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# Bulletin on Adverse Drug Reactions

## Lokmanya Tilak Municipal Medical College & General Hospital

Department of Pharmacology,

LTMMC & LTMGH, Sion, Mumbai - 22.

## *Committee Members for Bulletin on Adverse Drug Reactions*



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## From the Editor's desk

*Dear Friends and Colleagues*

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

*You are all aware that the first issue was inaugurated by Dr Y K Gupta, Coordinator, Pharmacovigilance programme Of India at the 17th Annual Meeting of SRS.*

*Our affords in field of pharmacovigilance was well received by all and I am happy to announce that our prestigious institute has now been included as one of the regional pharmacovigilance centre.*

*I believe it is another feather in the cap that out institute is recognised at the national level for Pharmacovigilance and it could never be possible without the direct or indirect support of all the clinical departments of our institute who contributed to the activity of Pharmacovigilance.*

*It also give me great pride to inform that this bulletin which was first intended for circulation only in our institute is now circulated to all the leading medical colleges in India as per the recommendations by respected Dean Madam.*

*The outcome of this activity has been very rewarding. We are not only getting words of appreciation from all the places but also back at home our ADR reporting from the clinical departments has increased by about 100%.*

*I would like to request to all the departments to continue and increase your support in ADR reporting and also to contribute to the bulletin in the form of case reports or articles to be published in the bulletin.*

*Finally, I would also like to thank all the members of Department of Pharmacology who worked wholeheartedly to bring to you this issue of the bulletin on ADR.*

*Thank you*

*Dr Sudhir Pawar*

# PHARMACOGENOMICS OF ADVERSE DRUG REACTIONS

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## Introduction

Adverse drug reactions (ADRs) are a significant cause of morbidity and mortality. On the basis of preventability, these adverse reactions have been classified as preventable and non-preventable. Some of the non-preventable ADRs have a genetic basis in their causality and can be prevented with the help of knowledge of Pharmacogenomics. [1]

Pharmacogenomics involves genome-wide analysis of the genetic determinant of drug efficacy and toxicity(Figure 1).[2] The two arms of pharmacogenomics are drug efficacy and drug toxicity. Here we discuss the potential role and applications of pharmacogenomics in predicting and preventing drug toxicity/ADRs.

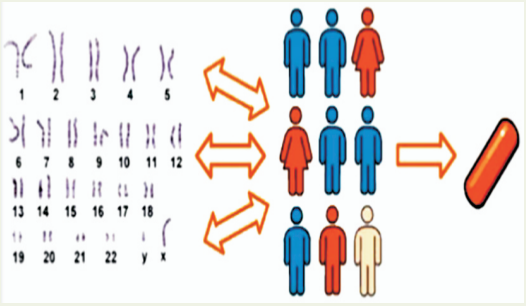

*Fig 1: Pharmacogenomics –Genome wide analysis*

## Need of pharmacogenomic testing

The genetic constitution of population is varied. In a given population, the response of individuals will vary in response to different drugs. Majority may have full response, some will be having partial response, some may not be responsive and few may have susceptibility to serious ADRs depending on the genetic variability. Thus there exists the need of pharmacogenetic testing to individualize the therapy and avoid possible serious ADRs.

## Genetic basis of ADRs

Genetic variations can be single nucleotide polymorphism (SNPs), gene deletion polymorphism; copy number variant (CNV) or variable number tandem repeats polymorphisms.[2] Adverse reactions in an individual can be due to genetic variations in genes for drug-metabolising enzymes, drug receptors, and drug transporters (Figure 2).[3]

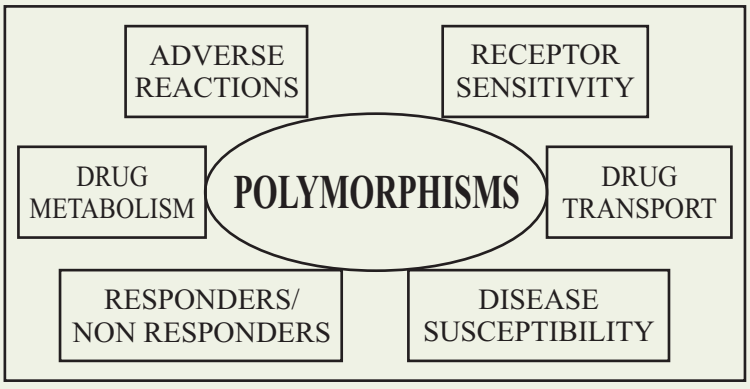


*Fig 2: Effects of polymorphism*

*1. Genetic variation in drug metabolizing enzyme*

The genetic variation in drug metabolizing enzymes has been amongst major factors in determining susceptibility to ADRs. The metabolizing status of an individual can be as an ultra-rapid metabolizer (UM) and poor metabolizer (PM) depending on genetic variability in drug metabolizing enzymes. For example, gene deletion polymorphism in CYP2D6 results in null enzyme activity and the individual is a poor metabolizer. The copy number variant polymorphism (extra copies of gene) in CYP2D6 results in increased capacity of metabolism and individual is a rapid metabolizer. The drugs affected by CYP2D6 include SSRIs, tamoxifen, codeine, β-blockers. [2, 3] Given the metabolizer status, the efficacy and toxicity of these will vary in an individual (Figure 3).

Another example is of oral anticoagulant warfarin which is metabolized by the enzyme encoded by gene cytochrome P4502C9 (CYP2C9). SNP in this gene results in commonly encountered variants CYP2C9*2 and CYP2C9*3 which have 12% and 5% of the enzyme activity, respectively. [4] Thus metabolism of warfarin is reduced with increased risk of bleeding including serious bleeding events and other complications. The population prevalence varies with 3 – 20% in Caucasians and 1 – 4% in Asians and American Africans. [2, 8]

The polymorphism of an enzyme Thiopurine methyl transferase (TPMT) which metabolizes immunosuppressant 6-mercaptopurine (6MP) results in reduced enzyme activity with 6MP toxicity i.e. myelosuppression. [2, 5] Other thiopurine analog azathioprine can also be affected. [2]

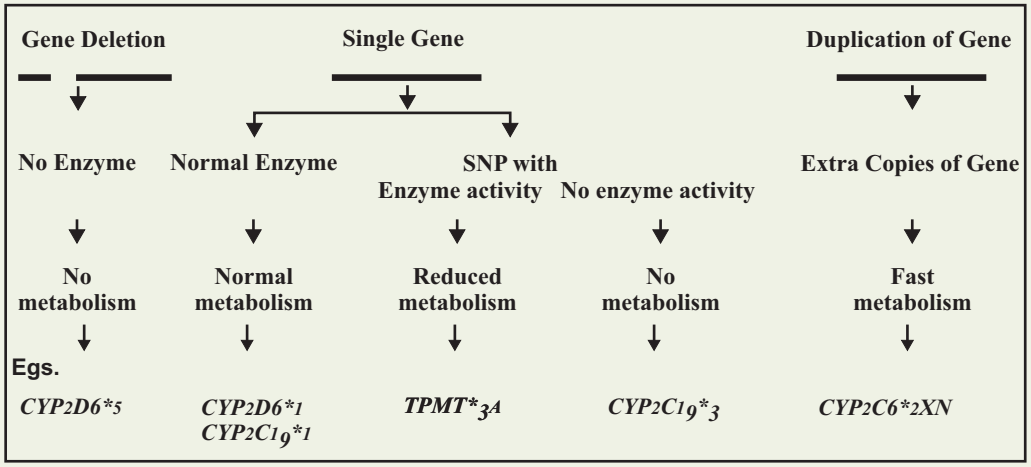


*Fig 3: Diagrammatic representation of genetic variations that may affect drug metabolism.*

*2. Genetic variation in drug receptors*

The most studied the genetic variations as regards to drug receptors is $\beta_2$ adrenergic receptor (ADRB2). The most studied SNPs are Arg16Gly, Gln27Glu and Thr164Ile. The Gly16 alleles predisposes individual to nocturnal asthma and have decreased response to beta-agonist therapy (albuterol). [3, 6]

Mutation on five genes coding for cardiac ion channels (LQT 1 - 5) resulted in sudden cardiac death due to long QT caused by drugs like anti-arrhythmics and other drugs which also tend to prolong QT interval. [5] Other receptors shown to be genetically polymorphic with possible alterations in clinical phenotype include G-proteins, Angiotensin-II receptor, Angiotensin converting enzyme, α-2 receptor, Dopamine $D_4$ receptor, endothelial NO synthase, $5HT_4$receptor.

*3. Genetic variation in drug transporters*

The efflux pump identified in various tissues is P-glycoprotein. The mutated variant for the multidrug resistance gene, MDR1, which codes for P-glycoprotein, may alter its function. Function of P-glycoprotein is to export substances from onside of the cell to outside. Its mutation affects its substrates which include chemotherapeutic agents, cyclosporine A, digoxin, verapamil, most HIV-1 protease inhibitors etc. The concentration of digoxin was elevated four times in person homozygous for mutation in MDR1. [3] Similarly, other drugs can get affected causing elevated concentration in plasma and more toxicity.

**Other genetic markers for adverse reactions**

Many of the adverse drug reactions have immunological basis in their causation. For immune-mediated toxic effects, much focus has been placed on the major-histocompatibility-complex (MHC) class I genes. Amongst the identified genomic markers, highest specificity is seen among the HLA allelic variants. [7]

The examples include HLA-B*5701 polymorphism responsible for abacavir induced hypersensitivity, HLA-B*1502 polymorphism resulting in increased risk of carbamazepine induced Stevens-Johnson syndrome and toxic epidermal necrolysis. [7, 8] HLA-B*1502 allele is present in 100% of carbamazepine-induced Stevens - Johnson syndrome cases is more common in Asians than in other races. [2,8] Both abacavir and carbamazepine should be avoided in individuals having these polymorphisms in HLA.

**Methods for Pharmacogenetic testing**

These include

- PCR with mutation-specific endonuclease
- PCR and allele-specific hybridization
- Oligonucleotide chip hybridization
- Laser lithography - guided oligonucleotide chip hybridization
- Rapid throughput pyrosequencing
- Taqman probe screening
- Genome wide SNP array

**AmpliChip**

The approval of world's first microarray based pharmacogenomic test has been called a "milestone" in personalized medicine. [10, 11] It tests for genetic variations in two common drug metabolizing enzymes CYP2D6 and CYP2C19 which metabolize majority (25%) of prescription drugs. [11]

For CYP3A4 which metabolizes more than 50% drugs, 39 allelic variants of the CYP3A4 gene have been described. However, functional characterizations of most CYP3A4 variants reveal a limited impact on protein expression or activity. [14]

**Current trends**

Currently there are only few pharmacogenomic tests that are used or recommended clinically. A survey of FDA-approved labels of drugs approved from 1945 to 2005 found that 69 labels contained information associated with human genomic biomarkers. [9] Despite great interest, the use in clinical practice is slow. A major challenge to its adoption is the current lack of evidence about their clinical utility and how to use the tests in clinical practice. [10] The genetic variations that have been established and are recommended for testing in clinical setting are given in table 1.

**Table 1 :** Genetic variations and adverse effects due to drugs

| Drug | Genotype involved | Clinical Effect |
|---|---|---|
| Warfarin | CYP2C9 and VKORC1 | Drug toxicity with increased bleeding events |
| Irinotecan | UGT1A1 | Increased risk of Neutropenia |
| Codeine | CYP2D6 | May result in fatal side effects in nursing babies |
| Tamoxifen | CYP2D6 | Poor or ultra-rapid metabolizer phenotype, Drug toxicity and poor efficacy will result with respective phenotype |
| Trastuzumab | HER2 | Drug should be given if tested positive for genotype |
| Azathioprine | TPMT | Myelosuppression; Drug should be given at lower doses or should be discontinued in case of toxicity |
| Abacavir | HLA-B*5701 | Hypersensitivity, Drug should not be given if tested positive for the genotype. |

Table 2 gives the different genetic variations some of which have been established in few numbers of studies and require further confirmation from large population studies.

Table 2 : Other genetic variations and their association with drugs [3, 12, 13]

| Drug | Genotype involved | Risk / Clinical effect |
|---|---|---|
| Antipsychotics | HTR2A | Susceptibility to tardive dyskinesia |
| Methotrexate | MTHFR | Increased toxicity |
| Succinylcholine | BCHEA | Prolonged apnoea |
| Cisplatin | GSTM3*3A | Increased risk of ototoxicity |
| Anti-tubercular (INH) | NAT2 (Slow acetylator) | Increased risk of drug induced lupus |
| Fluorouracil | Dihydropyrimidine dehydrogenase | Neurotoxicity, myelotoxicity |
| Diazepam | CYP2C19 | Prolonged sedation |
| Phenytoin | CYP2C9 | Phenytoin toxicity |
| Amoxicillin–clavulanate | HLADRB1*1501 | Hepatitis |
| Clozapine | HLA-B38, DR4 and DQ3 | Agranulocytosis |
| Hydralazine | HLA-DR4 | Systemic lupus erythematosus |
| Levamisole | HLA-B27 | Agranulocytosis |
| Oxicam | HLA-A2 and B12 | Toxic epidermal necrolysis |

**Conclusion**

Pharmacogenomics holds the promise to reduce the burden associated with non-preventable, genetically determined adverse drug reactions. The current problems in adoption of pharmacogenomics will soon be overcome. The advent of pharmacogenomic techniques to supplement clinical diagnosis gives the promising advancement towards personalized management of ailments in an individual.

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## SUMMARY OF ADRs IN LTMMC & LTMGH
## (April 2011 to July 2011)

| SR. NO | NAME OF REACTION | SUSPECTED DRUG | WHO CAUSALITY | CASE REPORTS IN LITERATURE |
|---|---|---|---|---|
| 1. | Encephalopathy | Methotrexate | Probable | Well Documented |
| 2. | Pseudotumour Cerebri | Vitamin A | Probable | Well Documented |
| 3. | Rash | Vancomycin | Probable | Well Documented |
| 4. | Thrombocytopenia | Rifampicin | Probable | Well Documented |
| 5. | Toxicity | Drug Interaction between Warfarin and Diclofenac/ Paracetamol | Probable | Well Documented |
| 6. | Rash | Ibuprofen | Probable | Well Documented |
| 7. | Fixed Drug Eruption | Co-trimoxazole | Probable | Well Documented |
| 8. | Hematuria & per Rectal Bleeding | Warfarin | Probable | Well Documented |
| 9. | Accidental poisoning, Toxicity & Death | Methotrexate | Possible | Well Documented |
| 10. | Steven-Johnson Syndrome | Carbamazepine/ Lamotrigine | Possible | Well Documented |
| 11. | Aseptic Meningitis | Bupivacaine | Possible | Well Documented |
| 12. | Hypoglycemia | Ringer's Lactate/Propofol/ Ketamine/ Midazolam/ Ranitidine/ Ondansetron/ Fentanyl | Unclassifiable | Cannot be commented |
| 13. | Tachycardia | Propofol/ Ketamine/ Ringer's Lactate | Possible | Well Documented |
| 14. | Hypoglycemia & Seizures | Glimepiride / Metformin/ Pioglitazone | Possible | Well Documented |
| 15. | Hypoglycemia | Unknown Oral Hypoglycemic Agent | Unclassifiable | Cannot be assessed |
| 16. | Hepatitis | Rifampicin/ Isoniazid/ Pyrazinamide | Possible | Well Documented |
| 17. | Abdominal pain, Vomiting & Giddiness | Efavirenz | Possible | Well Documented |
| 18. | Hypoglycemia | Glibenclamide/ Metformin/ Pioglitazone | Possible | Well Documented |
| 19. | Hyponatremia | Hydrochlorothiazide | Probable | Well Documented |
| 20. | Nausea & Vomiting | Stavudine/ Nevirapine/ Lamivudine | Possible | Well Documented |

| SR. NO | NAME OF REACTION | SUSPECTED DRUG | WHO CAUSALITY | CASE REPORTS IN LITERATURE |
|---|---|---|---|---|
| 21. | Rash | Artemether/ Lumefantrine | Possible | Well Documented |
| 22. | Rash | A.S.V. Serum/ Metronidazole/ Cloxacillin | Possible | Well Documented |
| 23. | Rash, Nausea, | Unknown Drug (? Chloroquine) | Unclassifiable | Cannot be |
| 24. | Hepatitis | Isoniazid/ Rifampicin/ Pyrazinamide | Possible | Well Documented |
| 25. | Hypoglycemia | Glibenclamide/ Metformin | Possible | Well Documented |
| 26. | Steven-Johnson Syndrome | Isoniazide/ Rifampicin/ Pyrazinamide/ Ethambutol/ Streptomycin | Possible | Well Documented |
| 27. | Cardiac Arrest | Pentazocine/ Ondansetron/ Tranexamic acid/ Pentobarbitone/ Succinylcholine | Unclassifiable | Cannot be Commented |
| 28. | Thrombocytopenic Rash | Unknown Drug | Unclassifiable | Cannot be Commented |
| 29. | Rash | Doxycycline/ Choroquine/ Paracetamol | Possible | Well Documented |
| 30. | Rash, Altered sensorium & Death | Metronidazole/ Ciprofloxacin/ Doxycycline/ Ceftriaxone | Rash- Possible Altered sensorium- Unclassifiable | Rash- Well documented Altered sensorium & Death- Cannot be Commented |
| 31. | Steven-Johnson syndrome progressing to Toxic Epidermal Necrolysis | Nevirapine/ Stavudine/ Lamivudine | Possible | Well Documented |
| 32. | Fixed Drug Eruption | Norfloxacin/ Tinidazole | Possible | Well Documented |
| 33. | Macular Rash | Co-trimoxazole | Probable | Well Documented |
| 34. | Toxic Epidermal Necrolysis | Phenytoin | Probable | Well Documented |
| 35. | Rash | Levofloxacin/ Azithromycin | Possible | Well Documented |
| 36. | Raised Liver Enzymes | Isoniazid/ Rifampicin/ Pyrazinamide | Possible | Well Documented |
| 37. | Rash | Cefoperazone | Probable | Well Documented |
| 38. | Rash | Ciprofloxacin/ Tinidazole | Possible | Well Documented |
| 39. | Rash | Ofloxacin/Ornidazole/Paracetamol Albendazole/ Pantoprazole | Possible | Well Documented |

## EVALUATION OF CASE FROM LTMMC and LTMGH

### Phenytoin induced DRESS syndrome complicated with second drug rash due to amoxicillin and / or ibuprofen

Dr. Ganesh Avhad*, Dr. Rachita S Dhurat**, Dr Smita Ghate***, Dr Ameet Dandale****

* - 3rd Resident MD, Skin and VD, ** - Prof and Head, Skin and VD, *** - Assoc Prof, Skin and VD, **** - Lecturer Skin and VD

**Case Report:**

A 26-year-old married woman presented with sudden onset of red colored lesions all over the body associated with low grade fever and malaise since 2 weeks. The patient was on phenytoin 100 mg three times a day for convulsion since 2 month prior to development of rash. For her rash prednisolone 60 mg was initiated, but there was worsening of the lesions with fever. She received oral amoxicillin and ibuprofen from a private practioner for fever. After 3 days of receiving oral amoxicillin and ibuprofen she developed further increase in intensity of rash with pus filled lesions around mouth. There was no mucosal involvement. There was no history of photosensitivity or previous drug allergy.

On general examination there was no pallor, cyanosis or icterus. Generalized bilateral, tender, mobile, firm 1.5 x 1.5 cm cervical, axillary and inguinal lymph nodes were palpable with bilateral pitting pedal edema.

Cutaneous examination showed perioral grouped 1 to 2 mm size pustules with pitting, tender facial edema. (Fig. 1)

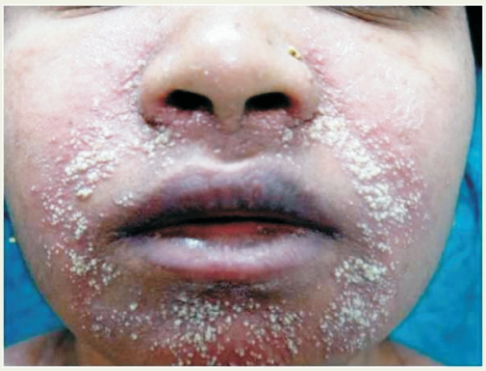

*Figure 1: Showing perioral pustules*

Generalized, tender, erythematous maculopapular rash was present all over the body sparing palms and soles with erythematous patches over the extremities. (Fig. 2, 3)

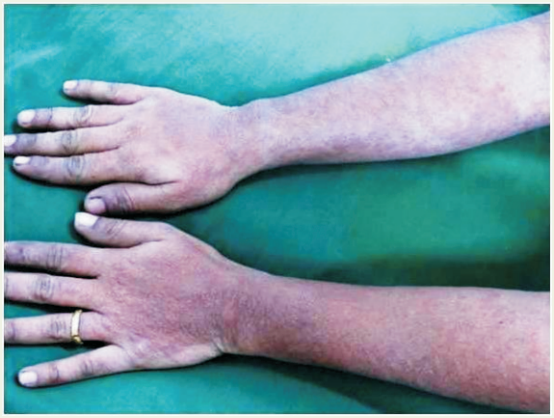

*Figure 2*

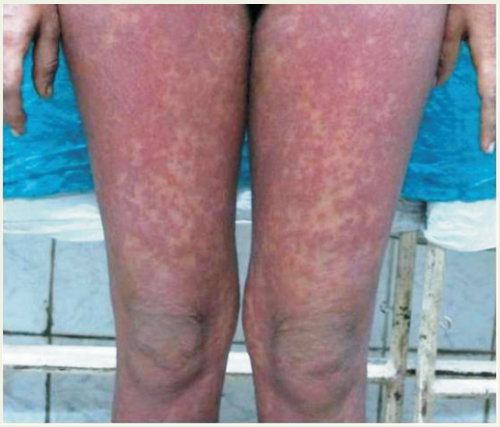

*Figure 3*

Her hematological investigations revealed hemoglobin 10.5 gm/dl; WBC count - 17,900; polymorphonuclear leukocytosis – 80%; lymphocyte – 68; monocytes – 10; eosinophils – 15; absolute eosinophil count – 1500 cells / cmm; increased liver enzymes serum glutamic oxaloacetic transaminase – 76 (Normal range 0-40 IU/L), serum glutamic - pyruvic transaminase – 216 (Normal range 0-40 IU/ L); erythrocyte sedimentation rate 20 mm at the end of hour. Gram staining and pus culture of pustule did not reveal any organisms. Urine microscopy, X- Ray chest were normal and HIV by ELISA were normal / negative.

Fine needle aspiration cytology of left axillary lymph node showed plenty of atypical lymphocytes in varying stages of maturation. Macrophages were also seen which is consistent with drug induced lymphadenopathy.

Histopathology of pustular lesion around oral cavity showed basket-weave orthokeratosis, subcorneal blister with moderate spongiosis. There was peri-vascular lymphocytic infiltrate with papillary dermal oedema and extravasation of red blood cells which is suggestive of acute generalized exanthematous pustulosis (Fig. 5)

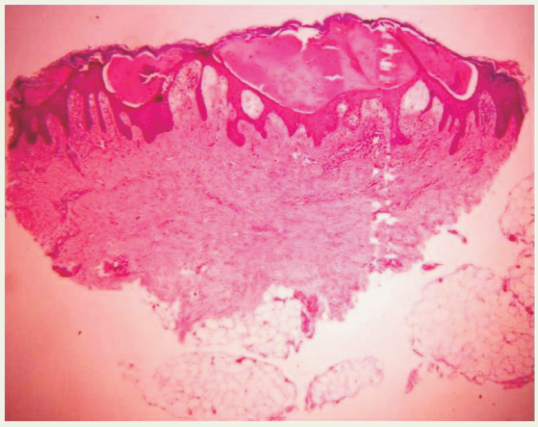

*Figure 4*

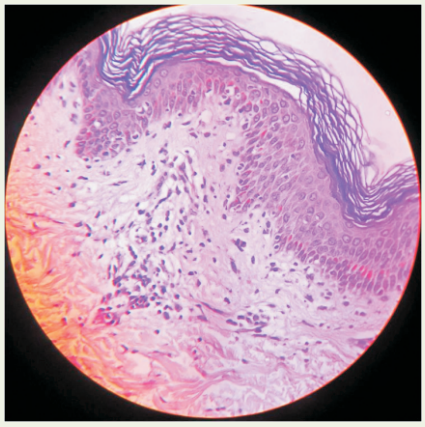

*Figure 5*

Histopatalogy of erythematous papule showed focal basal vacuolization, superficial and deep perivascular lymphocytic infiltrate with few eosinophils with few necrotic keratinocytes. (Fig. 5)

On the basis of clinicopathological and hematological correlation diagnosis of a combination of two drug reactions were:

1. DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) secondary to phenytoin
2. Acute generalized exanthematous pustulosis secondary to amoxicillin and / or ibuprofen

The patient was admitted and offending drugs were stopped. She was started on oral Prednisolone (60 mg), tab. Levocetrizine 5 mg and wet compresses four times a day over pustular lesions. The patient improved remarkably over a period of two weeks.

**Causality analysis of the ADR**

Here, the patient showed 2 ADRs and the causality analysis has been done separately for these drugs.

DRESS syndrome due to Phenytoin: There is a history of taking Phenytoin for 8 weeks prior to development of rash and low grade fever. The ADR is unlikely to be attributed to other disease or drugs and hematological, laboratory and histopathological evidence confirmed DRESS syndrome. There was also improvement in the patient on stopping Phenytoin. In this case, re challenge was not done, and hence as per the WHO scale, causality analysis it can be graded as "Probable".

Acute generalized exanthematous pustulosis due to Amoxicillin and / or Ibuprofen: There is a history of development of pus filled lesions around the mouth after 3 days of starting Amoxicillin and / or Ibuprofen. The AE can occur due to viral infection and either Amoxicillin (more commonly) or Ibuprofen. Hence, it can be explained by disease and other drugs (2 drugs are implicated here).
Hence as per the WHO scale causality analysis it can be graded as "Possible".
In this case, information on drug withdrawal is available and there is improvement on stopping the offending drugs. Re challenge information is not available.

**Discussion:**

Acute generalised exanthematous pustulosis (AGEP) is characterised by sudden and simultaneous onset of fever with edematous scarletiniform rash. It is soon covered by hundreds of nonfollicular, small, superficial pustules. The disease is self-limiting, fever and pustules lasting for 7 to 10 days, followed by desquamation. The aetiology of this condition is very varied. Often drugs and viral infections are implicated. Antibiotics are the main class of drugs implicated in the development of AGEP along with anticonvulsants and anti-inflammatory drugs. The most striking feature of AGEP is the short interval between the drug administration and the onset of the disease. [1]

DRESS syndrome is characterized by involvement of various organs and organ systems, particularly the skin, liver and hematologic system being with apparent cutaneous changes. [2]

DRESS syndrome usually occurs on first exposure to the associated offending medication; with a delayed onset classically begin 1 week to 8 weeks after starting drug therapy. In previously sensitized individuals, anticonvulsant hypersensitivity syndrome may occur within 1 day on re-challenge. It has no relationship to dosage or serum concentration of anticonvulsants. The reaction usually starts with low to high-grade fever, and over few days' cutaneous reaction develop. The cutaneous rash is most commonly an exanthema with or without pruritus which starts as a macular erythema which evolves into a red, symmetrical, confluent, papular rash. Initially, the upper trunk and face are affected, with later involvement of the lower extremities. This is followed by involvement of various internal organs, most commonly being the liver. [3]

Careful assessment is necessary as cutaneous changes do not necessarily reflect severity of internal organ involvement. Facial or periorbital swelling is a sign of a systemic and potentially severe reaction and helps in the diagnosis, because the typical erythematous, symmetric drug eruption often involves the body but spares the face. Rash usually resolve with desquamation. Tender local cervical nodes or generalized lymphadenopathy which usually involves axillary, cervical and inguinal nodes is another common feature of DRESS. [4.5]

Multiple drug reactions in an individual may pose challenge to treat for physician as complications of DRESS / AGEP are severe as in this case.
Treatment of these conditions includes discontinuation of the offending drug and systemic steroid 1 to 2 mg/kg/day to avoid potential progression of symptoms. [6]

It is also known that there exists cross reactivity between anticonvulsant drugs for developing DRESS syndrome and hence additional diagnostic methods should be sought to select safer alternative for seizure control.
Although no gold standard exists, in vitro lymphocyte toxicity assay or lymphocyte transformation tests (LTT), and in vivo patch tests may be helpful in such situations. Many studies have showed the usefulness of LTT and patch testing for the diagnosis of hypersensitivity to anticonvulsants. LTT shows similar results with patch test. But false negative reaction of LTT was also noted in patients with simultaneous positive patch test. [7]
Gabapentin and valproic acid could be considered as alternative therapeutic options in few cases. [8]

Finally, one has to take care that the prodromal symptoms of DRESS / AGEP can be misdiagnosed as bacterial or viral infection and a patient can be treated with antibiotics which can sensitise the patient, thereby worsening the existing condition. These prodromal symptoms of DRESS / AGEP should be recognized to avoid further complications as in our case.

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## Published Case reports on DRESS Syndrome

**Drug Hypersensitivity to Previously Tolerated Phenytoin by Carbamazepine-induced DRESS Syndrome**

*J Korean Med Sci 2006; 21: 768-72*

Cheol-Woo Kim, Gwang-Seong Choi, Chang-Ho Yun, Deok-In Kim

**Abstract.** Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome associated with anticonvulsant drugs is a rare but potentially life-threatening disease that occurs in response to arena oxide producing anticonvulsant such as phenytoin and carbamazepine. There have been many reports of cross reactivity among the anticonvulsants upon first exposure to the offending drugs. However, there has been few data describing the development of DRESS syndrome after switching medication from previously well-tolerated phenytoin to carbamazepine, and the induction of hypersensitivity to phenytoin by DRESS to carbamazepine. We experienced a case of a 40-yr-old man who had uncontrolled seizure that led to the change of medication from the long-term used phenytoin to carbamazepine. He developed DRESS syndrome after changing the drugs. We stopped carbamazepine and restored phenytoin for seizure control, but his clinical manifestations progressively worsened and he recovered only when both drugs were discontinued. Patch tests with several anticonvulsants showed positive reactions to both carbamazepine and phenytoin. Our case suggests that hypersensitivity to a previously tolerated anticonvulsant can be induced by DRESS to another anticonvulsant, and that the patch test may be a useful method for detecting cross-reactive drugs in anticonvulsant-associated DRESS syndrome.

**Drug Neosensitization During Anticonvulsant Hypersensitivity Syndrome**

*J Investig Allergol Clin Immunol 2006; Vol. 16(5): 321-326*

P Gaig, P García-Ortega, M Baltasar, J Bartra

**Abstract.** Anticonvulsant hypersensitivity syndrome (AHS) is a rare, severe drug hypersensitivity reaction included in the drug-related rash with eosinophilia and systemic symptoms syndrome (DRESS), in which a transient state of immune suppression and reactivation of latent virus infections have been observed. We describe 5 patients who developed neosensitization to different drugs taken during a previous episode of anticonvulsant-related DRESS, in whom skin prick, intradermal and/or patch tests were performed to confirm the diagnosis of drug hypersensitivity. In 1 patient, transient hypogammaglobulinemia was observed during the AHS. Four of the 5 patients developed a delayed skin eruption or a delayed systemic hypersensitivity reaction after intake of a drug that they had also taken during a previous anticonvulsant DRESS which had occurred months or years earlier; in the fifth, a possible reaction was prevented thanks to the allergy workup. The diagnosis of drug allergy was demonstrated by positive delayed reaction to intradermal test with

amoxicillin in 2 cases, positive patch tests to paracetamol and amitriptyline in 2 cases, and by clinical evidence of ceftriaxone erythroderma in one. The possibility of neosensitization to drugs administered during anticonvulsant-related DRESS should be considered. A transient state of immunosuppression induced during the anticonvulsant-related DRESS may trigger latent virus reactivation and massive nonspecific immune system response, which may lead to breakdown of tolerance to other drugs present at that time in the organism

**DRESS syndrome associated with carbamazepine and phenytoin**

*Eur J Dermatol 2004; 14: 339-42*

Jean-Pierre Allam, Teresa Paus, Christoph Reichel, Thomas Bieber, Natalija Novak.

**Abstract.** Drug Rash with Eosinophilia and Systemic Symptoms (*DRESS*) syndrome reflects a serious hypersensitivity reaction to drugs. Its clinical manifestations include diffuse maculopapular rash, exfoliative dermatitis, facial edema, lymphadenopathy, fever, multivisceral involvement and it is associated with a high mortality rate. We report a 62-year-old patient suffering from epilepsia presenting erythroderma following carbamazepine intake. Blood tests revealed eosinophilia, leukocytosis, elevated liver enzymes and high levels of Eosinophil Cationic Protein (ECP). We applied systemic steroids and anticonsulvant therapy was switched to phenytoin, which had been taken previously without adverse reactions. The skin eruptions persisted and the patient developed fever. Anticonvulsant medication was discontinued and skin eruptions finally resolved under steroid application. This case report demonstrates that cross reactivity between carbamazepine and phenytoin may not only lead to the development but also to the worsening of DRESS syndrome. ECP blood levels may represent a sufficient parameter to monitor the development of DRESS syndrome.

## DRESS SYNDROME – An update

Dr. Jaisen Lokhande*, Dr. Girish Joshi**
* - Assist Prof, Dept of Pharmacology, ** - Associate Prof, Dept of Pharmacology

The drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, previously referred to as the 'drug hypersensitivity syndrome', is an adverse drug reaction characterized by skin rash, fever, lymph-node enlargement and internal organ involvement.[1]
Many synonymous names and acronyms are attached to DRESS syndrome and includes HSS (Hypersensitivity Syndrome), AHS (Anticonvulsant Hypersensitivity Syndrome), DIHS / DHS [Drug (Induced) Hypersensitivity Syndrome], DIDMOHS (Drug-Induced Delayed Multiorgan Hypersensitivity Syndrome), and Drug-Induced Pseudolymphoma.[2]

The most frequently incriminated drugs are aromatic anticonvulsants (phenytoin, phenobarbital, and carbamazepine), sulfonamides, dapsone, allopurinol, minocycline, and gold salt (Table 1).

**Table 1:** Medicines more often reported to cause Drug Hypersensitivity Syndrome[3]

| | | |
|---|---|---|
| Abacavir | Dapsone | Nevirapine |
| Allopurinol | Diltiazem | Oxicam NSAIDs |
| Atenolol | Gold salts | Phenobarbitone |
| Azathioprine | Isoniazid | Phenytoin |
| Captopril | Lamotrigine | Sulphasalazine |
| Carbamazepine | Mexiletine | Sulphonamides |
| Clomipramine | Minocycline | Trimethoprim |

The incidence is approximately 1 in 1,000 to 1 in 10,000 exposures. In a recent record-linkage study, the risk for developing hypersensitivity within 60 days of the first or second prescription in new users of phenytoin or carbamazepine was estimated to be 2.3-4.5 per 10,000 and 1-4.1 per 10,000, respectively. Studies have shown 80% cross-reactivity between the anticonvulsants.

**Clinical Features:**

DRESS syndrome / Drug hypersensitivity syndrome usually occurs on first exposure to the associated medication, with a delayed onset. Reactions classically begin 1 week to 8 weeks after starting drug therapy. For phenytoin, the mean interval to onset is 17 to 21 days; and for carbamazepine, the onset is generally between 21 and 28 days. In previously sensitized individuals, anticonvulsant hypersensitivity syndrome may occur within 1 day on re-challenge. Anticonvulsant hypersensitivity syndrome has no relationship to dosage or serum concentration of anticonvulsants.
The reaction usually starts with low- or high-grade fever, and over the next 1 to 2 days a cutaneous reaction, lymphadenopathy and pharyngitis may develop. This is followed by involvement of various internal organs, as given below, most commonly the liver, although hematologic, renal or pulmonary impairment may occur (Table 2).

**Table 2 :** Involvement of organs based on severity of disease

| Organ Involved (%) | Mild | Moderate | Severe |
|---|---|---|---|
| Skin (90-100) | Maculopapular exanthema | Urticated lesions | SJS-TEN |
| Liver (50-60) | Mild elevation in LFT | Hepatitis | Fulminant hepatic necrosis |
| Muscle | Elevated creatine kinase level | Myositis | Rhabdomyolysis |
| kidney | Hematuria | Nephritis | Acute renal failure |
| Heart | Pericarditis | Carditis | Congestive cardiac failure |
| Lung | Mild cough | Pneumonitis | Adult respiratory distress syndrome |
| Hematological (50-80) | Eosinophilia (80%), neutrophilia, atypical lymphocytosis | Neutropenia, thrombocytopenia, hemolytic anemia | Aplastic anemia |

The pathophysiology of DRESS syndrome remains unclear, but a defect in detoxification of causative drug, immunological imbalance, and infections such as human herpes virus type 6 (HHV 6) have been suggested. The overall mortality in DRESS is about 10% and occurs in patients with severe multi-organ involvement.[4]

**Differential diagnosis**

Patients presenting with skin rash may be attributed to large number of causes however, the presence or absence of eosinophilia and with or without internal organs involved may help in short listing the more likely conditions.

Table 3 gives list of conditions for patients with eosinophilia and maculopapular rashes.[5]

Table 4 gives the list of disorders for patients with or without eosinophilia, drug induced skin eruptions and systemic symptoms (hepatic involvement more common and other organs/systems) whose diagnostic criteria are very similar to those of DRESS syndrome.[6]

**Table 3 :** Differential diagnosis in skin disorders associated with eosinophilia

| | Medical history | Laboratory test | Systemic symptoms | Skin lesion | Skin pathology |
|---|---|---|---|---|---|
| **DRESS syndrome** | Drug initiation or change within the past 2 months | Eosinophilia, leukocytosis, elevated liver enzymes, high ECP levels | Liver failure, renal failure, arthralgia, diarrhea | Maculopapular rash, exfoliative dermatitis, edema of the face | Lymphocytic infiltration, sometimes pseudolymphoma |
| **HES** | No association with drugs (without recognizable cause) | Eosinophilia > 6 months, in some cases leukocytosis, elevated liver enzymes, high ECP levels | Endocarditis, congestive heart failure, thrombosis, strokes, peripheral neuropathy, encephalopathy, hepatosplenomegaly, diarrhea, arthralgia | Erythroderma, edema, pruritus | Eosinophilic infiltration, cutaneous microthrombi embolism |
| **Wells' syndrome** | In some cases relation to drugs or insect bite at lesional site | Eosinophilia in > 50% of cases, leukocytosis and thrombocytosis may occur | None | Erythema and edema in initial phase, pruritic papular, annular plaques and urticaria-like eruptions, sometimes vesicles and blisters | Dermal infiltration of eosinophils, initially edema, cell debris between collagen bundles forming "flame figures" |

*ECP - Eosinophil Cationic Protein  HES - Hyper eosinophilia syndrome*

**Table 4 :** DRESS syndrome: most common differential diagnoses

| | **DRESS syndrome** | **SJS/TEN** | **Hypereosinophilic syndrome** | **Kawasaki disease** | **Still's disease** |
|---|---|---|---|---|---|
| Cutaneomucous features | Facial oedema, morbilliform eruption, exfoliative dermatitis, tight blisters | Blisters, atypical targets, cutaneomucous erosions | Urticaria, angio - oedema, morbilliform eruption, infiltrated papules or nodules | Conjunctival congestion; fissured lips, 'strawberry tongue'; palmar erythema, oedema of the hands, periungual desquamation; polymorphous exanthema | Salmon rash |
| *Haematological abnormalities* | | | | | |
| Eosinophilia | + | – | + | – | +/– |
| Presence of atypical lymphocytes | + | – | +/– | – | – |
| *Systemic involvement* | | | | | |
| Adenopathies | + | – | + | + | + |
| Hepatitis | + | + | + | +/– | + |
| Other organ involvement | Interstitial nephritis, pneumonitis, carditis | Tubular nephritis, tracheobronchial necrosis | Carditis, pneumonitis, encephalopathy, diarrhoea, vomiting or abdominal pain | Cardiovascular abnormalities, diarrhoea, vo miting or abdominal pain | Pleuritis, pericarditis |

+ = Usual; +/– = possible; – = very rare or absent.

There is no gold standard for diagnosis of DRESS, however at least two diagnostic criteria have been proposed for diagnosis. The RegiSCAR criteria[7] and the Japanese consensus group criteria[8] are detailed in the table below.

**Table 5 :** RegiSCAR criteria and Japanese consensus group criteria for diagnosis of DRESS

| ***RegiSCAR inclusion criteria*** for DRESS syndrome. | ***Japanese consensus group diagnostic cri teria*** for DIHS. Seven criteria needed for diagnosis of DIHS or the first five criteria required for diagnosis of atypical DIHS |
|---|---|
| Hospitalization | Maculopapular rash developing > 3 weeks after starting the suspected drug |
| Reaction suspected to be drug-related | Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug |
| Acute Rash* | Fever > 38° C |
| Fever > 38° C* | Liver abnormalities (ALT > 100 U/L) or other organ involvement |
| Lymphadenopathy in at least two sites* | Leukocyte abnormalities |
| Involvement of at least one internal organ* | Leukocytosis ( > 11 x $10^9$/L) |
| Blood count abnormalities (lymphopenia or lymphocytosis*, eosinophilia*, thrombocytopenia*) | |
| Atypical lymphocytosis (>5%) | |
| Lymphadenopathy | |
| Human herpesvirus 6 reactivation | |

*- *Three of the four starred criteria required for diagnosis*

**Management:**

**Acute period**: DRESS syndrome must be promptly recognized and all potential culprit drugs withdrawn. The typical delay between beginning the administration of a drug and the onset of the reaction is two to six weeks.

Systemic corticosteroids are often used (0.5 to I mg/kg). This therapy rapidly improves symptoms and laboratory measurements, but its impact on the long term disease course is not known. Relapses of rash and hepatitis may occur as corticosteroids are tapered.

When the skin rash results in exfoliative dermatitis supportive care consists of warming the environmental temperature and using local antiseptics and topical corticosteroids.

**Prevention of recurrence:** Consideration must be given to the likelihood of a particular drug to cause the syndrome when multiple drugs are involved. Patch tests and in-vitro lymphocyte tests have been used, but the sensitivity and specificity of these tests are variable, depending on the drug.

Cross-reactions are frequent between the three main aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital), and all three must be avoided by the patient if one has been causative. It may be difficult to find a safe alternative anticonvulsant therapy.

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## REGULATORY

### Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) between October - December 2010

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 October-December 2010 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** | **Used in following conditions** | **Potential Signal of a Serious Risk / New Safety Information** | **Additional Information (as of February 15, 2011)** |
|---|---|---|---|
| Asenapine maleate | Schizophrenia/Bipolar Disorder | Hypersensitivity | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Dronedarone HCl | cardiac arrhythmias | Liver failure | FDA Drug Safety Communication<br>The Warnings and Precautions a nd Adverse Reactions sections of the labeling for Multaq were updated February 11, 2011, to include liver failure.<br>Dronedarone HCl (Multaq) Labeling approved February 11, 2011 (PDF - 198KB) |
| Fenofibrate products | Hypolipidemic agent | Paradoxical decrease in HDL cholesterol | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Golimumab | immunosuppressive drug used for RA, Psoriatic Arthritis and Ankylosing Spondylitis | Hypersensitivity reactions and anaphylaxis | FDA is continuing to evaluate these issues to determine the need for any regulatory action. |
| Ibuprofen lysine | NSAID | Serious skin reactions (in pediatric patients) | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Morphine sulfate; Naltrexone HCl | opioid analgesic | Withdrawal symptoms (not associated with misuse) | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Oxycodone HCl controlled-release tablets [new formulation] | opioid analgesic | Choking and gastrointestinal obstruction | FDA is continuing to evaluate these issues to determine the need for any regulatory action. |
| Regadenoson | pharmacologic stress agent for radionuclide myocardial perfusion imaging | QT prolongation | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |
| Sevelamer HCl | to prevent hyperphosphatemia in patients with CRF | Choking (esophageal obstruction) | FDA is continuing to evaluate this issue to determine the need for any regulatory action. |

**Reference :** http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm249657.htm

**Examples of sound-alike and/or look-alike drug name pairs in international markets**

The existence of confusing drug names is one of the most common causes of medication error and is of concern worldwide. With tens of thousands of drugs currently on the market, the potential for error due to confusing drug names is significant. This includes non-proprietary names and proprietary (brand or trademarked) names. Many drug names look or sound like other drug names. Contributing to this confusion are illegible handwriting, incomplete knowledge of drug names, newly available products, similar packaging or labeling, similar clinical use, similar strengths, dosage forms, frequency of administration, and the failure of manufacturers and regulatory authorities to recognize the potential for error and to conduct rigorous risk assessments, both for non-proprietary and brand names, prior to approving new product names

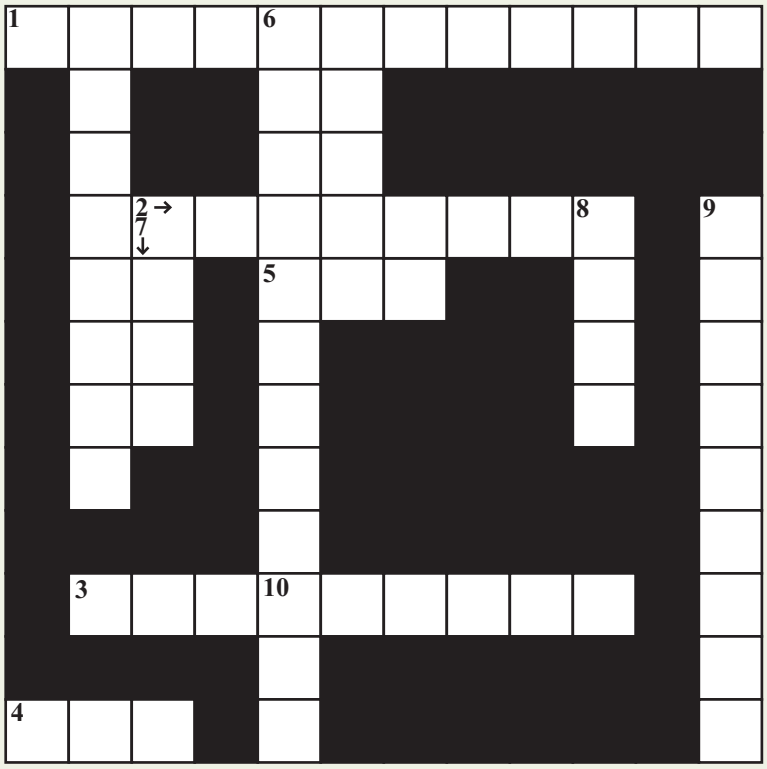
The following table includes examples of name pairs that have been confused in several countries around the world.

| ***Brand name*** **(Non-proprietary name)** | ***Brand name*** **(Non-proprietary name)** |
|---|---|
| *Avanza* **(mirtazapine)** | *Avandia* **(rosiglitazone)** |
| *Losec* **(omeprazole)** | *Lasix* **(frusemide)** |
| *Quelicin* **(succinilcolina)** | *Keflin* **(cefalotina)** |
| *Celebrex* **(celecoxib)** | *Cerebyx* **(fosphenytoin)** |
| **fluoxétine** | *Fluvoxamine* |
| *Reminyl* **(galantamine hydrobromide)** | *Amarel* **(glimepiride)** |
| **morphine** | **hydromorphone** |
| *Diamox* **(acetazolamide)** | *Zimox* **(amoxicillin)** |
| *Flomax* **(morniflumato)** | *Volmax* **(salbutamol sulphate)** |
| *Almarl* **(arotinolol)** | *Amaryl* **(glimepiride)** |
| *Taxotere* **(docetaxel)** | *Taxol* **(paclitaxel)** |
| *Dianben* **(metformin)** | *Diovan* **(valsartan)** |
| *Ecazide* **(captopril/hydrochlorothiazide)** | *Eskazine* **(trifluoperazine)** |
| *Avastin* **(bevacizumab)** | *Avaxim* **(hepatitis A vaccine)** |
| *Lantus* **(insulin glargine)** | *Lanvis* **(toguanine)** |

**Reference :** http://www.ccforpatientsafety.org/common/pdfs/fpdf/Presskit/PS-Solution1.pdf

**Crosswords 1**

Dr Sharmada Nerlekar (Assoc Prof, Dept of Pharmacology)



**ACROSS**

1. This oral antifungal is known to produce photodermatitis (12)
2. Heparin is known to cause this dermatological toxicity (8)
3. Phenylbutazone commonly causes this adverse effect on the skin (9)
4. An AKT drug causing lichenoid skin eruptions (3)
5. Barbiturates have a propensity to produce this syndrome (3)

**DOWN**

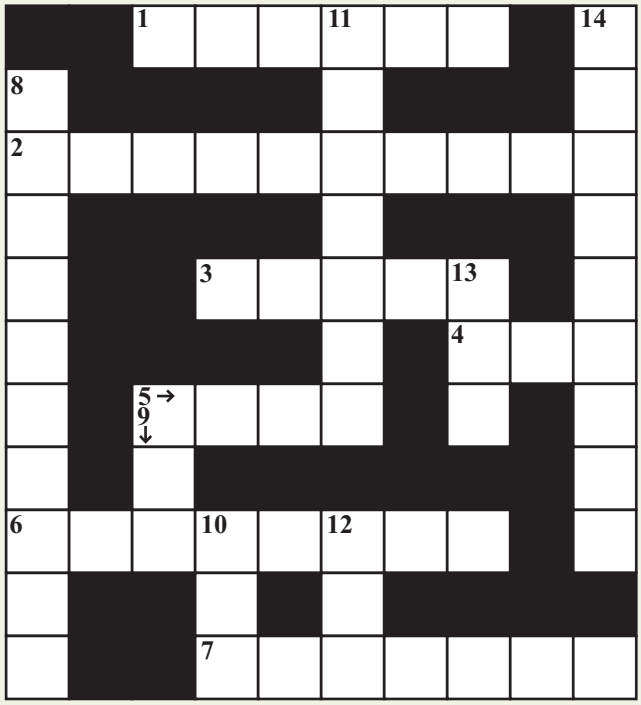
6. Apart from Phenytoin this antiepileptic can also cause Stevens-Johnson syndrome (12)
7. Iodides can produce this dermatological adverse reaction (4)
8. Hyperpigmentation is often due to this hormone (4)
9. Fixed drug eruptions are due to this ACE inhibitor in particular (9)
10. This AKT drug can skin rashes, orange sweat and cloth staining (8)

ANSWERS

1.Griseofulvin 2.Alopecia 3.Urticaria 4.PAS 5.SLE 6.Ethosuximide 7.Acne 8.ACTH 9.Captopril 10.Rifampin

## Crosswords 2

Dr Abhilasha Rashmi (Assist Prof, Dept of Pharmacology), Dr Girish Joshi (Assoc Prof, Dept of Pharmacology)




**ACROSS**

1. Deficiency of this vitamin manifests as Diarrhoea dermatitis and dementia. (6)
2. Livedo reticularis is the characteristic side effect of this anti-parkinsonia drug (10)
3. Drugs involved in acute phototoxic reactions caused by UV Rays are …….cyclines (5)
4. Severe form of Steven Johnson's syndrome with >30% involvement of body surface area, also called Lyell's syndrome (3).
5. Highest incidence of photosensitivity among quinolones is seen with ……floxacin (4)
6. Repeated large amount of topical application of steroids can lead to …….. syndrome (8)
7. ……. eruptions are the characteristic feature of acute barbiturate poisoning (7)

**DOWN**

8. Rapid IV injection of this antibacterial agent causes intense flushing due to histamine release known as "Red man syndrome" (10)
9. Hypersensitivity reactions to sulfa drugs can lead to this life threatening skin conditions in which epidermis separates from dermis (3)
10. Redness, warmth and swelling are common side effects with this vaccine against Haemophilus *influenzae* type B (3)
11. This crude preparation, indicated for treatment of Psoriasis, exerts a phototoxic reaction on skin when exposed to UV-A rays (7)
12. Alopecia and dermatitis are the major dermatological ADRs seen with CHOP regimen used for treatment of this cancer (3)
13. Allergic reactions are common with this equine antiserum against Tetanus (3)
14. This Vitamin A derivative used for treatment of acne should not be applied together with Benzoyl peroxide (9)

ANSWERS

**Across :** 1. Niacin 2.Amantadine 3.Tetra 4.TEN (Toxic Epidermal Necrolysis) 5.Spar 6.Cushing's 7.Bullous

**Down :** 8. Vancomycin 9. SJS (Stevens Johnson Syndrome) 10. HIB (Hemophilus Influenzae B) 11. Coaltar 12. NHL (Non Hodgkin's Lymphoma 13. ATS (Anti Tetanus Serum) 14. Tretinoin

The bulletin was inaugurated by Dr Y K Gupta, National Coordinator, Pharmacovigilance programme Of India at the 17th Annual Meeting of SRS. Other dignitaries present on the dais (from left to right) were Dr Rahul Mayekar (AP, Obs and Gynae), Dr Sudhir Pawar (HOD, Pharmacology), Dr Y K Gupta, Dr Sandhya Kamat (Dean, LTMMC and GH), Dr Laud (renowned Senior Orthopedician) and Dr Mohan Joshi (In-Charge - Gastroenterology Surgical Services).



Dr Sudhir Pawar presenting a memento to Dr Y K Gupta as a token of our appreciation

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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