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BULLETIN ON ADVERSE DRUG REACTIONS

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Bulletin on Adverse Drug Reactions

Lokmanya Tilak Municipal Medical College & General Hospital

Department of Pharmacology,

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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

You are aware that all medicines have benefits as well as potential risks. Even though clinical studies before approvals and launch of a drug detect most of the adverse drug reactions, some rare adverse drug reactions may be identified only in the clinics after its use in large number of patients and in special situations. This is where Pharmacovigilance and Adverse drug monitoring comes into picture.

All the clinical departments take measures to keep a check on adverse drug reactions and monitor the same. However there is a need to share the information amongst the various departments of the institute to formulate strategies for providing patient care.

This idea has resulted in conception of the "Bulletin On Adverse Drug Reactions" which will be circulated to all the departments in LTMMC and General hospital on a quarterly basis.

The aim is to detect, assess and prevent adverse effects or any other possible drug related problems, with the ultimate goal of achieving rational and safe therapeutic decisions in clinical practice. In the long term this will also reduce the burden on the hospital that may happen because of ADRs and its management.

We acknowledge all the clinical departments for your immense support to conduct this pharmacovigilance activity at this institute and look forward to your continued support.

Dr Sudhir Pawar

ASSESSMENT OF ADVERSE DRUG REACTIONS

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Introduction

Adverse drug reactions (ADRs) are an important clinical problem and a constant concern of the public health systems. In India, 0.7 % ADRs are responsible for admission in hospital and 3.7 % of the hospitalised patients experience ADRs with 1.8 % ADRs being fatal.[1,2] The globally reported percentage for hospitalized patients experiencing ADRs ranges from 1.5 – 35%[1]. Antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, and NSAIDs are responsible for between 60% and 70% of all ADRs.[3]

To reduce these figures and to minimize the patients suffering because of ADRs, it is essential to recognize the ADRs at the earliest, establish the causal relationship with drug and initiate measures to treat and prevent ADRs.

Some basic definitions and concepts are given below which may be helpful while assessing ADR.

***Adverse event* (AE)** is defined as "any untoward medical occurrence in a patient or clinical investigation in a subject who is administered a pharmaceutical product and which *does not* necessarily have to *have a causal relationship* with this treatment".[4]

***Adverse drug reaction* (ADR)** in defined as "a response to a drug which is noxious and unintended and which occurs at *doses normally used* in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function".[4] This implies there is a causal relationship with the drug causing ADR.

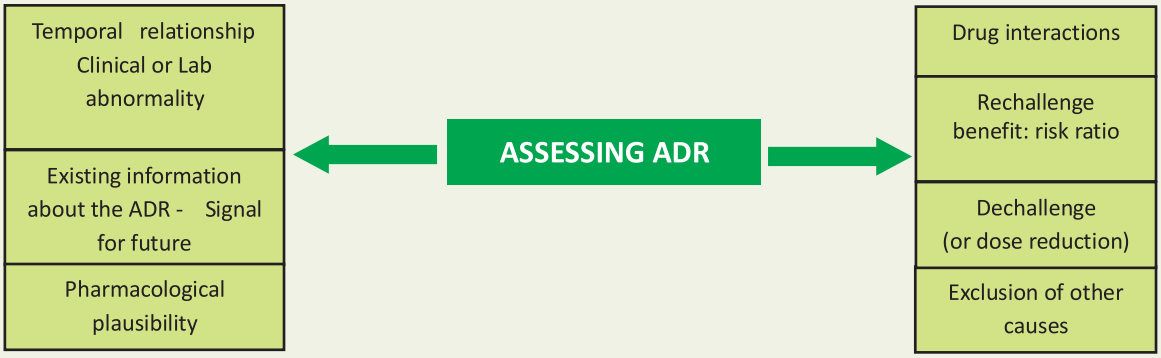
Aspects of ADR assessment

The different aspects of assessing an ADR include causality assessment, severity assessment, seriousness assessment and preventability assessment.

A) Causality assessment

The aim of the causality assessment is to establish a level of probability regarding the suspicion that a certain drug is responsible for an adverse event. The factors that are considered while assessing the adverse event for the causal relationship are discussed below.[1]

Factors considered for assessing ADRs



Temporal relationship: The onset of the reaction occurring within a defined time period after drug administration (as per literature) for that ADR is a very important indicator in assessing the causality.

Existing information about the ADR: If the given ADR is not documented, then it can be a signal for future. A signal is reported information on a possible causal association between an adverse event and a drug, the relationship being unclear or incompletely documented previously. It is based on one or more reports of an association between an intervention and an event. [6]

Pharmacological plausibility

Most type A reactions (dose related) are pharmacodynamically and pharmacokinetically plausible, and are relatively easy to diagnose. For example, renal toxicity due to gentamicin. However, the recognition of type B reaction (bizarre, non-dose related) might be difficult if previous reports on that

particular ADR are not available. Hypersensitivity to doxorubicin is one such example. One has to be very vigilant while assessing such reactions.

Dechallenge or dose reduction
It may result in improvement in condition or recovery. But this is not universal. Some of the ADRs may be irreversible. For example, pigmentary retinopathy associated with high doses of Thioridazine. Dose reduction may not improve the given condition.

Rechallenge
Benefit risk ratio is taken into consideration before rechallenge. In patient developing Steven – Johnson syndrome with Nevirapine, rechallenge is definitely a risk. Rechallenge though a risk, is justifiable in some important situations like drug treatment with Anti-Koch's therapy. Patient developing drug induced hepatitis due to Rifampicin/INH/ Pyrazinamide, one will not favour discontinuing all the 3 drugs without confirming which of them is a causative agent. Here rechallenge can be justified.

Other factors predisposing to ADRs
Other factors predisposing patient to ADRs that need to be considered while evaluating the adverse event are *pharmacodynamic and pharmacokinetic changes due to underlying disease, lifestyle factors, physiologic conditions, concurrent disease, patient compliance, genetic variability, medication errors, etc.*

Causality is assessed commonly with WHO causality assessment scale[7] as given in *table 1* and other scales like Naranjo's scale.

Table 1: WHO Causality Assessment Scale[7]

Grade	Assessment criteria
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
Probable/Likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Conditional / Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
Unassessible / Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

B) Serious and Severe assessment
Two terms that are used in relation to ADR are seriousness and severity of ADR. There is a difference between the terms "serious" and "severe". The term "severe" is used to describe intensity (severity) of an event (such as mild, moderate or severe). The event itself can be of relatively minor medical significance, such as a severe headache. This is not the same as the "serious" which is based on the patient and event outcome.

1. **Seriousness Assessment**[4]

A *serious adverse event (experience)* or reaction is any untoward medical occurrence that at *any dose* results in death; is life-threatening; requires inpatient hospitalization or prolong existing hospitalization; results in persistent or significant disability/incapacity, or cause congenital anomaly/birth defect.

2. **Severity Assessment**

It is done by the Hartwig – Seigel severity assessment scale. It divides the severity into 6 levels and score is calculated as *MILD* (requiring no change in treatment or change in dosage without need of antidote), *MODERATE* (requiring discontinuation of drug &/or patient transfer to higher level of care) and *SEVERE* (causing permanent harm or hemodynamic instability or death).

C) Preventability Assessment

Among various preventable factors, one is medication errors. Medication error is commonly 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*. Most medication errors do not cause any harm to patients but it has been said that < 1% may result in harm.[8] Schumock and Thornton scale is used for this purpose and is described in Table 2.

Table 2: Schumock and Thornton Preventability assessment scale

1	Was the drug involved in the ADR not considered appropriate for the patient's clinical condition?
2	Was the dose, route or frequency of administration inappropriate?
3	Was required therapeutic drug monitoring or other necessary laboratory test not performed?
4	Was there a history of allergy/previous reaction to the drug?
5	Was a drug interaction involved in the ADR?
6	Was a toxic serum drug level documented?
7	Was poor compliance involved in the reaction?
Result: If answer of any of 7 questions is “YES” then ADR is preventable.	

Conclusion

Adverse drug reactions are one of the important causes of patients’ morbidity and mortality in addition to increasing stay and cost burden to the hospital. Many of these can often be prevented by cautious use of drugs. The assessment of ADRs forms the most important area in pharmacovigilance as it is the cornerstone for signal generation. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The treating physician plays a key role in identifying these reactions. Thus with introduction of newer drugs in market the medicine safety lies in early detection, assessment and reporting of ADRs to generate early signals. Words of Harold Kaminetzsky (1963) must be remembered *“There are no 'safe' biologically active drugs. There are only safe physicians”*

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SUMMARY OF ADRS IN LTMMC & LTMGH
(January 2011 to March 31 st2011)

ADR Watch Team

SR No	Name of Reaction	Suspected Drug	WHO Causality	Case reports in Literature
1	Hypersensitivity	Penidura (Benzathine Penicillin)	Probable/ Likely	Well Documented
2	Hepatitis	AKT(Rifampicin, Isoniazid)/ Ofloxacin	Possible	1 report -fatal subfulminant hepatic failure with Ofloxacin
3	Gastritis & Hepatitis	AKT(Rifampicin, Isoniazid)	Probable/ Likely	Well Documented
4	Rash	Acyclovir/Phenytoin/ Ceftriaxone	Possible	Well Documented
5	Bleeding	Warfarin	Probable/ Likely	Well Documented
6	Drowsiness,Nystagmus Gum Hyperplasia	Phenytoin	Probable/ Likely	Well Documented
7	Hepatitis	AKT(R,I)	Possible	Well Documented
8	Hypersensitivity	Iron Sucrose	Probable	Post Marketing Surveillance Case reports of hypersensitivity
9	Anaphylaxis	Gelatin Infusion	Possible	Well Documented
10	Hypersensitivity	Vitamin B12	Probable	Few case reports documented
11	Toxicity(respiratory depression, altered sensorium)	Haloperidol	Probable	Well Documented
12	Maculopapular Rash	Efavirenz	Probable	Well Documented
13	Hypochromic Microcytic Anemia	Zidovudine	Probable	Well Documented
14	Nausea & Vomiting	Zidovudine/Lamivudine	Possible	Well Documented
15	Macular Rash	Co-trimoxazole	Probable	Well Documented
16	Maculopapular Rash	Nevirapine	Probable	Well Documented
17	Rash	Artemether + Lumefantrine	Possible	Well Documented
18	Steven-Johnson Syndrome	Co-trimoxazole	Probable	Well Documented
19	Acute Generalized Exanthematous Pustulosis (AGEP)	Phenytoin/ Valproate/ Ceftriaxone	Possible	Well Documented

EVALUATION OF CASE

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Case presentation

50 year old male patient, with a history of TB spine, had undergone debridement and spine stabilization with titanium cage between D8 and D9 spine one and half month back and was now posted for implant removal.

The patient recovered uneventful following the stabilization surgery and had shown improvement in his symptoms. No details were available about the drugs given during the peri-operative period then. The patient was started on AKT category II (Kanamycin, Cycloserine, Ethionamide, Pyrazinamide, Ethambutol, Levofloxacin).

Patient had a past history of tuberculosis which was treated as per medical advice however the details of drug history were not available.

On the day of implant removal, the general and systemic examination was within normal limits except for Grade II clubbing. His haematological parameters, X-Ray chest and 2D Echo were within normal limits. ECG showed left anterior hemiblock (LAHB). There was no history of allergy to any drugs or food.

At the time of surgery (10:30am), patient was started on IV succinylated gelatin used as plasma expanders and in about 4 to 5 minutes Inj Glycopyrrolate 0.2 mg IV, Inj Midazolam 1 mg IV, Inj Fentanyl 100mg IV, Inj Ondansetron 4 mg IV were given. Anaesthesia was induced with Inj Propofol 40 mg IV slowly till loss of consciousness.

During induction of anaesthesia, blood pressure dropped to 60 mm Hg. We suspected the symptoms of the patient to be either due to cardiovascular collapse or anaphylactic reaction and started treatment empirically. The operative procedure was abandoned and all the drugs were stopped.

Inj Ephedrine 10 mg was given IV bolus and fluid resuscitation started. A reddish rash (which was not a classical urticarial rash) was seen on patient's chest. IV succinylated gelatin was stopped and Inj Hydrocortisone 100mg was given IV. Patient's carotid pulse became non palpable. External cardiac massage was given along with IV Adrenaline 100 mcg and the patient was endotracheally intubated.

Blood pressure increased soon after and was recorded as 80 mm Hg and carotid pulse became palpable. Patient was started on Dopamine infusion 5 mcg/min and Inj Methylprednisolone 1gm IV given over half hour. Patient had come out of anaesthesia and meanwhile rash had also diminished.

Patient was put on mechanical ventilation and Noradrenaline drip (0.1mg/kg/min).

Arterial blood gas values done pre-operative and post-operatively were normal.

Patient was shifted to ICU and was kept on ventilator till evening and was weaned off and extubated at 08:30pm. He was then put on O_2 mask and ionotropic support till 10:00am on the next day. His ECG had shown LAHB and T inversion in V1-V6 leads, Troponin- T test done at 10:00pm and 04:30 am were negative and 2D Echo was within normal limits.

Patient's vitals recovered without support and he was shifted to the ward. At that time the patient had BP of 110/70, pulse was 101, RS- AEBE and clear, CVS- S1, S2 heard, CNS- conscious and oriented and P/A was soft.

Discussion :

The present case is an example of drugs' allergy to pre-operative medication. It resulted in increased morbidity with admission of the patient to ICU and postponement of the operative procedure.

Our patient received in total six different drugs namely IV Succinylated gelatin, Inj Glycopyrrolate, Inj Midazolam, Inj Fentanyl, Inj Ondansetron and Inj Propofol.

Interestingly, it was noted that the patient developed the symptoms soon after the dose of Propofol with the continuous infusion of Succinylated gelatin. Moreover as colloid plasma expanders and hypnotics are more likely to cause reaction compared to other drugs given, these two drugs (Propofol and Succinylated gelatin) were assumed to be the important culprits. The incidences of anaphylactic reactions to perioperative drugs differ as given in the table on page 11. Allergy to neuromuscular blocking agents, latex and antibiotics are the most frequent substances involved, allergy to other substances are by far less frequent.

As per WHO scale,[1] the reaction in the present case can be graded as "probable or likely" for Succinylated gelatin or Propofol.

It is to be noted that the patient was already on AKT for the past one and half months which he tolerated well and hence these drugs are less likely to cause the allergic reaction.

Colloid plasma expanders like succinylated gelatin are widely used during surgery and play a key role in resuscitation of severely hypovolaemic patients[2]. Anaphylactoid reaction to Succinylated gelatin, which contains Succinylated gelatin and other plasma expanders carries an estimated incidence of 0.07–0.15%[3,4]. However, this can prove life-threatening if not promptly recognized and accordingly treated. Severe anaphylaxis with Succinylated gelatin is rare (0.007%).

These reactions are normally type I, IgE-mediated and cause production of antibodies through prior sensitization, although in many cases they may occur without any previous documented exposure. The reaction is termed anaphylactoid when there is no known prior exposure for the production of the antibody-antigen reaction of true anaphylaxis[3].

Propofol is an injectable sedative–hypnotic agent indicated for induction of surgical anaesthesia in adults and children >3 years old and for maintenance of anaesthesia in adults and children >2 months of age[5].

It is to be noted that most anaesthetic agents can cause vasodilation, hypotension and potential cardiopulmonary dysfunction due to their direct and indirect effects on the cardiovascular system, and distinguishing this from an anaphylactic reaction can prove difficult.

In our case, the cardio-respiratory arrest could have been due to a number of different causes, including fat or pulmonary embolus. It was only after careful observation that the developing erythematous rash was noted and the possibility of anaphylaxis was considered.

Moreover, even though his ECG had shown LAHB and T wave inversion in V1-V6 leads, the ECG changes do not appear to be due cardiac damage as Troponin T test done at 10:00pm and 04:30 am were negative and 2 D Echo was within normal limit.

Diagnostic tests including serum tryptase levels could help in differentiation and confirmation of allergic reaction with other causes. However this does not define the causative agent.

A high index of suspicion and a prompt diagnosis should ensure successful resuscitation in the event of anaphylaxis as in the present case.

However in the present case it cannot be identified which drug resulted in the reaction. The standard diagnostic technique for this is skin prick testing.

As a preventive measure, the patients, their doctors and their kin should be informed regarding the drugs causing allergic reaction. In few countries, patients are given 'Medic Alert' bracelet indicating allergy to particular drugs.

It is also to be remembered that there is a large number of drugs which show cross reactivity and patients may be allergic to other drugs in the same group.

In case of Haemaccel and Succinylated gelatin which differ only in their linkage to urea or succinate, cross-reactivity between these two colloids has been documented by intradermal skin prick testing[6]. Consequently, any patient known to be allergic to one should be assumed as being allergic to the other until proven otherwise.

Cross reactivity also exists for food and medications. Propofol formulation includes both egg lecithin and soyabean oil, and its use is contraindicated in patients with hypersensitivities to these components[5].

Conclusion:

ADRs are known to increase the morbidity and mortality of patients and a lot of hospital resources and manpower have to be put in managing the same. In the present case the patient's procedure had to be abandoned and he had to be admitted for more days for managing the ADR. Prior patient history for food and drug allergy is very important. Detailed information to patients and their kin, regarding drug allergy should be provided to prevent such further incidences.

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APPRAISAL OF ANAPHYLACTIC REACTIONS DURING ANAESTHESIA

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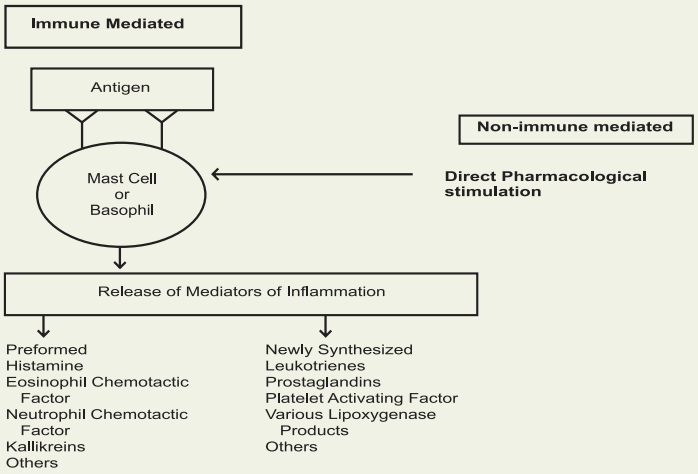
The term "anaphylaxis" was coined by Nobel Prize recipients Portier and Richet in 1902, derived from Greek word "prophylaxis" which means "protection", anaphylaxis means "opposite protection" or "against protection".[1] When occurring at the time of surgery, anaphylaxis is generally an unanticipated severe allergic reaction, often unpredictable in onset that can occur peri-operatively, when various anaesthetic as well as non-anaesthesia related drugs or procedures (e.g. disinfection) are administered. Because patients are under drapes and mostly unconscious or sedated, the early cutaneous signs of anaphylaxis are often unrecognized, leaving bronchospasm and cardiovascular collapse as the first recognized signs of anaphylaxis.[2] The frequency of these reactions occurring during anaesthesia has been estimated to vary between 1/1000 and 1/250000 procedures and the mortality from these reactions is in the range of 3-6%.[3]

The European Academy of Allergy and Immunology (EAACI) committee proposed the term allergic anaphylaxis which is mediated by an immunological mechanism (such as IgE, IgG, or complement activation by immune complexes) or non-immune mediated (previously known as anaphylactoid).Both these reactions are clinically indistinguishable.

Fig :1 MECHANISM OF ANAPHYLAXIS



Allergic anaphylaxis is most commonly caused by the interaction of an allergen with specific (IgE) antibodies. However, in allergic anaphylaxis, involving drug-specific IgE, previous contact is not obligatory, and sensitization may have occurred via cross-reactive substances.[4]

Clinical presentation:[5]

The clinical manifestations are classified in five stages of increasing severity:

- I - generalized cutaneous signs: erythema, urticaria with or without angioedema
- II - moderate multi-organ involvement, with cutaneous signs, hypotension and severe tachycardia, bronchial hyper reactivity (cough, ventilatory impairment)
- III - severe life-threatening multi-organ involvement that requires specific treatment: collapse, tachycardia or bradycardia, cardiac arrhythmias, bronchospasm; the cutaneous signs may be absent or occur only after the arterial blood pressure recovers normal value.
- IV - circulatory and/or respiratory arrest
- V - death due to inefficient cardio respiratory resuscitation

Evaluation of anaphylactic reaction during the peri-operative period:

Temporal correlation between causative agent administration and onset-of-symptoms:

Clinical signs and symptoms of anaesthetic anaphylaxis usually start within seconds to 72 hours post drug administration. In biphasic anaphylaxis, patient can experience second response within 1-72hrs after resolution of the initial response. Thus it is advisable to observe the patient for 24-36hrs in cases of anaphylaxis.[6]

Reactions to antibiotics are more frequent in the induction phase, neuromuscular blocking agent (NMBA) in the initiation and maintenance phases, and the non-steroidal anti-inflammatory drugs (NSAID) in the recovery phase. Anaphylaxis from natural rubber latex (NRL) and antiseptics exhibit a more delayed onset and generally occurs during maintenance anaesthesia or recovery.[2]

Detailed history to screen for prevalent risk factors

Risk Factors for developing peri-operative allergic reactions-

1. **Gender and age**: Neuromuscular blocking drugs and latex appear to cause anaphylaxis more commonly in female patients. Peri-operative allergic reactions rarely occur in children, and most that do occur are caused by latex.
2. **Comorbid conditions:** The conditions which may exaggerate risk of peri-operative anaphylaxis are atopy, mastocytosis & C1-esterase inhibitor deficiency.
3. **Food allergy:** Propofol should be used cautiously in patients giving history of allergy from eggs or soy, as lecithins are present in the propofol vehicle.[2]
4. **Previous anaesthesias:** One study showed that cough syrups containing pholcodine induce the production of specific IgE antibodies against the quaternary ammonium ions that are responsible for subsequent anaphylactic reactions to NMBAs. Up to 90% of allergic reactions to thiopental also occur in patients with previous exposure.[7]

Laboratory tests: None of the available diagnostic tests demonstrates absolute accuracy. False-positive test results might lead to unnecessary avoidance of a safe drug, whereas false-negative or equivocal results may causes extremely dangerous consequences.

Serum tryptase (> 25 µg/L): Tryptase is a neutral serine protease secreted by mast cell. An elevated total serum tryptase level only signifies mast cell degranulation but does not point out the causative drug per se. Test can be done as soon as 30 min after onset of symptoms, but sampling is recommended 60–120 min after onset of symptoms as half-life of tryptase is about 120 min. To enable comparison with baseline levels, a new sample should be collected >2 days after the reaction. Basophil activation gives false negative results while stressful situations yield false positive results.

Plasma histamine: Elevated histamine levels immediately following the adverse reaction will confirm the diagnosis of histamine release.[2]

Specific IgE (sIgE) Detection: The detection of drug-specific IgEs in serum is performed by a sandwich-type immunoassay. Assays for IgE antibodies to muscle relaxants, thiopentone, protamine and latex are available. These tests are usually performed several weeks after the reaction.[2,8]

Flow cytometric analysis: Flow-assisted allergy diagnosis relies on quantification of shifts in expression of basophilic activation markers after challenge with a specific allergen using specific antibodies conjugated with a fluorochrome or a dye. Currently, the most commonly used antibody in allergy diagnosis is anti-CD63 and, to a lesser extent anti-CD203c. This analysis can be fruitful when a specific IgE assay is unavailable.

Basophils activation assays: Allergen-induced mediator release tests quantify mediators released during effector cell degranulation, mainly peripheral blood basophils, following stimulation with specific antigen. Due to practical problems they are not used as routine diagnostic tests but are useful when cross-reactivity among muscle relaxants is investigated with a view to future anaesthesia in sensitized patients.

Progressive challenge testing: It is limited to local anaesthetics and latex, and is only done after SPT& IDT are negative. The test is considered negative if no adverse reaction occurs within 30 minutes after subcutaneous injection. Oral provocation tests are useful for the diagnosis of E-lactam hypersensitivity.[4]

Sensitivity test:

Skin prick test (SPT) & Intradermal test (IDT)

Skin tests are best done after a delay of at least six weeks. If the skin tests are done before six weeks then the chances of false negative results increase as the effector cell is refractory or IgE antibodies are depleted. The patient's informed consent must be obtained, and drugs that are known to inhibit skin test reactivity, such as antihistamines and psychotropic drugs, must be stopped several days before the test. Pregnancy, young age and treatment with beta-adrenergic blocking agents, oral corticosteroids and inhibitors of enzyme conversion are not contraindications to doing skin tests.

SPT being less painful is preferred first whereas IDT is used for confirmation or testing of cross reactivity.[2,4,5]

Table 1: Drugs commonly implicated in peri-operative anaphylaxis.[1,2]

Drug category	Incidence %	Most commonly associated drugs
Muscle relaxants	58.2	Succinyl choline, rocuronium, atracurium
Natural rubber latex	16.7	Latex gloves, tourniquets, catheters (Foley's)
Antibiotics	15.1	Penicillins & other β-lactams, vancomycin, quinolones
Colloids	4.0	Dextran, gelatine, albumin, hydroxyl-ethyl starch (HES)
Hypnotics	3.4	Propofol, thiopental, midazolam, etomidate, ketamine
Opioids	1.3	Morphine, pethidine, fentanyl
Other substances	1.3	Heparine, protamine, bupivacaine, aspirin, chlorhexidine, iodinated radiological contrast and dyes

Neuromuscular blocking agent (NMBA): These agents can produce anaphylactic reactions by following mechanisms:

- Immunological mechanism: IgE mediated (NH_4^+) being main antigenic epitope
- Non-specific stimulation of mast cells: d-TC, mivacurium, atracurium

Rocuronium and succinylcholine appear to be the most frequently incriminated agents. Life threatening reactions are typically IgE-mediated; although previous exposure is not essential for sensitisation to occur as exposure to quaternary ammonium groups found in cosmetics, over-the-counter medications and cleaning products may cause cross sensitisation. Diagnostic management of anaphylaxis from NMBA rests upon an evocative history corroborated by appropriate skin tests. NMBA-specific IgE assays to assess sensitization have been proved to be highly efficient.

Natural rubber latex (NRL):
IgE-mediated NRL allergy has become a well-defined condition. The at-risk individuals are those with genetic predisposition (i.e. atopics) and those with significant exposure such as healthcare workers and children requiring multiple or repetitive surgical and medical interventions (e.g. neural tube defects, spinal cord trauma, urogenital malformations) that need chronic bladder care with repeated insertion of NRL catheters or chronic indwelling catheters. In most patients, diagnosis of NRL anaphylaxis can readily be established by thorough history and quantification of sIgE, skin tests, or both. Although these tests are highly reliable, some patients might need additional tests such as basophil activation or challenge tests to establish diagnosis.

Antibiotics
Most commonly implicated antibiotics are beta-lactam antibiotics and vancomycin. Together, penicillin and cephalosporins account for 70% of peri-operative anaphylactic reactions to antibiotics, most being IgE-mediated.

Hypnotics & Opioids
Diagnosis mainly relies on skin prick testing & specific IgE quantification in the former while the same is not found to be useful for validating opioid allergy. Placebo controlled challenges can be utilised to aid diagnosis for the same if permissible.

Miscellaneous
For other drugs like antiseptics, heparin, oxytocin, radiocontrast dyes etc. the SPT remains the gold standard diagnostic investigation. Specific IgE assays are also available for heparin.[2]

Role of premedication in peri-operative anaphylaxis:[5]
For patients allergic to latex and to other drugs, premedication with an H_1 antihistaminic alone or with H_2 anti-histaminic, a corticosteroid or association of two or more of these drugs may be tried as this could prevent bronchospasm and haemodynamic variations caused by non-specific histamine release. The rate of severe reactions to dextrans can be decreased by administering dextran-I, which is a monavalent inhibitior of dextran binding.

Treatment of allergic reactions occurring during the course of anaesthesia:[4,9]
Treatment is aimed at interrupting contact with the responsible antigen, modulating the effects of the released mediators and inhibiting mediator production and release. Because the identification of the exact offending agent at the time of reaction is virtually impossible, all drugs as well as surgery should be interrupted unless otherwise impossible. Mainstay of treatment of anaphylaxis is control of airway, breathing, circulation & administration of appropriate doses of parenteral epinephrine. Patient must be

monitored for at least 24 hours due the risk of biphasic reaction. For assessing the tryptase levels in the patient, blood samples (5–10 ml clotted blood) should be collected as follows:

- Initial sample as soon as feasible after resuscitation has started – do not delay resuscitation to take the sample.
- Second sample at 1–2 h after the start of symptoms.
- Third sample either at 24 h or in convalescence as a measure of baseline tryptase levels.

Also allergy testing is advisable at 1 month.

The crucial role which an anaesthetist could play in peri-operative anaphylaxis in collaboration with a consulting allergist is to inform the patient about nature of the reaction and recommendations for subsequent anaesthesias. Reporting the event to the pharmacovigilance centre would definitely help to generate database and thus decrease the incidence of peri-operative anaphylaxis.

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SERIOUS WATCH ON 13 DRUGS BY FDA – WILL SOME DRUGS BE BANNED SOON?

Even after vigorous clinical testing, some adverse effects appear only after they are used in the general population. Serious adverse effects regarding 13 drugs have been reported to the FDA between July and September 2010. The FDA is currently keeping a careful watch to see if these drugs actually result in the reported side effects, and whether further regulatory changes like restricting their use may be needed. These drugs are mentioned below:

1. **Benzonatate (Tessalon):** Benzonatate is a local anesthetic used to control cough. Accidental ingestion has resulted in death in some children less than 10 years of age.

2. **Dronedarone HCl (Multaq):** Dronedarone used to treat arrhythmias or abnormal heart rhythms. It has been reported to increase the anticoagulant effect of warfarin when the two drugs were used together.

3. **Epoetin alfa (Epogen/Procrit):** Epoetin alfa is human recombinant erythropoietin. The formulation of epoetin alfa was reported to be contaminated with small glass flakes called lamellae. The lamellae could cause adverse effects like increased blood clotting and local reactions. The manufacturing company Amgen has recalled certain lots of the drug due to this contamination.

4. **Gemcitabine hydrochloride (Gemzar):** Gemcitabine is an anticancer drug. It has been reported to cause veno-occlusive liver disease or blockage of small hepatic veins.

5. **Lanreotide acetate (Somatuline depot):** Lanreotide is a drug similar to a hormone found in the body called somatostatin. It is used to treat adult patients suffering from excess growth hormone, a condition called acromegaly. It has caused severe cases of pancreatitis.

6. **Lanthanum carbonate (Fosrenol):** Lanthanum carbonate is used to reduce phosphate levels in the blood in patients with kidney failure. However, it has caused swallowing complications and obstruction in the digestive tract due to hardness of the tablet

7. **Levetiracetam (Keppra):** Levetiracetam is a drug used in the treatment of seizures. It has caused severe skin reactions like Stevens-Johnson's Syndrome and Toxic Epidermal Necrolysis.

8. **Lithium citrate**: is used for manic depressive psychosis. It has been found to increase the risk of certain patients manifesting a condition called **Brugada Syndrome**. Brugada Syndrome is a hereditary condition in which the patient suffers from ECG changes and sudden cardiac death.

9. **Lopinavir/Ritonavir oral solution (Kaletra):** This antiHIV formulation has been reported to cause serious adverse effects in neonates.

10. **Octagam 5%, Immune Globulin Intravenous (Human):** This formulation has been reported to cause increased cases of thromboembolism or blood clots. This formulation has been voluntarily withdrawn from the US market by its manufacturer.

11. **Pioglitazone HCl (Actos):** Pioglitazone is an anti-diabetes drug that could be associated with severe muscle damage called rhabdomyolysis. The condition often progresses to kidney failure.

12. **Ranolazine (Ranexa):** Ranolazine is used to treat angina. It has been found to increase the risk of rhabdomyolysis in patients taking cholesterol lowering drugs from the statin group.

13. **Sodium oxybate (Xyrem**): Sodium oxybate is a central nervous system depressant that has been reported to cause death in some patients.

Reference:http:www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm237585.htm

CROSSWORD-1

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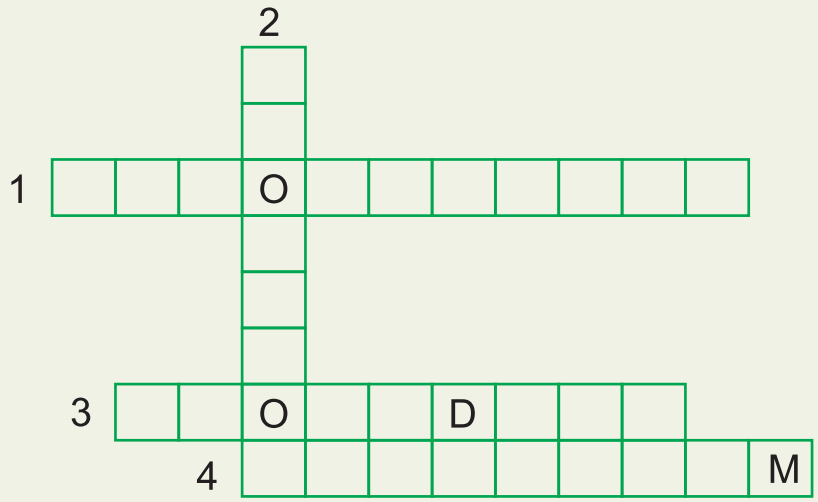

1. Across - GA degraded by soda lime. Hence, not used for closed circuit (11 letters).
2. Down - IV GA causing bradycardia (8 letters).
3. Across - IV GA inhibiting steroid production (9 letters).
4. Across - Amnesia is profound with this GA (9 letters)

Answers

1. SEVOFLURANE.
2. PROPOFOL.
3. ETOMIDATE.
4. LORAZEPAM.

CROSSWORD-2

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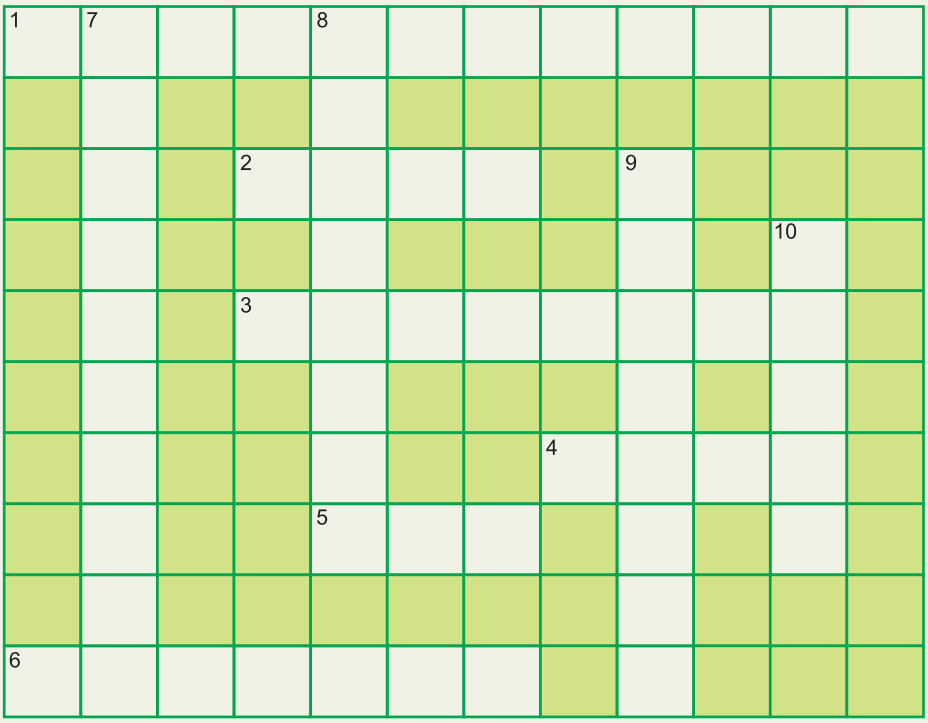

ACROSS-

1) Exposure to--------- for more than 4 hrs can cause megaloblastic changes in bone marrow.(7,5)
2) The ligand gated ion channel receptor which is the major target of anaesthetic action of drugs(4).
3) The only iv anaesthetic having significant analgesic property & produces CVS stimulation.(8).
4) ----------flurane shows nephrotoxicity after degradation by contact with sodalime.(4)
5) A valid measure of potency of inhalational general anaesthetics.(3)
6) Halothane anaesthesia is not repeated at intervals of less than 2-3 weeks to avoid the risk of--------- necrosis.(7)

DOWN-

7) Coronary steal phenomenon is seen with this inhalational anaesthetic(10).
8) Benzodiazepine safe in cases of liver dysfunction(8).
9) Enflurane is contraindicated in patients of----------(8).
10) Ideal anaesthetic gas (5).

ANSWERS TO GENERAL ANAESTHETIC CROSSWORD

ACROSS-1) NITROUS OXIDE, 2) GABA, 3) KETAMINE, 4) SEVO, 5) MAC, 6) HEPATIC.

DOWN-7) ISOFLURANE, 8) OXAZEPAM, 9) EPILEPSY, 10) XENON.

The bulletin was published by the contribution from all the members of the Department of Pharmacology, LTMMC and LTMGH, Sion

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

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