DECEMBER 2013 / VOLUME 3 / ISSUE 3

BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE & GENERAL HOSPITAL

Department of Pharmacology

LTMMC & LTMGH, Sion, Mumbai - 22

Committee Members for Bulletin on Adverse Drug Reactions

INDEX

From the Editor's Desk

Dear Friends and Colleagues,

It gives me great pleasure to present to you yet another issue of Bulletin on Adverse Drug Reactions.

First and foremost I would like to thank all the authors from various medical colleges who responded to our request for sending articles for publication in our bulletin.

The first article deals with an important issue of Counterfeit Medicines. Every year many lives are lost to counterfeit drugs. Counterfeit medicines cause huge revenue losses and more importantly risk of losing credibility of the pharmaceutical companies in the eyes of the consumer. The article handles these issues and also gives a brief overview on few methods to detect counterfeit medicine and some measures to reduce them.

The second article gives us a review of sexual dysfunction as an adverse effect of typical and atypical antipsychotic agents and the details of monitoring, prevention and management of this important adverse effect.

As in the previous issue, we have analyzed the ADRs from our institute and presented the data in easy chart form for your quick review which may be useful for comparison with the ADR trends in your institute.

I hope the readers find all the section of this bulletin interesting and informative and again request all the readers to contribute medical document for publication in this bulletin.

Finally, I would like to thank all the clinical departments from our institute for their valued contribution to Pharmacovigilance, to all the authors for contributing in the bulletin and to all the members of Department of Pharmacology for their efforts in bringing out the current issue of this bulletin.

Thank you

Dr. Sudhir Pawar

COUNTERFEIT MEDICINES

Dr. Bagle TR, Dr. Bhide SS***, , Dr. Kulkarni MV**, Dr. ManeYV***

**** Associate Professor, **Assistant Professor, *Resident,*
Department of Pharmacology & Therapeutics. Seth GSMC & KEMH, Mumbai.

Problem statement: Global and India

Medicines are supposed to treat or prevent illnesses. Almost 2 billion people lack access to essential medicines and by improving access to existing medicines 10 million lives each year could be saved.[1,2] Thus there is need of quality medicines as fake medicines can harm and even kill people.[3]

The World Health Organization (WHO) estimates that about 10% of the worlds and 25% of drug trade in poor countries consists of counterfeits.[4] In parts of Africa and Asia this figure exceeds 50%. The number of investigations of possible counterfeit drugs by United States-Food and Drug Administration (US-FDA) has jumped from about 5 per year in 1990s to more than 20 per year since 2000.[5]

In 1990 in Haiti, Nigeria, Bangladesh, India, and Argentina, more than 500 patients, predominantly children, are known to have died from use of the toxin diethylene glycol by fake paracetamol syrup.[5,6,7] In the United States (US), negligent production at Massachusetts compounding pharmacy sickened more than 600 people, killing 44, from September 2012 to January 2013.[8] In 2013 in India, around 200 children were ill and 21 kids were hospitalized after they were given iron and folic acid tablets during a government drive against anaemia.[9] Most of the counterfeit medicines in Nigeria originate in India, which led Nigerian Authorities threaten to ban import of drugs from India in 2003.[10] The vast majority of counterfeit medicines are currently thought to be produced in China, Russia and India.[11] Counterfeits affect both developed and developing countries[12] and these effects are difficult to detect and quantify.

Impact of counterfeit medicines:

Counterfeit medicines may include products with incorrect or wrong ingredients, or may be composed of toxic substances that directly cause illness and death.[1] The potential dangers posed by counterfeit drugs may multiply in health emergency situation; as the demand for the drug would vastly exceed legitimate supply of the drug. In such cases, opportunity for criminal counterfeiting may be significant. [12]

In1999 Newton et al demonstrated that 38% of shop-bought artesunate blister packs in South-East Asia were counterfeit, containing no artesunate.[13] If a drug contains too little active ingredient, not all the disease agents are killed and resistant strains are able to multiply and spread.[10]

According to the WHO 1 in 4 packets of medicines sold in street markets could be fake. The US- FDA estimates the worldwide sales of fake drugs exceed 3.5 billion USD per year[14] was projected to reach 75 billion US dollars in 2010. Thus, many pharmaceutical companies are deprived of their rightful profits. [1] Table 1 shows a glimpse of the counterfeit drugs that have hit the world.

Counterfeit/Substandard/Spurious/Falsified Medicines:

WHO broadly defines counterfeit medicines as medicines manufactured below established standards of safety, quality, efficacy and are deliberately and fraudulently mislabelled to hide their true identity and source. WHO's definition includes products without active compound, with insufficient quantities of active ingredient, with wrong drug or with correct ingredients in proper amounts but in fake packaging.[6, 11,15] The Council of Europe defines counterfeit as false representation regards to identity and/or source, extending this definition to include human, veterinary medicines and medical devices."[3]

The Drugs and Cosmetics (D & C) Act of India1940, chapter IV (Manufacture, sale distribution of drugs and cosmetics) which includes clauses: 17.Misbranded drugs, 17.A. Adulterated drugs, and 17.B. Spurious drugs, however the Indian D & C Act does not include the definition of counterfeit.[11, 16]

The WHO is currently engaged in negotiations with member states for its future role in tackling the issue of what is currently referred to as substandard/ spurious/ falsely labelled/ falsified/ counterfeit medical products (SSFFC). [3] Spurious, substandard, fake, and counterfeit drugs have been used interchangeably despite having differences in definition; this creates disarray and there is increased need for uniform international definition. Counterfeit medicines are part of the broader phenomenon of substandard pharmaceuticals. The difference is that they are deliberately and fraudulently mislabeled with respect to identity and/or source.

Table 1: Some brands of these drugs suffered at the hands of drug counterfeiters[1,5,13,18]

Sr.No	Country	Year	Drug
1	US	2012	Bevacizumab
2	WHO	2003	Fixed drug combination of Zidovudine, Lamivudine, Indinavir
3	US	2002	Erythropoietin
4	Ghana, Africa	2002	Halofantrine syrup
5	US	2001	Fixed drug combination of Zidovudine + Lamivudine
6	US	2001	Human growth hormone
7	Ghana	2002	Halofantrine Capsules
8	Brasil	1999	Oral contraceptive pills
9	Thailand	1984	Cotrimoxazole
10	US	1982	Paracetamol

Role of the Pharmaceutical Industry:

Falsified medicines are difficult to investigate and prosecute.[8] There is lack of proper legislation and stringent regulation in many countries.[6] The industry's history of secrecy over data about fake drugs, go back to over more than 20 years.[5] As per the WHO, the drugs industry has a great deal of data but was very reluctant to make them available.[17] Government's reluctance to publicize problems is reflected in lack of action against the problem of counterfeits, relative to their large impact on public health. There are no reliable accessible databases whereby health workers or public can access current details of which products are being faked in a locality.[5] The Pharmaceutical industry may play a major role to tackle the giant of counterfeit medicines.

Laws and Guidelines: World and India:

All those examples of pernicious deceptions mentioned above, are reported mostly in local newspapers and little are published in medical research. The accumulated evidence, suggests that mortality and morbidity arising from this murderous trade are considerable, especially in developing countries.[18]

The human right for adequate standard of living for health and well-being is an important right that is recognised in the International Bill of Human Rights. In the Indian Constitution, legal right to health is based on right to life and liberty.[11] Counterfeit drugs violate these rights. The problem of counterfeit drugs was first addressed at a conference in Nairobi, Kenya, in 1985. However, the counterfeit market has rapidly expanded, due to widespread use of internet to market counterfeit products.[19] WHO has taken lead in the global effort to combat counterfeit medicines and has created the first global partnership known as International Medicinal Products Anti-Counterfeiting Taskforce (IMPACT) in 2006 comprising of all 193 member states .[1,15,20]

The punishment for counterfeiters varies from imprisonment with or without fine to death worldwide.[1] While in India, death penalty has been discussed as a penal action in conviction of spurious drug case. The penalty for counterfeit drug manufactured in India is imprisonment for not less than 3 years and a fine of 5000 rupees.[11] A weak and incongruous penalty is incapable of making a great impact in preventing this lucrative crime.[1] In 2003, the Mashelkar Committee reported that only 15 states had functioning drug testing laboratories and out of these only seven were well equipped and 11 states had no drug testing facilities.[11] The report recognizes the lack of infrastructure and personnel to carry out these checks and recommends drastic up regulations and overhaul of the vigilance structure.[20] Thus India needs to upgrade its existing system for early detection of counterfeit drugs.

Consequences of counterfeit medications:[21]

The directly related consequences of counterfeit medicines to patients are many fold. It may result in increase in morbidity and mortality due to inadequate control of diseases, especially chronic conditions

like diabetes or hypertension. Another important result is increased drug resistance to anti-microbials. Other consequences are adverse effects due to incorrect ingredients. There are indirect effects in terms of economic loss, wastage of human efforts and increased burden on healthcare workers and other regulatory agencies. All these factors ultimately may lead to loss of confidence in the Health Care Systems.

Various methods to detect counterfeit medicines:

- The German Pharma Health Fund (GPHF) and China's National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) has developed the standard field test, 'Minilab' consisting of mobile labs in vans for analysing the authenticity of a wide range of essential drugs.[22]

- A combination of wired and wireless technologies provides information about location, condition, quality, and custodianship as products move through processes related to production, storage, and distribution. By smart devices such as sensors and radio frequency identification (RFID), it is possible to create a digital trail.[23]

- WHO has established a RAS (Rapid Alert system), world's first Web based system for tracking the activities of drug cheats.[23]

- In UK, the Yellow Card Scheme provides a facility for the public and healthcare professionals to report any side effects and other problems suffered by patients whilst taking a medicine.[3]

- In US, through the Med Watch Program health professionals can report suspected counterfeit drugs to the FDA.[11] There are products embossed with a unique code and consumers can check for authenticity of the product by sending a free Short Message Service (SMS) with a reply SMS telling that the product is original.[11]

- The Permanent Forum on International Pharmaceutical Crime is a forum consisting of members from 15 countries and its goal is to enhance protection of public health by combating pharmaceutical crime.[3]

- Organization of Pharmaceutical Producers of India (OPPI) working with International federation and Indian Pharmaceutical Alliance (IPA) have developed networks to counter the counterfeit drugs trade in India.[11]

Measures to curb counterfeiting:

Holograms, tracers, taggants and inks, provide a simplified means for consumers to deduce the authenticity of a drug. A microscopic tag having sequence of colors that denotes the unique code of the tag or Radio - Frequency Identification which is based on an electronic chip that emits radio

frequency waves encoding a specific ID or code can be used. Few other technologies to mention are providing a unique digital identity by Mass Encryption Technology, 2-D Data Matrix barcode, Quick Response Codes and Unique Identification Mobile Verification. Recently, work is on for developing an electronic pedigree (E- Pedigree) system to track drugs from factory to pharmacy.[24]

Conclusions:

Counterfeit drugs are a big challenge to the health care system worldwide. Poverty, lack of drug regulation, and light penalties makes this business flourish in developing countries.[11] As per Akunyili, drug counterfeiting is mass murder and one of the greatest atrocities of our time. It is a form of terrorism against public health as well an act of economic sabotage.[19] WHO has been struggling to define its role regarding counterfeit drugs on one hand and questions of intellectual property on the other. The world is in need of a comprehensive global strategy that unifies efforts of various stakeholders trans-nationally to combat poor quality drugs.[2]

In India, where illiteracy and poverty is rampant and consumer awareness is low, spread of fake and substandard drugs are a cause of an alarm.[25] The reports show India to be a major producer of counterfeit drugs in the world. It is also a major concern to the Indian pharmaceutical industry and government as it can jeopardize its reputation, and adversely affect India's rapidly growing pharmaceutical exports.[11]

Information on fake drug identity and distribution needs to be shared nationally and internationally between government, non-governmental organizations and consumer groups.[20,26] Solutions are at multiple levels of the chain and each has a unique role to play, these together can combat the menace of counterfeit medicines.

References:

1. Amon JJ. Dangerous medicines: Unproven AIDS cures and counterfeit antiretroviral drugs. Globalization and Health. 2008; 4:5. Available online from website http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2291042/
2. Editorial. Strenthening global action against poor quality drugs. Lancet. 2013; 381: 599
3. Medicine and Healthcare Regulatory Agency. Falsified medical products strategy 2012-2015. [Homepage on the Internet].cited on 2013 July 03. http://www.mhra.gov.uk/home/groups/ei/documents/websiteresources/con149816.pdf
4. Pincock S. WHO tries to tackle problem of counterfeit medicines in Asia. BMJ. 2003; 327:1126.
5. Cockburn R, Newton PN, Agyarko EK, Akunyili, White NJ. The Global threat of counterfeit drugs: Why industry and governments must communicate the dangers. Plos medicine. 2005;2(4):e100.302-308.
6. Mukhopadhyay R. The hunt for counterfeit medicine. Anal Chem. 2007 ;79(7):2622-7

7. Katherine LO, Selanikio JD, Hecdivert C, Placide MF, Louis M, Barr JR et al. Epidemic of paediatric deaths from acute renal failure caused by diethylene glycol poisoning. JAMA.1998;279(15):1175-80

8. Countering the problem of falsified and substandard drugs. [Internet]. Institute of Medicine; 2013. [cited on 2013 July 10.] Report. Available from: http://www.iom.edu/~/media/Files/Report%20Files/2013/Substandard-and-Falsified-Drugs/CounteringtheProblemofFalsifiedandSubstandardDrugs_RB.pdf.

9. Shekhar R, Jha DN. Iron pills leave 200 kids ill, 21 in hospital. Times of India. Mumbai edition.20 July 2013:11.

10. Morris J, Philip S. International Policy Network. Counterfeit medicines in less developed countries. Problems and solutions. 2006. [Homepage on the Internet].cited on 2013 July 10. counterfeiting.unicri.it/docs/Ctf%20medicines%20in%20less%20developed%20countries.pdf

11. Gautam CS, Utreja A, Singal GL. Spurious and counterfeit drugs: a growing industry in the developing world. Postgrad Med J. 2009;85(1003):251-6.

12. Progress Report of the department of justice's task force on intellectual property. [Internet].Department of justice; 2006. [cited on 2013 July 10.] Available from: http://www.justice.gov/opa/documents/ipreport61906.pdf

13. Dondorp AM. Newton PN. Mayxay M. Van Damme W. Smithuis FM, Yeung S et al. Fake antimalarials in Southeast asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. Trop Med Int Health.. 2004; 9(12):1241-6.

14. Burns W. Who launches taskforce to fight counterfeit drugs. Bull of World Health Organ.2006;84(9):689-690.

15. Counterfeit medicines. World Health Organisation Web site. http://www.who.int/medicines/services/counterfeit/impact/ImpactF_S/en/. 14 November 2006. Accessed on July 10, 2013.

16. Ministry of Health and Family Welfare. The Drugs and Cosmetics Act and Rules. [Homepage on the Internet].cited on 2013 July 10. http://cdsco.nic.in/html/copy%20of%201.%20d&cact121.pdf

17. Editorial. Counterfeit drugs: a growing global threat. Lancet. 2012;379(9817):685.

18. Swaminath G. Faking it-II: Countering and preventing counterfeiting of drugs. Indian J Psychiatry. 2009; 5(1): 9-11.

19. Grackin A. Counterfeiting and Piracy of pharmaceuticals. IEEE Eng Med and Biol Mag. 2008;66-9.

20. Srinivasan S, Jesani A. Standing committee report on CDSCO: hard facts confirm an open secret. Indian Journal of Medical Ethics.2012;9(3):148-50.

21. Newton PN, Green MD, Fernández FM. Impact of poor-quality medicines in the 'developing' world. Trends Pharmacol Sci. 2010;31(3):99-101.

22. Chika A. Bello SO. Jimoh AO. Umar MT. The menace of fake drugs: Consequences, causes and possible solutions. Res Jour Med Sci. 2011;5(5):257-61.

23. Newton PN. Murder by fake drugs Time for international action.BMJ.2002; 324(7341): 800-801.

24. Gupta et al. Counterfeit (fake) drugs & new technologies to identify it in india. IJPSR.2012; 3(11): 4057-64.

25. Charatan F. Fake prescription drugs are flooding the United States. BMJ.2001; 322(7300):1443-4

26. Lewis Katie. Chinas counterfeit medicine trade booming. CMAJ. 2009; 181(10): E237-8.

SEXUAL DYSFUNCTION AND OTHER LESSER KNOWN SERIOUS SIDE EFFECTS OF ANTIPSYCHOTICS

Dr. Mohammad Younis Bhat*, Dr. Samina Farhat, Dr. Zorawar Singh*****

Demonstrator, **Associate Prof. & Head,*Lecturer*
Department of Pharmacology, Govt. Medical College, Srinagar (J&K) India

INTRODUCTION

Psychosis is a symptom of mental illness characterized by a distorted or non-existent sense of reality with major disturbances in reasoning often with delusions and hallucinations.[1]Antipsychotic drugs or major tranquilizers are chemically diverse and interact with multiple neurotransmitter systems. The therapeutic effects of these drugs are believed to result from competitive blockade of dopamine receptors and serotonin (5HT) receptors, the adverse effects are attributed to blockade of variety of receptors like α1adrenergic receptors, dopamine (D2) receptors, dopamine (D4) receptors, histamine (H1) receptors, muscarinic receptors and serotonin (5HT2) receptors. Typical antipsychotic drugs have an equal or greater affinity for D2 receptors than for 5HT2 receptors.[2]

Adverse effects often are extension of pharmacological actions of these drugs. The most important are those on the cardiovascular, central, autonomic nervous and endocrine systems.[1,3] Endocrine disturbances occur due to effect of antipsychotic drugs on the hypothalamus or pituitary, and also because of their antidopaminergic action.[4] The hyperprolactinemic activity is presumed to be responsible for breast engorgement and galactorrhea that occasionally are associated with their use, sometimes seen even in male patients receiving high doses of neuroleptics. Some antipsychotic drugs reduce the secretion of gonadotropins and sex steroids, which can cause amenorrhea in women and sexual dysfunction or infertility in men.[5] Patients often refuse to take their medication on a regular basis because of unacceptable sexual adverse effects and sexual function is often sacrificed "for the sake of sanity" in psychotic disorders.[6] Studies have consistently shown an association between neuroleptic treatment and sexual dysfunction. The prevalence of sexual dysfunction in groups treated with neuroleptics is thought to be 60% in men and 30-90% in women, with thioridazine being one of the worst culprits.[7]

Sexual and reproductive function related side effects of antipsychotics are frequent, often under-estimated and badly tolerated.[8] It affects self-esteem, causes trouble for their sexual partners, interferes with their quality of life and compromises treatment compliance.[9],[10],[11],[12],[13] Patients themselves report that the sexual side effects of medication are distressing. Men may perceive sexual dysfunction as more distressing than women and can be a significant reason for non-adherence to prescribed antipsychotic treatment.[14],[15],[16]

The dopamine pathways in the brain that are relevant to efficacy and side effects of antipsychotic agents are the mesolimbic tract, tuberoinfundibular tract and the nigrostriatal tract. The prolactin is

secreted from the anterior pituitary in a pulsatile manner and is regulated by inhibitory and stimulatory influences from the hypothalamus. There are 13-14 peaks per day with an inter-pulse travel of about 95 minutes. The primary influence is tonic inhibitory, and dopamine has a major role in mediating this inhibition. Dopamine released into the hypophyseal portal blood from tuberoinfundibular neurons activates D2 receptors on lactotrophs in the anterior pituitary.[11]

All antipsychotics are dopamine blockers while some atypical antipsychotics also block serotonin receptors. Blockade of dopamine receptors by anti-psychotics in the tuberoinfundibular tract releases the inhibition of prolactin storage cells, resulting in elevation of prolactin levels. In contrast to dopamine, serotonin acts to stimulate prolactin release, thus having an inhibitory effect on dopaminergic influence. A consequence of this mechanism is that serotonergic influences can modulate prolactin release, but serotonin can only show this effect as long as the dopaminergic influence is present. Atypical antipsychotics are antagonists of both serotonin and dopamine, exerting opposite effects on prolactin release. The net effect would depend on relative strength of the two actions. Thus risperidone causes greater degree of prolactin elevation, olanzapine has only marginal effect and quetiapine has no effect on prolactin elevation.[17] When it comes to the proportion of cases where hyperprolactinemia was associated with sexual dysfunction, studies infer it to be 25-40%.[18] Thus it is not just hyperprolactinemia and there are other mechanisms that are involved in sexual dysfunction like dopaminergic, adrenergic, serotonergic and cholinergic actions of antipsychotics for sexual dysfunction.[19],[20]

Apart from effects on reproductive functioning, elevated prolactin levels have been associated with long term side effects in both women and men which include decreased bone density which may predispose to osteoporosis. Prolactin levels inversely affect estrogen and testosterone levels in both men and women. If prolactin is increased, testosterone and estrogen are decreased. This in turn is associated with decreased bone density, which may predispose patients to osteoporosis.[21] Sharavy et al suggested that cardiovascular disease is also a risk when estrogen levels are low and found that hyperprolactinemia with estrogen deficiency produced a significant decrease in nitric oxide production which increases blood pressure and predisposes patient to certain cardiovascular disorders.[22] Elevated prolactin levels have also been associated with cancers of breast and endometrium. Strungs et al reported that animal data have suggested that elevated prolactin can lead to breast carcinoma but studies in humans have been inconclusive.[23] Increased prolactin levels have also been found to have a direct effect on mood causing depression, anxiety and hostility as well as decreased libido in women.[24]

Monitoring of sexual dysfunction:

There are various aspects that make assessment of sexual dysfunction in clinical trials related to psychotropic drugs difficult. These include the potential biases associated with: [25]

(a) Patient selection (the study may include a greater number of patients who pay more attention to sexual matter and who are more willing to report on such matter)

(b) The assessment procedure used (self report, questionnaire or direct questioning)

(c) The type of measurement used (objective versus subjective) measurements

(d) The gender differences in the assessment

(e) The lack of baseline assessment.

An added difficulty is the differentiation between the effects of psychopathology and its course and the effect of psychotropic medication.[26] The best way of finding whether antipsychotic medication has a negative effect on sexual function is to compare subjects before and after they start medication. However, drug free patients are too unwell to answer intimate questions about sexual functioning. Patients are unlikely to voluntarily report symptoms they find embarrassing. Thus clinicians need to inquire about galactorrhea, gynecomastia and sexual dysfunction because many patients are reluctant to raise these type of problems without being asked. In the era of holistic medicine such an important facet of patient care has to cater for.

At present there are three scales available to assess sexual dysfunction in patients under antipsychotic treatment

(a) The Dickson and Glazer Scale for the assessment of sexual functioning inventory (DGSFi).[27]

(b) The Arizona Sexual Experience Scale (ASEX).[28]

(c) The Psychotropic - Related Sexual Dysfunction (PRSexDQ-SALSEX).[29]

Unlike the more traditional and lengthy scales for assessing sexual dysfunction, the ASEX is preferred as quantification of sexual dysfunction is limited by the paucity of validated, user-friendly scales. The ASEX which is a brief 5 item questionnaire designed to measure sexual functioning was developed for McGahuey et al. in the University of Arizona in response to the need for evaluating psychotropic drug induced sexual dysfunction. This scale quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm and satisfaction from organism. Possible total scores range from 5 to 30 with the higher scores indicating more sexual dysfunction. This scale has been assessed for internal consistency, test-retest reliability and convergent and discriminant validity. The ASEX can be completed in approximately 5 minutes and it was designed to be self or clinician administrated.[30] In addition, ASEX questionnaire can be used for heterosexual and homosexual population as well for those without sexual partners. Initially, the scale was tested to assess sexual dysfunction among selective serotonin reuptake inhibitors (SSRI) treated subjects28 and end stage renal disease.[31] Byerly et al. tested the psychometric properties of ASEX in patients with schizophrenia and schizoaffective disorders and demonstrated that ASEX represents an easy to administer tool for assessing sexual dysfunction in this population.[32]

Prevention and Management

If sexual dysfunction is identified secondary to psychotropic drugs, potential management strategies include:

- Wait for spontaneous remission over time.
- Switching to antipsychotics with least tendency of causing prolactin disturbances e.g. quetiapine. Though quetiapine does appear to significantly improve the rise in prolactin elevation and sexual dysfunction in short term treatment probably due to lesser affinity for D2 receptors within tuberoinfundibular tract and short-term treatment which is required with quetiapine. Also contributing are lesser adrenergic, serotonergic and cholinergic action of quetiapine. However, long term and larger sample studies are required to systematically evaluate this profile and confirm results.[33]
- If switching is not clinically feasible or advisable then following can be attempted:
  - Dose reduction
  - Addition of serotonin antagonist such as cyproheptadine[34] or partial 5HT1A agonist such as buspirone, adrenergic stimulants such as yohimbine[35] dopamine agonist such as amantadine, carbergoline or bromocriptine[36] or cholinergic agents such as bethanechol or neostigmine.[37] There is also evidence that PDE5 inhibitors such sildenafil, tadalafil, vardenafil are effective in patients with schizophrenia who have erectile dysfunction.[38]

Conclusion

- Atypical antipsycotics are not as a group much better than typical antipsychotics in causing sexual dysfunction. Amongst them, risperidone seems to induce more sexual dysfunction while with quetiapine, the incidence is less.
- Prolactin elevation is under-diagnosed but can have serious consequences. Clinicians must consider the long-term consequences of prolactin elevation with its potential effects on short-term and long-term health problems, poor compliance and depression.
- Further studies with larger sample size and dose comparison studies for individual antipsychotics should be attempted for better understanding of the lesser known side effects of these drugs.

References

1. Baldessarine R J and Tarozi F I. Pharmacotherapy of psychosis and mania in Goodman and Gillman's: The pharmacological basis of therapeutics. New York McGraw-Hill Eleventh Edition 2006; 18: 461.
2. Brenner G M, Stevens C W. Psychotherapeutic drugs. Pharmacology Saunders, Elsevier 2nd Edition 2006; 22: 234-236.
3. Baldessarine R J and Tarozi F I. Pharmacotherapy of psychosis and mania in Goodman and Gillman's:

The pharmacological basis of therapeutics. New York McGraw-Hill Eleventh Edition 2006; 18: 477-478.

4. Baldessarine R J, Campbell A, Ben J N. et al. Effects of apomorphine isomers on rat. Prolactin Neurosci Lelt 1994; 176: 269-271.

5. Schiavi RC, Segraves RT. The biology of sexual function. Psychiatric clinic. North Am 1995; 18: 7-23.

6. Theresa LC, James PG. Sexual pharmacology: Drugs that Affect Sexual Function.1st ed. Norton. 1996:307.

7. Shader and Grinspooet al. Shizophrenia, oligospermia, and the phenothiazines. Diseases of the Nervous System 1967; 28: 240-244.

8. Macdonald S, Halliday J, MacEwan T, et al. Nithsdale Schizophrenic surveys 24: Sexual dysfunction. Case control Study. Br J Psychiatry 2003; 182: 50-56.

9. Smith SM, O'Keane V, Muray R. Sexual dysfunction in patients taking conventional antipsychotic medication. J Psychiatry 2002; 181: 49-55.

10. Dickson RA, Glazer WM. Neuroleptic induced hyperprolactinemia Schizophr Res 1999; 35: 75-86.

11. Compton MT, Miller AH. Antipsychotic induced hyperprolacti-nemia and sexual dysfunction. Psycho Pharmacol Bull 2002; 36: 143-164.

12. Wirshing DA, Joseph MP, Mardes SR, Saunders CS, Wirshing WC. Sexual side effects of novel antipsychotics medications. Schizophr Res 2002; 56: 25-30.

13. Compton MT, Miller AH. Sexual side effects associated with conventional and atypical antipsychotic. Psycho Pharmacol Bull 2001; 54(3): 89-108.

14. Cutler AJ. Sexual dysfunction and antipsychotic treatment. Psychoneuroendocrinology 2003; 28 (Suppl. 1): 69-82.

15. DL Kelly and RR Conley. Sexual dysfunction and schizophrenic: a review. Schizophrenia Bulletin 2004; 30(4): 767-779.

16. DO Perkins. Predictors of non-compliance in patients with schizophrenia. Journal Clinical Psychiatry 2002; 63(2): 1121-1128.

17. S Smith. Effect of antipsychotics on sexual and endocrine function in women: implications for clinical practice. Journal of Clinical Psychopharmacology 2003; 23(3): S27-S32.

18. Rajiv Tandon. Safety and tolerabilities: how do newer generation atypical antipsychotics compare? Psychiatric Quarterly 2002; 73(4): 297-311.

19. Segraves RT. Effects of psychotropic drug on human erection and ejaculation. Arch Gen Psychiatry 1989; 46: 275-84.

20. Zajecha J, Fawcett J, Schalf M, Jerffriers H, Gey C. The role of serotonin in sexual dysfunction. Fluoxetine associated orgasm dysfunction. J Clin Psychiatry 1991; 52(2): 66-8.

21. Petty RG. Prolactin and antipsychotic medication. Mechanism of action. Schizophr Res 1999; 35 (Suppl): S67-S73.

22. Sharavy M, Nafri S, Abul Nasr A et al. Circulating nitric oxide levels in galactorrhea, hyperprolactinemic ammenorrheic women. Fertil Steril 1997; 68: 454-459.

23. Strungs I, Gray RA, Righy HB et al. Two case reports of breast carcinoma associated with prolactinoma. Pathology 1997; 29: 320-330.

24. Kellner R, Buchman MT, Fava M et al. Prolactin aggression and hostility: a discussion of recent studies. Psychiatry DCV 1984; 2: 131-138.

25. Demyttanarae K, De Fruyyt J and Sienaert P. Psychotropics and sexuality. International Clinical Psychopharmacology 1998; 13 (Suppl. 6): 35-41.

26. Peuskens J, Senaert P and DeHert M. Sexual dysfunction the unspoken side effect of antipsychotics. European Psychiatry 1998; 13(Suppl. 1): 23s-30s.

27. Dickson RA, Glazer W. Development of a scale to assess sexual functioning. Programs and abstracts from the 153rd Annual American Psychiatric Association Meeting. Chicago, Illinois, 2000.

28. McGahuey CA, Gelemberg AJ, Laukes CA, Moreno FA, Delgado PI, McKnight KM, Manber R. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther 2000; 26(1): 25-40.

29. Montejo AL, Rico-Villademoros F. Psychometric properties of the psychotropic-related Sexual Dysfunction Questionnaire (PRSexDQ-SALSEX) in patients with schizophrenia and other psychotic disorders. J Sex Marital Ther 2008; 34(3): 227-39.

30. Reynolds CF 3rd, Frank E, Thase ME, Houck PR, Jennings JR, Howell JR et al. Assessment of sexual function in depressed, impotent, and healthy men: factor analysis of a Brief Sexual Function Questionnaire for men. Psychiatry Res 1998; 24(3): 231-25.

31. Soykan A. The reliability and validity of Arizona sexual experiences scale in Turkish ESRD patients undergoing hemodialysis. Int J Impot Res 2004; 16(6): 531-4.

32. Byerly M, Nakonezny P, Fisher R, Magouirk B, Rush AJ. En empirical evaluation of the Arizona sexual experience scale and a simple one-item screening test for assessing antipsychotic related sexual dysfunction in outpatients with schizophrenia and schizoaffective disorder. Schizophr Res 2006; 81 (2-3): 311-6.

33. Seeman P, Tallerico T. Antipsycotic drugs which elcit little or no parkinsonism bind more loosely than dopamine to brain D2 Receptors, yet occupy high levels of three receptors. Mol Psychiatry 1998;3:123-134.

34. Cohen AJ. Fluoxetine induced young and anorgasmia treatment. Journal of Clinical Psychiatry 1992; 53: 174.

35. Savion M, Segenreich E, Kahan E, Servadio C. Pharmacologic, nonhormonal treatment of impotence. Evaluation of associated factors. Urology. 1987;29(5):510-2.

36. Matsuoka I, Nakai T, Miyake M, Hirai M, Ikawa G. Effects of bromocriptine on neuroleptic-induced amenorrhea, galactorrhea and impotence. Jpn J Psychiatry Neurol. 1986 Dec;40(4):639-46

37. Sullivan G and Lukoff D. Sexual side effects of antipsychotic medication. Evaluation and interventions. Hospital Community Psychiatry 1990; 41: 1238-1241.

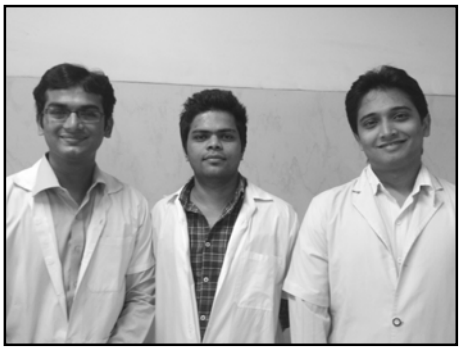
38. Smith S, Gillam A. Sexual dysfunction - the forgettable taboo. Mental Health Nurs 2005; 25: 6-9.

ANALYSIS OF ADVERSE DRUG REACTIONS REPORTED

(July 2013 - October 2013)

Compiled by Smruti Mulgaonkar*, Dr Swati Patil,**
Dr Neha Kadhe*, Dr Sudhir Pawar*****

- Technical Associate - Pharmacovigilance, **- Assistant Professor, **- Associate Professor, ****- Professor and Head, Department of Pharmacology, LTMMC & GH, Sion, Mumbai*



Total cases reported: 109

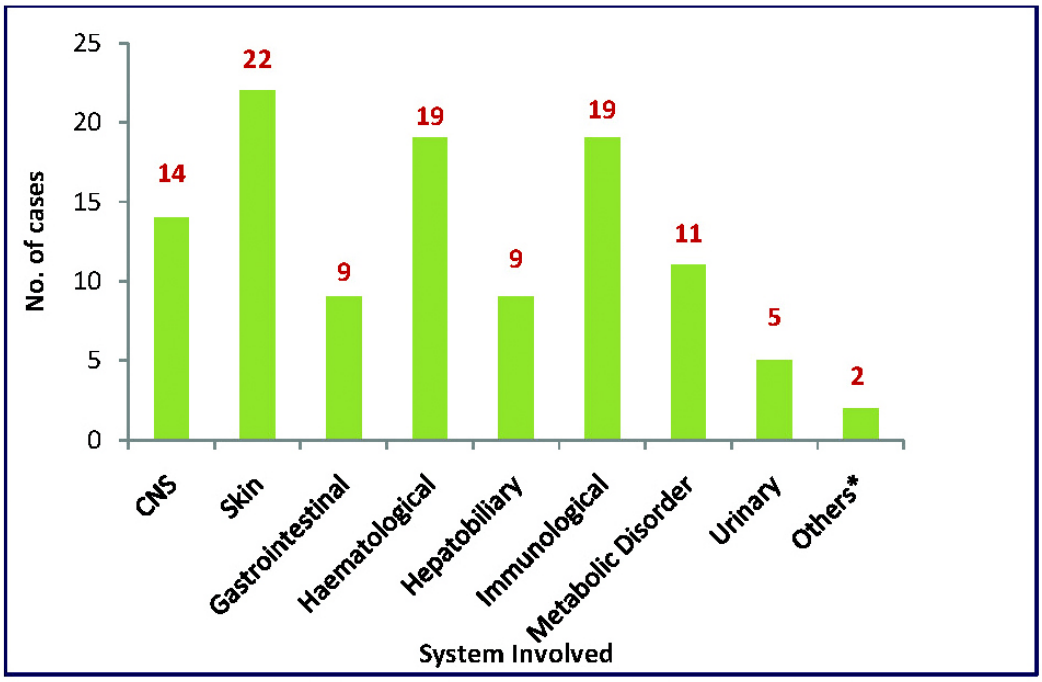
I. Age and Gender distribution

Age groups	Patients	Males	Females
<3yrs	20	10	10
3 - 17yrs	31	20	11
18 - 44yrs	33	15	18
45 - 60yrs	15	9	6
> 60yrs	10	3	7

II. Seriousness of reactions reported

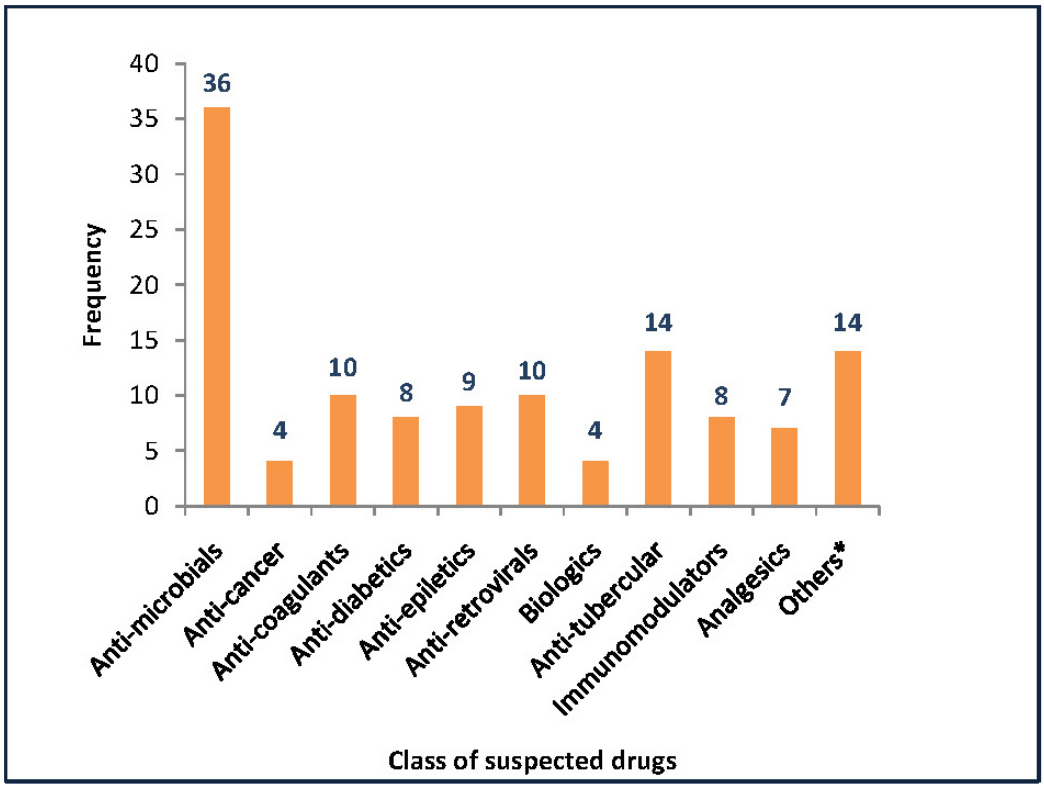
Seriousness of the reactions	Number of cases (Approx %)
Yes	100(91.74)
No	9 (8.25)

III. System wise distribution of the adverse drug reaction:



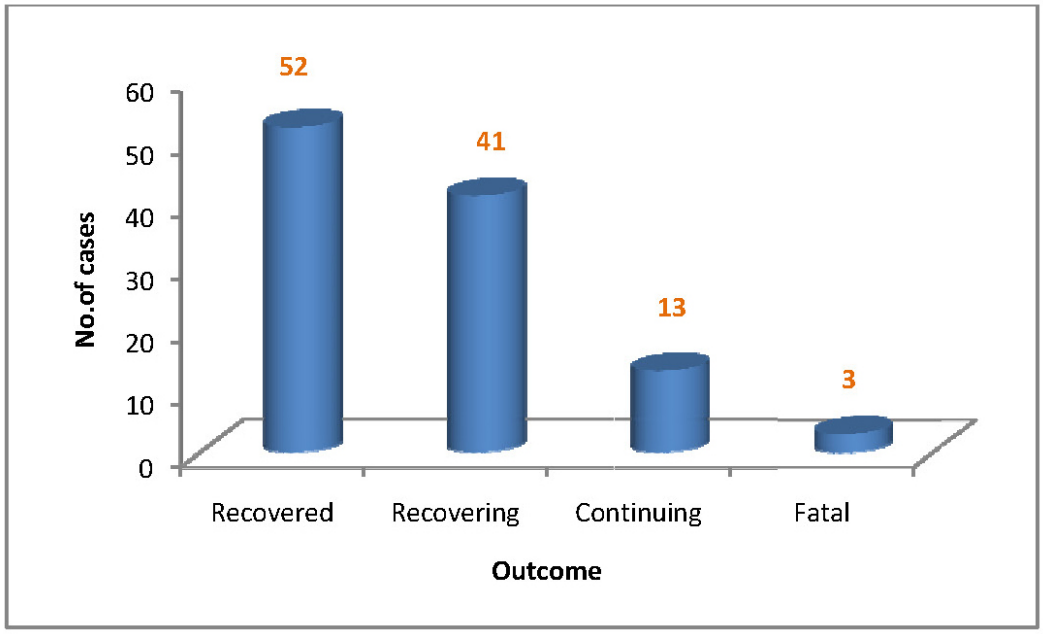
*Others include cases involving cardiovascular and respiratory system.

IV. Class of Suspected Drugs:

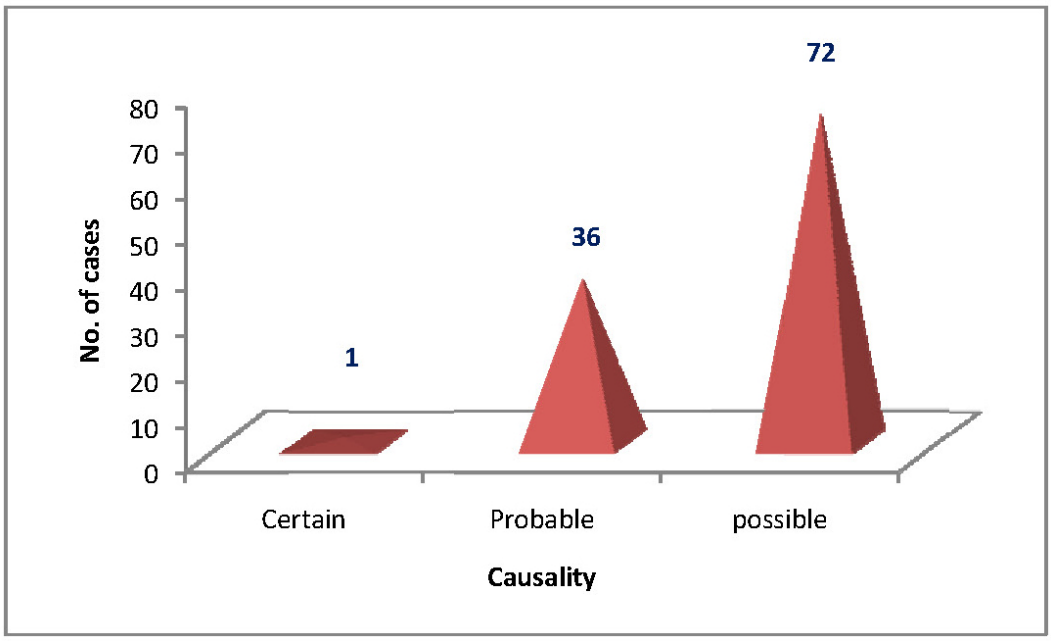


*Others include drug classes like Steroids, sedatives, anti-hypertensives, anti-leprosy, anti-adrenergics, anti-asthma, anti-alzheimer, muscle relaxants and diuretics.

V. Outcome of the reaction



VI. Causality assessment (WHO causality assessment scale)



CEFEPIME INDUCED NEUROTOXICITY: A CASE STUDY

Dr. Sunilkumar Jadhav**, Dr. Sarika Patil[###], Dr. Swati Patil***, Dr. Trupti Trivedi[##], Dr. Neha Kadhe**, Dr. Sudhir Pawar* Dr N D Moulick[#]**

Professor and Head, ** Additional Professor, * Assistant Professor, **** Resident*
Department of Pharmacology LTMMC & GH Sion, Mumbai.

[#]Professor and Head, [##]Associate Professor, [###]Resident
Department of Medicine LTMMC & GH Sion, Mumbai.

Introduction:

Cefepime is a semisynthetic, fourth generation cephalosporin antibiotic used to treat urinary tract and skin infections, as well as pneumonia. Cefepime is generally well tolerated but headache, rash, diarrhoea, nausea and vomiting have been reported as side effects.[1] Neurotoxic symptoms include lethargy, confusion, agitation, global aphasia, chorea-athetosis, seizures, non-convulsive status epilepticus (NCSE), myoclonus or even coma.[2]

In literature, there were several cases of cefepime associated reversible encephalopathy or Nonconvulsive status epilepticus (NCSE) in patients with variable level of impaired or relatively normal renal function. The incidence has been reported to be 1% in cefepime treated patients. Among renal-impaired patients, the incidence increases to 4.5 to 16.6%.[3]

Here we are presenting a case of cefepime neurotoxicity in a patient with no such alteration of renal parameters.

Case report:

A 50 yr old male was admitted to the medical ICU with history of bilateral lower limb weakness, breathlessness diagnosed as a case of Guillain- Barre (GB) syndrome on admission. Later he was also diagnosed as immunocompromised state (Human Immunodeficiency Virus-II positive) and tubercular pleural effusion. He was started on Antiretroviral therapy (Tab. Tenofovir 300 mg + Tab.Lamivudine 300mg + Tab. Lopenavir 200mg once daily) and Anti TB therapy (Cap. Rifampicin 450 mg + Tab. Isoniazid 300mg + Tab. Pyrazinamide 1500mg + Tab. Ethambutol 1200mg once daily). Patient also received IV Immunoglobulin therapy for GB Syndrome later on.

Patient was given antimicrobials for ventilation-associated pneumonia (VAP). On 4th March (day 1) patient was advised injection Cefepime 1gm thrice daily. On the same day, within 8hrs of cefepime injection patient was in state of disorientation, confusion and abnormal behaviour. On day 2 of cefepime injection patient's symptoms worsened and he became unresponsive.

On examination, the patient's general condition was moderate, afebrile, pulse was 100 beats per minute, blood pressure was normal and pallor ++ was present. Central nervous system examination revealed decreased power in lower limbs, areflexia, abnormal higher functions whereas neck rigidity was absent. Patient was on mechanical ventilator initially for respiratory failure, later on tracheostomy was done.

Investigations of the patient were as follows:

Investigation	Result	Normal range
Haemoglobin (gm%)	7.9	14 -17
Platelets (lakhs/mcl)	1.27	1.5- 4
S.Albumin (gm/dl)	2	3.5-5.5
S. Sodium (mEq/lit)	141	135 - 145
S. Potassium(mEq/lit)	3.2	3.5 - 5.0

Patients liver function tests as well as renal function tests were within normal limits. CD4 count was 342/mcl. Cerebrospinal fluid culture (CSF) was normal. His computerized tomography (CT) of brain was also normal.

Suspecting drug induced neurotoxicity, cefepime injection was withheld on 6th march (day 3). After stopping the drug patient recovered over 2-3 days.

Discussion:

Cefepime-induced neurotoxicity can present as confusion, disorientation, hallucination, agitation, myoclonus, convulsions, nonconvulsive status epilepticus and coma. Convulsions and non-convulsive status epilepticus are the most frequently described adverse neurological effects. The incidence of these adverse effects is not well known but the incidence has been regarded as underestimated.[1]

Neurotoxicity has been reported with first generation cephalosporins such as cefazolin, second generation such as cefuroxime, third generation such as ceftazidime and fourth generation such as cefepime and can range from encephalopathy to non-convulsive status epilepticus.[2]

The typical latent period for encephalopathy induced by cephalosporin use is 1 to 10 days and resolution occurs in 2 to 7 days following discontinuation.[2] The dose for toxicity ranges from 4 to 12 gm per day.[3] In our case, patient was given 1gm I.V 8 hourly for three days.

Predisposing factors for cephalosporin-induced neurotoxicity include excessive dosage, renal insufficiency, pre-existing central nervous system (CNS) abnormalities, and increased cerebral

penetration of the drug as in uraemia or CNS infection.[4] In our case, patient had Guillian-Barre syndrome which can predispose patient to neurotoxic effect of cefepime. Even low serum albumin predisposes to toxicity by increasing the unbound form of drug,[1] thereby predisposing to toxicity as seen in our case. As there was no evidence of septic, uremic or hepatic encephalopathy, we suspected cefepime-induced neurotoxicity.

Nonconvulsive status epilepticus (NCSE) is characterized by a decreased level of consciousness without convulsions, epileptiform discharges in the electroencephalogram (EEG), and a good response to anticonvulsant agents. Nonconvulsive status epilepticus causes many different neurologic deficits, particularly in alertness and cognitive functions, although it is a treatable disease with favourable prognosis.[5] The variable clinical presentation, however, is the reason for frequent misdiagnosis. An EEG abnormality serves as evidence supporting the impact of cephalosporin on the CNS. Given that the majority of patients using cephalosporin have co-morbidity which may be associated with mental alteration, EEG could be of benefit in the diagnosis and management of antibiotics-associated neurotoxicity.[4] However, EEG was not done in our case, hence; it could not be assertively labelled as NCSE.

The mechanisms involved in the development of cefepime neurotoxicity have not been clearly understood. Decreased gamma-amino butyric acid releasing from nerve terminals and subsequent increased excitatory neurotransmission, gamma-amino butyric acid transporter system dysfunction, and induction of endotoxins along with the release of tumour necrosis factor α have been proposed to explain the patho-physiology.[3]

Though the patient was receiving both cefepime and isoniazid, temporal relationship between the start of cefepime therapy and the manifestation of neurotoxicity symptoms as well as the withdrawal of cefepime and the disappearance of the symptoms strongly indicated that cefepime was the causative agent. Hence, the causality of reaction according to WHO Causality Assessment scale is Probable.

Cefepime over dosage may sometimes be difficult to diagnose, since treated patients often present co morbidities that could atleast partially account for the neurological symptoms. Thus, monitoring of renal function and cefepime blood concentrations appears to be of value in patients with renal failure, elderly patients and those with a history of neurological disease. Target trough concentrations of cefepime have not been well established. An association between high trough concentrations viz ≥ 22 mg/L and neurological adverse events has a 50% probability of inducing neurotoxicity.[6]

Cefepime is removed by haemodialysis (over 3h) and peritoneal dialysis (over 72h) to an appreciable extent, with 40 to 68% and 26% of the drug removed, respectively.[7] In cases with impaired renal function, once it is established that neurotoxicity is caused by the antibiotic, haemodialysis or haemofiltration may be required for adequate clearance of the drug. This may be in the form of high-volume continuous venovenous haemofiltration (CVVHF) to optimize drug clearance.[2]

Conclusion:

Cefepime is generally considered safe, however serious neurotoxic reactions can occur. As multiple differential diagnosis and co-morbid conditions can delay the diagnosis of cefepime neurotoxicity it requires very high index of suspicion.

In suspected cases of cefepime neurotoxicity blood concentration of drug and EEG may help in establishing the diagnosis of cefepime induced neurotoxicity.

References:

1. Baek SD., Park SJ, Baek CH, Koo TY, Kang JK, Kim SB. Neurotoxicity induced by cefepime in a patient with minimal change disease. Korean Journal of Nephrology 2010; 29(6):796-801.
2. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. Br J Clin Pharmacol. 2011;72(3):381-93.
3. Lin CJ, Chen SP, Wang SJ, Fuh JL. Cefepime-related encephalopathy in peritoneal dialysis patients. J Chin Med Assoc. 2011;74(2):87-90.
4. Kim KB, Kim SM, Park W, Kim JS, Kwon SK, Kim HY. Ceftiaxone-induced Neurotoxicity: case report, pharmacokinetic considerations, and literature review. J Korean Med Sci. 2012;27(9):1120-3.
5. Abanades S, Nolla J, Rodríguez-Campello A, Pedro C, Valls A, Farré M.Reversible coma secondary to cefepime neurotoxicity. Ann Pharmacother. 2004;38(4):606-8.
6. Maugard C, Lemaire-Hurtel AS, Gras-Champel V, Hary L, Maizel J, Prud'homme-Bernardy A, Andréjak C, Andréjak M. Blood and CSF monitoring of cefepime-induced neurotoxicity: nine case reports. J Antimicrob Chemother. 2012;67(5):1297-9.
7. Okomoto MP, Nakahiro RK, Chin A, Bedikian A. Cefepime clinical pharmacokinetics. Clin Pharmacokinet. 1993;25(2):88-102.

PUBLISHED STUDIES ON CEFEPIME INDUCED NEUROTOXICITY

Compiled by **Dr Jaisen Lokhande**

Assistant Professor, Department of Pharmacology, LTMMC & GH, Sion, Mumbai

Neurotoxicity Induced by Cefepime in a Patient with Minimal Change Disease

The Korean Journal of Nephrology 2010; 29: 796-801

Seung Don Baek, Se Jeung Park, Chung Hee Baek, Tai Yeon Koo, Joong Koo Kang, and Soon Bae Kim

A 71-year-old woman with minimal change disease visited our clinic complaining of pleuritic chest pain. Cefepime was given under the impression that she had pneumonia. Three days after cefepime administration, she became unconscious. A brain MRI scan was non-revealing and an EEG showed triphasic waves. As there was no evidence of septic, uremic or hepatic encephalopathy, we suspected cefepime-induced neurotoxicity. Cefepime was stopped and she underwent hemodialysis to decrease the blood levels of the drug. Following hemodialysis, she regained consciousness.

Reversible coma secondary to cefepime neurotoxicity

Ann Pharmacother. 2004 Apr;38(4):606-8.

Abanades S, Nolla J, Rodríguez-Campello A, Pedro C, Valls A, Farré M

OBJECTIVE: To describe a case of cefepime neurotoxicity associated with acute renal failure that resulted in nonconvulsive status epilepticus. **CASE SUMMARY:** A 66-year-old woman with acute myeloid leukemia had fever on the third day of the initial chemotherapy cycle. Empiric antibiotic treatment with cefepime 2 g every 8 hours was started; fluconazole and vancomycin were subsequently added due to the persistence of fever. Ten days after initiation of cefepime, the patient developed acute renal failure followed by altered consciousness (Glasgow coma scale 6) associated with nonconvulsive status epilepticus. Cefepime was discontinued. Epileptiform activity in the electroencephalogram disappeared with clonazepam, and the patient regained consciousness 48 hours after cefepime withdrawal. **DISCUSSION:** Acute renal impairment combined with the use of cefepime may account for nonconvulsive status epilepticus. An objective causality assessment revealed that the adverse event was probably due to cefepime. Cefepime's neurotoxic effects derive from high serum concentrations resulting from decreased renal clearance, increased unbound antibiotic, and blood-brain barrier dysfunction during uremia. **CONCLUSIONS:** The combination of cefepime treatment and acute renal failure may induce drug-related neurotoxicity. Nonconvulsive status epilepticus frequently passes unnoticed in severely ill patients without a history of epilepsy. This disorder should be included in the list of potential causes of coma. In this patient, early detection of nonconvulsive status epilepticus and withdrawal of the antibiotic resulted in full recovery.

Cefepime neurotoxicity despite renal adjusted dosing.

Scand J Infect Dis. 2011 Oct;43(10):827-9.

Gangireddy VG, Mitchell LC, Coleman T.

Neurotoxicity is a rare side-effect of cefepime. There are previous reports of cefepime neurotoxicity in patients whose dosages were not adjusted for their kidney disease. We report a toxic case of non-convulsive status epilepticus in a patient receiving renally-dosed cefepime. A 70-y-old woman was admitted with febrile neutropenia for which renally-dosed cefepime was started. On day 4 she developed altered mental status with orofacial myokymia. Blood and urine cultures were negative. Cerebrospinal fluid analysis was normal. Head computed tomography and magnetic resonance imaging showed no acute intracranial process. An electroencephalogram showed non-convulsive status epilepticus. Anticonvulsants were started, but she continued to have seizures. At this time, careful review of her medication list with temporal association of symptoms suggested cefepime as a probable cause and the drug was stopped. Within 24 h of discontinuation, her mental status began to improve and returned to baseline in 3 days. Our case illustrates that cefepime toxicity may still occur in patients who are dose-adjusted for renal insufficiency. It also underscores the importance of assessing for additional risk factors like history of stroke and seizures. Because cefepime-induced status epilepticus is completely reversible, prompt recognition and medication discontinuance can prevent further morbidity and mortality.

Cefepime-induced neurotoxicity: an underestimated complication of antibiotherapy in patients with acute renal failure.

Intensive Care Med. 2002 Feb;28(2):214-7.

Chatellier D, Jourdain M, Mangalaboyi J, Ader F, Chopin C, Derambure P, Fourrier F.

OBJECTIVES: To describe five new cases of life-threatening cefepime-induced neurotoxicity observed in a 2-year period. **SETTING:** A university intensive care unit. **PATIENTS:** Five patients recently treated with cefepime, admitted for seizures and coma. All suffered from acute renal failure, induced by sepsis and combined aminoside therapy, or by cefepime itself in one case.

INTERVENTIONS: All patients underwent hemodialysis, which led to complete neurological improvement in four of them. One patient remained comatose and subsequently died. **MEASUREMENTS:** Blood and CSF cefepime levels were measured by high performance liquid chromatography before and after hemodialysis. **CONCLUSION:** The frequency of cefepime-induced neurotoxicity is probably underestimated. Monitoring of renal function and close neurological survey in treated patients should allow an early diagnosis of this complication. Urgent hemodialysis seems the best therapeutic method to obtain a rapid neurological improvement.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by **Dr. Swati Patil**

Assistant Professor, Department of Pharmacology, LTMMC & GH, Sion, Mumbai

FDA MedWatch - Lexiscan (regadenoson) and Adenoscan (adenosine): Drug Safety Communication - Rare but Serious Risk of Heart Attack and Death 11/20/2013

Background: Lexiscan and Adenoscan are FDA approved for use during cardiac nuclear stress tests in patients who cannot exercise adequately. Lexiscan and Adenoscan help identify coronary artery disease. They do this by dilating the arteries of the heart and increasing blood flow to help identify blocks or obstructions in the heart's arteries. Lexiscan and Adenoscan cause blood to flow preferentially to the healthier, unblocked or unobstructed arteries, which can reduce blood flow in the obstructed artery. In some cases, this reduced blood flow can lead to a heart attack, which can be fatal.

Issue: The FDA is warning health care professionals of the rare but serious risk of heart attack and death with use of the cardiac nuclear stress test agents Lexiscan (regadenoson) and Adenoscan (adenosine). FDA has approved changes to the drug labels to reflect these serious events and updated recommendations for use of these agents. At this time, data limitations prevent FDA from determining if there is a difference in risk of heart attack or death between Lexiscan and Adenoscan.

The Warnings & Precautions section of the Lexiscan and Adenoscan labels previously contained information about the possible risk of heart attack and death with use of these drugs. However, recent reports of serious adverse events in the FDA Adverse Event Reporting System (FAERS) database and the medical literature prompted approval changes to the drug labels to include updated recommendations for use.

Recommendations: Screen all nuclear stress test candidates for their suitability to receive Lexiscan or Adenoscan. Avoid using these drugs in patients with signs or symptoms of unstable angina or cardiovascular instability, as these patients may be at greater risk for serious cardiovascular adverse reactions. Cardiac resuscitation equipment and trained staff should be available before administering Lexiscan or Adenoscan.

Reference : FDA Medwatch-Lexiscan (regadenoson) and Adenoscan (adenosine): Drug Safety Communication - Rare but Serious Risk of Heart Attack and Death [Internet]-2013 November 11[cited 2013 December 3]. Available from:http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety Alerts for Human MedicalProducts/ucm375981.htm

MEDICAL NEWS

I. Antibiotic and Calcium-Channel Blocker a Fatal Combination

Background: Clarithromycin is an inhibitor of the CYP3A4, the enzyme that metabolizes calcium-channel blockers. Previous research has shown that the antibiotic can send blood concentrations of calcium-channel blockers soaring by as much as 500%.

A warning from the US Food and Drug Administration states that "serious adverse reactions have been reported in patients taking clarithromycin concomitantly with CYP3A4 substrates, which includes hypotension with calcium-channel blockers metabolized by CYP3A4 (such as verapamil, amlodipine, diltiazem)."

Issue: The antibiotic clarithromycin prescribed for patients already taking antihypertensive calcium-channel blockers is associated with increases in hospitalization for acute kidney injury, hypotension, and death, according to new research.

Recommendations: Careful co-prescrition of clarithromycin and calcium channel blockers is essential. Azithromycin would be the preferred antimicrobial along eith calcium channel blockers. Because azithromycin is only a weak inhibitor of CYP34A, the type of intensification of the calcium-channel blocker that occurs with clarithromycin is not expected.

Reference : Nancy A. Melville. Antibiotic and Calcium-Channel Blocker a Fatal Combination. Medscape Medical News[Internet].2013 November 13 [cited 2013 December 3]. Available from: http://www.medscape.com

II. New Data Dispute Calcium Cardiovascular Risk in Both Sexes

Background: The use of calcium supplements, predominantly with vitamin D, is an important therapy for the prevention of osteoporosis and its clinical consequences. But concerns about the cardiovascular safety of calcium have emerged periodically; in 2 alarming meta-analyses there was a 27% increase in MI among individuals allocated to calcium supplements in the first study and a 24% increased risk in the second.[1] In other study, the effect on mortality appeared to be especially strong if a high dietary intake of calcium was combined with calcium supplements.[2]

Issue: Recent studies contribute further to the debate over the cardiovascular risk associated with supplementary or dietary calcium, each decidedly coming down on the side of no significant risk - to men or women. Results of both studies were reported at the recent American Society for Bone and Mineral Research (ASBMR) 2013 Annual Meeting.[3]

Recommendations: In recommendations issued in 2010, the ASBMR said that most adults 19 years of age and older require about 600 to 800 IUs of Vitamin D daily and 1000 to 1200 mg of calcium daily through food and with supplements, if needed. Thus, clinicians should continue to evaluate calcium intake, encourage adequate dietary intake, and if necessary, use supplements to reach but not exceed recommended intakes.[4]

Reference :

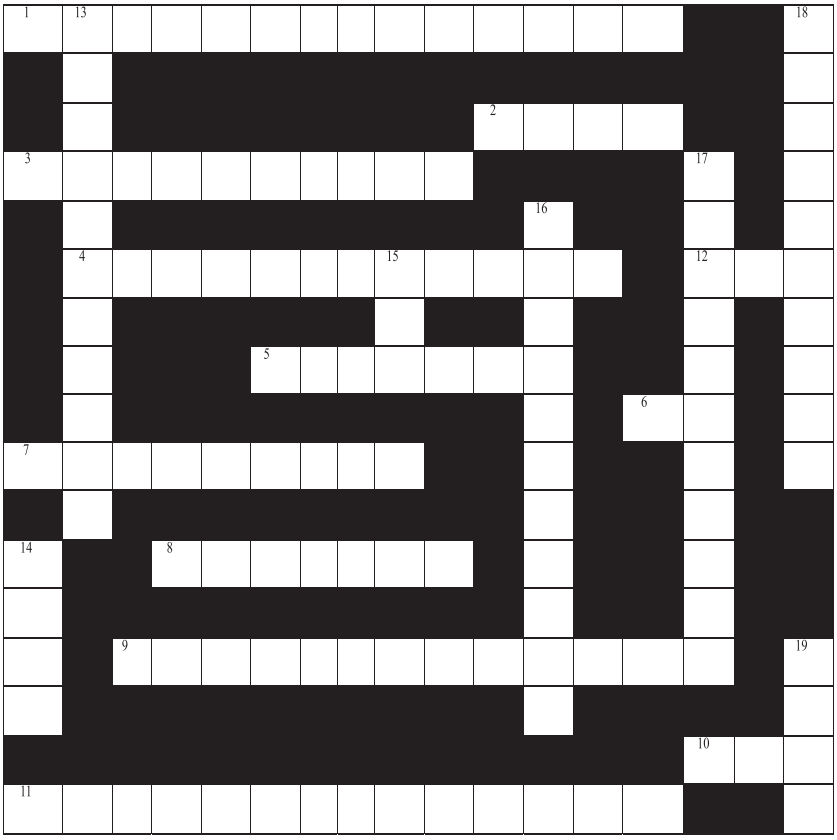
1. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010; 341:c3691.
2. Michaëlsson K, Melhus H, Warensjö Lemming E, Wolk A, Byberg L. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ. 2013; 346: f228.
3. American Society for Bone and Mineral Research 2013 Annual Meeting. Abstracts 1001 and 1002, presented October 4, 2013.
4. Nancy A. Melville. New Data Dispute Calcium Cardiovascular Risk in Both Sexes. Medscape Medical News[Internet].2013 October 08 [cited 2013 December 3]. Available from: http:/www.medscape.com

CROSSWORD

Dr Sharmada Nerlekar*, Dr Abhilasha Rashmi, Dr Nitin Shinde*****

-Associate Professor; **-Assistant Professor; * -Resident*

Department of Pharmacology, LTMMC & GH, Sion, Mumbai



Across

1) The ocular toxicity of cytarabine is ___. (14)
2) Ostarine, a first generation ___ intended for use in osteoporosis and andropause, has the advantage of being devoid of hepatotoxicity as compared to anabolic steroids. (4)
3) A common gastrointestinal complaint with diloxanide furoate is ___. (10)
4) ___ is contraindicated in ocular cysticercosis because of the risk of severe eye damage resulting from occlusion due to dead parasites. (12)
5) Streptogramins effective in treating nosocomial pneumonia caused by MRSA can cause infusion related arthralgia ___ syndrome. (7)
6) Estramustine clinically used in prostrate cancer treatment can cause acute ___. (2)
7) Adverse effects characteristic of warfarin include teratogenicity, alopecia, dermatitis and this gastrointestinal problem ___. (9)
8) Stoppage of megadoses of ascorbic acid has been reported to cause ___ scurvy. (7)
9) Being most toxic antifungal- antibiotic in use today, amphotericin- B is labeled as ___ drug. (13)
10) One of the adverse effects of erythropoeitin includes ___ like symptoms. (3)
11) The major adverse drug reaction of adefovir used to treat chronic Hepatitis B viral infection is ___ (14) but risk is low if treatment lasts for less than one year.
12) The aminoglycoside induced ___ toxicity can be lessened by co- administration of calcium (3).

Down

13) "Pharyngo-laryngeal dysasthesia" is an adverse effect of ___ used to treat colorectal cancer (11).
14) Cinacalcet, a calcimimetic approved for the treatment of secondary hyperparathyroidism in chronic renal failure can cause the adverse effect of ___ calcaemia (4).
15) L- asparginase used for induction in the treatment of ___ in a combination regimen, causes insignificant toxicity to the bone marrow (3).
16) The main adverse effect of maraviroc, a chemokine receptor 5 antagonist (CCR- 5) is that it is ___. (11)
17) The neuromuscular blockade produced by aminoglycosides can be reversed by an administration of intramuscular ___. (11)
18) This retinoid clinically used to treat cutaneous T-cell lymphoma can produce hypo- thyroidism as an adverse effect ___. (10)
19) Pyrazinamide as well as ethambutol may precipitate ___. (4)

MATCH THE ADR TO THE DRUG

Dr Sharmada Nerlekar*, Dr Abhilasha Rashmi, Dr Nitin Shinde*****

-Associate Professor; **-Assistant Professor; * -Resident*
Department of Pharmacology, LTMMC & GH, Sion, Mumbai

1.	Trazodone	a.	High risk of SLE.
2.	Dextropropoxyphene	b.	Worsens diabetes.
3.	Modafinil	c.	Esophagitis.
4.	Amrinone	d.	Water retention.
5.	Procainamide	e.	Blood dyscrasias.
6.	Dantrolene	f.	Lipid abnormalities.
7.	Desferrioxamine	g.	Histamine release.
8.	Ritonavir	h.	Insomnia & Headache.
9.	Carbamazepine	i.	Troublesome Diarrhoea.
10.	Alendronate	j.	Thrombocytopenia.
11.	Nifedipine	k.	Cardiotoxic Metabolite.
12.	Mianserin	l.	Priapism.

Answers : 1-l. 7-g. 2-k. 8-f. 3-h. 9-d. 4-j. 10-c. 5-a. 11-b. 6-i. 12-e.

CROSS WORDS ANSWERS:

1) Conjunctivitis 2) SARM (selective androgen receptor modulator) 3) Flatulence 4) Praziquantel 5) Myalgia 6) MI (myocardial infarction) 7) Diarrhoea 8) Rebound 9) Amphoterrible 10) Flu 11) Nephrotoxicity 12) Oto 13) Oxaliplatin 14) Hypo 15) ALL (Acute Lymphocytic Leukemia) 16) Hepatotoxic 17) Neostigmine 18) Bexarotene 19) Gout

We would like to request all the departments to contribute in ADR reporting.

Please feel free to contact us for the same.

Names	Extension No.	E-mail
Dr Sudhir Pawar	3162	dr.sudhirpawar@gmail.com
Dr Neha Kadhe	3206	nehakadhe@yahoo.com
Dr Manjari Advani	3205	manjari.advani@gmail.com
Dr Jaisen Lokhande	3164	dr_jaisen@yahoo.co.in
Dr Swati Patil	3161	drswati246@gmail.com
Dr Chandan Lahoti	3204	lahotichandan@gmail.com
Dr Vikhram Wankhade	3204	vikhramwankhade@gmail.com
Dr Sunil Jadhav	3204	drsuniljadhav123@gmail.com

Address for correspondence :

Department of Pharmacology,
College Building, LTMMC & LTMGH,
Sion, Mumbai-400022.
Tel.: 022-2406 3160
E-mail: ltmghbulletin@yahoo.com

NOVARTIS

Printing and distribution of
this bulletin sponsored by
NOVARTIS INDIA LIMITED