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BULLETIN ON ADVERSE DRUG REACTIONS

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Committee Members for Bulletin on Adverse Drug Reactions

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From the Editor's Desk

Dear Friends and Colleagues,

We are all aware that ADR monitoring is important not only in the post marketing phase but also in the early phases of clinical trials. Development of many investigational drugs have been suspended or terminated considering the safety issues detected in ongoing clinical trials.

The first article deals with the importance of ADR monitoring of drugs in clinical trials. The article deals with the role of Investigators, Ethics Committee and the Sponsors in handling serious adverse events during clinical trials.

Other features in this issue include a review article on Antiepileptic drugs and their ADRs and some measures for prevention and treatment of the same and an interesting case study on Hypervitaminosis D.

I hope the readers find the articles interesting and informative.

Finally, I would like to thank all the clinical departments for their continued support in ADR reporting and also to all the members of Department of Pharmacology for their efforts in bringing out current issue of the bulletin.

Thank you

Dr. Sudhir Pawar

ADVERSE EVENT REPORTING IN CLINICAL TRIALS

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'Medicine is a science of uncertainty and an art of probability'
William Osler

Introduction

Clinical trials are research studies, conducted in people, to answer specific questions about the safety and/or effectiveness of drugs, vaccines, other therapies, or new ways of using existing treatments. Reporting of adverse events (AEs) is a vital part of any clinical trial in order to ensure patient safety and help clinicians determine the risk-benefit ratio of a new drug/treatment. Various factors about an adverse event are considered when determining the existence or strength of a safety signal. These include the frequency, nature/type, time of onset and duration and presence of documented high-quality rechallenge/dechallenge information on the adverse event. There are many instances of drugs being withdrawn from the market following their launch due to serious adverse reactions; for example rosiglitazone and rimonabant. This results in loss of time and money spent by sponsors on their development. To reduce such losses, it is essential to have strong mechanisms in place to detect safety signals early in the drug development process. Keeping this in mind, we have reviewed the principles of safety reporting in clinical trials and its implications for drug development.

Why is AE reporting important?

By design, randomized controlled trials (RCTs) are efficacy trials and are not powered to look at AEs, especially rare AEs. Additionally, the reporting of AEs in RCTs, especially of new drugs, is frequently incomplete or inadequate.[1] Yet, safety data from RCTs are frequently used as evidence of a lack of difference between the active treatment and control arms in AE risk. Hence, adverse event monitoring in clinical trials is useful to detect adverse reactions before a drug is launched. One of the known examples underlining the importance of AE monitoring is withdrawal of rofecoxib due to increase in cardiovascular events. This was detected during the APPROVe (Adenomatous Polyp Prevention on Vioxx) study that attempted to assess the role of rofecoxib in lowering the incidence of benign sporadic colonic adenomas.[2] The discovery of this adverse effect led to a premature termination of the study.

Laboratory AEs occurring during clinical trials are often predictor of potential adverse drug reactions in the post-marketing phase. Drug induced liver injury during drug development is evidenced by a higher incidence of serum alanine aminotransferase (ALT) elevations in treated versus placebo populations and termed an "ALT signal". A cut-off of 1.2% increase in ALT ≥ 3× upper limit of normal (ULN) in treated versus placebo groups provides an easily calculated method for predicting post-marketing liver safety.[3] Hence, the investigator should be vigilant enough to pick up such laboratory AE signals.

Several drugs have been withdrawn from the market in the recent past following their marketing approval because of serious adverse reactions that increased the risks to patients. These include drugs like ximelagatran, a direct thrombin inhibitor, withdrawn in 2006 due to hepatotoxicity, tegaserod, a 5-HT4 agonist used in Irritable Bowel Syndrome which was withdrawn due to increased risk of cardiac ischemia in 2007, rimonabant in 2008 due to increased risk of depression and suicide and sibutramine and rosiglitazone in 2010 due to increased cardiovascular risk. Thus, it is important to detect, assess and document AEs early in drug development in order to prevent such withdrawals in the post-marketing phase.

Current lacunae in AE reporting

Some pitfalls arise from the fact that adverse events often are not the primary endpoints in clinical trials, hence deliberate non-reporting of certain AEs, incomplete reporting, inconsistent event definitions, various level of effort in reporting unexpected adverse events, and inappropriate use of statistical testing.[4] Earley *et al* reviewed the reporting of deaths in ClinicalTrials.gov records. It was observed that in 500 randomly selected records, only 123 records (25%) reported the number of deaths. The reporting of deaths and serious adverse events was variable. In a sample of 27 pairs of ClinicalTrials.gov records with number of deaths and the consistency with corresponding publications, the total deaths per arm could only be determined in 56% (15/27 pairs) but were discordant in 19% (5/27). In 27 pairs of ClinicalTrials.gov records without any information on number of deaths, 48% (13/27) were discordant since the publications reported absence of deaths in 33% (9/27) and positive death numbers in 15% (4/27).[5] These results highlight the fact that deaths are variably reported by investigators and emphasizes the need for unambiguous and complete reporting of the number of deaths in trial registries and publications.

Responsibilities of stake holders

Reporting and managing adverse events is the responsibility of all the stakeholders involved in clinical research. The Sponsor should ensure that people at the study site/s are trained in the reporting of adverse events as per the timelines to the Sponsor and the Ethics Committee.

Sponsor should also ensure that the documentation of the AE has been done in the case record form (CRF)/serious adverse events (SAEs) reporting form and should verify the data in these forms against the source documents. The Sponsor should expedite reporting to all concerned investigator(s)/institutions(s), to the IEC(s), where required, and to the regulatory authority(ies) of all adverse events that are both serious and unexpected. The Sponsor's policies and procedures should also address the costs of treatment and compensation of trial participants in the event of SAEs/deaths in accordance with the applicable regulatory requirement(s). When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).[6-8]

The Investigator too should ensure that his/her study team is trained in the capturing and management of AEs. Investigators should not only report AEs to the Ethics Committee and Sponsor within the given timelines but also medically manage the trial subject so that he/she gets the best possible treatment to manage the injury. Ethics Committees should review the submitted AE report/s and then assess the seriousness of the report and whether decisions need to be taken regarding progress of the study based on safety issues.

Current timeframes for reporting AEs and SAEs[6, 9]

As per the Schedule Y of Drugs & Cosmetics Rules, 2005 and the recent amendments of 2013, the Investigator(s) shall report all serious and unexpected adverse events including death to the Sponsor and Ethics Committee within 24 hours of his/her knowledge of their occurrence. Any unexpected serious adverse event (SAE) occurring during a clinical trial should be communicated by the Sponsor to the Licensing Authority and to the Chairman of the Ethics Committee of the study site within 10 calendar days. Subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed. The periodic safety update reports (PSURs) shall be submitted every six months for the first two years and annually thereafter for subsequent two years.

Compensation for trial related injuries

Recently there has been a lot of debate on the issue of providing compensation (when and how much) for adverse events especially serious adverse events that occur during a clinical trial. The latest notification from the Central Drugs Standard Control Organization (CDSCO) dated 30th January 2013 states that, any injury or death of the subject occurring in clinical trial due to following reasons shall be considered as clinical trial related injury or death and the subject or his/her nominee(s), as the case may be, are entitled for financial compensation for such injury or death:

a) adverse effects of investigational product(s)

b) violation of the approved protocol, scientific misconduct or negligence by the Sponsor or his representative or the Investigator

c) failure of investigational product to provide intended therapeutic effect

d) use of placebo in a placebo controlled trial

e) adverse effects due to concomitant medications excluding standard care, necessitated as part of approved protocol

f) for injury to a child-in-utero because of the participation of parent in clinical trial

g) any clinical trial procedure involved in the study

The SAE report, after due analysis (viz. causality), shall be forwarded by the Investigator to the Chairman of the Ethics Committee and Chairman of the Expert Committee constituted by the Licensing Authority and the Head of the Institution where the trial has been conducted within 10 calendar days of occurrence of the SAE. It is the investigator's responsibility to inform the trial participant/s through the informed consent process about the subject's rights to claim compensation in case of trial related injury or death. He shall also inform the subject or his/her nominee (s) of their rights to contact the Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial for the purpose of making claims in the case of trial related injury or death. Guidelines for calculating the amount of compensation to be provided to the injured trial subjects or his/her nominee has also been made available by the CDSCO.[10]

The Sponsor too should submit the SAE report, after due analysis, to the Chairman of the Ethics Committee and Chairman of the Expert Committee constituted by the Licensing Authority with a copy to the Licensing Authority and Head of the Institution where the trial has been conducted within 10 calendar days of occurrence of the SAE. The Sponsor should also make arrangements for the payment of the trial related injury which would include payment for the medical expenses incurred to treat the injury as well as financial compensation as per the recent Rules of the Drugs and Cosmetics Act. Once the quantum of the financial compensation to be paid is approved by the Licensing Authority and the same communicated to the Sponsor, the Sponsor has to pay the compensation within 30 days of the receipt of the order.

The responsibility of the Ethics Committee, in case of an SAE, is to submit its report on the SAE including death, including its opinion on the financial compensation to be paid, if any, by the Sponsor, to the Chairman of the Expert Committee constituted by the Licensing Authority with a copy to the Licensing Authority within 21 calendar days of its occurrence.[10]

Practical issues in AE reporting:

There are many practical shortcomings observed when reviewing AE reports submitted as a part of clinical studies. A few examples of these are missing mandatory items in the AE form like the AE outcome, use of unknown abbreviations or ambiguous terms, documenting of non-specific laboratory findings that have no clinical relevance to the AE, listing of symptoms rather than diagnosis, discrepancies between the date of onset of the AE and the that of first sign/ symptom listed in the form, failing to mark outcome of the event or making dual entries (eg. ongoing & resolved), not providing the date of resolution of the event, documenting medications used for the management of the AE/SAE as co-medication, not providing details of the concomitant medications, documenting patient clinical status rather than the expectedness of the AE with respect to the study drug, no details of whether unblinding was done or not etc. Sometimes, it has been observed that the AE form is not signed and/or dated by the Investigator and the causality assessment is missing. Other lacunae observed on the part of the Investigator are failure to adhere to the AE/SAE reporting timelines, to identify a serious adverse event and to follow-up the adverse event to resolution. All these issues affect the quality of the AE reporting, making it difficult for analysis. Thus, it is important that Investigators take additional precautions to avoid these errors when documenting AEs.

Recommendations:

Study protocols should clearly define how adverse events will be identified, managed, and reported. Safety data should be entered on case report forms designed for the study, and a quality control mechanism for ensuring the accuracy and integrity of the data should be established prior to the start of data collection. Another approach to augment safety data would be the use of adverse drug event questionnaires consisting of extensive checklists of symptoms organized by body system. Questionnaires should be administered at baseline and at predetermined intervals during and after a study preferably by a blinded investigator in order to capture the maximum information possible.[11]

Conclusion:

It is essential that the Sponsors and the Investigators particularly and other stake holders like Ethics Committees and the Regulators diligently heed their responsibilities in adverse event reporting. Improvements in adverse event reporting would permit a more balanced assessment of interventions and would enhance evidence-based practice. In addition to training of investigators in safety reporting, modification of approaches to adverse symptom reporting, such as patient self-reporting, should also be considered.

'There are no safe biologically active drugs; there are only safe physicians'

Harold Kaminetzsky

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ANTIEPILEPTICS: ADVERSE DRUG REACTIONS

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Epilepsy is one of the major neurological disorders affecting a large number of individuals worldwide. An epileptic seizure results due to abnormal central nervous system activity manifesting in convulsion and a brief period of unconsciousness in a few. The disorder has a long term impact on patient's lifestyle, education and employment. Apart from the older drugs such as phenytoin, phenobarbitone, carbamazepine, ethosuximide and valproic acid, last decade saw many newer antiepileptics (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, zonisamide, felbamate, topiramate and tiagabine) being available. These antiepileptic drugs control the seizure episodes but need to be continued for prolonged period. The main problem with the antiepileptic therapy is lack of compliance which is attributed mainly to the long term drug therapy and occurrence of unwanted adverse drug reactions (ADRs).

The ADRs of antiepileptics could be of 3 types viz. acute (dose related), idiosyncratic and chronic as given in Table 1. [1]

Table 1: Antiepileptics and ADRs (incidence)

Drug	Dose-related	Idiosyncratic	Long-term
Carbamazepine	GI distress, hyponatremia, mild leucopenia (10%), diplopia, dizziness	rash/exfoliation (7-10%), hepatitis, marrow aplasia (1 in 2 lakh)	osteomalacia
Phenytoin	ataxia, dizziness, diplopia, tremor, GI distress	rash/exfoliation (2-5%), hepatitis, marrow aplasia, lymphoproliferative disorders	osteomalacia, gingival hyperplasia (20%), facial coarsening/ hirsutism, cerebellar syndrome, mild peripheral neuropathy, folate deficiency
Phenobarbital	sedation (adults), hyperactivity (children), ataxia	connective tissue disturbance, rash (1-2%), hepatitis	osteomalacia, connective tissue disorders, sexual dysfunction, folate deficiency
Valproic acid	GI distress (16%), alopecia, weight gain, tremor, thrombocytopenia	encephalopathy, hepatic failure (1 in 20000 to 100000), pancreatitis, polycystic ovary syndrome (causality not yet proven)	

Drug	Dose-related	Idiosyncratic	Long-term
Clonazepam	sedation (50%), ataxia, behavioural disturbance	rare hepatic, renal, hematologic toxicity	
Ethosuximide	GI distress, headache, photophobia	rash, marrow aplasia, psychiatric disturbance	
Felbamate	GI distress, headache, insomnia, weight loss	rash, hypersensitivity, marrow aplasia, hepatic failure	
Gabapentin	sleepiness, dizziness, ataxia, fatigue, weight gain	rare rash	
Lamotrigine	dizziness, headache, diplopia, ataxia, nausea, sleepiness, rash	rash (8-10%), may be higher risk with valproic acid, rare hepatic failure	
Levetiracetam	sedation, fatigue, dizziness	psychiatric disturbances, leucopenia	
Oxcarbazepine	sedation, fatigue, headache, dizziness, GI distress, diplopia, hyponatremia	rash/exfoliation	
Tiagabine	dizziness, somnolence, "abnormal thinking"		
Topiramate	cognitive slowing, nephrolithiasis, paresthesias, weight loss, word finding difficulty, dizziness, fatigue, sleepiness		
Zonisamide	sedation, dizziness, headache, weight loss nephrolithiasis (1%), GI distress, fatigue paresthesias, irritability/agitation, metabolic acidosis	rash, marrow aplasia, rare hepatic damage, aplastic anemia, agranulocytosis, hyperthermia, psychiatric disturbances	

Antiepileptics and Pregnancy

Epidemiological studies have shown that the incidence of congenital malformations is doubled in babies born to mother taking antiepileptics. The common malformations include congenital heart defects, neural tube defects, cleft lip, and cleft palate. Phenytoin, carbamazepine, valproic acid, phenobarbitone and lamotrigine have all been associated with teratogenic effects. The newer antiepileptics produce teratogenic effects in animals but the occurrence of the same in humans is uncertain. Nonetheless good control of epilepsy is essential during pregnancy. Thus,

it is advised to prescribe monotherapy with minimal required dose and careful monitoring of the drug levels during pregnancy. Counselling the patient about antiepileptic therapy, regular monitoring and possible teratogenic effects is important to decrease the anxiety of the patient.[2,3]

Phenytoin and phenobarbitone (hepatic enzyme inducing drugs) cause deficiency of vitamin K dependent clotting factors in newborn. Therefore mother and newborn should receive vitamin K during last 2 weeks of pregnancy and at birth respectively.[2,3]

Pediatric issues[4]

Pediatric patients are more prone for ADRs due to antiepileptic drugs because of the immature detoxification mechanisms and a greater variability in dosing.

- Valproate has been implicated in hepatic toxicity in children
- Phenobarbital, phenytoin, carbamazepine, oxcarbazepine and lamotrigine cause higher incidences of rash in children than adults
- Topiramate and zonisamide have been associated with nephrolithiasis, oligohydrosis, hyperthermia and metabolic acidosis in children and adults
- Gingival hyperplasia, an adverse event seen in patients of all ages who take phenytoin, occurs much more commonly in developmentally impaired patients and young children.

Careful clinical assessment of patients will enable caregivers to detect adverse effects, and routine laboratory testing can reveal some occult problems. Family members should observe the patient for typical adverse effects and report them to the clinician when they witness even subtle changes.

Drug interactions of antiepileptics

Drug interactions are common with most of the older antiepileptics. This is because they are either inducers or inhibitors of hepatic microsomal enzymes. The newer antiepileptics are less commonly involved in drug interactions and these could be favoured while selecting antiepileptics especially in combination therapy. The important drug interactions are enumerated in Table 2.

Table 2: Important drug interaction of antiepileptics and other drugs[5]

Antiepileptic	Other drugs	Interaction and Consequences
Phenytoin	Carbamazepine, phenobarbital, valproic acid, tiagabine, lamotrigine, topiramate, zonisamide, steroids, digoxin, doxycycline, theophylline	Phenytoin being hepatic enzyme inducer, decreases plasma levels of these drugs
	Chloramphenicol, isoniazid, cimetidine, warfarin	These drugs inhibit phenytoin metabolism resulting in its increased plasma level
Carbamazepine	Carbamazepine (autoinducer), phenytoin, phenobarbital, valproic acid, topiramate, zonisamide, tiagabine, lamotrigine, haloperidol, OC pills	Carbamazepine being hepatic enzyme inducer, decreases plasma levels of these drugs
	Erythromycin, fluoxetine, isoniazid	These drugs inhibit carbamazepine metabolism resulting in its increased plasma level
Phenobarbital	Carbamazepine, Phenytoin, Valproic acid, Topiramate, Zonisamide, Tiagabine, Lamotrigine	Phenobarbital being hepatic enzyme inducer, decreases plasma levels of these drugs
Valproic acid	Carbamazepine, Phenytoin, Phenobarbital, Lamotrigine	Valproic acid being hepatic enzyme inhibitor, increases plasma levels of these drugs.
Topiramate, Zonisamide	OC pills	They are mild enzyme inducers leading to failure of OC pills.

Can we reduce the incidence of ADRs?

Though it is true that none of the antiepileptics are completely safe, the incidence of ADRs can be reduced by considering the following points:

1. *Monotherapy:* Therapy should be started with a single drug and substituted by another drug if the first drug fails. Except for patients with severe idiosyncratic reactions, where substitution is clearly preferable, choice is to evaluate the combination first and to slowly taper and finally discontinue the first drug. Tapering the first would ensure decrease drug load and thus decrease drug interactions and ADRs.[5] Polytherapy should be considered in patients with refractory epilepsy or patients suffering from more than one type of epilepsy.

2. *Dosing:* Slow titration up to average maintenance doses is generally advisable, because rapid dose escalation and higher-than-average doses cause adverse events. Higher-than average doses are more likely to improve seizure control in only an additional 20-30% of all responders. If the therapeutic benefit is not seen after further dose escalation, returning to the previous dose will avoid unnecessary toxicity.[5]

3. *Adverse drug interactions* can be minimized by avoiding enzyme-inducing or -inhibiting classic antiepileptics and using beneficial combinations of antiepileptics, if needed, for seizure control.[5]

4. *Selection of appropriate drug:* Selection of antiepileptics should be done considering the associated conditions. An obese patient with epilepsy may benefit from the use of topiramate or zonisamide, which have a tendency to produce weight loss. In patients with a history of drug-induced skin rash, valproic acid, gabapentin, topiramate, tiagabine, and levetiracetam carry a lower risk of cross-reactivity. In patients sensitive to cognitive dysfunction, drugs with a favorable profile include gabapentin, tiagabine, lamotrigine, oxcarbazepine, and levetiracetam.[6]

5. *For treating epilepsy in the elderly,* it is advisable to prefer non-metabolized, non-enzyme inducing new antiepileptics such as gabapentin and lamotrigine instead of classic enzyme-inducing carbamazepine, if possible. Slow dose escalation and lower than-average dosages are recommended; antiepileptic drug combination therapy should be avoided.[5]

6. *Monitoring the therapy:* Therapeutic Drug Monitoring (TDM) is an important aspect of antiepileptic therapy. The indications of TDM during the therapy are at the beginning of the therapy, any modifications of the dose, start of polytherapy, appearance of any ADRs and loss of efficacy. The reference ranges for different antiepileptics are given in Table 3.[7]

Table 3: Reference ranges of antiepileptics

Drug	Plasma levels (mg/L)
Phenytoin	10-20
Phenobarbital	10-40
Carbamazepine	4-12
Ethosuximide	40-100
Valproic acid	50-100
Felbamate	30-60
Gabapentin	2-20
Lamotrigine	3-14
Levetiracetam	12-26
Oxcarbazepine	3-35
Tiagabine	0.02-0.2
Topiramate	5-20
Zonisamide	10-40

Apart from monitoring the drug levels, certain other parameters should also be monitored during the therapy. For example liver function with valproic acid therapy (ADR: hepatitis), serum bicarbonate with zonisamide therapy (ADR: metabolic acidosis), complete blood count and liver function with felbamate therapy (ADR: bone marrow aplasia and hepatic failure).

Old versus newer antiepileptics [8]

It cannot be generalized that all the newer antiepileptics are better than the older antiepileptics. It is because ADRs of antiepileptics are drug specific. However the absence of hepatic enzyme induction/inhibition and fewer incidences of idiosyncratic reactions with most of the newer antiepileptics provide major advantage in the therapy. Data on long term ADRs of newer antiepileptics however is still lacking.

Conclusion

Good control of epilepsy with minimal ADRs has always been a challenge during the therapy with antiepileptics. Initiating the therapy in small doses with gradual titration, prescribing monotherapy, educating the patient regarding the possible ADRs and regular monitoring, reduces the incidence of ADRs, ensures compliance and thus results in a successful antiepileptic therapy.

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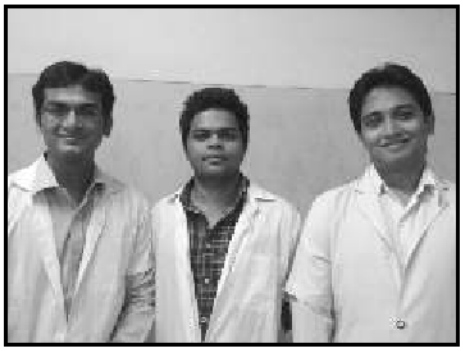

LIST OF ADVERSE DRUG REACTIONS
(November 2012 - February 2013)

Sr. No.	Adverse Drug Reaction	Suspected Drugs	Causality Assessment	Literature Documentation
1	Haemorrhage	Warfarin	Probable	Well documented
2	Tachycardia	Salbutamol, Cefpodoxime	Possible	Well documented
3	Skin Necrosis	Warfarin	Probable	Well documented
4	Gastritis	Chloroquine	Probable	Well documented
5	Abnormal muscle movements	Ketamine	Possible	Well documented
6	Rash	Ceftriaxone	Probable	Well documented
7	Fixed Drug Erruptions	Ofloxacin, Ornidazole	Possible	Well documented
8	Anaphylaxis	Iron-sucrose	Probable	Well documented
9	Rash	Piperacillin, Tazobactum, Amikacin, Co-trimoxazole	Possible	Well documented
10	Rash	Cefalexin	Probable	Well documented
11	Hypokalemia	Salbutamol, Terbutaline	Possible	Well documented
12	Neuropathy	Isoniazid	Probable	Well documented
13	Gastritis	Amoxicillin, Paracetamol, Metronidazole	Possible	Well documented
14	Hepatitis	Rifampicin, Isoniazid, Pyrazinamide, Stavudine	Possible	Well documented
15	Rash	Furosemide	Probable	Well documented
16	Rash	Nevirapine, Lamivudine, Tenofovir	Possible	Well documented
17	Encephalopathy	Glibenclamide	Possible	Well documented
18	Natriuresis	Artesunate	Probable	Well documented
19	Maculo-papular rash	Azithromycin	Probable	Well documented
20	Hyperpyrexia	Clindamycin	Possible	Well documented
21	Vomiting	Cyclophosphamide	Probable	Well documented
22	Hepatitis	Rifampicin, Isoniazid, Pyrazinamide,	Possible	Well documented
23	Cortical venous thrombosis	Ethinylestradiol, Norgesterol	Possible	Well documented
24	Hypocalcaemia	Magnesium sulfate, Valproate, Pantoprazole	Possible	Well documented
25	Metabolic Alkalosis	Piperacillin, Tazobactum	Possible	Well documented
26	Hypokalemia	Furosemide	Possible	Well documented
27	Intracranial bleed	Warfarin	Probable	Well documented
28	Rash	Co-trimoxazole, Paracetamol	Possible	Well documented
29	Hepatitis	Rifampicin, Isoniazid, Pyrazinamide	Possible	Well documented
30	Red Man Syndrome	Vancomycin	Certain	Well documented
31	Diarrhea	Amoxicillin + Clavulanic acid	Possible	Well documented
32	Thrombocytopenia	Linezolid	Possible	Well documented
33	Nephropathy	Iohexol	Possible	Well documented
34	Epistaxis	Warfarin	Probable	Well documented
35	Hepatitis	Rifampicin, Isoniazid, Pyrazinamide	Possible	Well documented
36	Hepatitis	Rifampicin, Isoniazid, Pyrazinamide	Possible	Well documented

37	Hypokalemia	Amphotericin B	Possible	Well documented
38	Myasthenia crises	Azithromycin	Probable	Well documented
39	Red Man Syndrome	Vancomycin	Probable	Well documented
40	Haemorrhage	Warfarin	Possible	Well documented
41	Metabolic alkalosis	Furosemide	Possible	Well documented
42	Vomiting	Zidovudine, Nevirapine, Lamivudine	Possible	Well documented
43	Hypersensitivity	Paclitaxel	Possible	Well documented
44	Hypersensitivity	Paclitaxel	Possible	Well documented
45	Hypersensitivity	Paclitaxel, Carboplatin	Possible	Well documented
46	Hypoglycaemia	Glimiperide, Metformin	Possible	Well documented
47	Rash	Ciprofloxacin, Tinidazole	Possible	Well documented
48	Pancytopenia	Zidovudine	Possible	Well documented
49	Rash	Ibuprofen, Paracetamol	Possible	Well documented
50	Nephrotoxicity	Cyclosporine, Tenofovir	Possible	Well documented
51	Hypoglycaemia	Glibenclamide, Metformin	Possible	Well documented
52	Hypoglycaemia	Glibenclamide, Metformin	Possible	Well documented
53	Convulsions	Co-trimoxazole	Possible	Well documented
54	Hepatitis	Rifampicin, Isoniazid, Pyrazinamide	Possible	Well documented
55	Metabolic alkalosis	Furosemide	Possible	Well documented
56	Erythema Multiforme	Amoxicillin + Clavulanic acid, Trimethoprim+sulfamethoxazole	Possible	Well documented
57	Encephalopathy	Metronidazole	Probable	Well documented
58	Haemorrhage	Warfarin	Probable	Well documented
59	Hepatitis	Rifampicin, Isoniazid, Pyrazinamide	Possible	Well documented
60	Psychosis	Isoniazid	Probable	Well documented
61	Rash	Nevirapine, Co-trimoxazole, Zidovudine, Lamivudine	Possible	Well documented
62	Angioedema	Ciprofloxacin	Probable	Well documented
63	Rash	Amoxicillin, Paracetamol	Possible	Well documented
64	Elevated Liver Enzymes	Valproate	Probable	Well documented
65	Hypoglycaemia	Glimiperide, Metformin	Possible	Well documented
66	Fever	Isoniazid	Probable	Well documented
67	Anaphylaxis	Clindamycin	Probable	Well documented
68	Metabolic alkalosis	Furosemide, Meropenem, Ciprofloxacin	Possible	Well documented
69	Red Man Syndrome	Vancomycin	Probable	Well documented
70	Cortical Venous Thrombosis	Levonorgestrol, Ethinylestradiol	Possible	Well documented
71	Allergic reaction	Iron-Sucrose	Probable	Well documented
72	Vertigo	Azithromycin	Probable	Well documented
73	Hyperthermia	Ketamine	Probable	Well documented
74	Convulsions	Imipenem-Cilastin	Possible	Well documented
75	Anaphylaxis	Fresh frozen plasma	Probable	Well documented
76	Hypocalcaemia	Magnesium sulfate	Probable	Well documented
77	Rash	Paracetamol, Diclofenac, Serratiopeptidase	Possible	Well documented
78	Intracranial bleed	Warfarin, Clopidogrel, Aspirin	Possible	Well documented
79	Anaphylaxis	Albumin, Heparin	Possible	Well documented
80	Thrombocytopenia	Linezolid	Probable	Well documented
81	Thrombocytopenia	Heparin	Probable	Well documented
82	Thrombocytopenia	Metronidazole, Isoniazid, Imipenem-Cilastin, Tigecycline.	Possible	Well documented

EVALUATION OF A CASE FROM LTMMC AND LTMGH

Hypervitaminosis D Leading to Transient Regression of Motor Milestones.

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** - Assistant Professor, ** - Residents, *** - Professor; Department of Paediatrics, LTMMC & GH, Sion, Mumbai*

Introduction:

Hypervitaminosis D is a condition where serum concentration of vitamin D's storage form i.e. 25(OH) Vitamin D becomes too high (upper limit of 25(OH) D - 100 ng/ml) causing systemic adverse effects. The immediate symptoms of vitamin D overdose are abdominal cramps, nausea and vomiting. Symptoms such as poor appetite, constipation (possibly alternating with diarrhoea), weakness, weight loss, tingling sensations in the mouth, confusion and heart rhythm abnormalities are also seen. The first biochemical parameter of vitamin D toxicity is hypercalciuria followed by hypercalcemia. Published cases of toxicity, for which serum levels and dose are known, all involve intake of ≥ 40,000 IU (1000 mcg) per day.[1]

We report a case of an 8 month old child with hypervitaminosis D who had transient regression of milestones secondary to vitamin D toxicity.

Case Report

8 months old female child, born of a non- consanguineous marriage, with a normal birth and development history was admitted with complaints of regression of motor milestones, vomiting and polyuria since 15 days. On enquiry, at the age of 6 months, on a regular visit to a general practitioner child was given Injection vitamin D 6 lakh IU orally, weekly for 8 weeks along-with calcium supplements. Therefore she had consumed total 48 lakh units of Vitamin D in a lipid soluble form over a period of 8 weeks.

On general examination child had tremulous upper limbs and head was wobbling in sitting position. Anterior fontanel was normal and pulsatile. On central nervous system examination, child was conscious, had no cranial nerve involvement, and was hypotonic with complete head lag, deep tendon reflexes were present and plantars were down going. Investigations revealed elevated serum calcium -12.2 mg/dl (normal range of 8.8-10.8 mg/dl). Serum phosphorus was 4 mg/dl (normal range of 3.8-6.5 mg/dl) and alkaline phosphatase was 150 U/L (normal range of 145-420 U/l) which were within normal range. Urinary calcium to creatinine ratio was high i.e. 2 (normal <0.6). MRI Brain was normal. Ultrasonography of abdomen did not reveal any nephrocalcinosis but there was metastatic calcification seen in the soft tissue of thighs. Serum

25Hydroxyvitamin D levels were above 100 ng/ml which were in the toxic range (normal range of 30 to 100ng/ml).

In view of hypercalciuria with hypercalcemia and elevated serum vitamin D level, diagnosis of hypervitaminosis D was confirmed. Hence, Vitamin D and calcium supplements were stopped. Patient was started on intravenous fluids, loop diuretics (furosemide 1mg/kg/dose 8hourly) and glucocorticoids (oral prednisolone 2mg/kg/24 hourly). Gradually the tremors subsided over 15 days. Levels of vitamin D and calcium done 1 week after starting the treatment were within normal limits. Child had regained the lost milestones over a period of 6 weeks.

Discussion

The physiological effect of vitamin D in pharmacological doses is to bind to an intracellular receptor, and the complex affects gene expression by interacting with vitamin D-response elements. In the intestine, this binding results in a marked increase in calcium absorption, which is highly dependent on 1,25-Hydroxy vitamin D. There is also an increase in phosphorus absorption, but this effect is less significant because most dietary phosphorus absorption is vitamin D independent. 1,25-Hydroxy vitamin D also has direct effects on bone resorption. 1,25-Hydroxy vitamin D directly suppresses parathormone (PTH) secretion by the parathyroid gland, thus completing a negative feedback loop. PTH secretion is also suppressed by the increase in serum calcium mediated by 1,25-Hydroxy vitamin D. 1,25-Hydroxy vitamin D inhibits its own synthesis in the kidney and increases the synthesis of inactive metabolites.[2-4]

The conventional treatment for hypervitaminosis D is hydration with intravenous fluids followed by loop diuretics. Vitamin D and calcium supplements should be discontinued and also a diet low in calcium and phosphorous needs to be followed. Glucocorticoids are used as one of the treatments as they decrease the intestinal calcium absorption and also decrease bone resorption.[5] Few other modalities for treating hypercalcemia are mithramycin and calcitonin which will inhibit osteoclast function. Drugs which accelerate vitamin D metabolism by inducing hepatic microsomal enzymes such as phenytoin and phenobarbitone can also be used.

In the present case, there is a reasonable time relationship between the intake of drug (Vitamin D) and the occurrence of ADR, the ADR is unlikely to be attributed to disease or other drugs and the patient recovered on stopping the offending drug. Based on the above finding, as per the WHO assessment scale the causality for Vitamin D causing the ADR is "Probable".

Conclusion:

From this case we would like to emphasise that vitamin D intoxication can be prevented if the dosages are carefully monitored. The systemic effects of hypervitaminosis D can be reversed if managed promptly.

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Answers to Crossword

Across

1. Dipyridamole
2. Cardiotoxicity
3. Rimonabant
4. MESNA
5. Dexrazoxane
6. Pancreatitis
7. Tacrine
8. INH (Isoniazid)
9. Orni(dazole)
10. ACE (Angiotensin Converting Enzyme)
11. ALA
12. RED

Down

13. Tamsulosin
14. Phenolphthalein
15. Aldesleukin
16. GIT
17. Aprepitant
18. Duloxetine
19. Teta(caine)
20. Bone

PUBLISHED CASE REPORTS ON HYPERVITAMINOSIS D

Compiled by **Dr Jaisen Lokhande***

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

Hypercalcemia due to hypervitaminosis D: report of seven patients.

J Trop Pediatr. 2009 Dec;55(6):396-8.

Joshi R.

We retrospectively studied seven children (six girls, one boy) aged from 7.5 to 25 months who presented to our institution after taking large doses of vitamin D (900 000-4 000 000 U) prescribed by medical practitioners for wrong indications like failure to thrive, etc. The clinical manifestations were constipation, decreased appetite, lethargy, polyuria, dehydration and failure to thrive. All patients had hypercalcemia (serum calcium ranging from 12 to 16.8 mg/dl), high 25[OH]D levels (ranging from 96 to >150 ng/ml), suppressed intact parathyroid hormone (ranging from <3 to 8.1 pg/ml). Hypercalciuria (urinary calcium/creatinine ranging from 1 to 2.45) was found in all patients, while nephrocalcinosis was present in five patients. All were treated with intravenous fluids, oral prednisolone, restriction of calcium in diet, while four patients received pamidronate infusion for reducing hypercalcemia.

Four Cases of Hypervitaminosis D Following Treatment for Vitamin D Deficiency

Endocr Rev. 2011;32:P2-117

Vanstone M. B., Oberfield S. E. and Carpenter T. O.

Background: Pharmacologic vitamin D (D) is reserved for D deficiency rickets or hypocalcaemia; recommended dosing has been assumed to be safe. Clinical Case(s)(1) An infant girl was treated for craniotabes with 1000-1400IU of D daily during her first 2 mos of life. 25OHD at 2 wks was 21ng/mL; at 2 mos, hypercalcemia (10.7 mg/dl) was present. 25OHD was 84 ng/mL. D was reduced to 400IU daily. At 5 mos, hypercalcemia persisted (11.0 mg/dL); 25OHD was 78 ng/mL. D was discontinued. Serum calcium (Ca) was normal by 6 mos.(2) An exclusively breastfed 4 mo-old African-American boy presented with seizures and rickets. Serum Ca was 5.5 mg/dL, alkaline phosphatase activity (AP) was 1110U/L, PTH was twofold elevated, 25OHD was < 5ng/ml, and 1,25(OH)2D was 7 pg/mL. After correction of serum Ca, he received 100 mg/kg/day of oral Ca, 4000 IU of D/day, and calcitriol (0.5 mcg/day). 1 wk later, serum Ca was 10.3 mg/dL and 25OHD was 33 ng/ml. Ca and D were decreased by half, and calcitriol was discontinued. 6 wks later hypercalcemia (10.4 mg/dL) persisted and 25OHD was 79 ng/mL. All

supplementation was stopped and hypercalcemia resolved 6 wks later (Ca 10.1 mg/dL, 25-OHD 40 ng/mL).(3) A 2-9/12 yr-old African-American girl presented with rickets; she had been exclusively breast-fed until 5 mos of age without D. She now drank 12-18 oz of milk/day. Biochemical findings (Ca 9.9 mg/dL, AP 661 U/L, PTH 102 pg/mL, 25OHD 5 ng/mL) indicated D deficiency and 2000IU/day of D was begun. 3 mos later, hypercalcemia (10.9 mg/dL) was present and 25OHD was 102 ng/mL. D was discontinued with normalization of serum Ca (9.9 mg/dL) 3 mos later; 25OHD was 24 ng/ml.(4) A 3-4/12 yr-old previously healthy girl presented with several wks of fatigue, vomiting, constipation, headaches, and recent polydipsia and nocturia. She was given oral D (600,000 IU/vial) in another country, receiving 6 vials (3,600,000 IU) over 3 wks. Serum Ca was 17.4 mg/dL and 25OHD was 300 ng/mL. A sonogram revealed mild medullary nephrocalcinosis. Acute hydration, furosemide, and dietary Ca restriction, with the later use of a single pamidronate dose corrected the serum Ca.

Conclusion: Hypervitaminosis / hypercalcemia can be unpredictable in small children. D therapy in this age group must be closely monitored as hypercalcemia occurred in 3 of our cases using dosages within well-recognized recommendations. Treatment guidelines for D deficiency may require modification for this age group.

Hypercalcemia in Children Receiving Pharmacologic Doses of Vitamin D

Pediatrics. 2012;129(4):e1060-e1063

Vanstone M. B., Oberfield S. E., Shader L., Ardeshirpour L. and Carpenter T. O.

Vitamin D deficiency causes rickets, requiring vitamin D at doses greater than daily dietary intake. Several treatment regimens are found in the literature, with wide dosing ranges, inconsistent monitoring schedules, and lack of age-specific guidelines. We describe 3 children, ages 2 weeks to 2 and 9/12 years, who recently presented to our institution with hypercalcemia and hypervitaminosis D (25-hydroxyvitamin D levels >75 ng/mL), associated with treatment of documented or suspected vitamin D-deficient rickets. The doses of vitamin D used were within accepted guidelines and believed to be safe. The patients required between 6 weeks and 6 months to correct the elevated serum calcium, with time to resolution of hypercalcemia related to age and peak serum calcium, but not to peak 25-hydroxyvitamin D level. With recent widespread use of vitamin D in larger dosages in the general population, we provide evidence that care must be taken when using pharmacologic dosing in small children. With limited dosing guidelines available on a per weight basis, the administration of dosages to infants that are often used in older children and adults has toxic potential, requiring a cautious approach in dose selection and careful follow-up. Dosage recommendations may need to be reassessed, in particular, where follow-up and monitoring may be compromised.

REGULATORY UPDATE

Compiled by **Dr Pankaj Patil*, Dr Girish Joshi****

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Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) between July - September 2012

The table below lists the names of products and potential signals of serious risks/new safety information that were identified for these products during the period July - September 2012 in the FAERS database. The appearance of a drug on this list does not mean that FDA has concluded that the drug has the listed risk. It means that FDA has identified a *potential safety issue*, but does not mean that FDA has identified a causal relationship between the drug and the listed risk. If after further evaluation the FDA determines that the drug is associated with the risk, it may take a variety of actions including requiring changes to the labeling of the drug, requiring development of a Risk Evaluation and Mitigation Strategy (REMS), or gathering additional data to better characterize the risk.

Product Name: Active Ingredient or Product Class	**Potential Signal of a Serious Risk / New Safety Information**	**Additional Information (as of December 1, 2012)**
Ofatumumab	Viral infections	FDA is continuing to evaluate this issue to determine if the current labeling, which contains information about viral infections, is adequate.
Lacosamide	Neutropenia	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Dalfampridine	Anaphylaxis	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Banana Boat Sunscreen Spray	Flammability	Drug Safety Recall FDA is continuing to evaluate this issue to determine the need for any regulatory action.

Adapted from: U.S. Food and Drug Administration E. Potential Signals of Serious Risks/ NewSafety Information Identified by the Adverse Event Reporting System (AERS) between july -september 2012. [homepage on the Internet]. 2012 [cited 2013 March 25]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm334542.htm

CROSSWORD PUZZLE ON ADVERSE DRUG REACTIONS

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**-Associate Professor, Department of Pharmacology; **-Assistant Professor, Department of Pharmacology*

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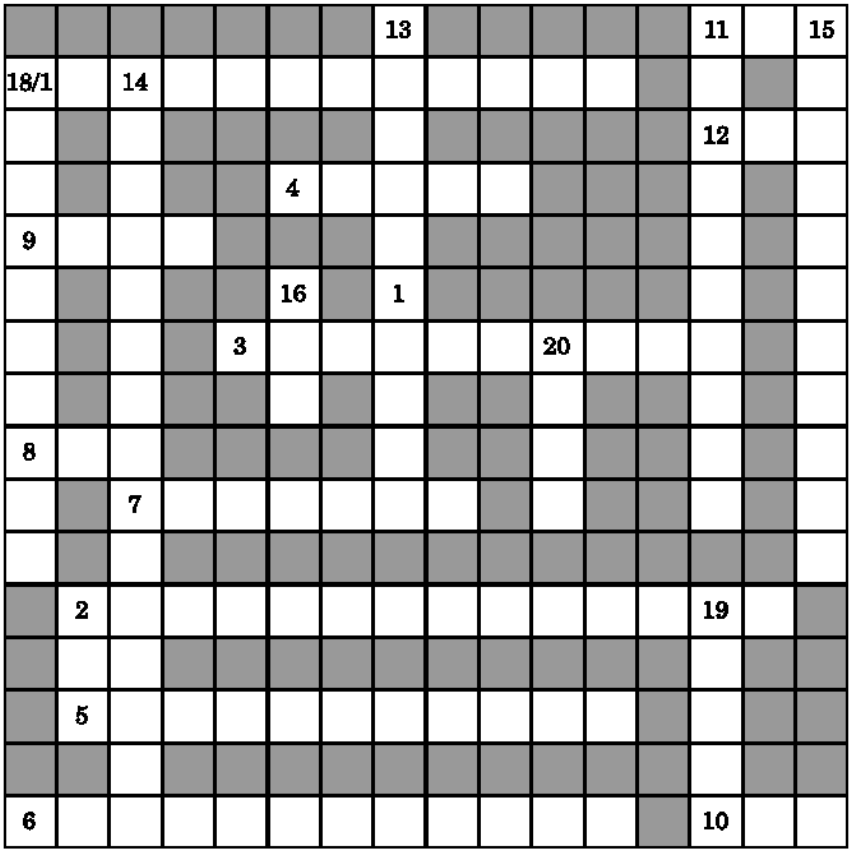

ACROSS

Q.1 This platelet inhibitor causes postural hypotension and coronary steal phenomenon in the elderly-----(12).

Q.2 In IBS with predominant diarrhoea in women, Alosetron is a safer alternative to Tegaserod due to risk of unpredictable-—(14).

Q.3 This cannabinoid antagonist used to treat obesity is banned due to its adverse effect of causing suicidal tendencies----(10).

Q.4 ----- is usually co administered with Cyclophosphamide to prevent haemorrhagic cystitis.(5).

Q.5 --- a cardioprotectant can be used with Daunorubicin/ Doxorubicin to minimize their cardiotoxicity.(11).

Q.6 Haemorrhagic---- is a side effect of Asparaginase.(12).

Q.7 The use of ---- in Alzheimer's disease is reduced as it produces significant although reversible hepatotoxicity in therapeutic doses.(7).

Q.8 ---- an anti-tuberculosis drug is known to cause peripheral neuritis in slow acetylators and hepatotoxicity in fast acetylators.(3)

Q.9 ---dazole and Tinidazole both are better tolerated than Metronidazole producing lesser incidence of nausea, epigastric distress and metallic taste.(4)

Q.10 ---- inhibitors can cause a dry cough possibly due to accumulation of Bradykinin in 5-20% of patients (3)

Q.11 Barbiturates are contraindicated in acute intermittent porphyria as they cause induction of -—synthetase enzyme in mitochondria.(3)

Q.12 Vancomycin can produce ---- man syndrome due to histamine release which can be prevented by giving slow infusion.(3)

DOWN

Q.13 This drug used for BPH causes intraoperative Floppy Iris Syndrome, problematic during cataract surgery.(10)

Q.14 This laxative-purgative due to its cardiotoxicity has recently been withdrawn from market in several countries.(15)

Q.15 Capillary Leak Syndrome is a peculiar side effect with this recombinant IL-2 used to treat metastatic renal cell carcinoma and melanoma.(11)

Q.16 Deferasirox, a new oral iron chelator, produces -— upset as a major side effect in 25% of the patients.(3)

Q.17 Very efficacious combination recently approved for chemotherapy induced emesis is with Dexamethasone and--- an NK1 receptor antagonist.(10)

Q.18 Selective Serotonin Norepinephrine Reuptake Inhibitors(SNRI) like ---, Venlafaxine and Milnacipran have advantage of fewer side effects in comparison with TCA group.(10)

Q.19 ---caine, a long duration ester group local anesthetic has highest possibility of producing cardiac arrhythmias.(5)

Q.20 Staining of teeth and ---- deformities are attributed to Tetracyclines and Fluorides.(4)

ALPHABET 'C' PUZZLE

Dr Abhilasha Rashmi*, Dr Sharmada Nerlekar,**

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1 C									
2	C								
3		C							
4			C						
5				C					
6					C				
7						C			
8							C		
9								C	
10									C

1. Because of its serious toxicities such as cardiovascular collapse, chances of anaphylactic shock and pulmonary hypertension, this PGF2α derivative is least preferred nowadays for inducing second trimester abortions.
2. Long term therapy of this Somatostatin analogue, can lead to biliary sludge or gall stone formation in over half of the patients.
3. This drug is a long acting new dihydropyridine group of calcium channel blockers, used to treat hypertension, which causes least ankle edema among all drugs of the same group.
4. Severe exacerbation of arrhythmia was demonstrated with this Class I C antiarrhythmic drug in the CAST trial, even when normal doses were administered to patients with preexisting ventricular tachyarrhythmias and myocardial infarction.
5. Hypotension & bronchospasm are not seen with R-cis isomer of this competitive neuromuscular blocker because it doesn't induce histamine release.
6. Long term use of this antimalarial acridine derivative can cause discoloration of skin and eyes.
7. Screening for tuberculosis should be done before starting this anti TNFα drug as activation of latent TB is seen with this drug used for treatment of rheumatoid, psoriatic and juvenile arthritis.
8. Reversible nephrotoxicity occurs in 5-25% and irreversible ototoxicity in 1-5% of patients receiving this aminoglycoside antibiotic for more than 5 days.
9. _____ are more prone to develop lactic acidosis, hepatomegaly and hepatic steatosis caused by NRTIs.
10. Benzbromarone is a newer and more potent _____drug that can be used in patients of gout refractory to probenecid or sulfinpyrazone.

ANSWERS:

1. CARBOPROST 3. LACIDIPINE 5. ATRACURIUM 7. ETANERCEPT 9. ALCOHOLICS
2. OCTREOTIDE 4. FLECAINIDE 6. QUINACRINE 8. GENTAMICIN 10. URICOSURIC

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

Please feel free to contact us for the same.

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