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BULLETIN ON ADVERSE DRUG REACTIONS

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From the Editor's Desk

Dear Friends and Colleagues,

It's truly a privilege to present to you the December issue of the "Bulletin of Adverse Drug Reaction".

The pharmacovigilance activity in our institution in the past two years has shown that majority of ADR's present as Cutaneous Adverse Drug Reactions. Thus to provide a concise and meaningful overview of these reactions, we have included a review article pertaining to it in this issue.

"There are no safe drugs, but safe physicians", hence we have incorporated an article on Medication errors as they are one of the most preventable causes of patient injury.

We are thankful to the Medicine department for providing the case study on Carbamazepine toxicity which emphasizes the need of dose optimization for the Indian population and highlights the importance of vigilant approach in such cases.

Other than this we also have included Crossword and Puzzle which would be a challenging exercise for all of you.

I hope the readers find these articles knowledge enhancing and utilizable in their clinical practice.

Finally, I would like to thank all the clinical departments for their valued contribution to Pharmacovigilance by reporting the adverse drug reactions and also to all the members of Department of Pharmacology for their efforts in bringing out the current issue of the bulletin.

I would also like to invite review articles and case reports on ADRs from all our readers.

Thank you

Dr Sudhir Pawar

CUTANEOUS ADVERSE DRUG REACTIONS: A REVIEW

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Introduction:

An adverse cutaneous reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompasses all adverse events related to the drug eruption, regardless of the aetiology.[1]

Although most of these conditions are benign and self-limited when the responsible drug is discontinued, several subtypes of drug eruptions are characterized by significant morbidity and mortality. The more dangerous types include erythroderma, leukocytoclastic vasculitis, anticonvulsant hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS).[2] Unfortunately, the definition and nomenclature of these severe (or dangerous) skin reactions have been confusing, and thus various publications on this issue can hardly be compared.[3] In this article the dangerous or severe skin reaction is referred to those involving mucous membrane and with systemic involvement.

Epidemiology:

Cutaneous ADRs (CADRs) are the most common, recognizable and reported form of ADRs. They represent over 30% of all reported ADRs,[4] and their incidence amongst hospitalized patients in India, accounts to 2-5%.[5-7] However, there is a lack of comprehensive data amongst out-patients. The dangerous drug eruptions have been estimated to occur in one out of every 1,000 hospitalized patients.[8]

Causative drugs:

In a study done by Chatterjee et al common offending drug groups for CADRs were antimicrobials (34.10%), anticonvulsants (32.88%), and anti-inflammatory drugs (21.51%).[9] Most of the studies have confirmed antibiotics as the commonest group causing CADRs.[10] Amongst antibiotics amoxicillin & cephalosporins are the most frequent ones whereas for antiepileptics it is carbamazepine.[11, 12] Other drug groups which also have the propensity to cause CADRs are antiretrovirals, antipsychotics(mood stabilizing), antidepressants, antihypertensives, oral contraceptives, antidiabetics and insulin, vaccines, radio contrasts and complementary medicines.[8,13,14]

Mechanism:

CADRs can be classified into immunologic and non-immunologic etiologies. Almost 75-80 % of CADRs are predictable (pharmacologically related) and non immunological in nature, the remaining 20-25% of adverse drug events are caused by unpredictable (idiosyncratic, intolerance, or anaphylactic reaction) effects that may or may not be immune-mediated.[1, 15]

The Gell and Coombs classification system describes the predominant immune mechanisms that lead to clinical symptoms of drug hypersensitivity. This classification system includes: Type I reactions (IgE-mediated), Type II reactions (cytotoxic), Type III reactions (immune complex) and Type IV reactions (delayed, cell-mediated). But for some reactions demonstration of exact immunological mechanism is difficult as in case of maculopapular rashes, erythroderma, exfoliative dermatitis, and fixed drug reactions and specific drug hypersensitivity syndromes.[16]

Predisposing factors: Factors predisposing to development of CADRs can be categorized in two broad groups viz. patient related and drug related as depicted in Table 1.

Table 1: Predisposing factors [1, 17, 18]

Patient related	Drug related
Age: Older patients, boys younger than 3 years and girls older than 9 years.	Drugs of low therapeutic index, high levels of drug-drug interactions and a tendency to form reactive intermediates or toxins.
Sex: Women are more likely than men to develop a skin drug eruption.	Drugs with large molecular weight and greater structural complexity (e.g., nonhuman proteins) are more likely to be immunogenic e.g. Heterologous antisera, streptokinase and insulin.
Genetic factors: Genetic variation in metabolism of drugs- HLA association (HLA-B*1502 and carbamazepine therapy; HLA-B*5801 and allopurinol therapy).	Route of administration: Common with topical> intramuscular> intravenous > oral.
Concomitant diseases: Viral infection (Epstein-Barr virus or HIV), systemic connective tissue disease, impaired renal and liver functions.	Duration: More common with chronic or frequent use.

Clinical presentation:

Drug reactions commonly manifest with dermatologic symptoms caused by the metabolic and immunologic activity of the skin. CADRs can also be distinguished in two types, depending on

the onset as acute or chronic. Acute-onset events are usually rather specific cutaneous 'syndromes', while chronic-onset events often present as dermatological diseases for example pigmentary changes, drug-induced autoimmune bullous diseases, lupus, pseudo lymphoma and acneiform eruptions.[19] The cutaneous symptoms of various drug hypersensitivity reactions are elaborated in Table 2 below:[16]

Table 2: Cutaneous symptoms of drug hypersensitivity reactions

Types of skin lesion	Associated immune mechanism
Exanthematous or morbilliform eruptions on trunk	Classic "drug rash" most common
Urticaria	IgE antibody mediated or direct mast cell stimulation
Purpura	Vasculitis or drug induced thrombocytopenia
Maculopapular lesions with distribution on the fingers, toes, or soles	Serum sickness
Blistering lesions with mucous membrane involvement	Stevens-Johnson syndrome or toxic epidermal necrolysis
Eczematous rash in sun exposed areas	Photoallergic reaction
Solitary circumscribed erythematosus raised lesion	Fixed drug eruption
Papulovesicular, scaly lesion	Contact dermatitis

Danger signs which should be looked for in any CADR are as follows:[20]

- Fever and facial oedema
- Hepatitis and eosinophilia
- Mucositis
- In cases of vasculitis, haematuria and proteinuria
- In SJS/TEN hypotension, diarrhoea, hypothermia and confusion suggest septicaemia

Diagnosis: Diagnosis of any CADR is complicated by various factors discussed below: [1,8,21-23]

(i) Establishing a diagnosis:

Diagnostic dilemma may arise between erythematous drug eruptions and viral eruptions. SJS/ TEN can be confused for erythema multiforme, mechanical or autoimmune blistering and skin disorders involving desquamation, in particular after pustulosis. Differential diagnosis of

Hypersensitivity Syndrome (HSS) or (DRESS) can be exfoliative dermatitis caused by psoriasis, dermatitis or lymphoma, angio-immunoblastic lymphadenopathy, viral eruption and vasculitis.

(ii) Attributing causality:

– Polypharmacy complicates causality assessment.

– Establishment of temporal relationship: Time between use of the drug(s) and the development of the adverse event(s) as well as treatment interruptions, responses to drug withdrawal and rechallenge. This information together with the known side-effect profile of the drug(s) will help in ascribing causality. Unless the patient has been previously sensitized to a drug, the interval between the initiation of therapy and the onset of reaction is rarely less than 1 week or more than 1 month. Moreover, the clinician must understand that adverse reactions can occur as late as 2 weeks after a medication has been discontinued. The knowledge of prior allergies helps to identify any cross-reactivity to current medications.

Laboratory work up:

Most allergological investigations are performed between six weeks to six months following the resolution of the ADR,[24, 25] and the choice of tests performed is dependent on the clinical reaction pattern and the underlying pathogenesis.[25] Drug challenges are not routinely recommended due to their inherent risks and ethical considerations, and they are absolutely contraindicated in severe cutaneous adverse reactions such as SJS, TEN, DRESS.[25] Various in-vivo and in-vitro tests that can be done are as discussed below.

In-vivo test: [26]

Skin testing: A crucial point is the interpretation of results of drug skin tests, whether negative or positive. Prick tests are used primarily for the evaluation of IgE mediated reactions such as urticaria, whereas patch testing is employed when a delayed Type IV reaction is suspected as the underlying pathogenesis (e.g. maculopapular drug exanthems, fixed drug eruptions, Acute generalized exanthematous pustulosis, DRESS). Skin testing is confounded with various factors as elaborated in Table 3 below:

Table 3: Drawbacks of Skin testing

Fallacies with positive skin tests:
Thresholds of specificity needs to be determined for many drugs in skin testing as it is well known for few drugs like beta lactam antibiotics, erythromycin and spiramycin.
Positive result needs to be compared with a negative control as positive drug patch test may have past relevance to contact dermatitis due to a drug, or to an excipient, without any relevance to the present CADR.

Fallacies with negative skin tests:

Skin testing is negative in 30-50% of patients. Negative results may have several explanations: the final responsible agent for the CADR is a drug metabolite that is not formed in the skin when the native drug is applied; there is no immune mechanism involved in the CADR; or concomitant factors that are responsible in inducing a transient oral drug intolerance, such as a viral infection, are not present at the time of testing.

In-vitro tests:

These include RAST (radioallergosorbent test), mast cell degranulation test, lymphocyte transformation test, lymphocyte toxicity assay, macrophage migratory inhibition factor test, interferon-gamma release test.[22] Another novel method of diagnosis is the CellScan method which is characterized by its ability to track and monitor the reaction of individual cells. By measuring the kinetic parameters of selected cells before and after adding the suspected drug, it is possible to identify the culprit drug.[27]

Management:

The first step is to review the complete medication list of the patient, including over-the-counter supplements. The second step is to find out any history of previous adverse reactions to drugs or foods.[20]

Drugs suspected of causing skin reactions should usually be withdrawn and not used again in that patient, although the risk-benefit potential needs to be considered before discontinuing any necessary medicine. Symptomatic treatment may be needed. Calamine lotion or systemic antihistamines may relieve pruritus and topical corticosteroids may help inflammation and itch. For more serious reactions, systemic corticosteroids may be indicated.[28]

Conclusion:

Thus a high index of suspicion is crucial in identifying a CADR which along with detailed past and present medical history would guide in establishing a causal association of the reaction with the drug. The diagnostic test for objective confirmation is associated with pitfalls. Once the patient is diagnosed of a drug hypersensitivity, future morbidity can be prevented by patient education and use of allergy card or bracelet. Though, pharmacogenetic testing is advisable before initiating therapy with drugs having high propensity to cause CADRs (e.g. Carbamazepine) it is expensive and not readily accessible.

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MEDICATION ERRORS

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Introduction:

Medications are blessings if health care providers prescribe, prepare, dispense and administer them to patients safely and appropriately. Despite their expertise and commitment to quality, errors and other adverse events with medications occur and sometimes cause human suffering. Each error can be tragic and costly in both human and economic terms. The large number of new drugs and technologies introduced each year further complicates medication use.[1]

As per the National Coordinating Council for Medication Error and Prevention (NCCMERP), medication errors [ME] are defined as: "Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including prescribing, order communication, product labeling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use".[2]

Epidemiology:

The 1999 Institute of Medicine (IOM) report on quality care entitled "To err is human: building a safer health system" brought into attention the occurrence, clinical consequences, and cost of adverse drug events in the hospitals. It stated that 44,000 to 98,000 Americans die each year as a result of medication errors.[3] In the Harvard medical practice study, a review of 31,429 records of patients identified an adverse event in 3.7% of the admitted patients. In 69% of these cases, the adverse events were considered preventable (implying error).[4] Worldwide, billions of dollars are being spent in managing the medication errors. It is reported that MEs cost Americans $37.6 billion each year and about $17 billion is associated with preventable errors. Errors also are costly in terms of loss of trust in the health care system by patients and diminished satisfaction by both patients and health professionals.

Phillips J. et al. did a retrospective analysis of medication errors between 1993 -1998 and found that the most common types of errors were from administering improper dose (40.9%), overdose (36.4%), wrong drug (19%) and wrong route of administration (9.5%). The investigators also found that the most common causes of errors were performance and knowledge deficits (44%) and communication errors (15.8%).[5]

The concern continues, as is seen in the most recent IOM report, "Preventing Medication Errors", which states that "a hospital patient is subject to at least one medication error per day, with considerable variation in error rates across facilities" Yet, despite numerous research findings, the actual rates cannot be estimated as they vary by site, organization, and clinician; because not all medication errors are detected; and because not all detected errors are reported.[6]

Although there is scanty data on medical errors in India, one study detected 457(35.5%) errors and severe morbidity which accounted to 2.4% in pediatric practice at a single teaching hospital over a period of six months.[7] In a study by Pote et. al., the medication errors were analyzed in a prospective observational study conducted in 3 medical wards of a public teaching hospital in India. According to it, drug-drug interactions were the most frequently (68.2%) occurring type of error, which was followed by incorrect dosing interval (12%) and dosing errors (9.5%).[8]

Types and causes of ME:[9]

Medications errors can occur at various stages of medication use cycle. The following is the treatment process where medication errors can occur:

- Choosing a medicine - irrational, inappropriate, and ineffective prescribing, under prescribing and overprescribing;
- Writing the prescription - prescription errors, including illegibility;
- Dispensing the formulation - wrong drug, wrong formulation, wrong label;
- Administering or taking the drug - wrong dose, wrong route, wrong frequency, wrong duration.
- Monitoring therapy - failing to alter therapy when required, erroneous alteration.
- Manufacturing the formulation to be used - wrong strength, contaminants or adulterants, wrong or misleading packaging.

There is considerable variation in classifying different types of medication errors. The Psychological classification is to be preferred, as it explains events rather than merely describing them. This classification system divides errors into mistakes, slips, or lapses. (See fig.1)

Mistakes may be defined as errors in the planning of an action and may be knowledge-based (e.g. giving a medication without having established whether the patient is allergic to that medication) or rule-based. Rule based errors can further be classified as either the misapplication of a good rule (e.g. injecting a medication into the non-preferred site) or the application of a bad rule or the failure to apply a good rule (e.g. using excessive doses of a drug). **Slips** and **lapses** are errors in the performance of an action - a slip through an erroneous performance

(e.g. writing the more familiar 'chlorpropamide' instead of 'chlorpromazine') and a lapse through an erroneous memory (giving a drug that a patient is already known to be allergic to). Technical error are the result of a failure of a particular skill (e.g. in the insertion of a cannula) and are therefore a subset of slips (skill-based errors).[10]

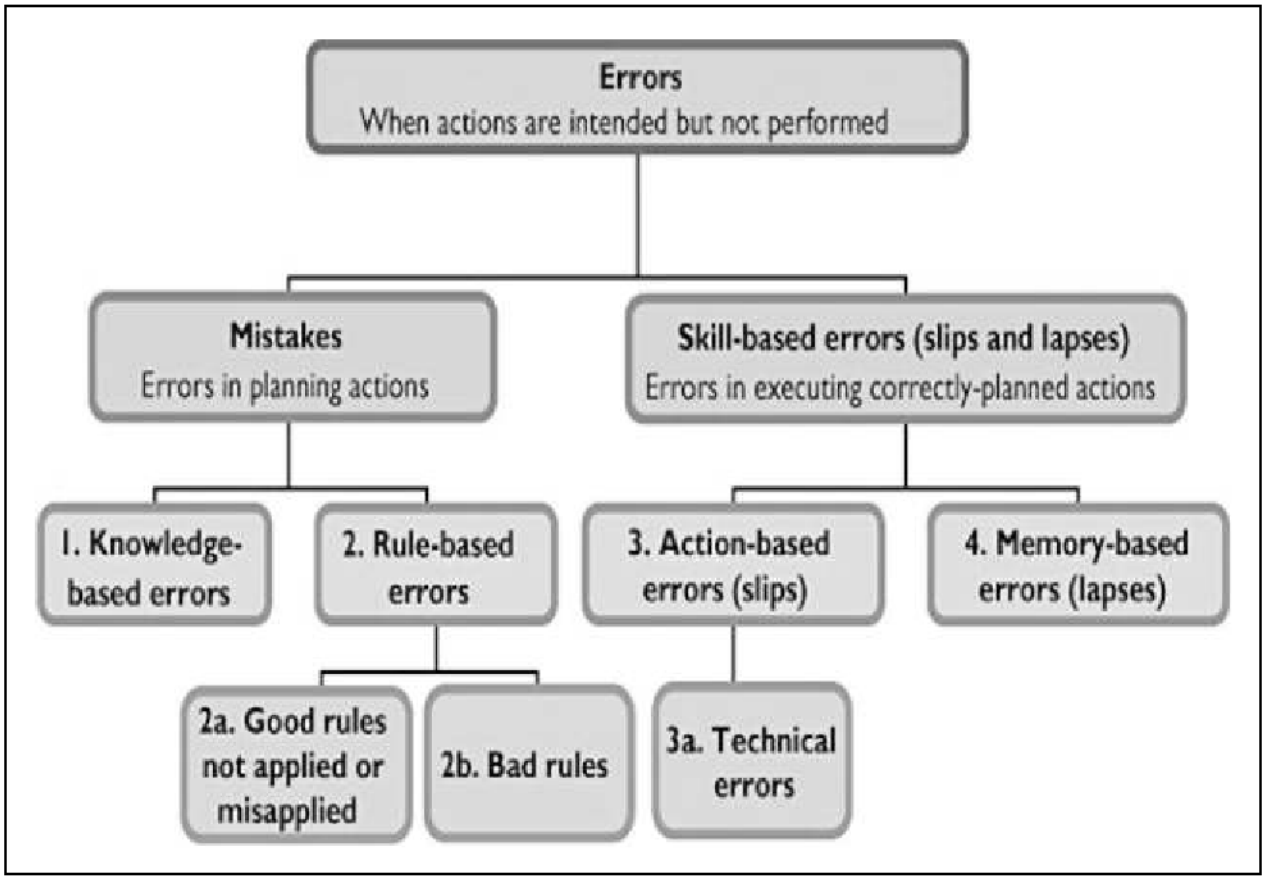

Figure 1: A classification of types of medication errors based on psychological principles[9]

Outcome of medication errors:

Probably most medical errors go unnoticed; a minority of medication errors results in ADRs. Medication errors can lead to slight to moderate harm to the patients with serious harm seen in a small number of patients.

In a UK hospital study of 36,200 medication orders, a prescribing error was identified in 1.5% and most (54%) were associated with the choice of dose; errors were potentially serious in 0.4%. In a survey of 40,000 medication errors in 173 hospital trusts in England and Wales in the 12 months to July 2006, collected by the National Patient Safety Agency, ~15% caused slight harm and 5% moderate or severe harm.[9]

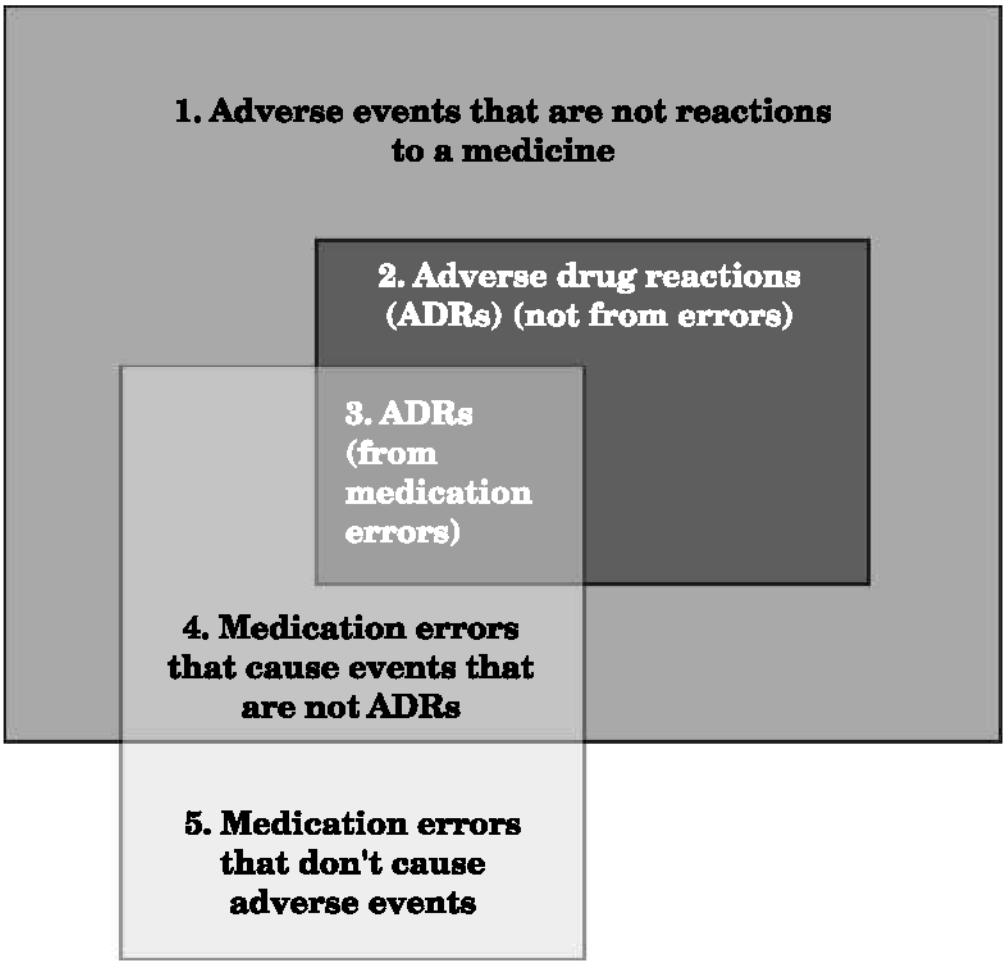

Figure 2: A Venn diagram showing the relation among adverse events, ADRs and medication errors; the sizes of the boxes do not reflect the relative frequencies of the events illustrated.[9]

Occasionally a medication error can result in an adverse event that is not an ADR (e.g. when a cannula penetrates a blood vessel and a haematoma results). Some ADEs are caused by preventable errors (e.g. coma due to an overdose of a sedative).

Prevention Strategies:

The common strategies employed to prevent medication errors are implementing patient education program, use of prior authorization programs, electronic technology like bar coding, e-prescribing etc, and adopting internal quality control procedures for workflow evaluation.

1. *Patient Education:* Errors can greatly be prevented/ minimized by providing adequate education on appropriate medication use. Healthcare professionals should educate the patients on name and indication, dosing regimen, administration guidelines, potential risks involved, precautionary measures, storage of medication and details of future consultation with physician.[11]

2. *Prior Authorization Programs:* Improving patient safety & reducing medication errors by promoting appropriate drug use is an integral function of prior authorization programs. Programs for checks/ rechecks and implementing policies and guidelines at prescribing, dispensing and administration levels can reduce the occurrence of medication errors. They should be taken up by healthcare systems as an objective to provide quality, cost effective prescription drug benefits.[11]

3. *Electronic Technology:* Use of electronic technology is an advanced method in the medication error prevention and management. Medication bar code system uses standard machine-readable bar codes and ensures administration of right medications to the patients. This system will help to register batch/lot number and expiry dates and thereby helps in product recall and thus patients do not receive expired medications. Data legally required to fill, label, dispense and/ or submit a payment request will be readily available in Electronic Prescription Record (EPR). Pharmacies in developed countries use this method as a tool to reduce medication errors by checking drug interactions, duplication therapy and drug contradictions. Computerized prescription order entry (CPOE) and E-prescribing can decrease the medication errors by eliminating illegible and poorly handwritten prescriptions, ensuring proper terminology and abbreviations, preventing ambiguous orders and omitted information. Electronic drug utilization review (DUR) technology helps pharmacists to conduct a review of prescription order at the time of filling to resolve potential drug-drug interactions, over use and under use of medications and medication allergies. Automated medication dispensing systems; though involves tedious work, high concentration, and proper record keeping strenuous to the pharmacist, medication errors can be reduced and patient safety can be improved by this technology.[10-12]

4. *Internal Quality Control Procedures:* These practices provide workflow evaluation and error reporting analyses, which lead to excellent protection from medication error. It provides additional safety checks, such as image displays, as part of the final dispensing review process, and the addition of descriptive text on prescription labels. These practices not only allow for final dispensing checks, but also allow for patient monitoring of consistency between label description and vial contents.[11]

Conclusion:

Medication errors are one of the most preventable causes of patient injury although the incidence of such errors varies widely as a result of differing definitions and methodologies. Medication errors not only lead to increased hospital stay, cost of treatment and disability, but also morbidity and mortality. Therefore, identifying the causes and attempting to prevent medication errors are vital. The majority of medication errors occur as a result of poor prescribing, emphasizing the need to improve prescribing skills. A multidisciplinary approach and different dimensions like

improved knowledge, adequate training and commitment of healthcare professionals are important in improving the patient safety through minimizing / preventing the medication errors.

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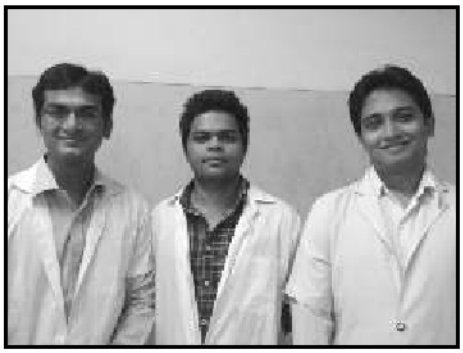

LIST OF ADVERSE DRUG REACTIONS
(July 2012- October 2012)

Sr. No.	Adverse Drug Reaction	Suspected Drugs	Causality Assessment	Literature Documentation
1	Hepatotoxicity	Carbamazepine	Probable	Well documented
2	Exfoliative Dermatitis	Carbamazepine	Probable	Well documented
3	Erythema multiforme	Cotrimoxazole, Nevirapine, Ceftriaxone, Clindamycin	Possible	Well documented
4	Nephropathy	Rifampicin	Probable	Well documented
5	Bleeding	Warfarin, Aspirin	Possible	Well documented
6	Stevens Johnson Syndrome	Cotrimoxazole	Probable	Well documented
7	Anaemia	Zidovudine, Lamivudine	Possible	Well documented
8	Lithium toxicity	Lithium	Probable	Well documented
9	Bleeding	Warfarin, Phenytoin	Possible	Well documented
10	Red man syndrome	Vancomycin	Probable	Well documented
11	Renal dysfunction	Gentamicin	Probable	Well documented
12	Hypersensitivity	Iron Sucrose	Probable	Well documented
13	Rash	Vancomycin	Probable	Well documented
14	Stevens Johnson Syndrome	Cephalexin, Phenylephrine	Possible	Well documented
15	Rash	Penicillin	Probable	Well documented
16	Vomiting	Chloroquine	Probable	Well documented
17	Rash	Bortezomib	Possible	Well documented
18	Metabolic Acidosis	Zidovudine, Lamivudine	Possible	Well documented
19	Gum hypertrophy	Phenytoin	Possible	Well documented
20	Anaemia	Zidovudine, Lamivudine	Possible	Well documented
21	Gastritis	Paracetamol, Artesunate, Pyrimethamine, Clindamycin	Possible	Well documented
22	Hypogylcemia	Glibenclamide	Probable	Well documented
23	Bleeding	Warfarin, Clopidogrel, Aspirin	Possible	Well documented
24	Rash	Chlorhexidine, Cetrimide	Possible	Well documented
25	Rash	Diclofenac	Probable	Well documented
26	Gastritis	Chloroquine	Probable	Well documented
27	Rash	Efavirenz	Possible	Well documented
28	Myopathy	Dexamethasone	Possible	Well documented
29	Gastritis	Chloroquine, Paracetamol	Possible	Well documented
30	Bleeding	Warfarin	Probable	Well documented

31	Rash	Levofloxacin	Probable	Well documented
32	Hepatitis	Isoniazid, Rifampicin, Pyrazinamide	Possible	Well documented
33	Rash	Amoxicillin, Metronidazole, Paracetamol	Possible	Well documented
34	Withdrawal syndrome	Chlordiazepoxide, Lorazepam	Possible	Well documented
35	Ptosis	Neostigmine	Unlikely	No documentation
36	Nephropathy	Rifampicin, Gentamicin	Possible	Well documented
37	Neurotoxicity	Carbamazepine	Possible	Well documented
38	Anaphylaxis	Cefotaxime, Ranitidine	Possible	Well documented
39	Rash	Amoxicillin	Possible	Well documented
40	Convulsions	Diazepam, Amitryptiline, Chlorpromazine	Possible	Well documented
41	Hypersensitivity	Antisnake Venom	Probable	Well documented
42	Rash	Quicklime	Unlikely	No documentation
43	Urticaria	Penicillin	Possible	Well documented
44	Bleeding	Heparin	Probable	Well documented
45	Mucosal ulceration	Methotrexate	Probable	Well documented
46	Bone marrow depression	Methotrexate	Possible	Well documented
47	Fixed drug eruption	Tinidazole	Certain	Well documented
48	Pancreatitis	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	Possible	Well documented
49	Thrombocytopenia	Rifampicin	Probable	Well documented
50	Rigors	Azithromycin	Probable	Well documented
51	Withdrawal syndrome	Opioid	Probable	Well documented
52	Rash	Cefotaxime	Probable	Well documented
53	Hepatitis	Isoniazid, Rifampicin, Pyrazinamide	Possible	Well documented
54	Hypotension	Amlodipine	Probable	Well documented
55	Rash	Paracetamol	Probable	Well documented
56	Anaemia	Zidovudine	Probable	Well documented
57	Hypokalemia	Amphotericin B, Vancomycin	Possible	Well documented
58	Rash	Cefpodoxime	Probable	Well documented
59	Vomiting and diarrhea	Cytarabine, Cyclophosphamide, 6-Mercaptopurine	Possible	Well documented
60	Rash	Warfarin	Possible	Well documented
61	Gastritis	Chloroquine	Probable	Well documented
62	Rash	Amoxicillin	Probable	Well documented
63	Rash	Amoxicillin, Ibuprofen, Paracetamol	Possible	Well documented
64	Urticaria	Primaquine, Ceftriaxone	Possible	Well documented
65	Rash	Ceftriaxone	Probable	Well documented
66	Anaphylaxis	Iron Sucrose	Probable	Well documented
67	Rash	Amoxicillin, Clavulanic Acid	Probable	Well documented

EVALUATION OF A CASE FROM LTMMC AND LTMGH

Unusual presentation of adverse effect of carbamazepine causing delay in diagnosis

Dr Divya Bajpai*, Dr Namita Soni, Dr N D Moulick*****

** - 3rd Year Resident, Department of Medicine; ** - Senior Registrar, Department of Medicine; *** - Professor and Head, Department of Medicine*

Introduction:

Carbamazepine is a widely used drug for the treatment of epilepsies, mood disorders and neuralgias. Having a broad dosing range (600 - 1800 mg day) can predisposes to overdosing in patients with a lower body mass. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) of has been well reported with the use of carbamazepine; however hyponatremia being the primary manifestation is often missed especially in the outpatient setting. We report a case of SIADH masquerading as primary illness (epilepsy) leading to delay in prompt diagnosis.

Case narration:

Mrs. V.K., a 55 year old diabetic lady, suffered from cerebrovascular accident (left temporo-parietal infarct) 8 months back and was started on carbamazepine 600mg/day as therapy for scar epilepsy. Her neurological deficit had recovered however presently she was symptomatic since last 10 days with complains of gait disturbances (imbalance while walking) and cognitive slowing (increased reaction time). She visited her private practitioner for above complaints who ascribed these symptoms to minimally deranged blood sugars. 6 days later she had one episode of generalized seizure after which the dose of carbamazepine was stepped up to 1000mg/day, 4 days following which she presented to our emergency department with 2 episodes of convulsions. She denied any other contributory history (fever, head trauma). Apart from carbamazepine she was on dual antiplatelets (clopidogrel 75mg/day, aspirin 150mg/day) and atorvastatin (40mg/day). She was thin built with a body mass index of 20.08.

Other physical examination showed stable vitals with signs of cerebral edema - obtunded mentation, brisk reflexes, bilateral Babinski reflex. However there were no focal neurologic signs and also no signs of hypovolemia (dry mucous membranes, decreased skin turgor, thready pulse). All laboratory tests were normal (including blood sugars) except hyponatremia (S. Na^+ 108m mol/l), decreased serum osmolality (226 mOsm/kg) decreased urine output (550ml/day), clinically conceived high urine osmolality (597mOsm/kg) and high urinary sodium excretion (urine Na^+ 97m mol/l). The serum potassium concentration was normal (4.84 mmol per litre) and remained stable during the rest of the patient's hospitalization. (Table 1)

Table 1: Laboratory parameters on the day of admission

Investigations	Value	Reference range
Random blood glucose	126 mg/dl	70 - 140 mg/dl
S. sodium	108 m mol/l	136 - 146 m mol/l
S. potassium	4.84 m mol/l	3.5 - 5.0 m mol/l
S. chloride	89 m mol/l	102 - 109 m mol/l
S. HCO3-	23 m mol/l	22 - 30 m mol/l
BUN	8 mg/dl	7 - 20 mg/dl
S. creat	0.9 mg/dl	0.6 - 1.2 mg/dl
S. albumin	3.2 mg/dl	3.0 - 5.0 mg/dl
S. calcium	9.8 mg/dl	8.7 - 10.2 mg/dl
S. osmolality	226 mosmol/kg	275 - 295 mosmol/kg
S. Cortisol (8 am)	25 µg/dl	5 25 µg/dl
TSH	2.6 µIU/mL	0.34 - 4.25 µIU/mL
S. uric acid	2.7 mg/dl	3.0 - 7.0 mg/dl
Urine sodium	97 m mol/l	25 - 250m mol/l
Urine potassium	22 m mol/l	25 - 100 m mol/l
Urine chloride	86 m mol/l	170 - 250 m mol/l
Urine osmolality	597 mosm/kg	50 - 1400 mosmol/kg

Patient was clinically euvolemic, with a generous urine Na^+ concentration and low plasma uric acid concentration. She was euthyroid, with no evidence of pituitary dysfunction, secondary adrenal insufficiency, neoplasm, pulmonary disease or acute intermittent porphyria. There was no other cause of hyponatremia like iatrogenic hyponatremia, hypovolemic hyponatremia, hyponatremia due to fluid abuse, congestive heart failure, cirrhosis, renal failure in the course of nephritic syndrome, pseudo-hyponatremia and reset osmostat syndrome. Thus the clinical presentation was consistent with the syndrome of inappropriate antidiuresis probably attributable to carbamazepine. Patient was started on furosemide 20mg IV twice a day with fluid restriction (<1L/day). Because of severe symptomatic hyponatremia, infusion of a 3% saline was administered once with which slow correction of serum sodium was achieved ($S.Na^+$ 117 m mol/l on day 2). Carbamazepine was discontinued and patient was shifted to Phenytoin 100mg IV thrice a day. Patient had no further convulsions during the ward course and her neurologic status steadily improved. On 5th day of hospitalization, her S. sodium levels were normal ($S.Na^+$ 140 m mol/l). Patient was discharged on day 6 after correction of all laboratory parameters (Table 2) and has been asymptomatic since then on regular follow up.

Table 2: Laboratory parameters during ward course

Investigations	Day 1	Day 2	Day 3	Day 5
S. sodium (m mol/l)	108	117	126	140
S. osmolality (m osmol/kg)	226	244	262	290
Urine osmolality(m osm/kg)	597	483	356	320

Discussion:

Drug induced SIADH is an important complication which can lead to life threatening complications if not recognized early. The present case is remarkable for the delay in diagnosis of hyponatremia which presented as subtle neurological symptoms like gait abnormalities and cognitive decline followed by convulsions which got concealed because of the primary illness and lead to further increase in dose of offending drug.

Carbamazepine induced SIADH is well known; with an incidence between 4 and 22%.[1] For oxcarbazepine, the keto-analogue of carbamazepine, the incidence appears even higher (51%).[2] Initially the underlying mechanism was thought to be carbamazepine induced stimulation of vasopressin secretion. However, Meinders et al. had described, a decrease in vasopressin levels with carbamazepine and have therefore suggested a renal effect.[3] This is supported with the finding that carbamazepine is able to improve central diabetes insipidus, in which endogenous vasopressin secretion is virtually absent.[4] Thereafter Stephens et al. proposed a combined central and renal effect.[5] As carbamazepine-induced water retention did not suppress vasopressin, this was the evidence that resetting of the osmoreceptors must also have occurred. However our patient promptly responded to fluid restriction and furosemide, the next appropriate step in the management would have been drugs antagonising the effects on renal V2 receptors like vaptans.

Factors predisposing to carbamazepine induced hyponatremia are advanced age, female sex and minor endocrinopathies.[6] Gender difference probably reflects the lower body mass in females as was seen in our patient (BMI=20.08) which warranted a lower dose. This emphasizes the need to review the dosages particularly in Indian population where requirements might be less than the west as is seen with most anti-epileptics.

In the present case, there is a reasonable time relationship between the intake of drug (Carbamazepine) 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 fact and as per the WHO assessment scale, the causality for Carbamazepine causing the ADR is "Probable".

In conclusion, the present case highlights the potentially dangerous complication of carbamazepine therapy which is easily avoidable by having a high index of suspicion and regular electrolytes monitoring especially in predisposed population.

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2. Nielsen OA, Johannessen AC, Bardrum B. Oxcarbazepine-induced hyponatremia, a cross-sectional study. Epilepsy Res 1988;2:269-71.
3. Meinders AE, Cejka V, Robertson G. The antidiuretic action of carbamazepine in man. Clin Sci Mol Med 1974;47:289-99.
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5. Stephens WP, Coe JY, Baylis P. Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. Br Med J1978;1:1445-47.
6. Kuz GM, Manssourian A. Carbamazepine-induced hyponatremia: assessment of risk factors. Ann Pharmacother 2005;39(11):1943-6.

PUBLISHED CASE REPORTS ON CARBAMAZEPINE INDUCED HYPONATREMIA

Compiled by – **Dr Jaisen Lokhande***

**Assistant Professor, Department of Pharmacology*

Carbamazepine-induced hyponatremia: assessment of risk factors.

Ann Pharmacother. 2005 Nov;39(11):1943-6. Epub 2005 Sep 27.

Kuz GM, Manssourian A.

Objective: To report a case of carbamazepine-induced acute hyponatremia resulting in seizures.

Case Summary: A 44-year-old white woman developed acute hyponatremia and 2 subsequent tonic-clonic seizures after ingesting twice her evening dose of carbamazepine (usual evening dose 600 mg). On admission, her serum sodium level was 122 mEq/L. An infusion of NaCl 0.9% was begun and, within 24 hours, the serum sodium level had returned to her previous level of 136 mEq/L. The woman's preadmission carbamazepine concentration was 8.6 microg/mL, and it was 11.3 micorg/mL on admission. Carbamazepine was withheld and, the following day, the concentration was 5.6 microg/mL. The woman had experienced a similar event 6 months earlier when she also took a large dose of carbamazepine.

Discussion: We attributed the acute hyponatremia and seizures to the large increase in dose of carbamazepine in the presence of other risk factors for hyponatremia. Hyponatremia associated with carbamazepine has been well described. The incidence ranges from 1.8% to 40% depending on the patient population studied. Severe hyponatremia in patients treated with monotherapy is uncommon. Several risk factors have been reported to increase the risk of hyponatremia including age >40 years, concomitant use of medications associated with hyponatremia, menstruation, psychiatric condition, surgery, psychogenic polydipsia, and female gender. Treatment is focused on removal of the precipitating factors or discontinuation of carbamazepine therapy. Use of the Naranjo probability scale indicated a highly probable relationship between acute hyponatremia and carbamazepine in our patient.

Conclusions: Hyponatremia with carbamazepine is well known. The factors associated with increased risk are less understood. An increased awareness of these risks, careful monitoring, and patient education are important in the prevention of neurologic complications.

Carbamazepine-induced hyponatremia

Pol Arch Med Wewn. 2007 Apr;117(4):73-5.

Krysiak R, Okopie B.

Treatment with some drugs may lead to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), the presence of which is more likely in some populations, including people who are elderly or who take diuretics. Resulting drug-induced hyponatremia is often mild and usually resolves following water restriction and withdrawal of the drug. In some patients, however, it may be a potentially fatal condition that is typically asymptomatic until it becomes severe. In this article, we describe the case of a 59-year-old man with arterial hypertension, already treated with hydrochlorothiazide, who presented with hyponatremia after starting administration of carbamazepine. After excluding other common causes of hyponatremia, a diagnosis of SIADH was established, carbamazepine was withdrawn and SIADH treatment introduced. Our study shows that routine assessment of blood electrolytes is reasonable not only in patients receiving diuretics but also in patients treated with other drugs affecting vasopressin secretion.

Hyponatremia-induced seizure during carbamazepine treatment.

World J Biol Psychiatry. 2007;8(1):51-3.

Holtschmidt-Täschner B, Soyka M.

Abstract

We report the case of a 54-year-old woman who was admitted for benzodiazepine withdrawal. After 6 weeks of carbamazepine treatment (600, then 200 mg) the patient suddenly suffered from a grand mal seizure. Laboratory findings revealed a clinical significant hyponatremia of Na 125 mmol/l (baseline: 143 mmol/l). CCT and ECG were normal. To our knowledge, this is the first description of a seizure related to hyponatremia in an adult carbamazepine-treated patient.

REGULATORY UPDATE

Compiled by – **Dr Girish Joshi***

* - *Professor (Additional), Department of Pharmacology*

Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) between April - June 2012

The table below lists the names of products and potential signals of serious risks/new safety information that was identified for these products during the period April - June 2012 in the AERS 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 August 1, 2012)
Cetirizine HCl	Oculogyric crisis	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Codeine sulphate	Respiratory depression or arrest resulting in death in children taking codeine who are CYP2D6 ultra-rapid metabolizers.	FDA Drug Safety Communication FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Docetaxel	Drug interaction with Dronedarone HCl resulting in death	FDA decided that no action is necessary at this time based on available information.
Fluoroquinolone products	Retinal detachment	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Levetiracetam	Potential for drug abuse, misuse, or dependence	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Mefloquine HCl	Vestibular disorder	FDA is continuing to evaluate this issue to determine the need for any regulatory action.

Product Name: Active Ingredient or Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of August 1, 2012)
Olmesartan medoxomil	Malabsorption resulting in severe diarrhea and weight loss.	FDA is continuing to evaluate this issue to determine if the current labeling, which contains information about diarrhea, is adequate.
Proton pump inhibitors (PPIs)	Pneumonia	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/New Safety Information Identified by the Adverse Event Reporting System (AERS) between April - June 2012. [homepage on the Internet]. 2012 [cited 2012 Dec 5]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm324020.htm

Telaprevir Linked to Potentially Fatal Skin Reaction

The label for the hepatitis C drug telaprevir now features a boxed warning on the risk for serious and sometimes fatal skin reactions, the US Food and Drug Administration (FDA) announced today.

Patients must stop taking telaprevir along with its partner drugs peginterferon and ribavirin if they experience a serious skin reaction, particularly a rash with systemic symptoms, or a progressive severe rash, according to the label change that FDA approved on December 14.

In combination with peginterferon and ribavirin, telaprevir is indicated for the treatment of chronic genotype 1 hepatitis C virus infection in adults with compensated liver disease, including cirrhosis, who are treatment-naive or who already have received interferon-based medications.

The boxed warning states that patients receiving telaprevir in combination treatment have experienced skins reactions that include Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, and toxic epidermal necrolysis. The fatal cases occurred in patients who continued to take the drug after developing a progressive rash and systemic symptoms.

Adapted from: Lowes R. Telaprevir Linked to Potentially Fatal Skin Reaction. [homepage on the Internet]. 2012 [cited 2012 Dec 20]. Available from: http://www.medscape.com/viewarticle/776403

FDA: Bleeding Risk with Dabigatran Similar to Warfarin

Bleeding rates associated with the use of Dabigatran etexilate appear to be no higher than bleeding rates associated with warfarin when used as an anticoagulant to reduce the risk for stroke in patients with non valvular atrial fibrillation (AF).

According to a safety communication sent today by MedWatch, the US Food and Drug Administration's (FDA's) safety information and adverse event reporting program, the finding "is consistent" with observations from the large clinical trial, the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial, used to approve dabigatran.

In the RE-LY trial, rates of fatal bleeding were 0.23% per year with 150 mg twice-daily dabigatran compared with 0.33% per year for warfarin. However, life-threatening bleeds were more common, numerically, in the 150-mg group than in the 110-mg group tested in the trial. The 110-mg dose is not approved in the United States.

The FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue, but the agency believes that dabigatran "provides an important health benefit when used as directed" and that healthcare professionals should adhere to the approved drug label.

Adapted from: Hitt E. FDA: Bleeding Risk With Dabigatran Similar to Warfarin. [homepage on the Internet]. 2012 [cited 2012 Nov 2]. Available from: http://www.medscape.com/viewarticle/773828

Answers to Crossword

(1) Acetazolamide (2) Hepatic (3) Trazodone (4) PVD(Peripheral Vascular Disease) (5) Mino(cycline) (6) CAD(Coronary Artery Disease) (7) Constipation (8) Gall(stones) (9) ANS(Autonomic Nervous System) (10) Neuro (11) L-DOPA (12) Somatrem (13) Red (14) Alopecia (15) Cimetidine (16) Tobra(mycin) (17) Methyldopa (18) Ataxia (19) Fits (20) Iris (21) Convulsion (22) Cardiac (23) Tramadol (24) DAM (Diacetyl Monoxime)

CROSSWORD PUZZLE ON ADVERSE DRUG REACTIONS

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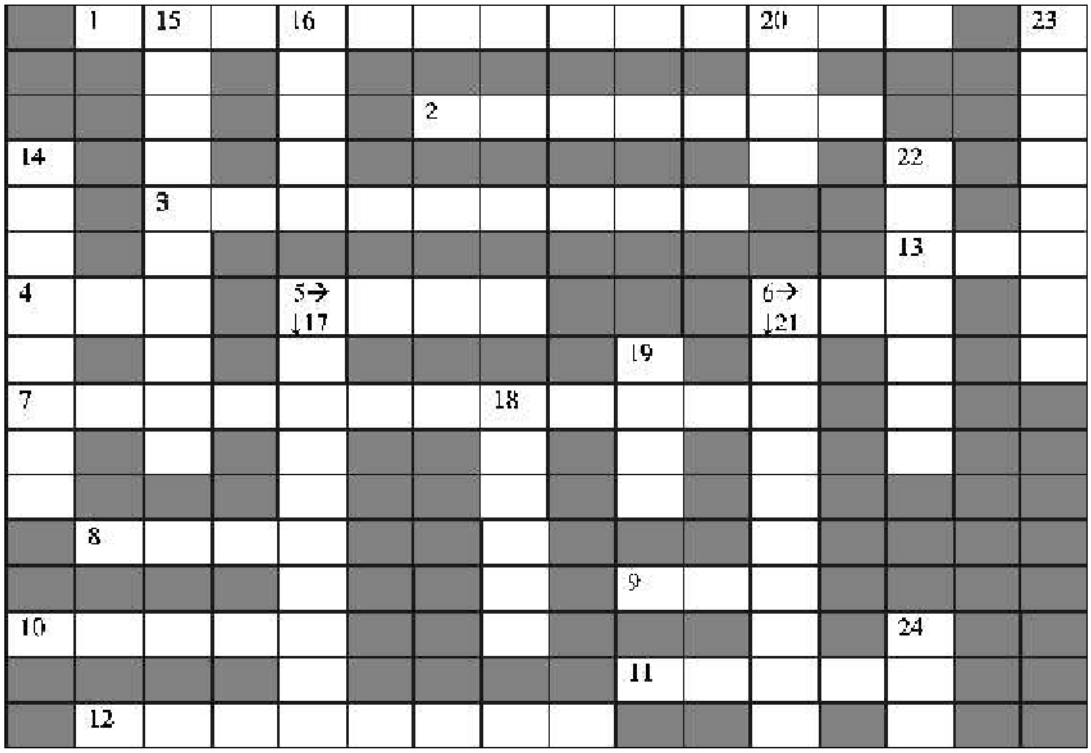
**-Associate Professor, Department of Pharmacology; **-Assistant Professor, Department of Pharmacology*



ACROSS

1. This diuretic can cause rare but serious bone marrow depression.(13)
2. Contraindication to Repaglinide is _____ disease.(7)
3. A TCA with low risk of cardiac arrhythmias and hence preferred in elderly is _____.(9)
4. Besides asthma, COPD and IDDM, _____ is an important contraindication to the use of β blockers.(3)
5. _____cycline in the dose of 200-400 mg/day causes ADRs like dizziness, vertigo and nausea in 35-70% of patients.(4)
6. Due to concerns regarding increased risk of MI with Rosiglitazone, this drug should be avoided in _____ patients with Diabetes Mellitus.(3)
7. TCAs very commonly cause this ADR of GIT.(12)
8. Bile acid sequestrants are known to increase incidence of _____ stones.(4)
9. Among Phenothiazine group of Antipsychotics, Chlorpromazine and Trifluopromazine have highest incidence of _____ related ADRs due to α blocking property.(3)
10. _____ paralysis is a rare side effect due to VERORAB Vaccine (inactivated rabies vaccine prepared on vero cells).(5)
11. _____, a dopamine precursor used in parkinsonism, is contraindicated in malignant melanoma.(5)
12. Raised ICT is a rare but notorious ADR with this human recombinant growth hormone.(8)
13. IV infusion of Vancomycin given rapidly can cause a shock like state called ____ man syndrome.(3)

DOWN

14. Oral contraceptive pills often cause this dermatological ADR(8).
15. Gynaecomastia is an embarrassing ADR seen in males when put on this H2 blocker(10).
16. _____mycin(an aminoglycoside) if used especially with furosemide can cause severe nephrotoxicity(5).
17. Autoimmune haemolytic anemia is a hematological toxicity seen with this centrally acting antihypertensive drug(10).
18. _____ and blackouts in the elderly are seen with midazolam(6).
19. Mianserin is known to produce a triad of these ADRs-blood dyscrasias, jaundice and ____(4).
20. Increased _____ pigmentation is a unique ADR with Latanoprost used to treat glaucoma.(4)
21. Penicillins given in high doses in patients with renal failure are likely to cause a _____.(10)
22. IV Domperidone given in excess is reported to cause _____arrhythmias.(7)
23. _____ analgesic agent , has a peculiar side effect of excessive sweating.(8)
24. _____ , a cholinesterase reactivator, used to treat OPC poisoning, has the advantage of being lipophilic.(3)

Answers on page 26

MATCH THE FOLLOWING DRUG INTERACTION WITH THE ADR PRODUCED

Dr Sharmada Nerlekar*, Dr Abhilasha Rashmi**

**-Associate Professor, Department of Pharmacology;*
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1.	NSAIDs and Fluoroquinolones	a.	Ventricular arrhythmias
2.	Cephalothin and Furosemide	b.	Cardiac arrest
3.	Erythromycin and Cisapride	c.	Risk of bleeding
4.	Carbenicillin and Aspirin	d.	Seizures
5.	Halofantrine and Mefloquine	e.	Nephrotoxicity
6.	Nicotinic acid and Simvastatin	f.	Myopathy
7.	Cimetidine and Phenytoin	g.	Precipitation of absence status
8.	Clonazepam and Valproate	h.	Hypertensive crisis
9.	Pethidine and Selegiline	i.	Hyperthermia
10.	Non selective MAO inhibitor and Levodopa	j.	Ataxia, vertigo, diplopia

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ANSWERS

1.-d 6.-f

2.-e 7.-j

3.-a 8.-g

4.-c 9.-i

5.-b 10.-h

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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