this commitment to reap the important Socio-economic benefits of nanotechnology for our people using this technology in industry and all other walks of life where useful.

Human Resource Development in Nanotechnology:

Since nanotechnology is going to influence the societies for next 40-50 years, there is need of producing specifically qualified and trained individuals for better, efficient and safe utilization of nanotechnology.Several universities across the world have therefore initiated degree programs for BS, MS and Ph.D studies. Some advanced countries have already introduced the programs for nanotechnology courses in schools and programs for awareness of public about the nanotechnology benefits and risks.

In Pakistan apart from the R&D activities mentioned above BS degree program in "Nanoscience and Nanotechnology"was started in Fall-2010 at the Preston Institute of Nano Science and Technology (PINSAT) of the Preston University, Islamabad.This is in line with the contemporary requirement as in about 100 institutions abroad the degree programs in nanotechnology are now being executed[15].In Pakistan PINSAT is the first and the only Institute for the BS degree program. Other universities will do so in times to come as the MS and Ph.D programs are already being done in a couple of other universities (P.U Lahore, IST Islamabad, CIIT Islamabad, GIKI Topi) and to feed these higher programs, BS programs will have to be strengthened.

Some Exotic Applications of Nanotechnology:

i. Treatment of Cancer and aids at cell size (tumor of about 100 times smaller than human hair thickness) – expected complete cure at the start.

ii. Treatments of Alzheimer and neurological diseases, never possible to treat before.

iii. Cardiac ,T.B, anthrax, efficient treatments of several diseases.

iv. MRI ,lab on chip (a tiny drop of blood giving tests of many diseases at the same time).

v. Nano sensors of sensing explosives several hundred times more sensitive than sniffing–dogs used today.

vi. Honey–Bee size small drones for military intelligence purposes.

vii. Dust free mirrors and glass coatings for big buildings.

viii. Wrinkle-free, stain-free clothes from tea, coffee, mud, ketchup stains.

ix. Shirt thickness bullet proof materials, fire proof nano materials etc.

Many defense applications like soldier cloaks, sensors for explosives, small and efficient communication systems, aerospace materials etc.

Nanotechnology in The Field of Medicine:

Similarly in the field of medicine and dentistry there has been revolution in the efficacy of the diagnostic and therapeutic aspects of healthcare[16,17].

In Medicine in the treatment of diseases like, Cancer, Aids, Alzheimer, neurological diseases etc have opened the way to treat them.Particularly world around the focus is on diagnostics and treatment of cancer using nanotechnology and immense literature is available on the internet regarding recent books on nanomedicine and nano research journals. [18,19]

In the field of pathology again a lot of literature is coming out. Even important project of developing "artificial retina" using graphene (the wonder nanomaterial of single atom thick layer of carbon

atoms,transparent, stronger that steel, conductor of electricity better than copper etc. and nanomaterial which earned 2010 Nobel Prize in Physics for Andre Geim and Konstantin Novoselov"for groundbreaking experiments regarding the two-dimensional material graphene".

A variety of ophthalmology researches are coming forth day by day[20, 21].

In pathology the nano markers of several diseases are found from one sample of blood[22].

The dental materials in particular are being produced having much better efficacy and performance In fact there is an enormous amount of applications of nanotechnology in almost any branch of medicine and dentistry, ranging from diagnostics to treatment of diseases more efficiently and treatment of those disease not possible before.

In the next 10–15 years, nanotechnology is likely to revolutionize the practice of medicine and have a significant impact on human health. Nanotechnology is already contributing to the development of new drugs, biologics, and medical devices and the augmentation of existing therapeutics. Over 200 companies are involved in nanomedicine research and development (R & D), 38 nanomedicine products are currently on the market and dozens of additional products are the pipeline. Current total annual sales have reached $6.8 billion, and the market is expected to grow to $12 billion by 2012. The U.S. Food and Drug Administration (FDA) has approved 9 different types of therapies that employ nanoscale materials, including products used for medical testing and imaging, drug delivery, wound healing, and bone and tissue repair. To date, drug delivery has been the most popular application of nanotechnology to medicine, accounting for 78% of sales and 58% of patent filings worldwide.[23]

Nanotechnology is expected to have a major impact on cancer treatment by making it possible to target chemotherapy to malignant tissues. In neurology, products under development include nanoparticles to aid drug delivery and neurosurgery, nanowires for monitoring brain activity, nanofiber brain implants, and nanoscaffolds to repair neural tissues

It is quite justified to call a revolution in Medicine and Dentistry due to the applications of Nanotechnology in these fields now commonly referred to as Nanomedicine and Nanodentistry.

The Fig. below illustrates briefly the aspects of nanomedicine.

Schematic illustration of nanotechnology revolutionizing biomedical sciences.

Nanodentistry:

Similarly in nanodentistry there are exotic things which are being done now and which were otherwise very cumbersome and time taking or were not treatable. Some of these are which nanodentistry will make possible for the new potential treatment opportunities in dentistry which include; one sitting in place of several sittings for a treatment, local an aesthesia, dentition re-naturalization, permanent hypersensitivity cure, complete orthodontic realignments during a single office visit, covalently bonded diamondised enamel, continuous oral health maintenance using mechanical dentifrobots, and creation of artificial bone and teeth.

Risks and Ethics of Nanotechnology:

As the use of nanomedicine expands , to minimize the risks to the human beings , the ethics, policy, and the regulatory aspects become very important [24].The risks of damage to human beings can occur through inhalation of nanomaterials, through interaction with skin, by injection and by swallowing. Those who work in the factories producing or using nanomaterials and for making the industrial products stand at risk. It is therefore important to proactively address the ethical, social and regulatory aspects of nanomedicine to minimize its adverse impacts on the environment and public health and to avoid a public backlash. At present, the most significant concerns involve risk assessment, risk management of engineered nanomaterials (ENMs), and risk communication in clinical trials.

Although socioeconomic benefits to the society are much greater than the known risks there is a genuine need for emphasis on doing extensive R&D in this area so as to give protection to the public. At present

there are no specific regulations with respect to the nanotechnology and nanomaterials but guidelines of regulations of toxic materials are used where necessary.

In certain countries the consumer associations are conscious of possibility of risks involved in the use of nanotechnology and are active in safeguarding the rights of human beings.

Conclusion:

Nanotechnology being the most recent and highly socioeconomic in its effect Pakistan needs to put it as its national priority as the advanced countries and some neighboring countries have done so.This is important if we have to safeguard our economic, strategic and security aspects as it is applied in all kinds of industries, moreimportantly toour export oriented Industries like Textiles at Faisalabad, Sports and Surgical goods at Sialkot. This is necessary to protect the exports in competition with other countries like Korea, India and Taiwan etc., who are using nanotechnology in their products to improve quality and would thus be a great threat to our export earnings. Also the development of Human resource in the form of degree programs and nanoeducation needs to be emphasized. With reference to this review article the emphasis on nanomedicine and nanodentistry R&D and education should be emphasized. Some courses on Nanomedicine should be introduced in the curriculum of MBBS and courses on nanodentistry in BDS degree programs should be introduced so that future doctors are well qualified and trained in the new revolutionary developments in medicine and dentistry based on nanotechnology.

The simple advice to the prospective medical doctors and students is that only go to the internet first to know the extent of mind boggling disease diagnostic and disease treatment opened by nanotechnology and then to the research journals of nanomedicine and nanodentistry and you will be so so fascinated that you will a whole life career in this revolutionary technology and serve our dear Pakistani people and the humanity at large to keep the healthy and productive. God bless you. Ameen.

Acknowledgments:

The author acknowledges the support of Dr Abdul Basit, Chancellor Preston University in provision of all facilities to do this work I am very grateful to Mr. Haroon Asghar for his help in preparing the manuscript.

References:

1. Feynman, Richard P. There's Plenty of Room at the Bottom. Engineering and Science, 23(5). pp. 22-36, (1960) . ISSN 0013-7812 http://resolver.caltech.edu/CaltechES:23.5.1960Bottom
2. Taniguchi, Norio "On the Basic Concept of 'Nano-Technology'". Proceedings of the International Conference on Production Engineering, Tokyo, 1974, Part II (Japan Society of Precision Engineering).
3. Engines of Creation: The Coming Era of Nanotechnology , Anchor Books, Random HouseINC.; New York, 1986 - www.anchorbooks.com.
4. Basdevant, J.-L.; Rich, J.; Spiro, M. Fundamentals in Nuclear Physics. Springer. p. 13, (2005), fig 1.1. ISBN 978-0-387-01672-6.
5. V.K.Khanna, Nanosensors: Physicsl, Chemical and Biological., CRC Press,Taylor & Francis Group,FL ,USA. 2012 and Challa.S.S.R.Kumar, Nanomaterials for Biosensors., Wiley & Sons, New Jersey,2007.
6. Charles P.Poole and Frank.J.Owens, Introduction to Nanotechnology, John Wiley and Sons Inc.; Hobkon, NewJersey,USA. 2003
7. National Science Foundation,USA and www.nanowerk.com/spotlight/spotid=1792.php And www.luxresearchinc.com
8. M/S Kaiser Consultants www.hkc22.com/nanomarkets.html
9. www.nano.gov/about-nni/what/funding
10. Bhattacharya, S. and M. Bhati "China and India: The two new players in the nanotechnology race." Scientometrics: 1-29.Feb 2012
11. Nanotechnology Ranking- Google Search 25th August 2014—"Iran TV Press dated 24 August 2014"
12. Nanotechnology Companies in India- [Google Search, 25 August 2014].
13. R.S,Bajwa and K.Yaldram., Research Output

in Nanoscience and nanotechnology: Pakistan Scenario., J.Nanopart Res.,14,721, 2012.

14. Pakistan Muslim League(N),Manifesto-2013, Chap.6, page 57.[Google search "Manifesto PML (N)].
15. Nanotechnology Education- [Google Search dated 25 August 2014].
16. Frank.J.Boem,Nanomedical Device and Systems Design: Challenges, Possibilities,Visions, CRC Press, Taylor & Francis Group, Florida,USA, 2013.
17. Bai X, More K, Rouleau CM, Rabiei A.Functionally graded hydroxyapatite coatings doped with antibacterial components; Acta Biomater.;6(6):2264-73,2010.
18. Mikkilineni M, Rao AS, Tummala M, Elkanti S. Nanodentistry: New buzz in dentistry, Eur J Gen Dent; 2:109-13, 2013.
19. Logothetidis, Stergios (Ed.) .,Nanomedicine and Nanobiotechnology - Springer Series: NanoScience and Technology. XII, p140, 2012.
20. Narayan, R. J.; Kumta, P. N.; Sfeir, Ch.; Lee, D-H; Choi, D.; Olton, D. (2004). "Nanostructured Ceramics in Medical Devices: Applications and Prospects". JOM56 (10): 38–43.
21. Nguyen P, Meyyappan M, YiuSC.,Applications of nanobiotechnology in ophthalmology—Part I,Ophthalmic Res.;44(1):1-16,2010. And Dr. Jose A. Garrido, Artificial retina: Physicists develop an interface to the Optical nerve, TUM, Munchen, Germany.7August, 2014, Research News.
22. Eric Stern, AleksandarVacic, Nitin K. Rajan, Jason M. Criscione, Jason Park, Bojan R. Ilic, David J. Mooney, Mark A. Reed & Tarek M. Fahmy., Label-free biomarker detection from whole blood., Nature Nanotechnology ;5, 138 - 142 ,2010.
23. JavadSafari,andZohreZarnegar, Advanced drug delivery systems: Nanotechnology of health design: A review.,DOI: 10.1016/j.jscs.2012.12.009.
24. David B. Resnik, and Sally S. Tinkle(Ed), Ethics in Nanomedicine, NIH Public Press, USA, 2012

GHRELIN: A VITAL MEMBER OF THE SURVIVAL KIT OF NATURE

Saadat Ali Khan, Sadia Ahsin, Tehreem Aftab, Tanzeel Ur Rehman[1], Tahira Amjad[2], Tahira Ayub[3]

Department of Physiology, Foundation University Medical College, Islamabad
[1]Department of Pharmaceutical Sciences, Riphah University, Islamabad
[2]Department of Community Medicine, Foundation University Medical College, Islamabad
[3]Department of Medical Education, Foundation University Medical College, Islamabad

ABSTRACT

Introduction:

Ghrelin, an endogenous ligand of growth hormone secretagogue receptor type 1a, is the only known appetite-stimulating hormone in humans. In addition it has many neuroendocrine, metabolic and nonendocrine roles which are reflected by widespread distribution of ghrelin and GHS-R expression. The present review summarizes the current knowledge of the structure, regulation, function and potential clinical applications of ghrelin.

Evidence acquisition:

Pubmed was searched and reference list of each article was screened. We reviewed 114 published articles in which various physiological and potential therapeutic roles of ghrelin were explored.

Content:

Ghrelin is synthesized mostly in the stomach and is liberated in response to acute and chronic changes in nutritional status. It stimulates ingestion of food and signals hypothalamus to control energy homeostasis. In addition, it is a potent stimulator of growth hormone release. The current knowledge on integration of ghrelin in various physiological functions of body, its structure, clinical significance and relation to leptin and obestatin have been summarized.

Conclusion:

Existing literature survey suggests that ghrelin has wide range of therapeutic effects however issues related to its downstream pathway, autocrine and paracrine role requires further investigation.

Introduction:

Ghrelin is a 28 amino acid acylated peptide hormone synthesized by enteroendocrine cells of stomach and epsilon cells of pancreas in response to negative energy balance.[1] This endogenous ligand was for the first time isolated from the stomach and named “ghrelin," after the word root “ghre" in Proto-Indo-European languages meaning “grow", since ghrelin has potent growth hormone (GH) releasing activity. Ghrelin plays important roles for maintaining growth hormone release and energy homeostasis in vertebrates. It has been considered as a natural ligand of growth hormone secretagogue type 1a (GHS-R1a) and has strong GH-releasing hormone activity.[2] Growth hormone secretagogues receptors are present in different parts of brain and in other peripheral tissues.[3] This distribution of growth hormone secretagogue receptor (GHS-R) is consistent with the GH-releasing effect of ghrelin and its profound endocrine and non-endocrine activities.[4] The present review summarizes the current knowledge of the structure, regulation, function and potential clinical applications of ghrelin. Pubmed was searched and reference list of each article was screened. We reviewed 114 published articles in which various physiological and potential therapeutic roles of ghrelin were explored.

Correspondence:
Dr. Tahira Ayub
Deparment of Medical Education
Foundation University Medical College, Islamabad.
E.mail: drtahira85@gmail.com

Structure of Ghrelin

Ghrelin is an acylated -peptide of 28 amino acids sharing structural resemblance to motilin.[5] Its esterification with octanic acid at 3rd serine residue increases the hydrophobicity of ghrelin molecule which is important for most of its biological actions.[6]

Naturally occurring variants of ghrelin have been

recognized, based on the acylation of the serine-3 or from alternative splicing of the same gene, like des-Gln14 ghrelin.[7] These molecules have same activity as ghrelin-28 but are present in lesser amount in the serum. The active form of ghrelin is the octanoylated form but major form of circulating ghrelin is nonacylated. Nonacylated ghrelin has no effect on the endocrine axis because it is unable to bind and activate the ghrelin receptor growth hormone secretagogue receptor 1a (GHSR1a) [8]

Figure I

Regulation of Secretion:

Ghrelin secretion varies throughout the day; with maximum secretion occurring before meals.[13] Circulating ghrelin levels have inverse relationship with body mass index. Ghrelin secretion rises in anorexia, falls in obesity and is optimal on recovery of ideal body weight.[9] Thus, ghrelin level adjustments in response to nutritional state, are opposite to those of leptin. Both hormones may signal metabolic control to the central nervous system.[14] Ghrelin secretion has inverse relation with body mass index except in Prader–Willi syndrome where obesity is linked with ghrelin hypersecretion.[15]

Different conditions affecting plasma ghrelin levels are shown in the table I.

Physiological Effects of Ghrelin:

Gh-releasing Activity:

Ghrelin has a strong dose-related growth hormone-releasing effect.[16] Ghrelin and growth hormone releasing hormone (GHRH) act together via partially different mechanisms. Growth hormone (GH) secretagogues need an intact endogenous growth hormone releasing hormone system to fully produce their growth hormone-releasing effect. They may act by stimulating growth hormone releasing hormone-secreting neurons and are inhibited by a GHRH antagonist or with a hypothalamus–pituitary discontinuation. Ghrelin may also act as somatostatin antagonist.[17] The growth hormone response to ghrelin is not responsive to exogenous somatostatin or cortistatin.[18] It is also refractory to other factors affecting growth hormone secretion, such as glucose, lipids, arginine, cholinergic agonists and antagonists, IGF-I and GH itself.[19]

Table I Conditions affecting plasma ghrelin levels

Increased ghrelin	Decreased ghrelin
Energy restriction	Feeding
Anorexia nervosa	Obesity
Cardiac cachexia	Total gastrectomy
Cancer cachexia	Hyperthyroidism
Ghrelinoma	Gastric bypass
Type 1 diabetes	Hypogonadism
Prader Wili syndrome	Cushing syndrome

Central Actions of Ghrelin:

Orexant Activity

Ghrelin and growth hormone secretagogue's orexigenic action is independent of their growth hormone-releasing action.[20] It occurs through a special network of neurons that are also moderated by leptin. Ghrelin released from stomach reaches the GHS-R in hypothalamus.[21] Ghrelin expression has also been found in a group of neurons near the third ventricle between the hypothalamic nuclei. These neurons send signals to neuronal circuits producing neuropeptide Y (NPY), agouti-related protein (AgRP), proopiomelanocortin (POMC) and corticotrophin releasing hormone (CRH).[22]

These neuropeptides have important role in the control of appetite and energy balance. Ghrelin binds presynaptic terminals of neuropeptide Y neurons and stimulates arcuate neuropeptide Y neurons. Thus ghrelin might control appetite and energy balance by stimulating orexigenic peptides and neurotransmitters release.[23]Pre-prandial rise in circulating ghrelin level reflect a role for ghrelin as a hunger signal leading to food intake.[24]

ROLE IN SLEEP, MEMORY AND ANXIETY-

LIKE BEHAVIOURAL RESPONSES

Ghrelin may stimulate slow-wave sleep in humans.[25] Ghrelin has shown to promote non-REM(Rapid Eye Movement) sleep in rodents. The cyclic Ghrelin release is correlated with the sleep–wake pattern and feeding behavior.[26]

It has been shown that Ghrelin might also be important in behavioral response to stress. Ghrelin has shown an anxiogenic action in rodents and its action is eliminated by a corticotrophin releasing hormone (CRH) antagonist.[27]Ghrelin injection in rats hippocampus, amygdala and dorsal raphe nucleus increase memory retention with rising dose.[28]

Entral Actions of Ghrelin:

Endocrine Actions

GHS-R1a and 1b as well as ghrelin are identified within the pancreas.[29] It can stimulate insulin secretion from rat pancreatic islets in vivo[30] however, insulin secretion from isolated rat pancreas after stimulation with glucose, arginine and carbachol was decreased by ghrelin.[31]

In addition ghrelin has been reported to produce a dose-dependent fall in the glucose-stimulated insulin release in mice in vivo.[32] In humans, acute administration of ghrelin blocks spontaneous and arginine-stimulated insulin secretion but does not affect the insulin response to the oral glucose tolerance test (OGTT).Ghrelin administration in humans improves plasma glucose levels and increases the hyperglycemic effect of arginine.[33] This effect may be indirect via catecholamine release or direct by the action on hepatocytes where it has been shown to modulate gluconeogenesis.[34] Ghrelin also causes increase in circulating somatostatin and pancreatic polypeptide (PP) levels in humans and this theoretically explains insulin decrease.[35] The negative outcome of insulin and glucose on ghrelin secretion suggest a link between ghrelin, pancreas and glucose metabolism.[36] It has been observed that long term administration of GHS in normal elderly humans was followed by hyperglycemia, glucose intolerance and insulin resistance.[37]

GHRELIN EXPRESSION IN GONADS, ADRENAL AND THYROID

It has been reported that Leydig cells of testis express ghrelin.[38]Ghrelin has been shown to decrease HCG- and cAMP-stimulated testosterone secretion in vitro.[39]In ovary, ghrelin expression has been seen in the ovarian interstitial cells and in young and mature corpora lutea but not in ovarian follicles.[40]Thus, ghrelin is likely to effect the gonadal axis at various levels and its secretion is, under the effect of gonadal steroids.

The adrenal gland has shown the maximum expression of GHS receptors.[41]However, ghrelin expression in the adrenals has been observed in few studies.[42] The physiological role of ghrelin at the adrenal level is still unclear, however, it has been suggested recently that it may regulate viability of adrenal cells.[41]

GHS-R1a and other GHS-R subtypes have been studied in different pathophysiological conditions of thyroid gland. Ghrelin expression within the thyroid has been found to be limited to parafollicular cells. An antiproliferative influence of ghrelin has been seen in follicular-derived thyroid carcinoma cell lines.[43] Ghrelin, however, has no effect on thyroid secretion and function.

Non Endocrine Actions

EFFECT ON GASTROINTESTINAL SYSTEM

Ghrelin has been reported to affect stomach motility and acid secretion. It can stimulate ileal peristalsis and inhibit cholecystokinin (CCK)-induced pancreatic protein secretion. These actions of ghrelin are mediated mainly by the cholinergic system.[44] Clinically most important is the prokinetic activity of ghrelin for which various applications have been hypothesized.

CARDIOVASCULAR ACTIONS

Different subtypes of receptors for ghrelin and synthetic GHS receptors have been observed in the cardiovascular system. Synthetic growth hormone secretagogues have protective action against cardiovascular damage in aged rats as well as in rats with growth hormone-deficiency, and those with post ischemic ventricular dysfunction. However ghrelin is much less valuable in providing this protection against ischemia.[45] Ghrelin like synthetic growth hormone secretagogues effects cardiac contractility and is found to improve cardiac function in normal subjects and in patients with dilated cardiomyopathy. It has been shown that ghrelin and growth hormone secretagogue

receptors are upregulated in atherosclerotic coronary arteries and in myocardium of patients with ischemic or dilated cardiomyopathy.[46] In addition to this ghrelin functions as antiapoptotic factor at the cardiovascular level. It has been shown to prevent cell death induced by doxorubicin, serum withdrawal or activation of FAS ligand in cultured cardiomyocytes and endothelial cells.[47]

MODULATION OF CELL PROLIFERATION

Ghrelin has also been shown to be expressed by several endocrine and nonendocrine neoplastic cells as well as their related cell lines.[48] This widespread distribution of ghrelin suggest an important autocrine/paracrine role of ghrelin in neoplastic conditions.[49] In addition, it has been observed that ghrelin may modulate the proliferation of several human tumor cell lines.[50]

Possible Clinical Applications

DIAGNOSIS AND TREATMENT OF GH DEFICIENCY

Ghrelin has strong GH-releasing activity and specificity, so it can be used in diagnosis and treatment of GH deficiency.[50] The commonly used GH stimulus for diagnosing GH deficiency is insulin induced hypoglycemia, in which blood glucose level falls to 40 mg/dl. This test can detect both GH and ACTH release in patients with pituitary disease. However, the hypoglycemic action of insulin is a disadvantage. At present, intravenous injection of ghrelin into humans does not show any side effects, suggesting the use of ghrelin in diagnosing GH deficiency. Individuals having growth hormone deficiency may be benefited by ghrelin treatment. The GH-releasing activity of ghrelin is similar to that of GHRH.[51] It has been observed that the combined administration of ghrelin and GHRH strongly stimulate growth hormone secretion, and their combined administration is the most effective stimulus for growth hormone release yet identified.[52] Even at small doses of 0.08 or 0.2 μg/kg ghrelin, the combined administration of ghrelin and GHRH significantly stimulated growth hormone release in a synergistic manner.[52]

TREATMENT OF OBESITY AND FEEDING DISORDERS

Ghrelin has been identified as the peripheral orexigenic signal that is effective parenterally[52] Thus blocking ghrelin's action may be helpful in reversing chronic obesity. However, appetite is regulated by several factors that may interact with and compensate for each other.[53]Thus ghrelin antagonist might only have a limited effect on obesity. In fact ghrelin-null mice showed no obvious abnormalities in feeding behavior. Ghrelin may prove useful orexigenic agent for the treatment of eating disorders such as anorexia nervosa.[54] Its administration can stimulate appetite and improve the nutritional status of these patients. But plasma ghrelin concentration in anorexia nervosa patients is already high which indicates disturbed sensitivity to ghrelin in these patients.

AS A PROKINETIC AGENT

Ghrelin stimulates gastric motility so it can be used in the treatment of postoperative gastric ileus. It has been observed to have a strong prokinetic effect, increasing gastric emptying and the small intestinal transit of liquid meals thus overcoming gastric ileus.[55] Studies have shown that central as well as intraperitoneal administration of ghrelin resulted in decreased ethanol-induced gastric ulcers.[56] This effect of ghrelin can be prevented by NG-nitro-L-arginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase suggesting that the gastroprotective effect of ghrelin might be mediated by nitric oxide.

TREATMENT OF CHRONIC HEART FAILURE

Ghrelin receptors are present in blood vessels and ventricles, suggesting relevance cardiac effects. It has been shown to decrease systemic vascular resistance and increase cardiac output in patients with heart failure. Ghrelin has also been shown to improve cardiac structure and function, and reduce the development of cardiac cachexia in rats with heart failure. [57]These results suggest that ghrelin has cardiovascular protective effects and regulates energy metabolism through growth hormone - dependent and independent mechanism.

RELATION TO LEPTIN

Serum concentrations of leptin and ghrelin have inverse relationship. Leptin is considered to be an inhibitor of ghrelin synthesis. Leptin levels are higher in obese than lean control whereas ghrelin is lower. During fasting ghrelin mRNA increase in stomach while leptin and leptin mRNA decrease. Leptin inhibits ghrelin transcription in vitro in dose

dependent manner. It has been reported to reduce ghrelin release from isolated rat stomach. [58] It has been shown that leptin cause satiety by depolarizing the POMC neurons, while hyperpolarizing neuropeptide Y cells.[59]Ghrelin significantly blocks this reduction of feeding in rats pretreated with leptin. This suggests that ghrelin may antagonize leptin action in the regulation of the neuropeptide Y system.

RELATION TO OBESTATIN

Obestatin is a 23 amino-acid peptide encoded by the preproghrelin gene. Both ghrelin and obestatin informs the central nervous system about the nutritional status and energy stores of body. Obestatin was initially described for its anorexigenic effects and its binding to G protein-coupled receptor 39 (GPR39). Recently it has been shown that obestatin inhibits exogenous ghrelin actions on food intake and it also antagonizes ghrelins actions on growth hormone secretion.60

FUTURE PROSPECTS

The multiplicity of ghrelin actions shows that it provides the crucial endocrine link for physiological processes regulating nutrition, body composition, and growth. Based on the existing knowledge, it is believed that ghrelin ensures that a sufficient amount of energy is available for growth hormone to stimulate growth and repair. The wide range of biological activities that have been linked with ghrelin continues to expand. As a result possible clinical applications for ghrelin, its agonist and antagonists are hypothesized. However, many issues including the regulation of ghrelin secretion, role of non-acylated ghrelin and obestatin, ghrelin receptor(s) and their downstream pathways, the autocrine/paracrine role of ghrelin still need further elaboration.

RECENT ADVANCES:

The sum effect of ghrelin is an increase in appetite and food intake, which, when coupled with ghrelin-mediated antiinflammatory activity, have led to the current interest in the use of this agent in human cachexia. Several experimental studies in animal models[61,62] and a few clinical trials of ghrelin (or ghrelin agonists) have shown modestly promising results of these agents as potential therapies for cachexia[63,64] .

To date, only a few pilot human trials of synthetic ghrelin or ghrelin agonist therapy in cancer cachexia have been published. The chief concern about the use of ghrelin or agonists is that it may stimulate tumor growth in cancer patients. More trials are needed to assess the safety and efficacy of these agents as potential therapies for cachexia.

References:

1. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999; 402:656–60.
2. Kojima M, Hosoda H, Matsuo H, Kangawa K. Ghrelin: discovery of the natural endogenous ligand for the growth hormone secretagogue receptor. Trends in Endocrinology and Metabolism, 2001b; 12: 118–22.
3. Papotti M, Ghe C, Cassoni P, Catapano F, Deghenghi R,Ghigo E, et al. Growth hormone secretagogue binding sites in peripheral human tissues. Journal of Clinical Endocrinology and Metabolism 2000;85: 3803–07
4. Van der Lely AJ, Tschop M, Heiman ML, Ghigo E. Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. Endocrine Reviews 2004; 25; 426–57.
5. Asakawa A, Inui A, Kaga T, Yuzuriha H, Nagata T, Ueno N, et al. Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motilin. Gastroenterology 2001b; 120: 337–
6. Broglio F, Benso A, Gottero C, Prodam F, Gauna C, Filtri L, et al. Non-acylated ghrelin does not possess the pituitaric and pancreatic endocrine activity of acylated ghrelin in humans. Journal of Endocrinological Investigation 2003b; 26: 192–6.
7. Hosoda H, Kojima M, Matsuo H, Kangawa K. Purification and characterization of rat des-Gln14-ghrelin, a second endogenous ligand for the growth hormone secretagogue receptor. Journal of Biological Chemistry 2000b; 275: 21995–22000.
8. Bednarek MA, Feighner SD, Pong SS, McKee KK, Hreniuk DL, Silva MV,et al. Structure–function studies on the new growth hormone-releasing peptide, ghrelin: minimal sequence of ghrelin necessary for activation of growth hormone secretagogue receptor 1a.

Journal of Medicinal Chemistry 2000; 43: 4370–6.

9. Ariyasu H, Takaya K, Tagami T, Ogawa Y, Hosoda K, Akamizu T, et al. Stomach is a major source of circulating ghrelin and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. Journal of Clinical Endocrinology and Metabolism 2001; 86: 4753–8.
10. Mori K, Yoshimoto A, Takaya K, Hosoda K, Ariyasu H, Yahata K, et al. Kidney produces a novel acylated peptide ghrelin. FEBS Letters 2000; 486: 213–6.
11. Hattori N, Saito T, Yagyu T, Jiang BH, Kitagawa K, Inagaki C. GH, GH receptor, GH secretagogue receptor, and ghrelin expression in human T cells, B cells, and neutrophils. Journal of Clinical Endocrinology and Metabolism 2001; 86: 4284–91
12. Volante M, Allia E, Gugliotta P, Funaro A, Broglio F, Deghenghi R, et al. Expression of ghrelin and of the GH secretagogue receptor by pancreatic islet cells and related endocrine tumors. Journal of Clinical Endocrinologyand Metabolism2002a; 87:1300–08.
13. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP ,et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. New England Journal of Medicine 2002b; 346: 1623–30
14. Kalra SP, Bagnasco M, Otukonyong EE, Dube MG, Kalra PS. Rhythmic, reciprocal ghrelin and leptin signaling: new insight in the development of obesity. Regulatory Peptides 2003; 111:1–11.
15. Haqq AM., Farooqi IS, O'Rahilly S, Stadler DD, Rosenfeld RG,Pratt KL,et al. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader–Willi syndrome. Journal of Clinical Endocrinology and Metabolism 2003; 88:174–8.
16. Arvat E, Di Vito L, Broglio F, Papotti M, Muccioli G, Dieguez, C, et al. Preliminary evidence that ghrelin, the natural GH secretagogue(GHS)-receptor ligand, strongly stimulates GH secretion in humans. Journal of Endocrinological Investigation 2000.23:493–5.
17. Tannenbaum GS, EpelbaumJ. Bowers CY. Interrelationship between the novel peptide ghrelin and somatostatin/growth hormone-releasing hormone in regulation of pulsatile growth hormone secretion. Endocrinology 2003; 144: 967–74.
18. Di Vito L, Broglio F, Benso A, Gottero C, Prodam F, Papotti M, et al. The GH-releasing effect of ghrelin, a natural GH secretagogue, is only blunted by the infusion of exogenous somatostatin in humans. Clinical Endocrinology 2002; 56:643–8
19. Broglio F, Benso A, Gottero C, Prodam F, Grottoli S, Tassone F, et al. Effects of glucose, free fatty acids orarginine load on the GH-releasing activity of ghrelin in humans. Clinical Endocrinology 2002b; 5: 265–71.
20. Inui A. Ghrelin: an orexigenic and somatotrophic signal from the stomach. Nature Reviews. Neuroscience 2001; 2: 551–60.
21. Horvath TL, Diano, Sotonyi P, Heiman M, Tschop M. Minireview: ghrelin and the regulation of energy balance –a hypothalamic perspective. Endocrinology 2001; 142: 4163–9.
22. Kalra SP, Kalra PS. Neuropeptide Y: a physiological orexigen modulated by the feedback action of ghrelin and leptin. Endocrine 2003; 22: 49–56.
23. Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, Grove KL, et al. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic 3circuit regulating energy homeostasis. Neuron 2003 b; 37: 649–61.
24. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001; 50: 1714–9
25. Weikel JC, Wichniak A, Ising M, Brunner H, Friess E, Held K ,et al. Ghrelin promotes slow-wave sleep in humans. American Journal of Physiological.Endocrinology and Metabolism 2003; 284: E407–15.
26. Tolle V, Bassant MH, Zizzari P, Poindessous-Jazat F, Tomasetto C, Epelbaum J, et al.Ultradian rhythmicity of ghrelin secretion in relation with GH, feeding behavior, and sleep-

wake patterns in rats. Endocrinology 2002; 143:1353–61.

27. Asakawa A, Inui A, Kaga T, Yuzuriha H, Nagata T, Fujimiya M, et al. A role of ghrelin in neuroendocrine and behavioral responses to stress in mice. Neuroendocrinology 2001 a; 74:143–7.
28. Carlini VP, Monzon ME, Varas MM, Cragnolini AB, Schioth HB, Scimonelli TN, et al. Ghrelin increases anxiety-like behavior and memory retention in rats. Biochemical and Biophysical Research Communications 2002; 299: 739–43.
29. Date Y, Nakazato M, Hashiguchi S, Dezaki K, Mondal MS, Hosoda H, et al. Ghrelin is present in pancreatic alpha-cells of humans and rats and stimulates insulin secretion. Diabetes 2002b; 51:124–9.
30. A deghate E, Ponery AS. Ghrelin stimulates insulin secretion from the pancreas of normal and diabetic rats. Journal of Neuroendocrinology 2002; 14: 555–60
31. Egido EM, Rodriguez-Gallardo J, Silvestre RA, Marco J. Inhibitory effect of ghrelin on insulin and pancreatic somatostatin secretion. European Journal of Endocrinology 2002; 146: 241–4
32. Salehi A, de la Cour C, Hakanson R, Lundquist. Effects of ghrelin on insulin and glucagon secretion: a study of isolated pancreatic islets and intact mice. Regulatory Peptides 2004; 118: 143–50
33. Broglio F, Gottero C, Benso A, Prodam F, Destefanis S, Gauna C, et al. Effects of ghrelin on the insulin and glycemic responses to glucose, arginine, or free fatty acids load in humans. Journal of Clinical Endocrinology and Metabolism 2003d; 88: 4268–72
34. Broglio F, Benso A, Castiglioni C, Gottero C, Prodam F, Destefanis S, et al. The endocrine response to ghrelin as a function of gender in humans in young and elderly subjects. Journal of Clinical Endocrinology and Metabolism 2003 a; 88:1537–42.
35. Arosio M, Ronchi CL, Gebbia C, Cappiello V, Beck-Peccoz P, Peracchi M. Stimulatory effects of ghrelin on circulating somatostatin and pancreatic polypeptide levels. Journal of Clinical Endocrinology and Metabolism 2003; 88:701-4.
36. Ukkola O. Ghrelin and insulin metabolism. European Journal of Clinical Investigation 2003; 33: 183–5.
37. Broglio F, Gottero C, Benso A, Prodam F, Volante M, Destefanis S, et al Ghrelin and the endocrine pancreas. Endocrine 2003e; 22:19–24.
38. Barreiro ML, Gaytan F, Caminos JE, Pinilla L, Casanueva FF, Aguilar E, et al. Cellular location and hormonal regulation of ghrelin expression in rat testis.Biology of Reproduction 2002a; 67: 1768–76.
39. Tena-Sempere M, Barreiro ML, Gonzalez LC, Gaytan F, Zhang FP, Camino JE ,et al. Novel expression and functional role of ghrelin in rat testis. Endocrinology 2002; 143:717–25.
40. Caminos JE, Tena-Sempere M, Gaytan F, Sanchez-Criado JE, Barreiro ML, Nogueiras R, et al. Expression of ghrelin in the cyclic and pregnantrat ovary. Endocrinology 2003; 144: 1594–1602.
41. Andrei PG, Malendowicz LK, Trejter M, Neri G, Spinazzi R, Rossi GP,et al. Ghrelin and growth hormone secretagogue receptor are expressed in the rat adrenal cortex:evidence that ghrelin stimulates the growth but not the secretory activity of adrenal cells. FEBS Letters 2003; 536, 173–9.
42. Tortorella C, Macchi C, Spinazzi R, Malendowicz LK, Trejter M, Nussdorfer GG. Ghrelin, an endogenous ligand for the growth hormone-secretagogue receptor, is expressed in the human adrenal cortex. International Journal of Molecular Medicine 2003; 12:2 13-7.
43. Volante M, Allia E, Fulcheri E, Cassoni P, Ghigo E, MuccioliG,et al. Ghrelin in fetal thyroid and follicular tumors and cell lines: expression and effects on tumor growth. American Journal of Pathology 2003; 162: 645–54.
44. Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z, et al. Ghrelin stimulates gastric acid secretion and motility in rats. Biochemical and Biophysical Research Communications 2000; 276: 905–8.
45. Frascarelli S, Ghelardoni S., Ronca-Testoni S, Zucchi R. Effect of ghrelin and synthetic

growth hormone secretagogues in normal and ischemic rat heart. Basic Research in Cardiology 2003; 98: 401–5.

46. Enomoto M, Nagaya N, Uematsu M, Okumura H, Nakagawa E, Ono F, et al. Cardiovascular and hormonal effects of subcutaneous administration of ghrelin, a novel growth hormone releasing peptide, in healthy humans. Clinical Science 2003; 105: 431–5.
47. Baldanzi G, Filigheddu N, Cutrupi S, Catapano F, Bonissoni S, Fubini A, et al. Ghrelin and des-acyl ghrelin inhibit cell death in cardiomyocytes and endothelial cells through ERK1/2 and PI 3-kinase/AKT. Journal of Cell Biology 2002; 159: 1029-37.
48. Korbonits M, Bustin SA, Kojima M, Jordan S, Adams EF, Lowe DG, et al. The expression of the growth hormone secretagogue receptor ligand ghrelin in normal and abnormal human pituitary and other neuroendocrine tumors. Journal of Clinical Endocrinology and Metabolism 2001a; 86: 881–7
49. Jeffery PL, Herington AC, Chopin LK. The potentialautocrine/paracrine roles of ghrelin and its receptor in hormone dependent cancer.Cytokine Growth Factor Review 2003; 14: 113–22
50. Baldelli R, Otero XL, Camina JP, Gualillo O, Popovic V, Dieguez C, and Casanueva FF. Growth hormone secretagogues as diagnostic tools in disease states. Endocrine 2001; 14: 95–9.
51. Peino R, Baldelli R, Rodriguez-Garcia J, Rodriguez-Segade S, Kojima M, Kangawa K, et al. Ghrelin-induced growth hormone secretion in humans. Eur J Endocrinol 2000; 143: R11–4.
52. Drazen DL, Woods SC. Peripheral signals in the control of satiety and hunger. Curr Opin Clin Nutr Metab Care 2003; 6: 621–9.
53. Bays HE. Current and investigational anti obesity agents and obesity therapeutic treatment targets.Obesity Res 2004; 12: 1197–1211.
54. Muccioli G, Tschop M, Papotti M, Deghenghi R, Heiman M, and Ghigo E. Neuroendocrine and peripheral activities of ghrelin: implications in metabolism and obesity. Eur J Pharmacol 2002; 440: 235–54.
55. Trudel L, Tomasetto C, Rio MC, Bouin M, Plourde V, Eberling P, et al.Ghrelin/motilin-related peptide is a potent prokinetic to reverse gastric postoperative ileus in rat. Am J Physiol Gastrointest Liver Physiol 2002; 282: G948–52.
56. Sibilia V, Rindi G, Pagani F, Rapetti D, Locatelli V, Torsello A, et al. Ghrelin protects against ethanol-induced gastric ulcers in rats: studies on the mechanisms of action. Endocrinology 2003; 144: 353–9.
57. Chang L, Ren Y, Liu X, Li WG, Yang J, Geng B, et al. Protective effects of ghrelin on ischemia/reperfusion injury in the isolated rat heart. J Cardiovasc Pharmacol 2004; 43: 165–70.
58. Kamega J, Tamura H, Shimizu T, Ishii S, Sugihara H, Oikawa S. Effects of insulin, leptin, and glucagon on ghrelin secretion from isolated perfused rat stomach. Regul Pept 2004 ; 119 : 77-81.
59. Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, Horvath TL, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature 2001; 411:480-4.
60. Zhang JV, Ren PG, Avsian-Kretchmer O, Luo CW, Rauch R, Klein C, et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science. 2005; 310:996-9.
61. Kamiji MM, Inui A. The role of ghrelin and ghrelin analogues in wasting disease. Curr Opin Clin Nutr Metab Care 2008;11:443–51.
62. DeBoer MD, Emergence of ghrelin as a treatment for cachexia syndromes.Nutrition 2008;24:806–14.
63. Strasser F, Lutz TA, Maeder MT, et al. Safety, tolerability and pharmacokinetics of intravenous ghrelin for cancer-related anorexia/cachexia: a randomised, placebo-controlled, double-blind, double-crossover study. Br J Cancer 2008;98:300–8.
64. Garcia JM, Polvino WJ. Effect on body weight and safety of RC-1291, a novel, orally available ghrelin mimetic and growth hormone secretagogue: results of a phase I, randomized, placebo-controlled, multiple-dose study in healthy volunteers. Oncologist 2007;12:594–600.

ROLE OF INTRAVENOUS IMMUNOGLOBULINS IN THE TREATMENT OF CHRONIC UNREMITTING PHARYNGO-FACIAL VARIANT OF GULLIAN-BARRE SYNDROME IN CHILDREN

Syed Zulfiqar Haider, Parveen Akhtar, Lubna Akhtar[1], Awais Tahir

Department of Paediatrics, Fauji Foundation Hospital, Rawalpindi
[1]Department of Anatomy, Foundation University Medical College, Islamabad

ABSTRACT

Pharyngo-facial variant is a rare variant of Gullian-Barre Syndrome (GBS) which can occur with or without other well-known signs and symptoms of the syndrome. It can take an acute or a chronic clinical course. We describe a four years old girl who was a diagnosed case of this variant and presented with the history of inability to close her eyes, dysphonia, drooling dysphagia and recurrent pneumonia for the last one year. Her clinical examination showed palsy of VII, IX and X cranial nerves. Electrophysiological studies confirmed palsy of both facial nerves. She was given Intravenous Immunoglobulin (IVIG) therapy and significant improvement occurred.

Keywords:

Pharyngo-facial variant of Gullian-Barre Syndrome, Electrophysiological studies, Intra-venous immunoglobulin (IVIG)

Introduction:

Gullian-Barre syndrome is a polyneuropathy which involves the peripheral nerves, nerve roots and the cranial nerves[1]. Many variants of this syndrome have been described. One such variant is pharyngo-facial GBS, which occurs in 4.7% of cases of GBS[2]. It involves cranial nerves with or without other clinical sign of GBS[3]. It can take an acute, chronic unremitting or a remitting-relapsing course[4]. There is no known cure for GBS. However there are therapies that reduce the severity of illness, treat complications and speed-up recovery. Currently plasma exchange and high dose IVIG therapy are used. Researchers and clinicians are continuously working for the refinement of these modalities. International research has shown that pharyngo-facial GBS in adults and childhood chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) improves with IVIG therapy[5,6]. We present a case of chronic unremitting pharyngo-facial GBS in a 4 year old girl, who showed significant improvement following Intravenous Immunoglobulin (IVIG) therapy, which has not been reported so far.

Correspondence:
Dr. Syed Zulfiqar Haider
Deparment of Paediatrics
Fauji Foundation Hospital, Rawalpindi
E.mail: drsyedzulfiqarhaider@gmail.com

Case Report:

Our patient, a 4yr old female child was admitted with complaints of difficulty in breathing along with fever, in May 2014 at Fauji Foundation Hospital, Rawalpindi. On examination, in addition to the signs of pneumonia she also had oropharyngeal incoordination, inability to close her eyes and incomprehensible speech (Fig-1, 2). The treatment of pneumonia and supportive care was started.

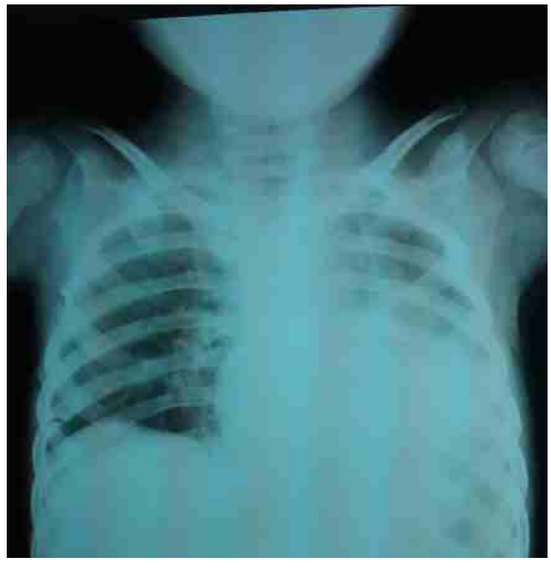


Figure 1: Chest X-ray showing left sided pneumonia.

Figure 1a: Child's eyes remain open during sleep and NG tube in place due to marked oropharyngeal incoordination.

Past history revealed that prior to this admission she was admitted thrice to different tertiary care hospitals during the last one year. She was alright one year back, when following an upper respiratory tract infection she developed inability to close her eyes. This was followed in a week by the appearance of nasal twang to voice, drooling and difficulty in swallowing. A local general practioner prescribed some medicines which were used for three months but no improvement occurred. The child was then brought to the ENT department of a tertiary care hospital in Rawalpindi where adenotonsillectomy was done but the complaints persisted.

A month later the child developed fever and difficulty in breathing. She was hospitalized in a tertiary care hospital at Islamabad. She had the clinical signs of pneumonia and obvious facial weakness. The neurological examination showed intact higher mental functions, sensory and motor systems and palsy of VII, IX and X cranial nerves. The MRI brain was normal, which ruled out space occupying lesions, degenerative disorders and neoplasms of the brain. The electrophysiological study revealed normal peripheral nerve conduction and muscle responses. Thus a diagnosis of aspiration pneumonia with cranial variant of GBS was made which deteriorated to the extent that she developed respiratory failure requiring ventilation. She was successfully weaned off after eleven days. After recovery from pneumonia, she was discharged but oropharyngeal incoordination, inability to close eyes and incomprehensible speech persisted. She was sent home with a nasogastric tube in place. This was followed by two more episodes of aspiration pneumonia treated at different hospitals in Rawalpindi and Islamabad.

During the present admission at Fauji Foundation Hospital, electrophysiological study of the facial nerves showed absent bilateral facial nerve conduction and unevoked compound muscle action potentials. The peripheral nerves were normal. This was in keeping with the diagnosis of pharyngo-facial variant of GBS.

Literature review showed substantial evidence of efficacy of IVIG in such cases. We gave IVIG 1gm/kg/day on two consecutive days. No known side effects of IVIG therapy were observed. A gradual improvement in the neurological deficit was observed and on the two week follow-up, the eye closure had improved considerably, drooling had decreased and the child was able to eat with less difficulty. Her speech also improved (Fig 3).

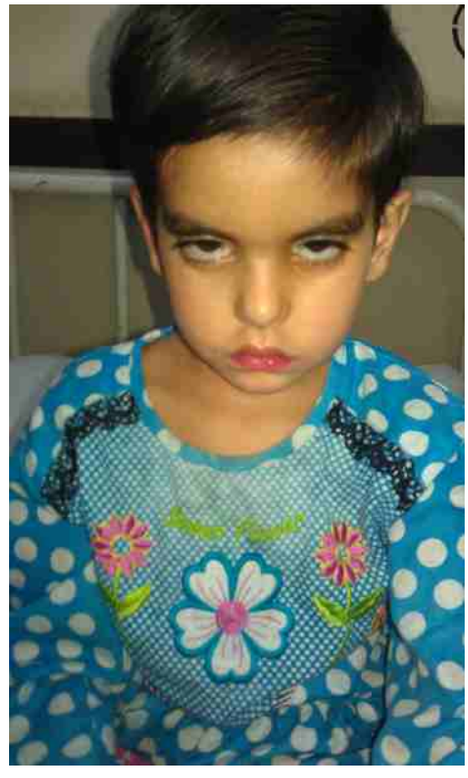


Figure 2: Child on two weeks follow-up

On four weeks and two months follow up no further improvement occurred. Though some residual deficit persisted the quality of life has improved considerably.

Discussion:

GBS is a polyneuropathy with diverse etiologies and clinical course. Our patient had the chronic unremitting pharyngo-facial GBS mainly involving VII, IX and X cranial nerves. International research shows that the use of IVIG in such cases has promising results[5, 6].

Unal-Cevik et al reported a similar case of an adult patient, in which IVIG therapy was given for the treatment of pharyngo-facial variant of GBS. Partial improvement of bilateral facial paralysis was observed[5].

Similarly, McMillan et al conducted a large cohort study in children and reported favorable long-term outcome in children with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) following IVIG therapy[6]. This study showed the efficacy of IVIG therapy in CIDP but did not specifically target pharyngo-facial GBS.

In light of the literature review we gave IVIG therapy to our patient and the improvement was encouraging. On two weeks follow-up, the eye closure improved considerably and drooling was decreased enabling the child to eat with much less difficulty. The quality of speech also improved. It appears that in our patient with chronic unremitting pharyngo facial GBS treatment with IVIG played a beneficial role. This is in accordance with the results of the above mentioned studies in which there was improvement with IVIG therapy.

Conclusion:

We therefore suggest IVIG therapy may have a significant role in improving quality of life in chronic unremitting Pharyngo-Facial variant of GBS.

References:

1. Dididze MN. Clinical variants of Gullian-Barre syndrome: some aspects of differential diagnosis. Georgian Med News. 2009 Jan; (166):48-51.
2. Lin JJ, Hsia SH, Wang HS, Lyu RK, Chou ML, Hung PC et al. Clinical variants of Gullian-Barre Syndrome in children. Pediatr Neurol. 2012 Aug; 47(2):91-6.
3. Yu JY, Jung HY, Kim CH, Kim HS, Kim MO. Multiple Cranial Neuropathies Without Limb Involvements: Gullian Barre Syndrome Variant? Ann Rehabil Med. Oct 2013; 37(5): 740-44.
4. Kliegman RM, Stanton BF, St.geme JW, Schor NF, Behrman RE. Nelson text book of Pediatrics. 19th edition. Elsevier, Saunders 2011.
5. Unal-cevik, Onal MZ, Odabasi Z, Tan E. IVIG-responsive multiple cranial neuropthy: a pharyngo-fascial variant of Gullian-Barre syndrome. Acta Neurol Belg. 2009 Dec; 109(4):317-21.
6. Mcmillan HJ, Kang PB, Jones HR, Darras BT. Childhood chronic inflammatory demyelinating polyradiculoneuropathy: combined analysis of a large cohort and eleven published series. Neuromuscul Disord 2013 Feb 23(2):103-11.

A QUEER CASE OF THE MARCUS GUNN JAW WINKING SYNDROME

Sana Nadeem

Department of Ophthalmology, Fauji Foundation Hospital, Rawalpindi

ABSTRACT

The Marcus Gunn 'jaw winking' syndrome is characterized typically with congenital, ipsilateral, variable ptosis, and retraction and bizarre movements of the affected eyelid with movements of the jaw. We present a case of right sided unilateral Marcus Gunn syndrome with bilateral mild ptosis, with intermittent, downward flicking movements of the left eye, in a 16 year old boy. Marcus Gunn syndrome with bilateral ptosis and contralateral eyelid flickering is extremely rare and so far not been reported in Pakistan.

Keywords:

Marcus Gunn syndrome, ptosis, jaw winking.

Introduction:

The Marcus Gunn (Jaw-Winking) syndrome was described for the first time in 1883 by Marcus Gunn, who observed a peculiar ptosis in a young girl, with winking of the lid associated with jaw movements.[1, 2] 'Jaw winking' is a misnomer since the eyelid elevates rather than falling. It is a rare congenital synkinetic syndrome with an occurrence of 4-6% in all cases of ptosis[2]. Usually unilateral and isolated, but may occasionally be bilateral[3], or associated with ocular or systemic abnormalities. Mostly sporadic and non-familial, but familial cases with autosomal dominant inheritance have been reported. There is no predilection for gender or race[2, 4].

The wink phenomenon i.e. intermittent elevation of the ptotic lid occurs in conjunction with contraction of the ipsilateral external pterygoid muscle, which is elicited by opening the mouth, thrusting the jaw to the contralateral side, chewing, sucking, and less commonly by jaw protrusion, smiling, swallowing and teeth clenching. Jaw winking becomes less noticeable with age, as patients may learn to limit or mask it1-4.

Correspondence:
Dr. Sana Nadeem
Department of Ophthalmology
Fauji Foundation Hospital, Rawalpindi.
E.mail: doctorsana@hotmail.com

Case Report:

A 16 years old boy presented to the out-patient department of Holy Family Hospital, Rawalpindi with the complaints of blurred vision and eye strain. His vision was 6/9 right eye and 6/6 left eye. During examination, he was found to have winking movements of the right upper eyelid associated with movements of the jaw. Upon inquiry, we found that these movements were observed by his parents since birth. The family history was negative and there was no co morbid systemic abnormality.

The boy was found to have mild bilateral ptosis. [Figure 1]. The Margin reflex distance (MRD1) was 3 mm right eye and 3mm left eye, Levator function was normal; 15 mm in both eyes, symmetrical palpebral fissure heights of 9 mm in both eyes, upper lid creases 5.5 mm both eyes, with the pretarsal show being slightly higher on the left side, being 3 mm right eye and 4 mm left eye respectively. Right lid retraction was marked on opening the jaw i.e. 5 mm [Figure 2A], and also on ipsilateral jaw movement [Figure 2B], and lessened with contralateral jaw movement [Figure 2C]. Upon closer examination, it was observed that the left eyelid showed very mild drooping of 1 mm upon opening of the jaw, and movement of the jaw to the left. This drooping could be described as intermittent flicking of the left eyelid and occurred simultaneously with the right eyelid retraction. This could be a milder variant of the rarely described 'See-saw' Marcus Gunn phenomenon in

which ipsilateral lid retraction is accompanied by contralateral ptosis which corresponds to the jaw movements. The patient had normal range of extra ocular movements. Bell's phenomenon was intact.

Both anterior and posterior segments were unremarkable. Vision was corrected to 6/6 right eye with - 0.5 DS correction. A diagnosis of right sided Marcus Gunn (jaw winking) syndrome was established surprisingly with bilateral ptosis and downward flicking of the contralateral eyelid.

The eyelids being almost symmetrical in primary position and the patient not having cosmetic issues with the winking movements. We explained the syndrome to the patient and his father, reassured them of the condition and sent him home with a spectacle prescription.

Discussion:

The Marcus Gunn syndrome is also known as trigemino-oculomotor synkinesis.[1, 2] The etiology is largely unknown, but the pathophysiology involves the abnormal congenital misdirection of the mandibular division of the trigeminal nerve (Cranial Nerve V) which innervates the external pterygoid muscle into the superior division of the oculomotor nerve (Cranial Nerve III) which innervates the levator palpebrae superioris (LPS); thus the latter has a dual innervation. In the true Marcus Gunn phenomenon, trigeminal innervation to the pterygoids is associated with excitation of the oculomotor branch to the levator; with resultant coincidental intermittent elevation of the ptotic upper lid with contraction of the pterygoids; there being a directly proportional relationship between the ptosis severity and wink amplitude, the amplitude of the wink being higher in downgaze.[1, 5]

The exact level of this abnormal connection is disputed, with no anatomical basis for this hypothesis demonstrated so far.Various theories that have been proposed include aberrant

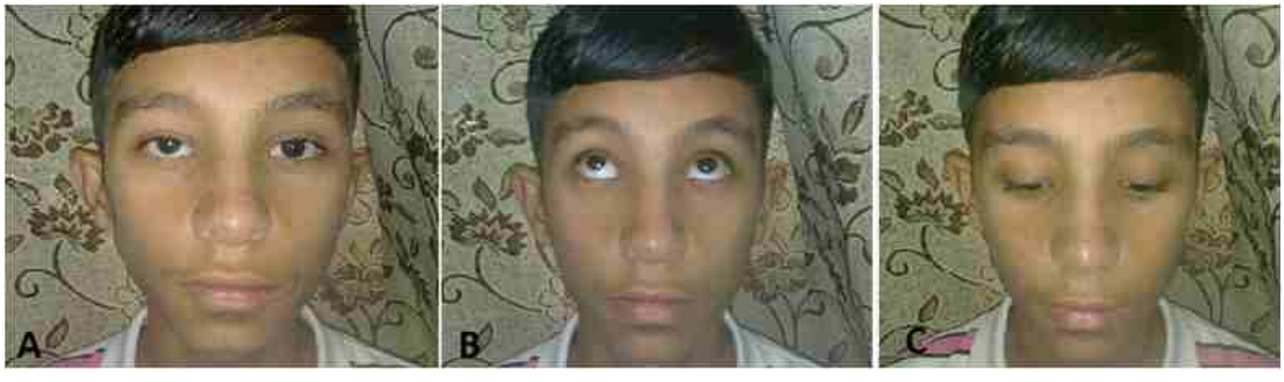


FIGURE 1:
A: Mild bilateral ptosis R > L in primary position B: Normal lid position on up gaze
C: Normal lid position on down gaze

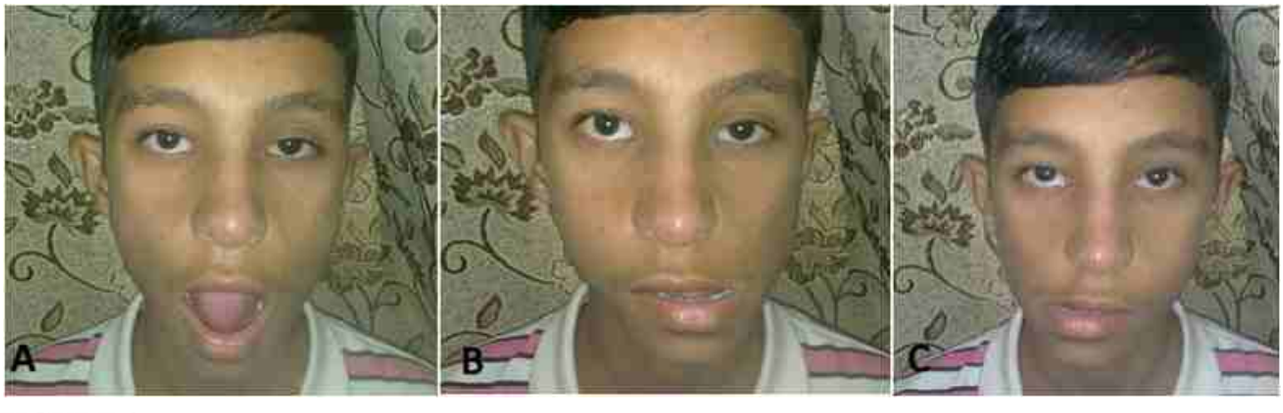


FIGURE 2:
A: Right lid retraction on jaw opening, and corresponding mild drooping of the left lid
B: Right lid retraction on jaw movement to the left side, the left ptosis accentuated
C: Right lid retraction lessened on jaw movement to the right side

connection, functional interference and atavistic reversion.[3]

In the Inverse Marcus Gunn phenomenon[6], the eye closes with contraction of the pterygoids, with EMG studies revealing that trigeminal innervation to the pterygoid muscles leads to inhibition of the branch of the oculomotor nerve supplying the LPS.

The very rare 'See-saw Marcus Gunn syndrome'[6] is characterized by ipsilateral classical Marcus Gunn phenomenon and contralateral inverse Marcus Gunn phenomenon resulting in see-saw movements of the eyelids.It is possible that this boy represents a mild variant of this rarely described syndrome.

Measurement of lid retraction in this syndrome is done with a millimeter ruler. The amount of jaw-winking is the excursion of the upper eyelid with synkinetic mouth movement. Jaw-winking is classified as: Mild < 2 mm; Moderate 2-5 mm; Severe ≥ 6 mm.[3]

Ocular associations of the Marcus Gunn syndrome are amblyopia (30-60%), anisometropia (25%), strabismus (50-60%), double elevator palsy (25%), superior rectus muscle palsy (23%), monocular elevation deficit (MED), Duane retraction syndrome and congenital fibrosis of the extraocular muscles (CFEOM).[1-3]

Systemic associations although rare include cleft lip and palate, the CHARGE Syndrome in bilateral cases, and renal stones.[3]

If the jaw-winking is cosmetically insignificant i.e. <2 mm, it can be ignored in the treatment of the ptosis. Surgical treatment is still controversial. Many techniques are described for the correction of jaw winking ptosis, usually reserved for severe cases. Management involves correction of ptosis along with correction of winking response, as ptosis correction alone may lead to worsening of wink. In mild ptosis, a Muller muscle and conjunctival resection (MMCR) or a Fasanella-Servat procedure is the best option. For moderate to severe ptosis, a levator resection may be indicated. Severe, large amplitude winking needs bilateral levator ablasion, followed by frontalis suspension procedure.[1-4]

Our patient did not have cosmetically significant ptosis and the jaw winking was moderate i.e. 5mm, but still the patient, nor his family showed much concern about it being a cosmetic issue, so there was no need of surgical management. Surprisingly, it was his first presentation to an ophthalmologist.

Acknowledgements:

Special thanks to Dr. B A Naeem (Ophthalmology Department, Fauji Foundation Hospital, Rawalpindi.) for his utmost guidance; Dr. Sikandar, Dr. Saira Satti, Dr. Afia Matloob Rana, Dr. Ambreen Gul, Dr. Fatima Sidra, Dr. Salman Tariq, (Post graduate trainees), Dr. Rabeeah, and Dr. Atiqa (House surgeons) of the Ophthalmology Department, Holy Family Hospital, Rawalpindi, for bringing me this rare case. This patient presented to us in my last few days at Holy Family Hospital as a Senior Registrar.

References:

1. Yanoff M, Duker JS. Ophthalmology. Second Edition. Mosby: St Louis 2004; p 656-666.
2. Angmo D, Bajaj MS, Pushker N, Ghose S. Marcus Gunn Jaw-Winking Phenomenon: A Review. DJO 2011; 21(3).
3. Betharia SM, Kishore K, Kumar H. Unusual Marcus Gunn phenomenon in adults. Indian J Ophthalmol 1992; 40:20-3.
4. Pratt SG, Beyer CK, Johnson CC. The Marcus Gunn phenomenon. A review of 71 cases. Ophthalmology 1984; 91:27-30.
5. Yu-Hisang Su Y, Cheung-TerOng C. Marcus Gunn Jaw-winking syndrome. Acta Neurologica Taiwanica 2010; 19(1).
6. Kumar V, Goel N, Raina UK, Ghosh B. "See-saw Marcus Gunn syndrome." Ophthal Plast Reconstr Surg 2011 Nov;27(6):144-5.

CASE REPORT: A PATIENT WITH PNEUMOMEDIASTINUM AND SURGICAL EMPHYSEMA FOLLOWING TREATMENT FROM A HOMEOPATHIC DOCTOR

Kanwal Fatima Khalil, Asma Ambreen

Department of Medcine, Fauji Foundation Hospital, Rawalpindi

ABSTRACT

Introduction:

Pneumomediastinum is an uncommon radiographic finding of potential clinical significance. Secondary pneumomediastinum (SPM) has a variety of etiologies that can lead to potentially morbid outcomes. A 22-year-old lady presented with complaints of trismus and shortness of breath after ingestion of an unknown medicine for dyspepsia from a local homeopathic doctor. She developed pneumothorax and pneumomediastium following an attempt of naso gastric tube insertion at a peripheral hospital. With intensive supportive management requiring admission to an intensive care unit, she survived. The medicine prescribed to her by local GP showed presence of strychnine. Blood samples sent for chemical analysis confirmed the diagnosis. Pneumomediastinum is uncommon and occurs when air leaks into the mediastinum. The diagnosis can be confirmed by chest X-ray showing a radiolucent outline around the heart and mediastinum or thoracic CT scan. Treatment is usually conservative.

Keywords:

pneumomediastinum, strychnine, homeopathic remedies, blood poisoning

Introduction:

Pneumomediastinum is an uncommon radiographic finding of potential clinical significance. Secondary pneumomediastinum is a morbid condition with distinctive etiologies, radiologic findings, and outcomes.1

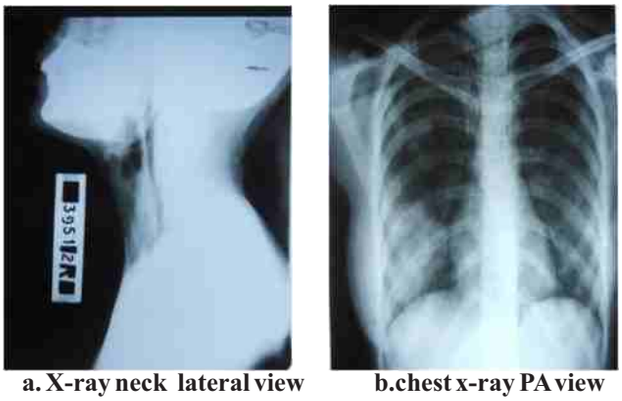
Secondary pneumomediatinum develops as a consequence of a distinct underlying pathology or thoracic injury resulting in intrathoracic dissection of air through mediastinal planes. Secondary pneumomediastinum has been identified as result of blunt thoracic trauma, high pressure mechanical ventilation, pulmonary barotrauma in divers, intrathracic infections like pneumocystis carinii pneumonia (PCP), cavitary pulmonary disese, surgical procedures and oesophageal or tracheobronchial disruptions.[1]

The mortality rate associated with pneumomediastinum may be as high as 50-70% as seen in Boerhaave syndrome (esophageal rupture following vomiting). Other predisposing conditions associated with high mortality rates include trauma, asthma, and tracheobronchial perforation. [2]

Correspondence:
Dr. Kanwal Fatima Khalil
Deparment of Medicine
Fauji Foundation Hospital, Rawalpindi
E.mail: khalil.kanwal@gmail.com

Case report:

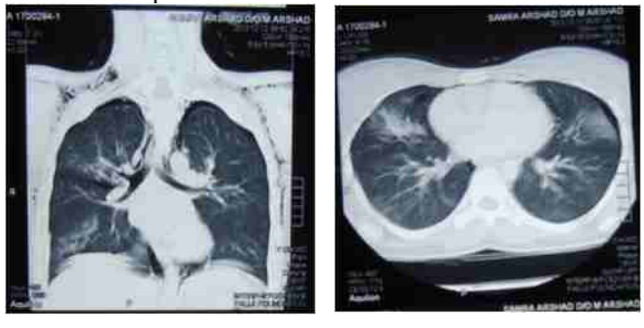
A 22 years old lady was referred for, sudden onset shortness of breath and facial and neck swelling, to ENT department. On examination she was very sick and in obvious respiratory distress. Her BP was 100/60mmhg, pulse 132/min, regular. Temp 38 C, R/R 36/min. O2 sat on room air was 90%. She was having jerky movements of upper limbs. Chest examination revealed surgical emphysema and reduced breath sounds in right lower chest. Clinical examination of other systems revealed trismus, periodic jerky movements of upper limbs, hyperreflexia in lower libs with clonus. Immediately after presentation, chest X-ray was done that showed surgical emphysema and pneumomediastinum as shown in fig 1.



a. X-ray neck lateral view b.chest x-ray PA view

Fig 1. Xray neck (a) and CXR (b) showing surgical emphysema & Pneumomediastinum

Blood complete picture showed neutrophilic leukocytosis. Rest of the laboratory investigations were normal. A provisional diagnosis of retropharyngeal abcess and lung abcess was made. Vigorous antibiotic and oxygen therapy started. An emergency CECT neck and chest was performed that confirmed marked surgical emphysema involving neck and chest, pneumomediastinum and bilateral small pneumothoracies. CT scan of the neck did not reveal retropharyngeal or parapharyngeal abcess. Figure 2 shows CT scan of chest of this patient.



a. HRCT chest b. HRCT chest

Fig 2: HRCT chest showing surgical emphysema(a) with pneumomediastinum and bilateral small pneumothoracis(b)

A suspicion of strangulation was made by the radiologist but the patient denied any physical or sexual assault and there were no marks of physical abuse on her body.

On detailed history from the father, it was found that patient was alright 3 days back when she develops dyspepsia and epigastric pain for which she took medicine in the form of some syrup from a homeopathic doctor. Following ingestion of that medicine she developed difficulty in swallowing and inability to open her mouth. She was unable to eat or drink due to limited mouth opening. She was taken to a local hospital as her condition was not improving. The doctor considered it as malingering and a forced attempt was made to pass a nasogastric(N.G) tube while five people were holding the patient. Patient developed vomiting, cyanosis, laboured breathing and fits.

Forced N.G intubation or fits was the likely cause of injury to the respiratory passages leading to pneumomediastinum and pneumothorax. Serum toxicology screen was carried out that showed high strychnine levels. Analysis of the medicinal syrup prescribed by the quack also confirmed the presence of nux vomica. Patient improved with antibiotics and oxygen. She was managed conservatively and observed. She was asymptomatic 48 hours later . Repeat CXR was normal after 2 weeks.

Discussion:

Pneumomediastinum, or mediastinal emphysema, is the presence of free air in the mediastinal structures. The Macklin effect, first described in 1939, highlights the sequence of events in the development of pneumomediastinum as follows: alveolar rupture, air dissection along the bronchovascular sheath, and free air reaching the mediastinum.

The dissection of free air may not be confined solely to the mediastinum. The mediastinum communicates with the submandibular space, the retropharyngeal space, and vascular sheaths within the neck. [2]

Primary or Spontaneous Pneumomediastinum (SPM) is caused by increased pressure gradient between the alveoli and pulmonary interstitium .Spontaneous pneumomediastinum is a rare condition.

Common causes of increased intra-alveolar pressure include acute asthma exacerbation, Valsalva maneuvers, childbirth, intense athletic activity, coughing or vomiting. Decrease in intrapleural pressure or in the lung interstitium, as in vasoconstriction, or loss of integrity of the alveolar-capillary membrane, as in interstitial lung disease, predisposes patients to SPM. The other known causes. Unusual causes include arthroscopy, dental extraction, adenoid-tonsillectomy, diving, trombone playing and performing a maximal expiratory pressure manoeuver. [3,4]

Sadarangani et al provide a case report of pneumomediastinum precipitated by weight lifting.5 Spirometry has been associated with the development of pneumomediastinum in 3 individual case reports.

Secondary causes include gas-forming microorganisms during an infection, and increasing intrathoracic pressure from trauma causing a disruption of bronchiolar, alveolar, or rarely, esophageal tissue, with leakage of air into the interstitial tissues.[5,6]

Pneumomediastinum differs from pneumothorax in that, in the latter, there is a disruption of the parietal pleura with collection of air in the pleural space; in pure pneumomediastinum the pleura remains intact. Symptoms include chest pain (26–70%), dyspnea (26–46%), cough (26–45%), sore throat (18%), neck pain (4–38%), rhinolalia (65%), hoarse voice (65%), neck and/or chest swelling (87%) . Signs include systolic crepitations (Hamman's sign), an abnormal crunchy or bubbling sound heard during cardiac auscultation (8–17%), subcutaneous emphysema (12–100%), neck swelling (14%), and hoarse voice and rhinolalia (65%).[7]

Diagnosis is made by chest x-ray. Small pneumomediastinum not visible, will be seen on chest CT although the use of CT only to confirm the diagnosis of SPM in an otherwise well-appearing patient is probably not warranted.[8]

Treatment is most often conservative; complications, although not common, include tension pneumopericardium; massive subcutaneous emphysema causing clinical effects can be drained with a silastic drain. Concurrent pneumothorax is found in 6–32% of cases and should be treated conventionally. Resolution of free air typically takes 2–4 days; recurrence is rare, but has been reported[7,8].

This is a case of a 22-year-old female who presented with pneumomediastinum following a forced attempt of passing a nasogastric tube. She had no identifiable underlying lung condition. She developed trismus due to overdosage of nux vomica prescribed by the homeopathic doctor.

The homeopathic remedy nux vomica, prepared with strychnine, was created as well as proved by the founder of the alternative stream of medicine homeopathy, Dr. Samuel Hahnemann way back in 1805.9 Nux Vomica is one of the commonly prescribed homeopathic medications and is used to treat problems related to the digestive and nervous systems. The common adverse effects of Nux Vomica are severe nausea, vomiting, convulsions of all muscle groups, which become longer and more closely spaced with time, spasms of the facial muscles causing cyanosis of the face, dilated pupils, prominent eye balls, and frothing at the mouth, loss of consciousness and a clear mind, immense reflex sensitivity, death due to asphyxiation caused by muscle spasms.

The presumed pathophysiology behind pneumomediastinum in this case appears to be increased intrathoracic pressure as a result of patient's exertion or air leak as a result of trauma to the respiratory passages during the procedure of NG intubation. Studies have demonstrated pneumomediastinum after generalized tonic clonic seizures and it may be the underlying cause in this case.[10]

Conclusion:

Pneumomediastinum and subcutaneous emphysema following a simple procedure like NG intubation is usually an uncommon complication. It needs to be considered as a differential diagnosis in a patient presented with sudden onset dyspnea, as it carries a high morbidity and mortality . Physicians must be aware of the risks associated with mixed medications used by Quacks and homeopathic doctors and complications of simple procedures like NG intubation which can compromise the life of a patient. Malingering should only be suspected when all the medical causes are ruled out.

References:

1. M Caceres, RL Braud , R Maekawa , DS Weiman , HE Garrettr. Secondary pneumomediastinum: a retrospective comparative analysis. Lung, Sep-Oct 2009; 187(5):341-6.
2. Zylak CM, Standen JR, Barnes GR, Zylak CJ. Pneumomediastinum revisited. Radiographics. Jul-Aug 2000; 20(4):1043-57.
3. M. Z. Gunluoglu, L. Cansever, A. Demir, C. Kocaturk, H. Melek, S. I. Dincer, and M. A. Bedlrhan, “Diagnosis and treatment of

spontaneous pneumomediastinum," Thoracic and Cardiovascular Surgeon, vol. 57, no. 4, pp. 229–231, 2009.

4. Perna, E. Vilà, J. J. Guelbenzu, and I. Amat, "Pneumomediastinum: is it really a benign entity? When it can be considered as spontaneous? Our experience in 47 adult patients," European Journal of Cardio-thoracic Surgery, vol. 37, no. 3, pp. 573–575, 2010
5. Sadarangani S, Patel DR, Pejka S. Spontaneous pneumomediastinum and epidural pneumatosis in an adolescent precipitated by weight lifting: a case report and review. Phys Sportsmed. Dec 2009;37(4):147-53.
6. F. Al-Mufarrej, J. Badar, F. Gharagozloo, B. Tempesta, E. Strother, and M. Margolis, "Spontaneous pneumomediastinum: diagnostic and therapeutic interventions," Journal of Cardiothoracic Surgery, vol. 3, no. 1, article 59, 2008.
7. Caceres M. , Ali S. Z. , Braud R. , Weiman D. , and Garrett Jr. H. E., "Spontaneous pneumomediastinum: a comparative study and review of the literature," Annals of Thoracic Surgery, vol. 86, no. 3, pp. 962–966, 2008.
8. Esayag Y., Furer V., and Izbicki G., "Spontaneous pneumomediastinum: is a chest X-ray enough? A single-center case series," Israel Medical Association Journal, vol. 10, no. 9, pp. 575–578, 2008.
9. Posadzki P, Alotaibi A, Ernst E. Adverse effects of homeopathy: a systematic review of published case reports and case series. The International Journal of Clinical Practice. 2012;66(12):1178–1188.
10. CurranH, RossJ. Bilateral pneumothoraces and pneumomediastinum complicating a generalized tonic-clonic seizure. CJEM. 2008;10:176-8.

SELECTED ABSTRACTS FROM PAPERS PRESENTED AT 1ST YOUNG SCIENTISTS RESEARCH CONFERENCE, HELD AT FOUNDATION UNIVERSITY MEDICAL COLLEGE, 2ND JUNE, 2014.

The "1st Young Scientist Research Conference 2014" was held at Foundation University Islamabad Campus on June 2, 2014. It was a truly momentous occasion on an unprecedented scale, providing an exemplary platform for young researchers to exhibit their potential in the field of research. A large number of articles were received from various Medical Colleges, both public and private, all across Pakistan. Thirty-nine articles were chosen for oral presentation whereas a total of 42 were designated for poster exhibition. The articles were meticulously assessed by a panel of eminent and highly revered judges. The present edition of FUMJ has included abstracts from a few of the very best articles presented at the conference.

ROLE OF RICE CROP IN THE SPREAD OF DENGUE

Mohsin Yousuf

Islamic International Medical College, Rawalpindi

ABSTRACT

Introduction:

Dengue is a mosquito borne infection found in tropical and subtropical regions of the world. WHO estimates that there may be fifty million dengue infected individuals worldwide. It is observed that dengue is endemic in those countries which are on the top of the list in rice crop production. Rice crop needs stagnant water for four to six month for its growth, which acts as a reservoir for mosquitos. It is observed that rice crop, its time of cultivation and frequency of reported cases are correlated with each other.

Aims & Objectives:

To find out the role of rice crop in the spread of dengue in rural areas of northern Punjab.

Methodology:

It was a retrospective cohort research study conducted from 2011 to 2013 on the population of rural areas of Faisalabad, Lahore and other endemic areas of Punjab. Sample size of 2651 had been taken; Lahore (1525) Faisalabad (945) and others (181). Data was collected from community, Government hospitals and Government of Punjab. Data was analyzed by using Microsoft Excel.

Results:

Out of 2651 patients (44.5%) belonged to those areas where rice crop is cultivated. The timing of their infection (May to November) is similar to the time of rice crop cultivation. In Faisalabad 444 out of 945 (47%) belonged to the rural area of Faisalabad. In Lahore 640 out of 1525 (42%) belonged to the rural area of Lahore.

Conclusion:

This calculation revealed that dengue is also spreading to the rural areas and rice crop has a big role in dengue spread.

Keywords:

Dengue, rice crop, stagnant water

IMPACT OF TERRORISM ON THE DEVELOPMENT OF POSTTRAUMATIC STRESS DISORDER (PTSD) AMONG THE RESIDENTS OF KHYBER BAZAAR AND ITS IMMEDIATE SURROUNDING AREAS IN PESHAWAR, KHYBER PAKHTUNKHWA, PAKISTAN

Syed Asad Abbas

Institute of Management Sciences, Hayatabad - Bara Road, Peshawar

ABSTRACT

Objective:

This study evaluated the frequency of posttraumatic stress disorder (PTSD) and the severity of PTSD symptoms in survivors, rescuers and witnesses of terrorist attacks on Khyber bazaar, Qissa Khawani bazaar and All Saints Church in Peshawar.

Methodology:

Cross-sectional survey carried out on a sample of 100 survivors, rescuers and witnesses of terrorist attacks using structured interviews to assess the severity of posttraumatic stress five months after the attacks. The study period extended from January 24th to March 24th, 2014 (a total of 8 weeks). PTSD symptoms were measured using Posttraumatic Symptom Scale Interview (PSSI), conferring a diagnosis of PTSD at 5 months. Additionally, the severity of PTSD symptoms was also determined using PSSI scores, severity ranged from 0-51.

Results:

Of the 100 survey respondents, 88% were males and 12% were females. 40% had attained 10 years of education, matriculation but irrespective of the gender or educational status, all had some degree of PTSD symptoms. The frequency of PTSD was calculated to be 80%. 66% percent respondents were diagnosed as having moderate PTSD while 11% of the sample suffered from severe PTSD level. Age, gender, occupation and education level did not have any correlation with PTSD development.

Conclusion:

The contemporary findings indicate that any person who has witnessed or survived catastrophes of terrorist activities like bomb blast or suicide attacks is at risk for developing PTSD and there is necessity to deliver specialized post-disaster mental health facilities to the people having substantial levels of PTSD after calamities of such great intensity.

Keywords:

Anxiety Disorder, Frequency, Mental Health, Posttraumatic Stress, PTSD, Terrorism

ASSESSMENT OF KNOWLEDGE REGARDING REUSE OF DISPOSABLE PLASTIC BOTTLES IN MEDICAL STUDENTS

Umay Kalsoom Hadi, Mabroor Ghani, Amna Batool Gardazi, Amna Naveed, Aamna Malik, Lubna Hussain

Foundation University Medical College, Islamabad

ABSTRACT

Objective:

The study was done to assess the level of knowledge regarding hazards of reuse of plastic water bottles and to create awareness about the hazards of reuse of disposable plastic bottles.

Methodology:

Descriptive cross-sectional study consisting of 300 students of Foundation University Medical College. Study period was from January 2014 to September 2014. Data was collected using structured questionnaire and analyzed by SPSS 17.

Result:

Results showed that 79.3% of population studied was aware of the hazards of plastic bottles and 20.7% were not aware. About 42.2% people had knowledge about diseases caused by reuse of plastic bottles while 57.5% did not. Despite being aware of the hazards, 57.1% of the population was using plastic bottles on regular basis. 36.4% of people thought that GIT disturbances, 12.4% thought that infectious diseases, 39.3% thought that cancers are caused by reuse of plastic bottle while 12% had no idea. 51.3% people sometimes,36.4% always and 12.4% never place plastic bottles in their cars.

Conclusion:

Despite having sufficient knowledge regarding reuse of disposable bottles majority of people regularly use them.

Keywords:

Disposable plastic bottles, Knowledge, Resue

LEVELS AND SOURCES OF STRESS IN MEDICAL STUDENTS AT A PAKISTANI MEDICAL SCHOOL PERTAINING TO YEAR OF STUDY AND GENDER

Nimra Ishfaq

CMH Lahore Medical College & Institute of Dentistry

ABSTRACT

Objective:

The study primarily aims to examine levels and sources of stress in students at a Pakistani Medical School with regards to year of study and gender. This study also looks at the effects of demographics on self reported stress.

Methodology:

A cross sectional survey was distributed to 350 medical students of year 1, 4 and 5 at Combined military hospital medical college, Lahore during April 2014. It contained a consent form, general demographic information and the questionnaire consisting of 40 items to identify the levels and sources of stress.

Results:

The response rate was 241/350 (68.84%). Year 1 reported a Moderate stress level of 1.890, Year 4 reported a High stress level of 2.039 and year 5 reported a Moderate stress level of 1.925 where academics were the stressors. Males reported lower stress levels than females ($p<0.000$). The common sources of stress were academic and social. Linear regression analysis indicated that daily hours of study was positively co-related with academic stressors ($p<0.026$) and social stressors ($p<.0.028$). Daily hours of sleep was negatively co-related with academic stressors ($p<0.045$). Year of Study ($p<0.036$) and Marital Status ($p<0.024$) were negatively co-related with social stressors.

Conclusion:

The stress levels and sources did change with year of study. Stress and stressors were found to be gender specific with males reporting lesser perceived stress.

Keywords:

Medical students, stress

NITROFURANTOIN - A NEGLECTED ANTIMICROBIAL FOR URINARY TRACT INFECTIONS

Sehrish Siddique, Ruqiya Bashir

Foundation University Medical College, Islamabad

ABSTRACT

Objective:

To determine the susceptibility of uropathogens againts antimicrobials and to compare the efficacy of nitrofurantoin with other antimicrobials.

Methodology:

Patients of all age groups and gender reporting to outdoor clinic of Fouji Foundation Hospital Rawalpindi for some urinary infection problem from July 2013 to December 2013 were included in the study. A total of 100 uropathogens were included in the study. The urine samples were cultured quantitatively on cystine lactose electrolyte deficient agar .The isolates were identified using Gram stain, catalase, coagulase and oxidase test and standard biochemical tests using Analytical profile index-20E. The susceptibility against various antimicrobials was performed using standard antimicrobial disks (oxoid) and adapting the method of Clinical Laboratory Standard Institute.

Results:

Escherichia coli was the most common isolates (65%) followed by Klebsiella pneumoniae (12%) ,Pseudomonas aeruginosa (9%), Providencia species (4%), Proteus mirabilis (3%), Acinetobacter baumannii (3%). All the isolates except for MRSA revealed best susceptibility against Imipeneum from 67% to 100%.All the isolates excluding Pseudomonas species,Proteus species and Acinetobecter revealed very good susceptibility against nitrofurantoin. Nitrofurantoin showed better activity as compared to ciprofloxacine (p=0.0011) for Escherichia coli and (p=0.0209) for Klebsiella pneumoniae. However, there was no significant difference between nitrofurantoin and gentamicin (P=0.2142) and (P=0.3016) for hese two organisms respectively.

Conclusion:

Among oral antimicrobials nitrofurantoin revealed best activity against uropathogens. Nitrofurantoin is recommended to be used in community acquired urinary tract infections as first line drug.

Keywords:

Antimicrobials, Nitrofurntoin, Urinary tract infections

THE EFFECT OF ENERGY DRINK ON REACTION TIME, HEMODYNAMIC AND ELECTROCARDIOGRAPHIC PARAMETERS IN HEALTHY MEDICAL STUDENTS

Waheed A, Zafar A, Cheema A, Mukhtar Q, Malik A

CMH Lahore Medical College & Institue of Dentistry, Lahore

ABSTRACT

Objective:

To evaluate the cardiovascular effects and reaction time associated with energy drink in healthy medical students.

Methodology:

In this randomized control design, a total of 30 healthy volunteers, 19-21 years of age of either sex were divided at random into three groups namely A, B and C. At the time of study, subjects were fasting overnight and were abstaining from caffeine for 48 hours. Baseline pulse and blood pressure were taken whereas heart rate, QTc interval and mean reaction time of each of three groups were measured by using power laboratory. The subjects of group A had consumed nothing while those belonging to group B and C were asked to consume 250ml (1 can) and 500ml (2 cans) of energy drink respectively and measurements were retaken after 1 and 2 hours interval.

Results:

The pulse rate, heart rate, blood pressure and QTc interval increased significantly in group C at 2 hour as compare to group A and B. In group C, at 2 hours, pulse rate increased by 16.1% (p= 0.001), systolic blood pressure increased by 9.5% (p= <0.001), diastolic blood pressure increased by 10.1% (p= 0.002), heart rate significantly increased by 17.3% (p= 0.015) and QTc interval prolonged by 12.4% (p= 0.002). A decrease in mean reaction time was noticed by 20.0% (p= <0.001).

Conclusion:

Energy drink consumption increases the HR, BP, QTc interval as well as performance. The more the energy drink consumed, the higher the changes are likely to be.

A COMPARATIVE INVESTIGATION TO OBSERVE THE EFFECT OF THE RECITATION OF AL-QURAN AND CLASSICAL MUSIC ON ALPHA BRAIN WAVE IN MEDICAL STUDENTS

Tehleel Javaid, Zohra Asghar, Saira Tariq ,Qandeel Nawadat, Mahnoor Mir

Foundation University Medical College, Islamabad

ABSTRACT

Objectives:

- *To determine the role of Qur'anic recitation in producing alpha wave increments on EEG in healthy subjects.*
- *To compare the level of increments, if any in alpha waves on EEG between Qur'anic verses and Classical music.*

Materials and Methods:

16 healthy volunteers aged 20-25 years, comprising 8 males and 8 females were selected, from the undergraduate MBBS program of FUMC. A 10-minutes baseline EEG was recorded for each participant prior to the procedure at FFH, to rule out any neuropsychiatric disorder. After adjusting the electrodes properly, a 5-minutes baseline EEG was recorded .The participant was then exposed to the recitation of chapter 36 (Surah Yaseen) of Al-Quran for 5 minutes using earphones. A period of EEG at rest was recorded for 5 minutes after the exposure to Qur'anic recitation. Subsequently, the subject was exposed to Pachelbel's Canon in D-major, which has been used as a "relaxing music" in researches. Statistical analysis was performed using SPSS version 21. Paired sample t-test was used to determine the significance of difference in increments.

Results:

Mean values of Maximum negative alpha amplitude for Qur'anic Recitation, Baseline and Classical music were -39.9μV, -36.5μV, -35.8μV respectively. Maximum negative alpha amplitude was higher for Qur'anic recitation vs. Baseline (p=0.033) and Qur'anic recitation vs. Classical music (p = 0.006).

Conclusion:

The results reveal that Qur'anic recitation increments alpha brain waves more than classical music which has been scientifically proven to be relaxing for mind. Therefore Qur'anic recitation can help in achieving a more relaxed state of mind and may be used as potent tool in music therapy as a part of CAM (Complementary and Alternative Medicine).

Keywords:

Alpha Brain Wave, Classical Music, Quranic Recitation

OPTIMISTIC BIAS AMONGST SHEESHA SMOKER AND NON-SMOKER UNIVERSITY STUDENTS

Waleed Ahmad Raja, Muhammad Saad Aziz, Maaz Tambra, Temoor Naeem, Nabhan Zakir, Dr. Nabeela Fazal Babar

Department of Community Medicine, Foundation University Medical College, Islamabad

ABSTRACT

Objective:

To examine and compare the risk perceptions of sheesha smoking amongst smokers & non-smokers.

Methodology:

A survey using a specially designed questionnaire was carried out on 320 Students of a private University by using Consecutive sampling technique. Data was collected by administering a structured questionnaire to university students only if they were willing to take part in the study. Data was analyzed on SPSS version 20.

Results:

The study participants were 320 university students, majority of them were between the ages of 22-24 years. 47.2% of the participating students confessed that they smoke sheesha. Among sheesha smokers, 67.5 % were males and 32.4% were females. Out of 151 sheesha smokers, 71 (47%) were also cigarette smokers. Majority of the sheesha smokers, 61(98%) and only 2% of non-smokers believed that it to be addictive. They believed that one can quit smoking easily. Nearly half, 47.1% of smokers and 46.2% of non-smokers did not believed it to be health hazardous. 57 (76%) sheehsa smokers believed that sheesha smoking is socially more acceptable as compared to cigarette smoking whereas 49 (32.4%) non-smokers also believed that so.

Conclusion:

The optimistic bias regarding smoking risks appears to be held by both smokers and non-smokers. The results of our study indicate a need for proper education of students starting from a young age (which is habit forming age) so that they are aware of the health hazards of sheesha smoking.

Keywords:

Sheesha, smoking, university students

GUIDELINES FOR AUTHORS

The FUMJ agrees to accept articles prepared in accordance with the "Uniform Requirements of manuscripts" prepared by the International Committee of Medical Journal Editors (ICMJE) in Vancouver in 1978 and revised in 2010. Detailed requirements are available at their website www.icmje.org. Salient requirements are reproduced here for guidance of the authors.

Submission Of An Article:

All material submitted for publication should be sent exclusively to the Foundation University Medical Journal. Work that has already been reported in a published paper or is described in a paper, sent or accepted elsewhere for publication of a preliminary report, usually in the form of an abstract, or a paper that has been presented at a scientific meeting, if not published in a full proceedings or similar publication, may be submitted. Press reports of meeting will not be considered as breach of this rule but such reports should not be amplified by additional data or copies of tables and illustrations. In case of doubt, a copy of published material should be included with a manuscript to help the editors decide how to deal with the matter.

Ethical Considerations:

If the article includes tables, illustrations or photographs, which have been previously published, a letter of permission for publication should be obtained from author(s) as well as the editor of the journal where it was previously printed. Written permission to reproduce photographs of patients whose identity is not disguised should be sent with the manuscript; otherwise the eyes will be blackened out.

Format of Articles:

The material submitted for publication may be in the form of an original research, a review article, a case report, recent advances, adverse drug reports or letter to the editor. Original Articles should normally report original research of relevance to basic or clinical medicine and may appear either as papers or as short communications. The papers should be of about 2000 words, with nor more than six tables or illustrations; short communications should be about 600 words, with one table or illustration and not more than five references. Review article should consist of structured overview of a relatively narrow topic providing background and recent developments with reference of original literature. An author is eligible to write a review article only if he/she has published at least three original research articles and some case reports on the same topic.

Letters should normally not exceed 400 words, have not more than 5 references and be signed by all the authors; preference is given to those that take up points made in articles published in the journal. Editorials are written by invitation.

Clinical case reports must be of academic and education value and provide relevance of the disease being reported as unusual. Brief or negative research findings may appear in this section. The word count of case report should be 800 words with a minimum of 3 key words. It should have a non-structured abstract of about 100 – 150 words (case specific) with maximum of 5 – 6 references. Not more than 2 figures shall be accepted.

Authors should keep one copy of their manuscripts for reference, and send three copies to the Editor FUMJ. The author should also submit an electronic copy of the manuscript typed in MS Word. Any illustration or photographs should also be sent in duplicate.

Each manuscript should include a title page (containing mail address, fax and phone numbers of the corresponding author), structured abstract, text, acknowledgements (if any), references, tables and legends. Each component should begin on a new page, in the following sequence; title page, abstract and 3-5 key words; text; acknowledgement; references; tables and legends for illustrations.

The manuscript should be typed in double spacing on 8" x 11" white bond paper with one inch margin on both sides. There should be no more than 40 references in an Original Article and no more than 60 in a Review Article. The CD containing soft copy of the article should be sent with the manuscript.

Tables, Graphs and Illustrations:

Tables and illustrations should be merged within the text of the paper, and legends to illustrations should be typed on the same sheet. Tables should be simple, and should supplement rather than duplicate information in the text; tables repeating information will be omitted. Each table should have a title and be typed in double space without horizontal and vertical lines on an 8 1/2" x 11' paper. Tables should be numbered consecutively with Roman numerals in the order they are mentioned in the text. Page number should be in the upper right corner. If

abbreviations are used, they should be explained in foot notes and when they first appear in text. When graphs, scattergrams, or histogram are submitted, the numerical data on which they are based should also be provided. All graphs should be prepared on MS Excel and sent as a separate Excel file. For scanned photographs highest resolution should be used.

SI Unit:

System International Unit (SI Unit) measurements should be used. All drugs should be mentioned by their generic names. Trade names may however, be mentioned in brackets, if necessary.

Abstract:

Abstracts of original article, comprising of upto 250 words, should be in structured format with following sub-headings.

i. Objective, ii. Design, iii-Place and duration of study, iv. Patients/materials & Methods, v. Results, vi. Conclusion.

Review article, case reports and others require a short, unstructured abstract.

Introduction:

This should include the purpose of the study. The rationale for the study should be summarized. Only pertinent references should be cited; the subject should not be extensively reviewed. Data or conclusions from the work being reported should not be presented.

Methods:

Study design and sampling methods should be mentioned. The selection of the observational or experimental subjects (patients or experimental animals, including controls) should be described clearly. The methods and the apparatus used should be identified (manufacturer's name and address in parentheses), and procedures described in sufficient detail to allow other workers to reproduce the results. References to established methods should be given, including statistical methods; references and brief description for methods that have been published but are not well known should be provided, new or substantially modified methods should be described, giving reason for using them, and evaluating their limitations all drugs and chemicals used should be identified precisely, including generic name(s), dose(s) and route(s) of administration.

Results:

Results should be presented in a logical sequence in the text, tables and illustrations. All the data in the tables or illustrations should not be repeated in the text; only important observations should be emphasized or summarized.

Discussion:

The author's comment on the results supported with contemporary references. Critical analysis of similar work done by other workers, its comparison with own work with possible reasons for any differences found should be included.

Conclusion:

Conclusion should be provided under separate heading and highlight new aspects emerging from the study. It should be in accordance with the objectives.

References:

Reference should be numbered in the order in which they are cited in the text. At the end of the article, the full list of the references should give the names and initials of all authors (unless there are more than six when only the first six should be given followed by et al). The author's names are followed by the title of the article; title of the journal abbreviated according to the style of the Index Medicus (see “List of Journals Indexed”, printed yearly in the January issue of Index Medicus); year volume and page number; e.g. Farrell RJ.

Rational approach to iron deficiency anaemia in pre menopausal women. Lancet 1998; 352:1953-4.

References to books should give the names of editors, place of publication, publisher and year. The author must verify the references against the original documents before submitting the article.

Peer Review:

Every paper will be read by two staff editors or members of the editorial board. The papers selected will then be sent to 2-3 reviewers. If statistical analysis is included, further examination by a statistician will be carried out.

Copyright:

ADDENDUM

to the original article entitled
"Assessment of quality of Soan River water"
Babar NF, Hussain A, & Zaidi N
Foundation University Med J 2014; 1(1): 35-41

The authors are grateful to Major General Mahmood Ahmed (Retd) for his constructive suggestions and inspiration for the study. Assistance of the following students is acknowledged in data collection
Ahmed Zeb Khan
Syed Kumail
Abdul Hannan
Adeel Usman
Ahsan Nawaz
Ali Imran
Umair Javaid

Publication Office:
Editor FUMJ, C/O Department of Pharmacology & Therapeutics,
Foundation University Medical College, DHA Phase-I, Islamabad, Pakistan 46000
Online issue available at: www.fui.edu.pk
E mail (for electronic submission of articles): fumj@fui.edu.pk