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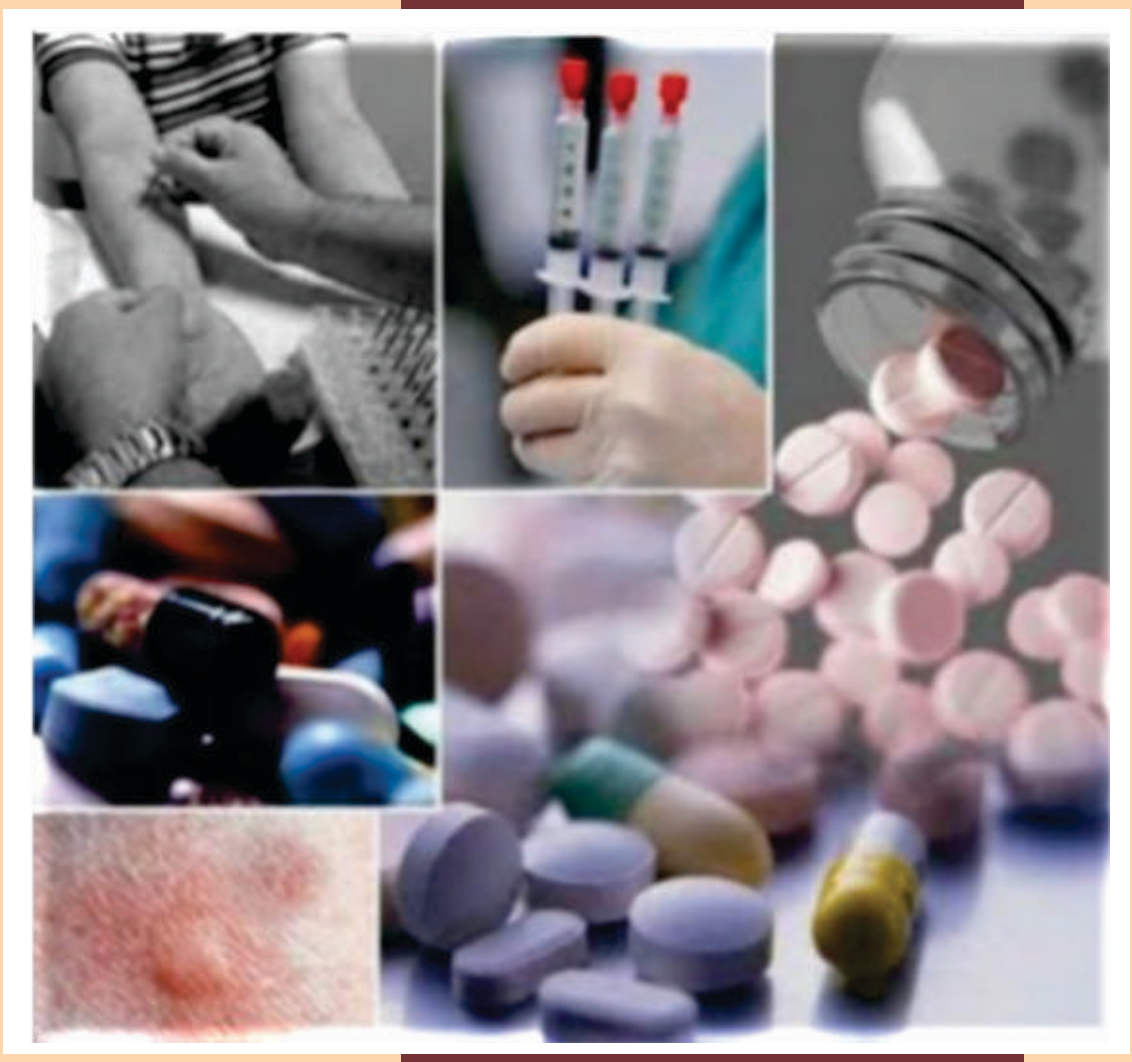
LOKMANYA TILAK MUNICIPAL COLLEGE & GENERAL HOSPITAL



DEPARTMENT OF PHARMACOLOGY,

LTMMC & LTMGH, Sion, Mumbai – 22.

Committee Members for Bulletin on Adverse Drug Reactions

Lokmanya Tilak Municipal Medical College & General Hospital, Mumbai

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From the Editor's Desk . . . . ✍

Dear friends and colleagues,

It gives me immense pleasure to put forth this year's second issue of Bulletin on Adverse Drug Reactions.

The first article in this issue features a review of adverse event monitoring of medical devices which is also known as Materiovigilance. The purpose of materiovigilance is to study, follow and report adverse incidents that might result from using a medical device. We hope this article helps us have a better understanding of adverse reactions to medical devices which can be preventable and also help in improving the quality of medical devices, providing patients using them with increased and better safety.

Today, we live in a world where materialistic beauty holds utmost importance in our lives where film and TV stars are idolised beyond measure. Hence, physical appearance plays an important part of our lives, as a result of which the use of cosmetics, cosmeceuticals, and other such products are increasing day by day. With the increase in use of these products the adverse reactions caused by them is also increasing. The second article deals with these adverse reactions associated with the use of cosmetics and other such products.

In this issue we also discuss an interesting case of phenytoin induced seizures. We have also summarised the ADRs from our institute to provide a glimpse of pharmacovigilance activity at our institute. The puzzle and crossword will surely make it more interesting and entertaining.

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

Thank you,

Dr. Sudhir Pawar

ADVERSE EVENT MONITORING OF MEDICAL DEVICES

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Introduction

A Medical device means, any instrument, apparatus, implement, machine, appliance, implant, reagent for in-vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of :

- diagnosis, prevention, monitoring, treatment or alleviation of disease
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury
- investigation, replacement, modification, or support of the anatomy or of a physiological process
- supporting or sustaining life
- control of conception
- disinfection of medical devices
- providing information by means of in-vitro examination of specimens derived from the human body
- aids for persons with disabilities
- devices incorporating animal and/or human tissues
- devices for in-vitro fertilization or assisted reproduction technologies
- disinfection substances;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.[1]

Need for Adverse events monitoring in medical devices

Medical devices accounts around $3 billion market in India. All medicines carry some risk of harm and so do medical devices. It is therefore important to monitor their effects, both intended and unwanted to get an evidence-based assessment of risk versus benefit. Each year drug regulating authority receives several hundred medical device reports of suspected device-associated deaths, serious injuries and malfunctions. India had no proper system for registering medical device associated adverse events (MDAE) or for tracking the safety record of medical devices, creating awareness among health care professionals and monitoring the risk-benefit profile of medical devices.

Hence there was a need for Monitoring of medical devices which ultimately led to formation of Materiovigilance Programme of India.

About Materiovigilance

Several horrific cases of malfunctioning of medical devices have been reported like babies suffering severe burns due to short circuits in incubators or hip implants causing blood poisoning. In view of these incidences, the health ministry has approved a Materiovigilance Programme in an effort to ensure safety of medical devices. Materiovigilance is an important tool to ensure that a marketed device is safe. It was launched with a vision to improve patient safety and welfare in Indian population by monitoring medical device safety and thereby reducing the risk associated with use of medical devices. Since its inception it has certainly helped increase awareness of MDAE among industry associations and healthcare providers.

Materiovigilance means close monitoring of any undesirable occurrence resulting from a medical device by means of having a system in place which comprises identifying, collecting, reporting, and estimating undesirable occurrences and reacting to them, or safety corrective actions after their post-marketing phase. In addition to protection of health and safety of patients, Materiovigilance programme reduces the likelihood of recurrence of the harmful incidents elsewhere, thereby improving medical devices quality by and large. Materiovigilance programme of India was launched by DCGI on 6th July 2015 at Indian Pharmacopoeia Commission, Ghaziabad. Indian Pharmacopoeia Commission functions as National Coordination Centre (NCC) for MvPI. Sree Chitra Tirunal Institute for Medical Sciences & Technology (SCTIMST), Thiruvananthapuram, is the National Collaborating Centre; National Health System Resource Centre (NHSRC), New Delhi, is the Technical support partner, and Central Drugs Standards Control Organisation (CDSCO), New Delhi, functions as regulator.[1]

Materiovigilance Programme of India (MvPI) is meant to enable safety data collection in a systematic manner so that regulatory decisions and recommendations on safe use of medical devices being used in India could be based on data generated here. The programme is meant to monitor medical device-associated adverse events (MDAE), create awareness among healthcare professionals about the importance of MDAE reporting in India and to monitor the benefit-risk profile of medical devices. It is also meant to generate independent, evidence-based recommendations on the safety of medical devices and to communicate the findings to all key stakeholders.[1]

Classification of Medical devices:

In the Indian regulatory system, medical devices are considered as drugs by the Ministry of Health and Family Welfare. Each regulatory authority has classified medical devices in its own way. In general, the basis for medical device classification is:[2]

1. The risk associated with the medical device
2. Manufacturer's intended purpose for the device
3. The device's indications for use

The US Food and Drug Administration (FDA) has classified medical devices into three classes (Table 1) on the basis of level of control necessary to assure the safety and effectiveness of the device and on the basis of information about marketing requirements and has grouped them into 16 medical specialties

Table 1: Classification of Medical Devices

Class I	General controls	e.g. Elastic bandage and examination gloves
Class II	General and special controls	e.g. Infusion pumps, surgical drapes, and ultrasound imaging systems
Class III	General controls and premarket approval	e.g. Heart valves, and silicone gel-filled breast implants

In comparison to the regulated countries, medical devices in India are not classified on the basis of risk. Rather, the 10-device category of medical devices has been notified to be regulated as drugs.[3]

Criteria for reporting:[4]

The criteria are

→ An adverse event has occurred

→ Device product is associated with event;

→ The adverse event led to:

1. A serious threat to public health;
2. Serious deterioration in state of health of patient, user or other person;
3. No death or serious injury occurred but might lead to death or serious injury if recurs.
4. Death of a patient, user or other person.

Timeline for reporting a Medical Device Adverse Event (MDAE) as per MvPI is as depicted in Table 2.

Table 2: Timeline for reporting

REPORTER	WHAT TO REPORT	TO WHOM	WHEN
Manufacturers	Medical device adverse event (MDAE) or incident on MDAE-reporting form with causality assessment report and future preventive or corrective steps that would be taken in a defined timeframe	MvPI	Within 30 calendar days of becoming aware of an event
Manufacturers	Reports for an event on MDAE reporting form with remedial action to prevent an unreasonable risk of substantial harm to public health	MvPI	Within 5 work days of becoming aware of an event
Healthcare service provider	Medical device adverse event or incident on MDAE-reporting form with causality assessment report	MvPI	MDAE Reporting form within 5 work days of becoming aware and root cause analysis in next 30 calendar days

The USFDA[5-7] requires reporting of events not only by the manufacturer, whether domestic or foreign, but also by the user facility and distributor. The manufacturer must submit four reports depending on the event reported: first, 30-day reports for death, serious injury, or malfunctions; second, 5-day reports for events requiring immediate remedial action; third, baseline report to provide basic data on the device, subject to MDR report; and finally, annual certification. The user facility and distributor need to report death and serious injury within 10 working days on FDA form 3500A. The user facility is also required to submit semi-annual reports to FDA (form 3419) from January 1 to July 1. Eventually, form 3500A should report events for each device, and only one report must be submitted for the same patient or same event irrespective of the multiple sources of information for an event. Voluntary reports may be submitted at any time for adverse events, product problems, and product use errors through completion of online MedWatch FDA form 3500.

Who can Report?

All healthcare clinicians, biomedical engineers, clinical engineers, hospital technology managers, pharmacists, nurses and technicians can report medical device adverse events (MDAEs). Pharmaceutical companies can also send adverse events specific to their product to NCC. In India, CDSCO considers that an adverse event should be reported by the manufacturer.

Why to Report?

As a stakeholder it is a responsibility to report adverse events associated with use of medical devices and safeguard the health of public

What to Report?

In order to foster the habit of reporting MvPI encourages reporting of all types of adverse events related to medical devices- irrespective of whether they are known or unknown, serious and non-serious, frequent or rare.

How and Whom to Report?

- Use of the 'Medical Device Adverse Event (MDAE) reporting form.
- Research Associates from Medical Device Adverse Event Monitoring Centres (MDMCs) after filling the MDAE form would submit it to the National Collaboration Centre (mvpi@sctimst.ac.in).
- NCC-PvPI helpline 1800-180-3024 (Toll free) also provides assistance in medical device adverse event reporting.
- Directly e-mail on mvpi@sctimst.ac.in or mvpi.ipcindia@gmail.com

Current status

The members of MvPI met recently at the IPC in May 2017 to discuss plans to gauge the progress of the ambitious programme. It was decided that biomedical engineers with experience will be recruited and PvPI will provide them with the necessary training. The MvPI members also suggested that the medical devices manufacturers should be involved in interactive sessions with them. It was also decided that steps will be taken by the MvPI to increase the awareness of the programme and encourage reporting of Medical Devices Adverse Events (MDAEs).[8] The regulatory structure has an established licensing component, a proactive inspection component and a responsive compliance/investigation component. The licensing component plays a major role in pre-market approval and device registration. Post-market surveillance, including a responsive investigational component, is in a nascent stage in India. Support of clinical engineering apart from other sciences within medical faculty could play a significant role in regulating medical devices by post-market surveillance.

Conclusion

Patient safety is a fundamental principle of health care. Delivering safe care and preventing harm, particularly "avoidable harm", is one of the greatest challenges in today's complex, pressurized and fast moving environments. With the population of 1.3 billion people we need a robust reporting infrastructure in India. The regulators should define clearly the medical device and classify the devices on the basis of risk involved. One of the biggest issues is underreporting of MDAEs which is still largely done by manufacturers of devices. More combine efforts are needed from expertise of clinical medicine and biomedical engineering / clinical engineering in making medical devices safer for the benefits of patients and healthcare provider.

Annexure: List Of Notified Medical Devices

1	Disposable Hypodermic Syringes	In addition to medical devices given, following products are regulated as 'Drugs' under Drugs & Cosmetics Act & Rules there under: -
2	Disposable Hypodermic Needles	
3	Disposable Perfusion Sets	
4	In vitro Diagnostic Devices for HIV, HBsAg and HCV	
5	Cardiac Stents	
6	Drug Eluting Stents	
7	Catheter	Blood Grouping Sera
8	Intraocular lens	Ligatures, Sutures and Staplers
9	I V Cannulae	Intra Uterine Devices (Cu-T)
10	Bone Cements	Condoms
11	Heart Valves	Tubal Rings
12	Scalp Vein Set	Surgical Dressings
13	Orthopaedic Implants	Umbilical Tapes
14	Internal Prosthetic Replacements	Blood and Blood Component Bags

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ADVERSE REACTIONS WITH THE USE OF COSMETIC AGENTS

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Definition

Section 3(aaa) of Drugs and Cosmetics Act defines "cosmetics" as "any article intended to be rubbed, poured, sprinkled or sprayed on, or introduced into, or otherwise applied to, the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and includes any article intended for use as a component of cosmetic.[1] The term cosmeceutical was created over 25 years ago to define products with active substances that cannot be considered cosmetics or drugs. Cosmeceuticals are increasingly popular, with sales representing one of the largest growing segments of the skin care market. The products are found in many forms, including vitamins, peptides, growth factors, and botanical extracts. Cosmeceuticals contain topically applied vitamins having an increasing role in skin care. Cosmeceuticals are active cosmetics that are sold over-the-counter, having profound effects on skin appearance and functioning. Agents include single-entity and combination products containing hydroquinones, retinoids, topical antioxidants, and minerals.[2]

Classification

Cosmetic products may be classified into various types such as:[3]

1. Decorative products eg: make-up
2. Nail care products eg: polish and removers
3. Skin care products eg: moisturizers
4. Soaps and bath additives eg : bubble bath
5. Oral hygiene products eg: toothpaste and mouthwash
6. Shaving products eg: foams, after shave
7. Sun protection eg: sunscreen creams and lotions
8. Hair care products eg: shampoo, dyes, regrowth treatment
9. Fragrances eg: perfumes and colognes
10. Deodorants and antiperspirents
11. Foot care products eg: antifungicides
12. Baby care products eg: baby salve, baby oil, baby powder

History

Ancient Indians of both genders applied a number of different makeup products. While makeup is generally seen as merely superficial, cosmetics to Indians were a means of practicing their religion and culture. The caste or class system in India is based on birth and wealth. Many Indians still consider fair skin a hallmark of beauty due to its association with status. In addition, mothers apply kohl to their infant's eyes soon after birth to "strengthen the child's eyes" and others believed it could prevent the child from being cursed by the evil eye.[4]

Introduction

Since few decades there is a big boost in cosmetic industries, by the production of the various types of the cosmetics which are needed for the care and beautification. The Indian cosmetics industry is estimated at Rs. 15,000 crore and is expected to grow at over 10% annually. It was assumed that cosmetics were supposed to help women look beautiful, but recent changes in the fast growing industry and advertising have smartly lured even men into buying "men" cosmetics thus expanding the industry even further.[5]

Therefore, given the widespread use of cosmetics, it is important to monitor their side-effects. "Unlike drugs and medical devices, cosmetics permeate daily life. It is estimated that an average woman uses 12 personal care products daily which comprise of 168 unique ingredients and on an average, a man uses 6 personal care products with around 85 unique ingredients. According to a research, of the 10,500 chemical ingredients used in personal care products, only 11% have been safely assessed. In addition to allergens, cosmetics and toiletries contain several hazardous ingredients including 100 carcinogens and 15 endocrine disruptors particularly phthalates.[6]

The most recent former commissioner of the FDA, Dr. Robert M. Califf stated that challenge of overseeing cosmetic safety is "daunting" for regulators. The global cosmetics industry was expected to reach $265 billion in revenue in 2017, yet, the FDA's Office of Cosmetics and Colors had a budget of about $13 million for 2017. "For products that are used routinely, small effects over time within large populations can be almost impossible to detect without active surveillance". "Even when health risks are substantial, as with tobacco products, the path to identifying and interpreting those safety signals clearly enough to justify regulatory action is often long and tortuous".[7]

Types of ADR's

In a retrospective study with 1609 participants, in a period of 5 years, 12.2% suffered from adverse effects of cosmetics and toiletries, out of which 63.3% were women and 36.7% were men. Most common complaint was itching (70.9%), dryness of skin (63.3%), and burning sensation in skin (50%).The skin manifestations ranged from rhagades, scales, blisters, spots, and redness to no visible

changes. Other complaints were eye irritation as manifested by burning and watery eyes, shortness of breath following perfume spray, local lymph node swelling following deodorant use, sneezing following aftershave application, and nausea following perfume application. Face and hands were the most frequently affected location.[8] Most common adverse drug reaction (ADR) following permanent makeup procedure were tenderness, swelling, itching, and bumps. The duration of suffering ranged from 5.5 months to 3 years. With increased use of cosmetics, the rate of sensitization to many allergic components has increased. Hair dye is reported as one of the most common causes of contact dermatitis in India. Kumkum dermatitis was highly prevalent in southern part of India. Sticker bindi use is also found to be an important risk factor for occurrence of contact dermatitis. Apart from the active product, other ingredients of cosmetic products are also implicated in adverse reactions following the use of cosmetics. Although lots of ADRs occur at the population level, reporting to the regulatory authority is very low. Cosmetic product-related adverse effect identification and analysis is mainly industry driven. Although lots of efforts are made by manufacturers, potential conflict of interest may bias the findings.[9]

Regulation

In India, cosmetics are regulated as per Drugs and Cosmetics Act 1940 and Rules 1945. Part-XIII (regulates import and registration of cosmetics), part-XIV (manufacture of cosmetic for sale or for distribution) and part-XV (regulates labelling, packing and standards of cosmetics). Rule 145 and 135 prohibits the use and import of arsenic and lead containing compounds. Cosmetics containing mercury are prohibited as per provisions of rules 135A and 145 D. Rule 134-A prohibits import of hexachlorophene containing cosmetic. Rule 134 specifies that cosmetic products should contain color, dye or pigment as per specified by schedule Q and Bureau of Indian Standards. Gazette notification G.S.R 426(E) divides cosmetics into 4 gross categories: skin products, hair and scalp products, nail and cuticle products and products for oral hygiene.[9]

Currently, cosmetic manufacturers have no legal obligation to report health problems from their products to the FDA. Cosmetics also do not need to go through a pre-market approval process before they are sold in stores, and regulators do not assess the safety and effectiveness of the claims on the products. Instead, people and doctors are asked to report any health complications to the FDA's database (called the Center for Food Safety and Applied Nutrition's Adverse Event Reporting System, or CFSAN). If FDA finds any increase in ADR due to cosmetics which is of concern, they can investigate.[7]

Causative Agents

The skin is the largest organ of the body; over 70% of what is placed over the skin manages to seep into the body and the bloodstream. The various harmful allergens present in cosmetics may be grouped under phthalates, parabens, metals, chlorofluorocarbon propellants, dioxanes etc. Some of the harmful

chemicals present in cosmetic products are coal tar colours (make-up and hair dye), diethanolamine (shampoo), formaldehyde and its releasers (eye shadow, mascara, nail polish, shampoo, blush etc), glycol ethers (deodorant, perfume), lead (hair dyes, lipsticks), mercury (skin-lightening cream), parabens (deodorant, shampoo, cream, baby product, shaving cream, make-up etc), phenylenediamine (hairdyes), phthalates (fragrance, nailpolish, hair products, cream, lotion etc).[6] Moreover, cosmetics are used almost on a daily basis; hence even minute amounts of chemicals which are applied regularly will cause a cumulative effect.

Hazardous chemicals in cosmetics:[6]

1. *Antibacterials:* Overuse of antibacterials affect their effectiveness in fighting disease-causing organisms such as E. coli and Salmonella enterica. Triclosan which is widely used in soaps, toothpastes and deodorants has been detected in breast milk and it interferes with testosterone activity in cells.

2. *Coal Tar:* Coal tar, a known human carcinogen is used as an active ingredient in dandruff shampoos and anti-itch creams. Coal-tar-based dyes such as FD&C Blue 1, used in toothpastes, and FD&C Green 3, used in mouthwash have been found to be carcinogenic in animal studies when injected under the skin.

3. *Diethanolamine (DEA):* DEA is a hormone disruptor, with limited evidence of carcinogenic property and is known to deplete the body of choline needed for fetal brain development. DEA can also show up as a contaminant in products containing related chemicals such as cocamide DEA.

4. *1,4-Dioxane:* 1,4-Dioxane is a human carcinogen that can appear as a contaminant in products containing sodium laureth sulfate and ingredients that include the terms "PEG," "-xynol," "ceteareth," "oleth" and most other ethoxylated "eth" ingredients. The FDA monitors products for the contaminant but has not yet recommended an exposure limit. Manufacturers can remove dioxane through vacuum stripping. A 2007 survey by the Campaign for Safe Cosmetics found that most children's bath products contain 10 ppm or less, but an earlier 2001 survey by the FDA found levels in excess of 85 ppm.

5. *Formaldehyde:* Formaldehyde has adverse effects on health, which includes immune-system toxicity, respiratory irritation and cancer in humans. Yet it still turns up in baby bath soap, nail polish, eyelash adhesive and hair dyes as a contaminant or break-down product of diazolidinyl urea, imidazolidinyl urea and quaternium compounds.

6. *Fragrance:* The term "fragrance" may imply phthalates, which act as endocrine disruptors and may cause obesity, reproductive and developmental harm. Phthalates should be avoided by selecting essential-oil fragrances.

7. *Lead and Mercury:* Neurotoxic lead may be present in certain cosmetic products as a naturally occurring contaminant of hydrated silica, one of the ingredients in toothpaste, and lead acetate is found in some brands of men's hair dye. The mercury found in the preservative thimerosol, is used in some mascaras and is known to cause damage to the brain. Heavy metals are known to cause various health problems such as cancer, reproductive and developmental disorders, neurological problems, cardiovascular, skeletal, blood, immune system, kidney problems, headache, vomiting, nausea, diarrhea, lung damage, contact dermatitis, and brittle hair and hair loss. Some are hormone disruptors while others are respiratory toxins.

8. *Nanoparticles:* Tiny nanoparticles, which may penetrate the skin and damage brain cells are appearing in an increasing number of cosmetics and sunscreens. Most problematic are zinc oxide and titanium dioxide nanoparticles used in sunscreens to make them transparent. These days a few manufacturers have started advertising their lack of nanoparticle-sized ingredients on labels.

9. *Parabens:* (methyl-, ethyl-, propyl-, butyl-, isobutyl-) Parabens which have weak estrogenic effects are common preservatives that appear in a wide array of toiletries. Butyl paraben has been shown to damage sperm formation in the testes of mice and sodium methylparaben is banned in cosmetics by the European Union (E.U). Parabens break down in the body into phydroxybenzoic acid, which has estrogenic activity in human breast-cancer cell cultures.

10. *Petroleum Distillates:* Petroleum distillates which are possible human carcinogens are prohibited or restricted for use in cosmetics in the E.U but are found in several U.S brands of mascara, foot odour powder and other products.

11. *p-Phenylenediamine:* It is commonly found in hair dyes and can bring damage to the nervous system causing lung irritation and severe allergic manifestations.

12. *Hydroquinone:* Found in skin lighteners and facial moisturizers, hydroquinone is neurotoxic and allergenic, and there's limited evidence that it may cause cancer in laboratory animals. It may also appear as an impurity not listed on ingredients labels.

Misbranded and Spurious Cosmetics

Misbranded and spurious cosmetics are defined as per provision of Drugs and Cosmetics Act 1940 and Drug and Cosmetics rule 1945. Cosmetics are called misbranded if it contains an unprescribed colour, inappropriate labeling or contains false/misleading product information. Cosmetics are labelled as spurious when its name resembles another cosmetic, the product resembles another cosmetic or if manufacturer information is misleading/fictitious or does not exist which can deceive customers. Spurious cosmetics are commonly reported in Indian market. Spurious cosmetics in branded bottles are found to be sold to parlors and salons. In one Food and Drug Administration raid in beauty parlors in Pune, officials seized lots of cosmetic products with no license number displayed on the

label. High level of lead is reported in many cosmetic products. Impurities such as high level of heavy metals (lead, zinc, and cadmium) are reported in many cosmetic products (lipsticks, lip glosses, eyeshadows, and henna hair dye). Hair technicians in salon and parlour are at risk of chemicals in cosmetics and hand dermatitis is quite common among them. Female hair technicians are at particular risk for fertility disorders and adverse pregnancy outcomes which is of special concern. Hair technicians are also more prone to development of asthma due to exposure to ammonium persulfate. A study by Shah et al shows that 43% of the Indian samples of sindoor exceeded the limit of lead content in sindoor comparative to US Samples. Public health interventions should focus on primary prevention to ensure that lead-adulterated sindoor is not available for sale. Even commonly used "kajal" is found to contain high levels of lead. The different lead-containing compounds found in kajal are minium (Pb_3O_4) and galena (PbS). Other compounds reported are zincite (ZnO), magnetite (FeO) and amorphous carbon. High level of these compounds can be harmful to human body more specifically for pregnant woman.[9]

List of restricted/ prohibited substances notified by the Government of India are :[10]

- Prohibition of manufacture of cosmetics containing colours other than those prescribed: Dyes, colours and pigments other than the one specified by the Bureau of Indian standards (IS:4707 part 1 as amended) and Schedule Q [under rule 144].
- Permitted synthetic organic colours and natural organic colours used in the cosmetic shall not contain more than 2 ppm of Arsenic calculated as Arsenic trioxide, 20 ppm of lead calculated as lead, 100 ppm of heavy metals other than lead calculated as the total of respective metals. [under rule 144-A].
- Manufacture of cosmetic containing hexachlorophene. Soaps may contain hexachlorophene not exceeding 1% w/w. [under rule 144-A].
- Lead and Arsenic compounds for the purpose of colouring cosmetics. [under rule 145].
- Manufacture of cosmetic containing mercury compounds. [under rule 145-D].
- Fluoride content in tooth paste shall not be more than 1000 ppm. [under rule 149-A].
- Manufacture and sale of all cosmetics licensed as tooth paste/tooth powders containing tobacco.

Cosmetics and Pregnancy

Cosmetic use during pregnancy and its developmental effect is another issue which needs to be dealt carefully. There is no clear-cut answer to this issue. Regarding skin care products, except hydroquinone and topical retinoids risk of malformations and other adverse effects do not seem to be increased with use of cosmetics.[11] With regard to chemical peeling agents, trichloroacetic and salicylic acid is preferably to be avoided or to be used with caution. Use of botulinum toxin is another controversial

area. Sclerotherapy also needs to be used with caution and it is better to avoid during the first trimester and after 36 weeks of pregnancy. Fat transfer procedure and sclerotherapy are not recommended during lactating period.[12] Couto et al reported an association between first trimester use of hair dye or hair strengthening products and development of acute lymphoblastic leukemia and acute myeloid leukemia in their children.[13] In studies conducted later no such outcomes were observed but it is preferable to avoid such treatment during pregnancy.[14]

Evaluation of the safety/toxicity of a cosmetic product[15]

In vitro tests	**In vivo tests**
Screening for severe irritancy	Screening toxicological profile
Phototoxicity	Determination of no-observed adverse effect (NOAEL)
Percutaneous absorption Mutagenicity / genotoxicity	Adverse effects at higher exposure

Need of Cosmetovigilance in India

Population of India is huge and similar is the market of cosmetics. Contact dermatitis and other dermatosis are common in India and cosmetics are implicated in the same. Adverse reactions to traditional agents are also commonly reported for example kajal and kumkum dermatitis. Import of cosmetics tested in animals is prohibited in India as per section 135 B of Drugs and Cosmetics Act. Like other diseases, disorders related to cosmetics also lead to pharmacoeconomic loss. Hence besides proper regulation of these agents, a proper vigilance system is also required to protect health of Indian population. Thus, the process of cosmetovigilance is evolving and coming up as a strong regulatory science to protect public health and beauty.[9]

Conclusion

In today's world, exposure to man-made chemicals has become unavoidable. However, we do have a choice when it comes to our personal care products. Although, cosmetic products are not often associated with serious health hazards, this does not mean that they are always safe to use, especially with regard to possible longterm effects as the products may be used extensively over a long period of time. Cosmetics and skincare products may contain ingredients whose safety is not certain or which are known to cause health risks. Many of the cosmetics particularly hairdyes and shampoos may contain ingredients classified as known or probable human carcinogens. Again many of these products may contain penetration enhancers increasing penetration through the skin. Proper use of cosmetovigilance can help to control or rule out hazardous ingredients in cosmetics and thus improve our confidence on use of these agents.

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ANALYSIS OF ADVERSE DRUG REACTION REPORTED

(March 2018 to June 2018)

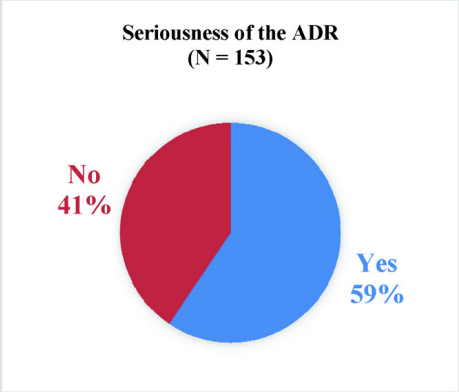
Compiled by Dr. Nitin Gawari, Dr. Nayana Nair, Dr. Pranesh Pawaskar
3rd year residents; Department of Pharmacology, LTMMC & GH, Sion, Mumbai.

Total no. of cases : N = 153

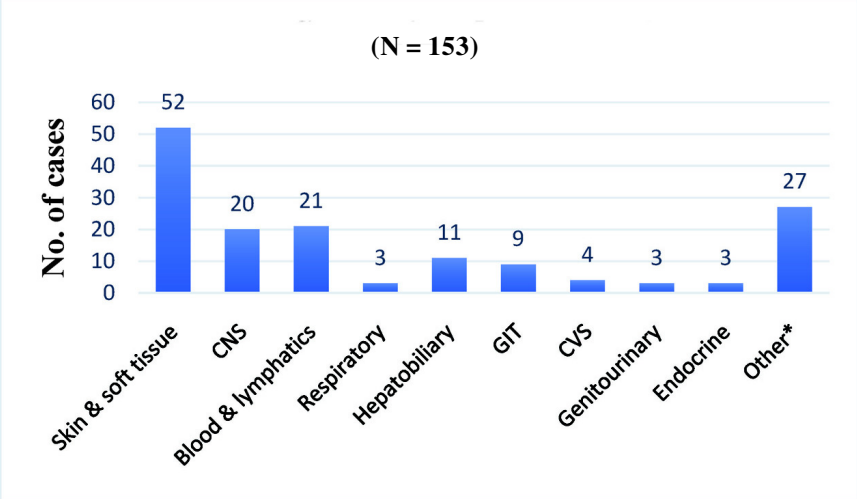
1. Age and Gender distribution

Age group (years)	No. of patients	Males	Females
<3	21	12	9
3-17	39	18	21
18-44	55	31	24
45-60	26	16	10
>60	12	8	4
Total	153	85	68

2. Seriousness of the ADR

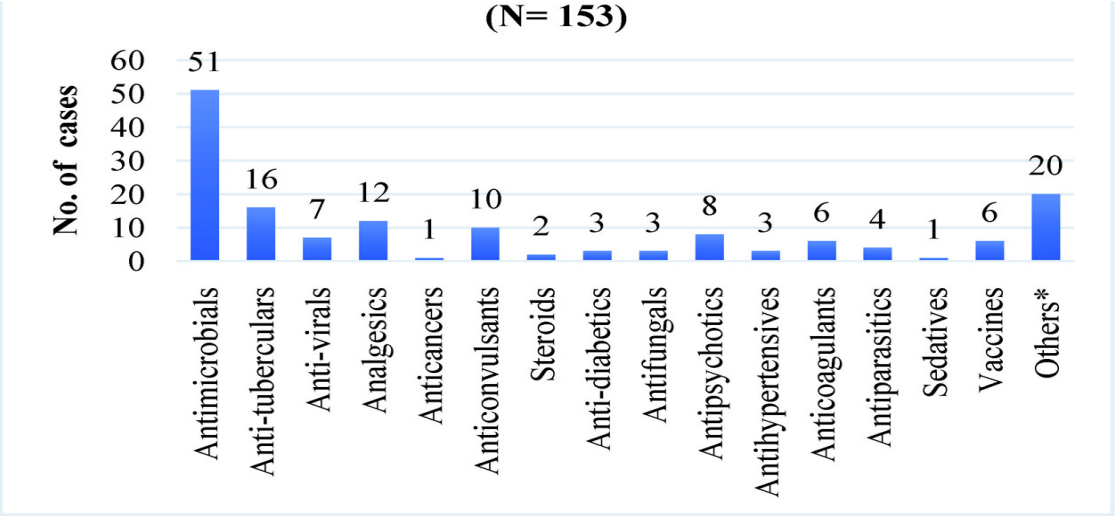


3. System involved in ADR :



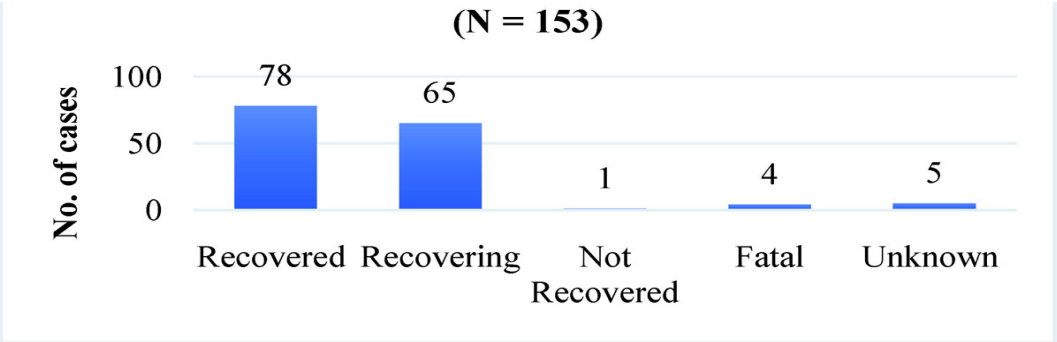
Others* system include fever with or without chills, immunological, renal system, electrolyte disorder and ocular system.

4. Class of the suspected drug:

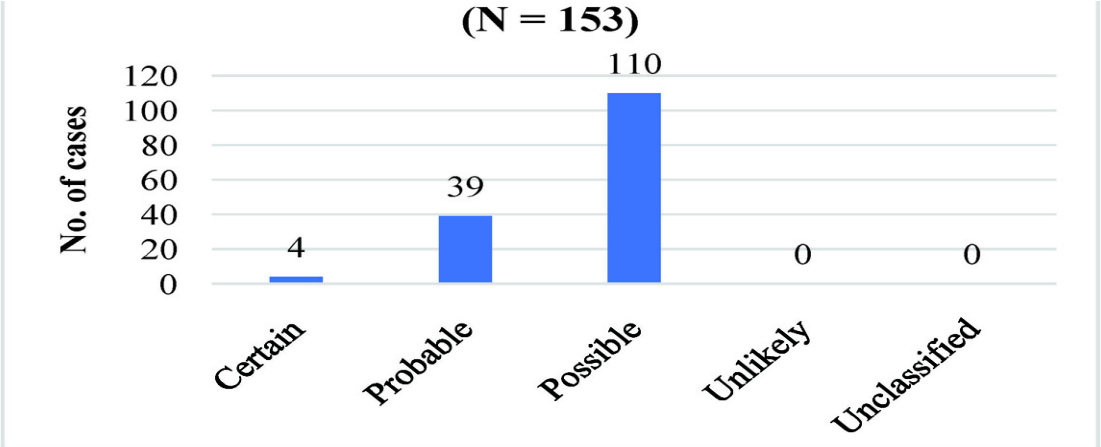


Others* class of drugs include ADR of anti-platelet, laxative, vitamin supplements, electrolytes and proton pump inhibitors.

5. Outcome of the reaction:



6. Causality assessment (WHO UMC Classification)



EVALUATION OF A CASE PHENYTOIN INDUCED PARADOXICAL SEIZURES

Dr. Harshad Katyarmal*, Dr. Priyanshu Shah**

**Second year resident, Department of Pharmacology*

***Assistant Professor, Department of Medicine, LTMMC & GH, Sion, Mumbai.*

Introduction

Seizure is a paroxysmal event due to abnormal excessive or synchronous abnormal activity in brain. Seizures are a common toxic complication of drugs and poisons, as well as drug withdrawal syndromes. Studies have estimated that 6% of new-onset seizures and up to 9% of status epilepticus cases are due to drug toxicity. Antidepressants, stimulants including cocaine, diphenhydramine , isoniazid account for majority of cases.[1] Bupropion is the most common drug to cause seizures (23%). Many reports of aggravation of seizures due to antiepileptic drugs have been published. Most such reports are anecdotal and speculative, and suggest that many such reactions are idiosyncratic. Seizure aggravation may include increase in the frequency or severity of existing seizures, emergence of new types of seizure, or the occurrence of status epilepticus.This is best documented for the use of carbamazepine in idiopathic generalized and myoclonic epilepsies. The lowest risk of seizure aggravation appears to be with valproate.[2] Among anti-epileptics seizures are also seen with, phenytoin, lamotrigine, and vigabatrin.[3] Phenytoin at toxic concentration (>40 mcg/ml) can cause seizures.[4] The present case is about a patient who developed paradoxical seizures, which was the only presentation of phenytoin toxicity.

Case History

A 19 year old female patient a known case of central nervous system tuberculoma since one year clinically presented with, two episodes of seizures, drowsiness and altered sensorium. She was on anti-tubercular regime HRZE (Isoniazid, rifampicin, pyrazinamide, ethambutol) since one year. She was on anti-epileptics (Levetiracetam, phenytoin) since 6 months for multiple seizure episodes which were well controlled. But she developed 2-3 episodes of seizures a day since last 2 days prior to getting admitted to our hospital. She was admitted to our hospital and was started on intravenous mannitol and dexamethasone suspecting raised intracranial tension. As provisional diagnosis of breakthrough seizure was made, tablet clobazam was added to her medications 2 days later.

On investigation her complete blood counts, blood glucose, serum electrolytes, liver function and kidney function parameters were within normal range. CT findings were consistent with previous finding of tuberculoma. On investigating level of phenytoin in blood, it was found in toxic range (>20) i.e. 52 g /mcg. So phenytoin was stopped on same day i.e. five days after admission. After withdrawal of phenytoin there was no new episode of seizure. All other anti-tubercular drugs were continued.

Thus the diagnosis of phenytoin induced paradoxical seizures was confirmed. The adverse drug reaction is serious and moderate in severity as per Modified Hartwig Seigel scale. The causal association of the reaction with phenytoin is 'PROBABLE' as per WHO UMC causality assessment scale.

Discussion

The term seizure refers to a transient alteration of behaviour due to the disordered, synchronous, and rhythmic firing of populations of brain neurons. Epilepsy refers to a brain function disorder characterized by the periodic and unpredictable occurrence of seizures. Seizures can be provoked (i.e., by chemical agents or electrical stimulation) or unprovoked.[4] Seizures may be either focal or generalised. Generalised seizures arise within and rapidly engage networks distributed across both cerebral hemisphere and focal seizure limited to one cerebral hemisphere only.[5]

Drug induced seizure can occur as direct result of altering neural pathway and specific excitatory or inhibitory neurotransmitter and receptors within those pathways. Gamma Aminobutyric acid (GABA) mediated receptor and pathway are inhibitory while those mediated with glutamine are excitatory . Seizures occur generally as a result of inadequate inhibitory influences (e.g., gamma aminobutyric acid, GABA) or excessive excitatory stimulation (e.g. glutamate) although many other neurotransmitters play a role.[1]

Seizure-inducing effects can be observed in the treatment of epileptic patients with antiepileptic drugs. This may be a paradoxical reaction (for example the increase of complex focal seizures due to carbamazepine, vigabatrin or phenytoin treatment) or a result of anti-epileptic drug-induced encephalopathy.[6] A study conducted by Sane et al showed that seizures most commonly occur after overdose of sodium valproate followed by phenytoin and carbamazepine.[7] The pathophysiology of seizure aggravation is poorly understood including nonspecific effects such as those associated with sedation, drug induced encephalopathy, and paradoxical or inverse pharmacodynamic effects.[2]

Phenytoin is used in all types of seizures except absence seizure. It is the most commonly prescribed antiepileptic drug due to its cost and availability. Phenytoin is known for its side effects such as gingival hyperplasia, nystagmus, myopathy, and drug-induced lupus, but rarely causes seizures. Phenytoin induced seizure is usually brief and generalized, preceeded by other signs of toxicity and occurs after an acute overdose.[8] Phenytoin has a narrow therapeutic range of 10-20 mcg/ml. At plasma concentrations below 10 mcg/ mL, elimination follows first order. However, at higher concentrations, including those in the therapeutic range (10-20 mcg/mL), the metabolic pathway becomes saturated and elimination shifts to zero order.[9] At toxic level (<40 mcg /ml) it can cause nystagmus, ataxia, drowsiness and (<40 mcg /ml) paradoxical seizures.[10] Phenytoin is primarily absorbed in the duodenum and is 90% protein-bound. For most patients, this binding is predictable and is linear throughout the therapeutic range. Predisposing factors for toxicity include: (a) hypoalbuminemia, (b) chronic renal

failure, (c) hepatic dysfunction secondary to hepatitis or cirrhosis, (d) Genetic defects in phenytoin metabolism, and (e) inhibition of phenytoin metabolism by other drugs. A study done by Chua et al demonstrates that fall in phenytoin levels after overdose varies in individuals as they have different rates of metabolism.[10]

Our patient is a known case of CNS tuberculoma that itself can cause seizures. However that may not have triggered seizures as CT- scan findings were consistent with previous findings of tuberculoma showing no change in size of the lesion. Liver enzymes & bilirubin were also normal ruling out liver abnormality that might hamper metabolism of phenytoin. Patient was receiving isoniazid which increases serum phenytoin levels. Phenytoin metabolism carried by cytochrome P450 enzymes (especially 2C9 & 2C19), drugs that alter the function of these enzymes can place the patient at risk for toxicity.[11] The incidence of patients experiencing CNS toxicity while receiving phenytoin and isoniazid concomitantly ranges from 11% to 27%. Isoniazid produces a reversible inhibition of phenytoin metabolism.[12] While with dexamethasone the exact mechanisms for these conflicting phenomena remains unknown, but increased levels are attributed to competition on protein binding.[13]

Stopping phenytoin mostly resolves the condition. There is no specific treatment available, only supportive treatment is given. Knowledge of the elimination rates assist the clinician in deciding on the best time to reinstitute phenytoin treatment, hence preventing phenytoin levels from dropping to sub-therapeutic levels and development of seizures. Oral phenytoin therapy can be restarted when levels fall to or below 15mcg/ml.[10] Seizures in the setting of phenytoin toxicity should be treated with appropriate doses of benzodiazepines, with the use of phenobarbital for persistent or recurrent seizures.[14] Some studies suggest use of activated charcoal to be beneficial in both acute and chronic phenytoin toxicity.[11] Peritoneal dialysis & haemodialys is found to be ineffective in acute intoxication.[15,16] Newer technologies like Molecular Adsorbents Recirculating System (MARS) removes albumin-bound toxins based on the principle of albumin dialysis are being studied.[17]

Conclusion

Seizures due to antiepileptic drugs may be idiosyncratic in nature and related to the genetic polymorphism exhibited by these drugs. Paradoxical seizures may be the only presentation of phenytoin toxicity in some patients. As phenytoin exhibits saturation kinetics slight increase in plasma levels due to any drug interactions can precipitate toxicity.

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PUBLISHED LITERATURE ON DRUG INDUCED SEIZURES

Compiled by Dr. Swati Patil

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

Seizure Induced by a Therapeutic Dose of Venlafaxine ER: A Case Report.

J Psychiatr Pract. 2018 Mar;24(2):117-120.

Ye C, Ninneman M, Christian JS, Zhang F, Musselman D.

Venlafaxine is a selective serotonin and norepinephrine reuptake inhibitor commonly used for the treatment of depression. Although listed as an adverse reaction, seizure activity associated with a therapeutic dose of venlafaxine has rarely been documented. We report the case of a 44-year-old woman undergoing antituberculosis therapy who suffered complex partial seizures after ingestion of a low therapeutic dose of venlafaxine extended release (ER). Her first seizure was observed soon after venlafaxine ER was titrated from 37.5 to 75?mg daily, with a total of 9 witnessed complex partial seizures. After titrating the dose of the venlafaxine ER back down to 37.5?mg daily and beginning lamotrigine anticonvulsant therapy, the patient exhibited no further seizures. The development of seizure activity under therapeutic dosing of venlafaxine should be brought to the attention of the health care prescriber. The potential for drug-drug interactions involving venlafazine, particularly in combination with multiple drugs, such as isoniazid and levofloxacin, needs to be recognized.

Refractory idiopathic absence status epilepticus: A probable paradoxical effect of phenytoin and carbamazepine.

Epilepsia. 2000 Jul;41(7):887-94.

Osorio I, Reed RC, Peltzer JN.

They performed a retrospective chart review of all cases of idiopathic generalized epilepsies treated by the authors between 1985 and 1994. They compared seizure frequency and mean intravenous benzodiazepine dose required to control absence status epilepticus, intraindividually in subjects on carbamazepine or phenytoin before and after discontinuation of these compounds, and interindividually to subjects without treatment or receiving other drugs. Bouts of absence or tonic-clonic status epilepticus and seizures in subjects treated with phenytoin or carbamazepine at therapeutic concentrations were considerably more frequent and proved intractable to treatment with valproic acid or benzodiazepines, compared with a cohort of subjects also with idiopathic generalized epilepsies, but naive to, or receiving subtherapeutic or therapeutic doses of other agents.Our observations strongly suggest that therapeutic concentrations of phenytoin and carbamazepine exacerbate idiopathic generalized epilepsies. Subjects in whom absence is one of the seizure types seem at a particularly high risk for responding paradoxically. These findings underscore the value of accurate classification

of seizures and particularly the syndromic approach to diagnosis and point to the potential for iatrogenic complications with indiscriminate use of antiseizure drugs.

Low-dose Clozapine-induced Seizure: A Case Report.

Clinical Psychopharmacology and Neuroscience 2017;15:190-193

Bolu A, Akarsu S, Pan E, Aydemir E, , Oznur T.

Seizures are believed to be a dose-dependent side effect of clozapine. In this case report, we describe a patient who had tonic-clonic seizures after using a low dose clozapine who did not have any seizure risk. The 29-year-old male patient had been followed-up with a diagnosis of schizophrenia for about 5 years. When using clozapine 200 mg/day he had a tonic-clonic seizure with bilateral diffuse epileptic activity in electroencephalography (EEG). In the literature, there are a few case reports about low-dose clozapine-induced seizure. Seizures were observed in our case with a low dose of clozapine (200 mg/day) making this case remarkable. EEG monitoring at regular intervals and examination of plasma levels of clozapine could be useful in preventing the development of seizures.

Seizure risk associated with neuroactive drugs: data from the WHO adverse drug reactions database.

Seizure. 2010 Mar;19(2):69-73.

Kumlien E, Lundberg PO.

Using the WHO adverse drug reactions (ADR) database, VigiBase, we surveyed reports of suspected seizures from 1968 until February 2006. Case reports of ADRs, that were classified as convulsions were collected and compared to the total number of ADRs reported. To explore the association between the use of neuroactive drugs and reports of epileptic seizures. The total number of ADRs was 7,375,325. The number of convulsive events was 71,471. The ratio of convulsive ADRs to the total number of ADRs reported for each drug was evaluated and expressed as a percentage. The 10 drugs most frequently associated with convulsive ADRs were maprotilene (14.42%), escitaloprame (9.78%), buproprione (9.49%), clozapine (9.0%), chlorprothiexene (8.89%), amoxapine (8.74%), donepezil (8.40%), rivastigmine (6.41%), quetiapine (5.90%) and trimipramine (5.69%).Based on the reports in VigiBase, ADR reports relating to antidepressants, antipsychotic and cholinomimetic drugs included seizures more often than other neuroactive drugs.

REGULATORY UDATE AND MEDICAL NEWS

Compiled by Dr. Swati Patil

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

FDA Drug Safety Podcast: FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes.

On July 10, 2018, FDA announced it is strengthening the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects. The low blood sugar levels can result in serious problems, including coma, particularly in older people and patients with diabetes who are taking medicines to reduce blood sugar. This affects only the oral or injectable fluoroquinolone formulations. Blood sugar disturbances, including high blood sugar and low blood sugar, are already included as a warning in most fluoroquinolone drug labels; however, they are adding that low blood sugar levels, or hypoglycemia, can lead to coma. A range of mental health side effects are already described in the Warnings and Precautions section of the fluoroquinolone drug labels. The new label changes will make the mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. Mental health side effects to be added are disturbances in attention, disorientation, agitation, nervousness, memory impairment, and delirium.

Health care professionals should alert patients to the symptoms of hypoglycemia and inform them about the risk of psychiatric adverse reactions that can occur after just one dose. Stop fluoroquinolone treatment immediately if a patient reports any central nervous system side effects, or blood glucose disturbances. Health care professionals should not prescribe fluoroquinolones to patients who have other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections, as the risks outweigh the benefits in these patients.

FDA Drug Safety Podcast: FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. [Internet]. [Cited in July 2018]. Available from:https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm613184.htm.

FDA Drug Safety Podcast: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir.

On May 18, 2018, FDA alerted the public that serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir used to treat human immunodeficiency virus (or HIV). Dolutegravir is an FDA-approved antiretroviral medicine used in combination with other antiretroviral medicines to treat HIV, the virus that can cause acquired immunodeficiency syndrome (or AIDS).

Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects. To date, in this observational study there are no reported cases of babies born with neural tube defects to women starting dolutegravir later in pregnancy.

Health care professionals should inform women of childbearing age about the potential risk of neural tube defects when a dolutegravir-containing regimen is used at the time of conception and early in pregnancy. Health care professionals should weigh the benefits and the risks of dolutegravir when prescribing antiretroviral medicines to women of childbearing age. Alternative antiretroviral medicines should be considered. Discuss the relative risks and benefits of appropriate alternative antiretroviral therapies.

If the decision is made to use dolutegravir in women of childbearing age, health care professionals should reinforce the consistent use of effective birth control. Perform pregnancy testing before initiating a dolutegravir-containing regimen in women of childbearing age to exclude pregnancy.

FDA Drug Safety Podcast: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir. [Internet]. [Cited in July 2018]. Available from: https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm608708.htm.

FDA Drug Safety Podcast: Risk of serious and potentially fatal blood disorder prompts FDA action on oral over-the-counter benzocaine products used for teething and mouth pain and prescription local anesthetics.

On May 23, 2018, FDA warned that over-the-counter (or OTC) oral drug products containing benzocaine should not be used to treat infants and children younger than 2 years. These products carry serious risks and provide little to no benefits for treating oral pain, including sore gums in infants due to teething. Benzocaine, a local anesthetic, can cause a life-threating condition, called methemoglobinemia, in which the amount of oxygen carried through the blood is greatly reduced. They have urged manufacturers that they should stop marketing OTC oral drug products for treating teething in infants and children younger than 2 years. They have also urged manufacturers of OTC oral drug products containing benzocaine for adults and children 2 years and older to make the following changes to the labels of their products:

- Add a warning about methemoglobinemia;
- Add contraindications directing parents and caregivers not to use the product for teething and not to use in infants and children younger than 2 years; and
- Revise the directions to direct parents and caregivers not to use the product in infants and children younger than 2 years.

Health care professionals using local anesthetics during medical procedures should take steps to minimize the risk for methemoglobinemia by monitoring patients for signs and symptoms suggestive of methemoglobinemia; using co-oximetry when possible; and having resuscitation equipment and medications readily available, including methylene blue. We have been monitoring the risk of methemoglobinemia with the use of OTC and prescription local anesthetics and previously communicated about this risk in 2014, 2011, and 2006. FDA estimates that more than 400 cases of benzocaine-associated methemoglobinemia have been reported to FDA or published in the medical literature since 1971.

FDA Drug Safety Podcast: Risk of serious and potentially fatal blood disorder prompts FDA action on oral over-the-counter benzocaine products used for teething and mouth pain and prescription local anesthetics.[Internet]. [Cited in July 2018]. Available from: https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm609486.htm.

MATCH THE FOLLOWING DRUG WITH ITS SPECIFIC ADR

Dr. Sharmada Nerlekar*, Dr. Abhilasha Rashmi*

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1	Amodiaquine	A	Peripheral Neuropathy
2	Thiacetazone	B	SIADH
3	Bortezomib	C	Dyspepsia
4	Atazanavir	D	Histamine release
5	Paromomycin	E	Diarrhoea
6	Primaquine	F	Hyperuri caemia
7	Vincristine	G	Neutropenia in HIV Patients
8	Nelfinavir	H	Xanthopsia
9	Exemestane	I	Hypocalcemia
10	Etidronate	J	Ototoxicity
11	Desferrioxamine	K	SJS
12	Cinacalcet	L	Visual Disturbances
13	Pyrazinamide	M	Haemolysis
14	Digitalis	N	Osteomalacia
15	Colestipol	O	Jaundice

Answers : 1 - G; 2 - K; 3 - A; 4 - O; 5 - J; 6 - M; 7 - B; 8 - E; 9 - L; 10 - N; 11 - D; 12 - I; 13 - F; 14 - H; 15 - C

ALPHABET 'S' PUZZLE

Dr. Abhilasha Rashmi*, Dr. Sharmada Nerlekar*
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1 S									
2	S								
3		S							
4			S						
5				S					
6					S				
7						S			
8							S		
9								S	
10									S

Clues

1. Mild chronic salicylate intoxication called _____ exhibits symptoms like dizziness, headache, tinnitus, dimness of vision, mental confusion, lassitude, sweating, hyperventilation, nausea, vomiting and occasionally diarrhea.
2. Two second generation H1 antihistaminic drugs, Terfenadine & _____were withdrawn from the market in 1998 due to their ability to induce a potentially fatal arrhythmia, Torsades de pointes.
3. The primary side effect of this recombinant human brain natriuretic peptide is hypotension which may persist for a prolonged period requiring inotropic support.
4. Apart from haemorrhagic cystitis, _____ in high doses cause a chronic, irreversible toxicity to proximal tubules which is attributed to chloroacetaldehyde and acrolein.
5. Ototoxicity with loop diuretics like _____ occurs most frequently with rapid intravenous administration and least with oral administration.
6. Teratogenecity is seen with H1 antihistaminic drugs like Hydroxyzine, Fexofenadine and _____, while other drugs are safe.
7. Peripheral neuropathy is the most common adverse effect with Bortezomib, which is a boron containing _____ inhibitor used for treatment of multiple myeloma & mantle cell lymphoma.
8. Chronic use of Class I (most potent) topical glucocorticoids like _____ can cause skin atrophy, striae, telengiectasias, purpura & acneiform eruptions.
9. Nausea, vomiting, diarrhea, uterine cramps, shivering, fever, hypotension & tachycardia are common side effects seen with this PGF2? analog injected intramuscularly for control of postpartum hemorrhage.
10. Nephrotoxicity, neurotoxicity, GI complaints, hypertension, hyperkalemia and hyperglycemia are associated with the use of this calcineurin inhibitor immunosuppressant.

ALPHABET 'S' PUZZLE: ANSWERS :

1. Salicylism
2. Astemizole
3. Nesiritide
4. Ifosfamide
5. Furosemide
6. Azelastine
7. Proteasome
8. Clobetasol
9. Carboprost
10. Tacrolimus

NOTES

NOTES

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

Please feel free to contact us for the same.

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