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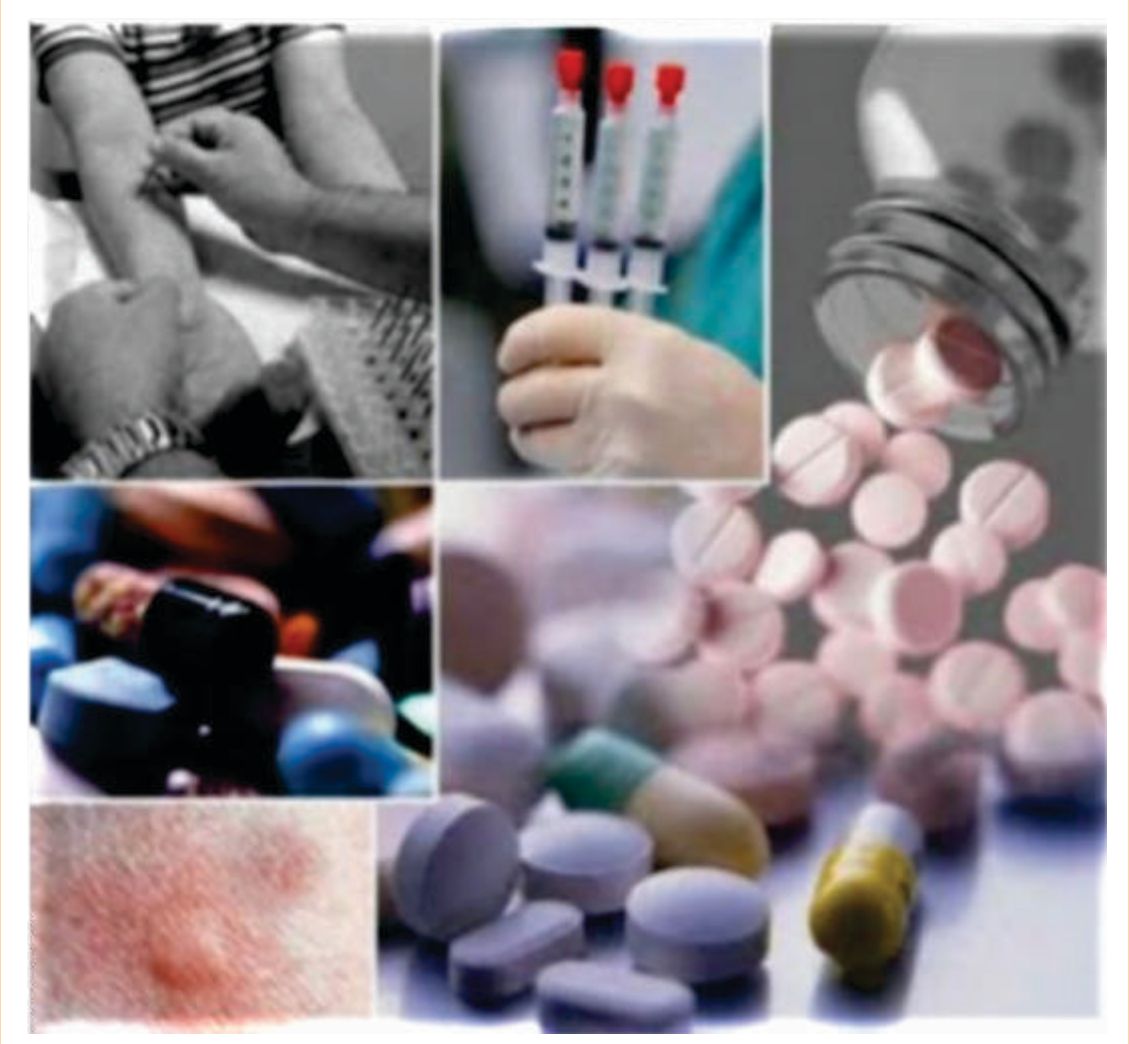
BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL COLLEGE & GENERAL HOSPITAL



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From the Editor's Desk . . . . ✍

Dear Friends and Colleagues,

I am delighted to put forth the very first issue of Bulletin on Adverse Drug Reaction of this year.

As we all know, all drugs come with an expiry date which is an approximate judgement of its shelf life. The first review article elaborates on how it is determined and safety issues with expired drugs. Hairs are an integral part of one's personality. Our second review article highlights the usual offending medications for causing alopecia. It also provides overview of different types, mechanism and management of drug induced alopecia.

In this issue we also discuss an interesting case of D-Penicillamine Induced Pancytopenia. We also have a summary of analysis of ADRs from our institute to provide the glimpse of pharmacovigilance activity at our institute. The puzzle and crossword will surely make it more interesting.

I hope all the readers find this issue informative and interesting.

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

Thank you,

Dr. Sudhir Pawar

DRUG INDUCED ALOPECIA

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Introduction

Considerable number of drugs may interfere with the hair cycle and lead to alopecia.[1] Drug-associated hair loss is usually reversible after interruption of treatment or withdrawal of offending drug. Prevalence and severity of alopecia depends on the drug as well as on individual predisposition. Some drugs produce hair loss in most patients receiving appropriate dosages while other drugs are only occasionally responsible for hair abnormalities.[2]

Alopecia inducing agents can affect the hair follicles via two major mechanisms: anagen effluvium or telogen effluvium. In the former, hair loss occurs within 2 to 3 weeks of drug administration, whereas in telogen effluvium, the delay is usually 2 to 4 months. Clinically, both are classified as diffuse non-scarring alopecias.[3]

When temporal association between the onset of hair loss and commencement of a medication can be established, the medication is commonly thought to have caused the hair loss.[4] However, hair loss, and in particular telogen effluvium, may occur in response to a number of triggers including fever, haemorrhage, severe illness, chronic ailments, stress, and childbirth, and a thorough exclusion of these potential confounders is necessary before the hair loss can attributed to the medication.[5,6] Many reports in the literature that attribute hair loss to particular medications have not adequately explored the nature of the hair loss and excluded other potential unrelated causes of hair loss; therefore, they are difficult to interpret.[7]

In a study conducted by E. K. Choi et al[8] drug induced alopecia has been negatively associated with body image and psychosocial wellbeing, and positively associated depression in women with breast cancer. Despite the substantial number of reports of drug-induced alopecia in the literature, not infrequently is there a questionable causal relationship because of inadequate documentation and confounding factors.[1,4]

Normal hair physiology

Hair follicle cycles through three different phases: anagen, catagen and telogen.[9] During anagen, which is the longest phase, the active follicle produces hair continuously. Duration of anagen impacts the length of the hair, however, this differs between individuals and location of hair. The next transient phase, catagen, involves the hair follicles regressing and in part undergoing apoptosis to prepare for the next phase.[10] Telogen is the resting phase and lasts for about 3 to 4 months. Thereafter, the

telogen hair is shed and the cycle is re-entered. In a normal scalp 80-90% of hair are in anagen. This mitotic activity in anagen follicles is one of the fastest tissue turnover processes in the body. Due to the increased mitotic activity, anagen follicles are most vulnerable to toxic insults, while catagen and telogen follicles are not as susceptible to toxic insults owing to their significantly reduced mitotic activity.[1] Thus, regions with the most proportion of anagen follicles, such as the scalp, are more vulnerable to exogenous noxious events such as drugs.[11]

Pathophysiology

The mechanism of hair loss in drug induced alopecia may involve a direct effect on the follicle through interruption of anagen growth, premature precipitation of telogen (telogen effluvium), or androgenic transformation of normal terminal hair to vellus hair in genetically susceptible individuals[12]. The fraction of hair in anagen and telogen, the density of the hair follicles, and the regional distinctions in the duration of anagen and telogen account for the varying severity of drug-induced alopecia in different regions.' Indirect effects may be associated with a drug-induced systemic disorder, such as hypothyroidism, or a severe skin disease e.g., lichenoid eruption complicated by cicatricial alopecia or toxic epidermal necrolysis.[1]

Types of drug-induced hair loss

A. Telogen effluvium

Telogen effluvium is the most common form of hair loss induced by drugs(table 1) and is characterized by excessive shedding of hair in telogen.[6] Drugs can induce telogen effluvium through different mechanisms. In most cases, drugs induce telogen effluvium by advancing the follicle into premature rest. Telogen effluvium can result as a consequence of discontinuation of drugs that can prolong anagen phase such as topical minoxidil and oral contraceptives. Some drugs have been associated with premature detachment of the hair shafts from the follicles with shortening of the normal telogen phase (systemic retinoids).[7] Hair loss typically begins about 12 weeks after beginning of treatment. Daily hair shedding is variable, Severe hair shedding (more than 250 strands per day) is uncommon and is almost exclusively seen with antineoplastic agents, interferons, antiretroviral drugs, and heparin. Loss of pubic or body hair can occasionally occur.[13]

Table 1: Drugs associated with telogen effluvium and anagen effluvium

Drugs Associated with Anagen Effluvium	Drugs Associated with Telogen Effluvium	
	Probable Causal Association	Possible Causal Association
Bleomycin	Beta-blocker	Amiodarone Carbamazepine
Carmustine	Bromocriptine	Oral contraceptives
Colchicine	Captopril	Tricyclic antidepressants
Cyclophosphamide	Carbimazole	Enalapril
Cytarabine	Cimetidine	Heparin
Dactinomycin	Coumarins	Proguanil
Doxorubicin	Fluoxetine	Minoxidil
Etoposide	Gold salts	Methyldopa
5-Fluorouracil	Interferons	Methysergide
Hydroxyurea	Lithium	
Ifosfamide	Retinoids	
Mechlorethamine	Thiouracil	
Methotrexate	Sulfasalazine	
Vinblastine	Valproic acid	
Vincristine		
Vindesine		

B. Anagen effluvium

Anagen effluvium is usually associated with telogen hair loss. Anagen effluvium is almost exclusively seen after intake of cytotoxic drugs Hair shedding is usually acute and severe and may produce loss of most of the scalp hair, eyebrows, and eyelashes; other body hair are less commonly involved.[14] Drugs associated with anagen effluvium are summarised in table 1.

C. Cicatricial alopecia

Diffuse and permanent hair thinning attributable to hair follicle destruction is uncommon and almost exclusively seen after busulphan conditioning for bone marrow transplantation or after radiation therapy for CNS tumors.[14-16]

Drugs causing reversible hair loss

a. Anticoagulants

Telogen effluvium is a common side effect of treatment with anticoagulants. It occurs in up to 50% of patients treated with high dosages of heparin, heparinoids, or coumarin derivatives.[17] Low molecular weight heparin enoxaparin is commonly associated with anticoagulant induced hair loss, characteristically, there is a latent period of few weeks between anticoagulant exposure and increased hair shedding and hair loss. Less commonly, warfarin-induced alopecia has been described in literature.

b. Antineoplastic agents

Alopecia is the most common cutaneous adverse reaction of antineoplastic drugs. Hair loss is more frequent and severe in patients receiving combination chemotherapy than in those treated with monotherapy. Severity of hair loss varies among patients submitted to the same therapeutic regimen. In most patients, hair loss starts after the first or the second cycle of administration of chemotherapy and therefore 4 to 8 weeks after the start of treatment.[18][14] Evaluation of hair shedding in a group of patients submitted to polychemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil revealed that mean daily hair shedding was 125 hair per day but some patients may shed more than 1000 hair daily .[7] Hair regrowth is usually rapid after discontinuation of therapy but hair morphology may be altered. In rare cases, hair regrowth is not complete and a permanent hair thinning persists.[19]

Table 2: Risk of hair loss with various antineoplastic drugs

High risk of hair loss	Medium risk of hair loss	Low risk of hair loss
Adriamycin	Amsacrine	Capecitabine
Cyclophosphamide	Bleomycin	Carmustine
Daunorubicin	Busulphan	Carboplatin
Docetaxel	Cytarabine	Cisplatin
Epirubicin	5-Fluorouracil	Fludarabine
Etoposide	Gemcitabine	6-Mercaptopurine
Ifosfamide	Lomustine	Procarbazine
Irinotecan	Melphalan	Raltitrexed
Paclitaxel	Methotrexate-	
Topotecan	Mitoxantrone	
Vindesine	Mitomycin C	
Vinorelbine	Thiotepa	
	Vincristine	
	Vinblastine	

c. Antiretroviral

Telogen effluvium and hair loss in patches resembling alopecia areata are common side effects of indinavir therapy, occurring in up to 10% of patients. Leg, thigh, pubic, thoracic, and axillary hair are also frequently affected. Combined treatment with indinavir and ritonavir may be associated with severe hair loss since ritonavir increases the plasma concentration of indinavir.[20,21] The combination of lopinavir plus ritonavir has also been associated with hair loss.[20]

d. Cardiovascular Drugs

Beta-adrenoceptor antagonists, commonly used to treat hypertension, have been reported to be associated with alopecia. Metoprolol and propranolol have both been described to lead to reversible hair loss from a telogen effluvium.[22] Another group of antihypertensives, the angiotensin-converting enzyme inhibitors, may also be associated with alopecia. Captopril is one of a several drugs in this group and has been shown to induce a diffuse hair loss. Often the hair loss is in association with other known cutaneous adverse effects. Amiodarone, a popular antiarrhythmic medication, has rarely been reported to be associated with alopecia. Hair regrowth was reported on cessation of the medication.

e. Oral Contraceptives

Telogen effluvium is commonly observed following interruption of long-term oral contraceptive therapy.[21,23,24] It has been postulated that the estrogen contained in the contraceptives prolongs anagen duration.[7] An alternate proposition is that a certain oral contraceptives contain antiandrogens such as cyproterone acetate or drospirenone which arrest androgenetic alopecia, and that cessation of these agents leads to a resumption of a previously suppressed propensity towards androgenetic alopecia.[6]

f. Retinoids

Retinoids routinely used in dermatology for various conditions, may cause hair loss with visible alopecia in a sizeable population. The hair loss is dose-related, and body hair may also be affected. In a few cases, alopecia is severe.[7] Vitamin supplements containing vitamin A commonly induce mild hair loss. In addition, acitretin may also induce changes in hair colour, including repigmentation and texture.[25]

g. Antimicrobials

Isoniazid is an important medication used in combination for the treatment of tuberculosis. Isoniazid induced hair loss has been reported in a 30-year-old woman receiving combination treatment for pulmonary tuberculosis. Hair loss was reported a month after initiating treatment with isoniazid, and after stopping the treatment, hair regrowth was observed at 2 months.[26] The exact mechanism of isoniazid-induced alopecia is not understood. Other antituberculosis medications may also cause alopecia.[13]

h. Minoxidil

Telogen effluvium occurs 2 to 3 months after topical minoxidil interruption. Hair loss is often severe and results from concurrent telogen entry of all follicles which were stimulated to enter into growth phase by minoxidil. Minoxidil prompts resting follicles to reenter anagen and therefore induces detachment of the old club hair which causes hair loss at the beginning of minoxidil therapy. [27]

i. Psychotropic drugs

There are reported cases of alopecia following the use of psychotropic drugs but data about frequency

of hair loss are not available for most drugs. Mood stabilizer lithium causes hair loss in up to 20% of long term users,[28] which in some cases may be attributed to lithium-induced hypothyroidism.[27] Valproic acid and divalproex frequently cause dose-dependent hair loss that may affect up to 12% of patients. Carbamazepine on the other hand is only very rarely responsible for hair loss.

j. Dopaminergic therapy

Reversible telogen effluvium has been documented in patients treated with dopaminergic drugs for Parkinson's disease including levodopa, ergot alkaloid and nonergot alkaloid dopamine receptor agonists eg. bromocriptine, cabergoline, pramipexole, ropinirole, pergolide. Hair loss has been reported more commonly in female patients.[29]

k. Antidepressants

Telogen effluvium has been primarily reported in patients taking the serotonin reuptake inhibitor fluoxetine.[30] It usually occurs a few months after the beginning of therapy but can occasionally take more than a year to present. Hair loss has been occasionally reported with tricyclic antidepressants but not with mono- amine oxidase inhibitors.[28]

Permanent alopecia/cicatricial alopecia

i. Busulphan

Busulphan used for allogeneic or autologous bone marrow transplantation produces permanent alopecia in up to 50% of patients.[31]

ii. Anti-hypertensive agents

Lichen planopilaris can be precipitated by antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers. Drug induced lichen planopilaris is usually aggressive and unresponsive to systemic corticosteroid treatment. [31]

Diagnosis of drug induced alopecia

The diagnosis of drug-induced alopecia involves the same approach as the evaluation of any suspected drug reaction.[7] Obtaining detailed drug history with special emphasis on drug intake for past four months prior to the onset of hair loss can help identify known causative agents. The causative role of the drug is often difficult to prove; normalization of hair loss may, in fact, take few months after drug discontinuation. A causal association is markedly strengthened, if there is improvement on dechallenge. Although deliberate rechallenge is rarely performed, recurrence of alopecia on rechallenge is strongly suggestive that the medicine was responsible.[12] Role of present medical ailment should be evaluated as a possible contributing factor in alopecia. Pull test and examination the hair under the microscope to determine type of alopecia can aid diagnostic procedure.[32]

Prevention and Management strategies

Telogen effluvium usually resolves spontaneously, it may precipitate or aggravate androgenetic alopecia in susceptible individuals. Discontinuing the causative drug may not reverse alopecia which may necessitate treatment with finasteride or topical minoxidil.[7] Cancer chemotherapy induced hair loss often has a severe negative impact on the patient's quality of life. Available options include scalp hypothermia and topical minoxidil.[12]

Currently scalp hypothermia represents the only available preventive measure especially for cancer chemotherapy associated alopecia. The efficacy of scalp cooling depends on the cytostatic regimen used. In particular, scalp cooling is effective when anthracyclines or taxanes are used as a monotherapy rather than combination. Proposed rationale for scalp cooling is it causes vasoconstriction, which reduces the blood flow to the hair follicles during peak plasma concentrations of the chemotherapeutic agents and so reduces cellular uptake of these agents. Also reduced scalp temperature, biochemical activity, which makes hair follicles less susceptible to the damage of chemotherapeutic agents.[19] Topical minoxidil has been shown to accelerate hair regrowth after chemotherapy but not prevent hair loss.[13]

Summary

Drug induced alopecia usually presents as a diffuse, non-scarring alopecia most commonly involving the scalp, which in majority of cases is reversible. A high index of suspicion should be maintained regarding medication-induced alopecia, especially if other causes have been excluded. Prevention and treatment of drug induced alopecia is important along with treatment of the disorder under therapy as it can have negative psychological impact and hamper overall recovery from the primary disorder.

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DRUGS AND EXPIRY DATES

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With a splitting headache, you reach into your medicine cabinet for some aspirin only to find the expiration date on the medicine bottle is more than a year out of date. So, does medicine expire? Do you take it or not? If you decide to take the aspirin, will it be a fatal mistake or will you simply continue to suffer from the headache? This is a dilemma many people face in some way or another. The website of Harvard Medical School (HMS) Family Health Guide says that the expiration dates on the medications and vitamins are a conservative estimate by the manufacturers to ensure quality. In most instances, expired medications are safe but may not be as effective or potent once past their expiry date.[1]

Definition[2]:

The expiry date is the point in time when a pharmaceutical product is no longer within an acceptable condition to be considered effective. The medication reaches the end of its 'shelf life'.

Depending on the product, the expiry date may be set as a fixed time:

- after manufacture
- after dispensing
- after opening of the manufacturer's container.

The shelf life of products is determined by either the breakdown of the active drug or by risk of contamination. Not all drugs deteriorate at the same rate.

The expiration date doesn't really indicate a point at which the medication is no longer effective or has become unsafe to use. Medical authorities state expired medicine is safe to take, even those that expired years ago. A rare exception to this may be tetracycline, but the report on this is controversial among researchers. It's true the effectiveness of a drug may decrease over time, but much of the original potency still remains even a decade after the expiration date. Excluding nitroglycerin, insulin, and liquid antibiotics, most medications are long-lasting. Placing a medication in a cool place, such as a refrigerator, will help a drug remain potent for many years.[3]

Calculating the drug expiry date[3]

At some point after major clinical trials are concluded, but before FDA approval, a series of quality standards are established for each new drug. These are the manufacturing and testing specifications,

which includes upper and lower limits for the amount of the Active Pharmaceutical Ingredient (API) in each dose unit (e.g., 500mg per tablet). The final dosage form may be a mix of the API as well as fillers, binders, and other ingredients to ensure the API is delivered to the body in a reliable and predictable manner. But what certainty do we have that this new dosage form will maintain all of these properties over time? What happens after it sits on a shelf for two or three years, or more? Few companies have the patience to wait, so drug products are put through accelerated degradation testing, or "stress" testing, to estimate how quickly a drug will deteriorate. Depending on the dosage form, stress testing may include short-term exposure to extremes of heat, light, oxidation, and humidity. After exposure over different time periods, the quantity of the API, and the other product characteristics, will be assayed again. Not only does this help us understand how stable a drug is, it illustrates the degradation pathways - what chemical reactions could be expected to occur over time. For liquid and injectable drugs, there will be additional tests for bacterial purity and chemical stability. All of these tests predict the overall stability of the dosage form - not just the amount of drug, but how that drug will be absorbed into the body. All of this is used to estimate what the expiry date should be: the date to which the manufacturer warrants the original product characteristics will be retained.

Expiry dates for drugs can vary dramatically. One of the drugs with shortest expiry is injectable epinephrine (Epipen) used for anaphylaxis and other indications. Epinephrine injections need to be stored in proper place as per the instructions by the manufacturer. Other drug products are highly sensitive to moisture, requiring dispensing in specialized containers with desiccants to trap moisture and enhance stability. Many liquid antibiotics have very poor stability, so they must be prepared in the pharmacy at the time of dispensing. Refrigeration is necessary for other drugs, ranging from vaccines to eye drops, which keeps the dosage form stable.

It is important to keep in mind that the expiry date of a drug is based on testing of previously unopened products, stored in its original container, and maintained under typical conditions. Once you open a bottle, or transfer it to another container (like a prescription vial), the manufacturer's expiry date is no longer reliable. That doesn't mean a drug will become ineffective rapidly, but the stability could be compromised once it has been introduced to light, heat, and humidity. Humidity's effects are frequently noticeable with old bottles of Aspirin (acetylsalicylic acid) which breaks down via hydrolysis to salicylic acid and acetic acid giving old bottles a characteristic vinegar odour.

FDA ruling[4]

Before 1979, it was not mandatory for drug manufacturers to mention the expiration date on the products. For the first time in 1979, the Food and Drug Administration (FDA), US, made it necessary under the law for all drug manufacturers to mention the date up to which the full potency and safety of the drug was certified. This resulted into the start of a new era of discarding drugs that had passed the date of expiry mentioned on their packing. Thus it caused huge losses to the bulk purchasers of the drugs, especially in government health departments and the US Army, forcing them to replace the

unused expired drugs with a fresh stock. In 1985, this loss was noticed by the US Army authorities when they were faced with the task of destroying and replacing the stockpiled expired drugs worth more than a billion dollars. This triggered the process of testing the efficacy and safety of the expired drugs. The task of testing was assigned to the FDA by the US Army.

Accordingly, the FDA tested more than a hundred prescriptions and over-the-counter medications and observed that 90 per cent of the expired drugs were still safe and potent; the oldest drug tested had expired 15 years back at the time of testing. The study pointed out that the expiry date did not really indicate a point at which the medication was no longer effective or had become unsafe to use. At present, there is a programme being run jointly by the Department of Defence and the FDA, US, known as "Shelf Life Extension Program" (SLEP)[5] that is meant to defer drug replacement costs for date-sensitive stockpiles of pharmaceuticals by extending their useful life beyond the manufacturer's original date of expiry. The SLEP started in 1986 and has started providing online service since 2005.

Dos and Don'ts[6]

- Most outdated medications, whether prescription or over-the-counter, are usually not harmful. If the medications have been stored under good conditions, they usually retain much of their potency for at least one to two years following their expiry date, even after the container is opened. One should not consume any pills that have become discoloured, turned powdery, or smell bad; any liquids that appear cloudy or filmy; or any tubes of cream that are solidified or cracked. To help maintain potency, the medications should be stored in a closet or cabinet located in a cool and dry room.
- The medicine kit should not be stored in the bathroom where the heat and humidity from hot water showers/ steam can cause medications to break down, lose potency and, occasionally, even become harmful. Similarly, their storage in the kitchen next to the gas stove, washbasin or dishwasher is not advisable.
- It should be ensured that the bottles are tightly sealed after use. Also, the medications should not be mixed in one container because chemicals from different medications can interact to interfere with potency or cause toxic side effects. If two or more medications have been mixed, they should be discarded. A few medications, like insulin and some liquid antibiotics, do degrade quickly and should never be used beyond the expiry date.
- If there are any doubts about the safety or potency of a particular expired drug, it is wise to consult a pharmacist who does not have any conflict of interest.

Are expired drugs still safe?

Again, the evidence is reassuring - with some caveats. The best way to verify long-term stability

would be to stockpile supplies, let them sit for years, and even decades, and then test them. Americans can thank their government for doing such testing - the Department of Defense/FDA Shelf Life Extension Program has been in place for over 20 years. It tested 122 different products, stored unopened and in their original containers, and found that about 88% are stable for at least one year after expiry with an average of 5 years after the expiry date. However, this was under ideal conditions - not typical use consumer use, where bottles are usually partially consumed, and partially exposed to moisture and light. Epipen's active ingredient degrades consistently after the expiration. So never suggest people carry an expired Epipen - but don't hesitate to recommend its use in life-threatening anaphylactic situations where no other alternatives exist. Similarly, one may be less concerned about drug potency if taking something like Excedrin for a headache, versus medication to treat epilepsy, where small changes in the dose delivered could affect drug levels. Because of sterility concerns, throw out an eye drop that has been open for several months, even if the expiry date still says it's OK to use - that expiry date was for the unopened drug, not a bottle that's been used.

FDA Exemptions[7]

The FDA grants some exemptions for certain drugs. Any drug that uses a company's previous stock of tested chemicals can accelerate the testing process. This saves the company time and money. At one point the FDA gave an exemption to drug companies that had to reduce the amount of iron in their medications. The iron in the drugs needed to be reduced, but in order to minimize manufacturer burdens the FDA allowed drug companies to skip shelf-life testing.

Emergency Use Authorities and Enforcement Discretion[8]

In addition to SLEP, there are other ways that, when appropriate, FDA can allow certain medical products to be used beyond their manufacturer-labelled expiration dates.

One way is through issuing an Emergency Use Authorization (EUA) under section 564 of the FD&C Act since use of a product beyond its labelled expiry date is considered unapproved. However, before FDA can issue a EUA, specific type of determination must be in place, the Health and Human services (HHS) Secretary must issue a declaration to justify the issuance of the EUA, the section 564 statutory criteria for issuing a EUA must be met, and FDA must determine that it is safe to use the product beyond its labelled expiration date.

Another way FDA can approach expiration dating challenges is through FDA's expiration dating extension authority under section 564A(b) of the FD&C Act, which was established by Pandemic and All-Hazards Preparedness Reauthorization Act(PAHPRA) in 2013. Before PAHPRA, the distribution, dispensing, or use of products with extended expiry, and any related labeling adjustments, were possible through a EUA or FDA enforcement discretion.

Expiration Dating Extension Updates[8]

FDA acknowledges the stockpiling challenges of federal and state, local, tribal, and territorial (SLTT) stakeholders (for example, related to doxycycline, ciprofloxacin, oseltamivir phosphate, and certain auto-injector products) and remains committed to finding appropriate solutions to address such challenges. The draft guidance report of the updates is published by FDA.

Drug disposal[6]

- Disposal of the expired drugs properly is equally important to avoid the harmful environmental effects and prevent accidental use of discarded expired drugs by the children and animals. A 1996 report of how expired medications are being disposed off found that 1.4 per cent of respondents returned medications to a pharmacy, 54 per cent disposed of medications in the garbage, 35.4 per cent flushed medications down the toilet or sink, 7.2 per cent did not dispose of medications, and 2 per cent related that they used all medications before expiration.
- Ideally, one should follow the advice and instructions for the disposal of the expired medications as rendered by the manufacturer, if they are provided with. However, if there are no such instructions, it is advisable to take out the medicines out of their containers and mix them with something like cat/ dog litter or dirty household waste to which the children and pets are not attracted to. Finally they should be disposed off after sealing them in plastic bags. The expired medicines should not be flushed down the toilet unless specifically instructed to do so because of the earlier reported risk of the resistant bacteria in the aeration tanks of sewage treatment plants by the antibiotic substances present. The exceptions to the rule are narcotics and controlled substances, which are often flushed to prevent unintentional use, overdose and illegal abuse.

Conclusion

There's no single rule for expired drugs and supplements, owing to the variety of products, regulatory requirements, and other factors that can influence a product's safety and efficacy. In general, expiry dates are conservative, and consumers can have confidence that drug labeling claims will be accurate up to, and in some cases well beyond, the labelled expiry date. But the reality is that we don't store drugs under ideal circumstances. So when absolute certainty is required, stick to drug products that are not expired. When absolutely necessary, expired drugs are probably safe, however, the potency may be compromised. And before you flush or toss those expired drugs, find ways to dispose of them in a way that minimizes the environmental impact and potential for harm.

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ANALYSIS OF ADVERSE DRUG REACTION REPORTED

(November 2017 to February 2018)

Compiled by Dr. Nayana Nair, Dr. Pranesh Pawaskar, Dr. Nitin Gawari

2nd Year Residents; Department of Pharmacology, LTMMC & GH, Sion, Mumbai.

Total no. of cases : N = 126

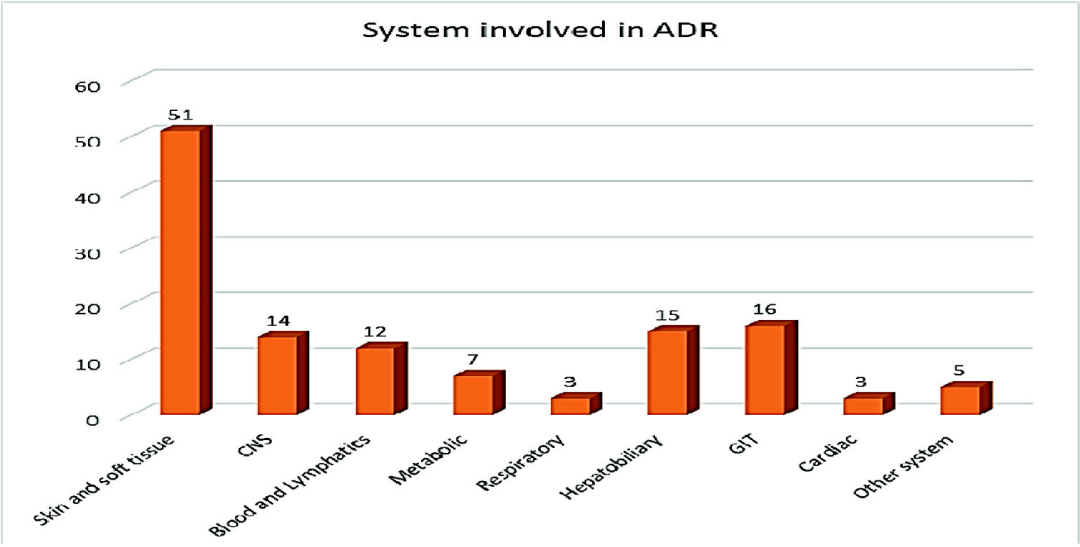
1. Age and Gender distribution

Age group	No. of patients	Males	Females
<3 yrs	9	4	5
3 - 17 yrs	40	16	24
18 - 44 yrs	36	9	27
45 - 60 yrs	26	10	16
> 60 yrs	15	5	10
Total	**126**	**44**	**82**

2. Seriousness of the ADR

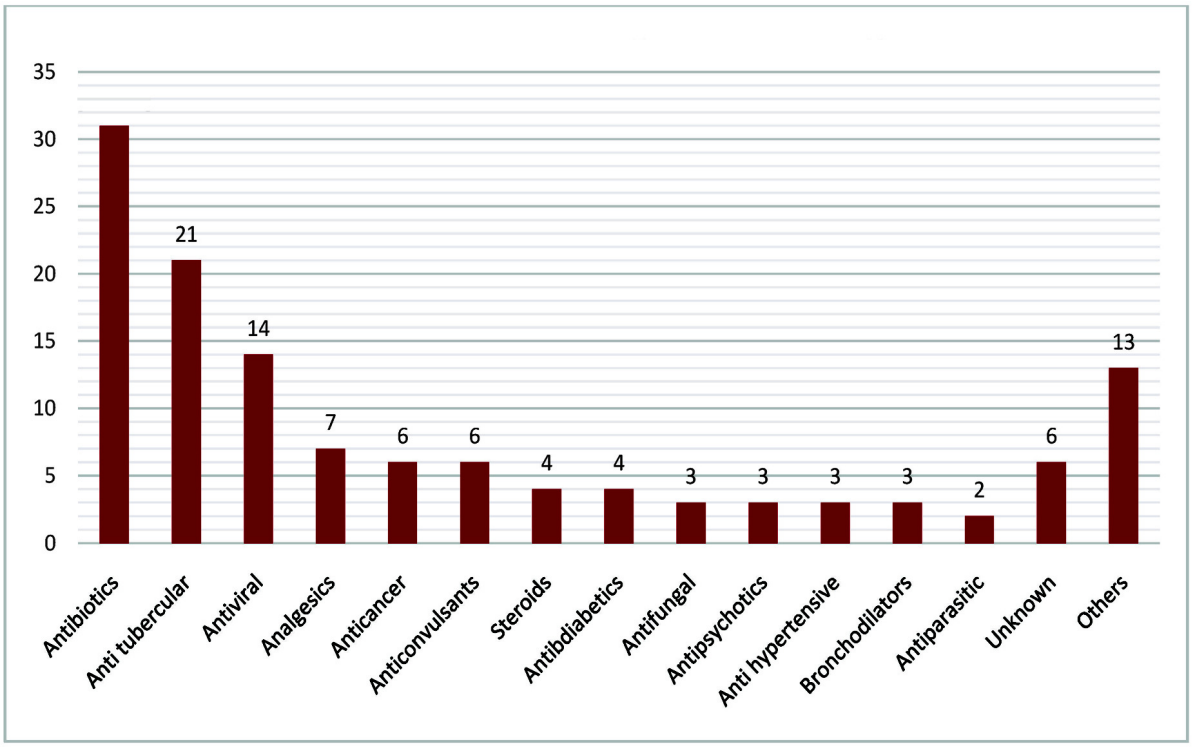
Seriousness of ADR	N = 126
Yes	114
No	12

3. System involved in ADR : N = 126



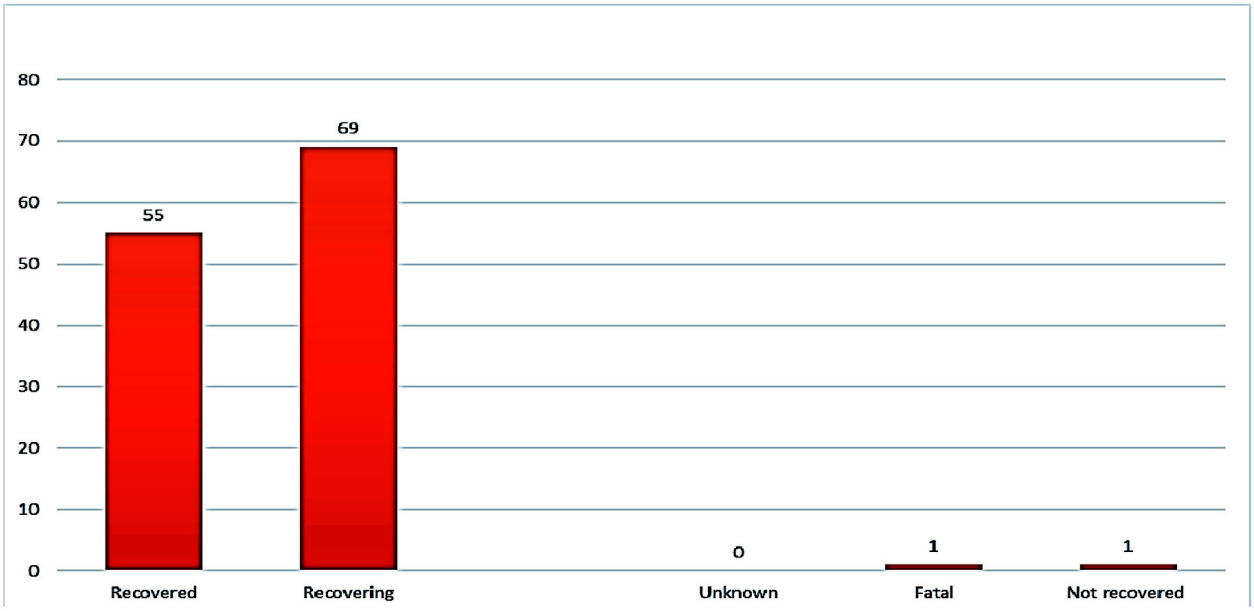
Other system fever with or without chills, immunological, renal system, electrolyte disorder and ocular system.

4. Class of the suspected drug

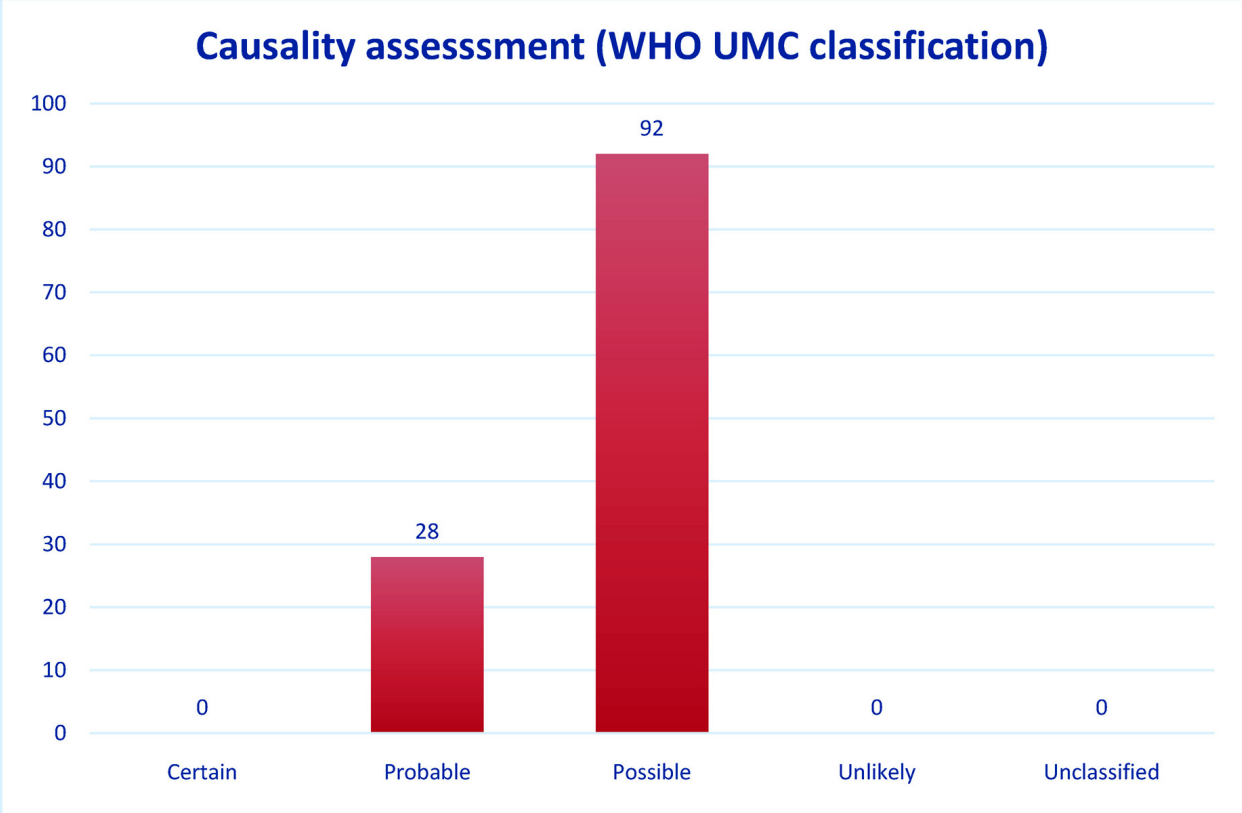


Other system one ADR each of anesthetic agent, antigout agent, antiplatelet, vitamins supplements and proton pumpinhibitors.

5. Outcome of the reactions : N = 126



6. Causality assessment (WHO UMC Classification) : N = 126



No causality assessment was done for unknown drugs = 06

EVALUATION OF A CASE

D-PENICILLAMINE INDUCED PANCYTOPENIA - A CASE REPORT

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Introduction

Wilson's disease (WD), also called hepatolenticular degeneration, is an autosomal recessive inheritance disorder of copper metabolism characterized by the multiple mutations in the ATP-ase 7B gene of chromosome 13q with prevalence of approximately 1 in 30,000 live births [1]. Early treatment for WD usually leads to better prognoses. The drugs, also named as anticopper agents, are commonly used in clinics including D-penicillamine, trientine, sodium dimercapto-succinate, dimercapto-succinic acid, zinc and tetrathiomolybdate [2].

As the conventional anticopper, earliest first choice for WD, D-penicillamine has worldly been of the advantage of high excretion amount of urine copper. Studies have confirmed that D- penicillamine has a better curative effect on WD patients but shows negative influences on neurologic function, seen in 10% - 50% patients with WD. About half of those patients suffered from irreversible damage [2,3]. The above study was in patients who also had underlying liver damage. D-penicillamine may cause series of adverse reactions such as: gastrointestinal symptoms and anaphylactic reaction at the early stage, leukocytopenia, thrombocytopenia, haemolytic anemia and autoimmune systemic diseases in the long-term usage. [4,5]

Pancytopenia is a common haematological condition often encountered in day to day clinical practice. It is defined as a decrease in all the three cell lines of blood viz., red blood cells, leucocytes, and platelets. Many diseases affect production of these cells by bone marrow resulting into pancytopenia i.e., simultaneous presence of anaemia, leukopenia, and thrombocytopenia. Pancytopenia is defined as haemoglobin of < 9 gm/dl, WBC < 4,000/cmm, and platelets < 100,000/cmm. Severe pancytopenia is defined as absolute neutrophil count < 500/cmm, platelet count < 20,000/cmm, and corrected reticulocyte count < 1% [6,7].

Haematological disorders arise through a variety of mechanisms and etiologies. Drug-induced haematological disorders can span almost the entire spectrum of haematology, affecting red cells, white cells, platelets, and the coagulation system. Most recent reviews of drug-induced haematological

disorders focused on specific drugs or cytopenia's [8]. There are very few cases noted with D-penicillamine related pancytopenia. One such case is presented in here.

CASE

18-yrs old female presented with complaints of fever associated with chills and rigors for 8 days, and history of generalized body pains, cough and cold. She was a known case of Wilson's disease for 6 years and was taking Tablet D-Penicillamine 250mg twice a day. On general examination patient was found to be conscious, febrile. On systemic examination pulse rate was 90 beats/min, blood pressure was 110/70mmHg, all other systems were normal. She did not have petechiae, purpura, overt or focal neurological signs. A partial Kayser Fleischer ring was identified.

Laboratory investigations showed Hb 9 g/dL (N=12-15g/dL), WBC- 1,500 Cells/µmm (N=5000-10,000 Cells/µmm) and platelet count was 69,000 /cmm(N=1.5-4.0 lakhs/cmm). All other parameters were within normal range. On bone marrow examination, decreased hematopoietic stem cells were noted. D-penicillaminewas suspected to be the cause of pancytopenia.Treatment with D-penicillamine was stopped after confirmation of pancytopenia by complete blood count(CBC) and bone marrow report.

Patient was treated with Inj. Ceftriaxone 1.5g, IV, twice a day; Inj. Paracetamol 650mg, IV, thrice a day; Inj. Pantoprazole 40mg, IV, once a day; Inj. Vitamin K 10mg, IM, once a day; Tab. Zinc 50mg/ thrice a day and Tab. Pyridoxine 25mg/ twice a day. Patient recovered 10 days after stopping D-penicillamine with improvement of laboratory;Hb was 10 g/dL,WBC was 5,200 Cells/µmm and platelet count was 1.02 lakhs /cmm.

In this case, there was a reasonable time relationship between drug intake and occurrence of ADR, noalternative disease or drugs likely to cause this clinical presentation and positive improvement on de-challenge. Thus, as per WHO UMC causality is"probable" for the occurrence of the ADR of pancytopenia and administration of D-penicillamine. Severity was assessed by Hartwig scale and it was a moderate reaction. [9,10]

DISCUSSION

Treatment of WD is based on several chelating agents (D-penicillamine and trientine) and zinc salts for medical therapy. In general, the approach for treatment is dependent on whether the patient is symptomatic or asymptomatic and on the predominant manifestation of the symptoms (neurological or hepatic). Although it is clearly effective, D-penicillamine has serious toxicity. The side-effects include immunological conditions (lupus-like reactions, nephrotic syndrome, myasthenia gravis and Good-pasture syndrome), skin defects (degenerative changes and elastosis perforans serpiginosa) and joint disorders (arthropathy). [11,12]

D-penicillamine is the mainstay of treatment of Wilson's disease. It is a sulphur containing metabolite of penicillin. It acts as a copper chelating agent. It should be started as small dose because large amount of released copper from liver will deposit in CNS and may worsen the neurological symptoms. After treatment, copper gets quickly mobilized by tissues and is eliminated in urine.[13,14] Our patient was on penicillamine therapy since last six years.

Pancytopenia may present clinically as anaemia, leukopenia, and/or thrombocytopenia. Anaemia may present with fatigue, breathlessness, and cardiac symptoms. Neutropenia may present with febrile illness due to increased susceptibility to infections. Patients with thrombocytopenia may present with mucocutaneous bleed or bruising which was not present in this case. Pancytopenia should be suspected on clinical grounds in any patient presenting with unexplained anaemia, prolonged fever and bleeding tendency.[8] In our case, patient presented with acute febrile illness which lead to suspicion of pancytopenia which was confirmed by bone marrow examination.

The D-Penicillamine was stopped and Zinc tablet 50mg was prescribed on 2nd day of admission and patient was reviewed after 10 days, when her anemia, leukopenia and thrombocytopenia had improved.[15]

Other drugs implicated in inducing pancytopenia include antirheumatic drugs, anti-thyroid medications, anti-tuberculous drugs, NSAIDs, and anticonvulsants. Specific drugs cited includechloramphenicol, butazone, sulfonamide, gold salts, penicillamine, amidopyrine, trimethoprim/sulfamethoxazole, methimazole, and felbamate.[16]

The haematological adverse effects of the chelating agent penicillamine include leukopenia, thrombocytopenia, agranulocytosis and rarely aplastic anaemia. Penicillamine by chelating and excreting copper leads to copper deficiency which induces anemia and other cytopenia's. Copper is an essential cofactor for many redox enzymes essential for optimal erythropoiesis, including cytochrome oxidase and ceruloplasmin ferroxidase and it is hypothesized that decreased activity of these enzymes may lead to anemia. Patient responded well to the administration of Zinc which acts as a anticopper agent. The safety and long-term efficacy of zinc as maintenance therapy has been well shown in both adults and children.[17,18] For prevention of such adverse effects 24-hour urine copper 4 times peryear initially, then at least twice per year, Serum freecopper 4 times per year initially, then at least twice peryear should be monitored.[19]

Conclusion

WD is a rare disease with drug treatment modalities including D-penicillamine, trientine and zinc salts. D-penicillamine is usually a frequent offender in neurological toxicities when used in WD but can also lead to pancytopenia as seen in our patient. Physician neds to be vigilant to suspect this adverse effect with penicillamine therapy. Such patients improve on stopping the drug and substituting with zinc salts.

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PUBLISHED CASE REPORTS ON D-PENICILLAMINE INDUCED BONE MARROW TOXICITY

Compiled by Dr. Jaisen Lokhande

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D-Penicillamine Induced Aplastic Anemia - A Case Report

Vinay Aluri*, Pravallika Guttu, Shourya Shaga, Dr. Uma Maheswara Rao V

European Journal of Biomedical and Pharmaceutical Sciences.2016;3(3):494-496

Acquired aplastic anemia is characterized by pancytopenia anemia, neutropenia, and thrombocytopenia with a hypocellular bone marrow and no gross evidence of increased peripheral blood cell destruction. In this case the patient has taking D-penicillamine since 1 year in the treatment of Wilson disease, which has been lead to decreased hematopoietic stem cells. Adverse effects of penicillamine include Agranulocytosis, Alopecia, Anorexia, epigastric pain, nausea, vomiting, diarrhea Aplastic anemia. Practioners should consider the use of D-penicillamine with Zinc in the treatment of Wilson's disease.

Toxicity of D-penicillamine in rheumatoid arthritis. Report of 63 patients including two with aplastic anemia and one with the nephrotic syndrome.

Weiss AS, Markenson JA, Weiss MS, Kammerer WH.

Am J Med. 1978 Jan;64(1):114-20.

To assess toxicity of D-penicillamine a retrospective chart review was performed on 63 patients with rheumatoid arthritis receiving penicillamine. These patients had a total of 83 courses of therapy. The mean age of patients was 52 years and the mean duration of disease was 10.07 years. Laboratory data showed an increase in hematocrit values from 36 per cent to 40 per cent and a decrease in the erythrocyte sedimentation rate from an average of 50 to 29 mm/hour. The platelet count also decreased with treatment from 394,000 to 267,000/mm3. The over-all complication rate was 53 per cent. Life-threatening complications occurred in two patients including one case of aplastic anemia and one case of nephrotic syndrome. One additional patient was referred with aplastic anemia. Minor complications include rash in 18 per cent, loss of taste in 6 per cent, dyspepsia in 11 per cent, oral ulceration in 7 per cent and proteinuria of less than 3 g/day in 8 per cent. In summary, 53 per cent of the courses of penicillamine were associated with toxicity including one episode of aplastic anemia and one case of nephrotic syndrome. Therapy was stopped due to complications in 39 per cent of the patients in this series.

Development of Fatal Bone Marrow Suppression during D-Penicillamine Therapy in Three Patients with Rheumatoid Arthritis

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Japanese Journal of Clinical Immunology.1983;6(2): 132-138

Three patients with advanced rheumatoid arthritis developed fatal pancytopenia in one case and fatal agranulocytosis in the other two, during the course of D-penicillamine therapy. One patient with classical rheumatoid arthritis experienced fatal pancytopenia after four year treatment of 600mg/day of D-penicillamine which had successfully inhibited acute arthritic episodes during that time. Without any abnormal data suggestive of blood crisis in routine peripharal blood analysis, the patient had begun to complain of palpitation and arrhythmia. The later blood count revealed severe anemia (Hb 6.2g/dl)with leukopenia (2100/mm3). Every effort of suporting therapies including transfusions of fresh blood and platelets, injections of high doses of corticosteroid and protection against life-threatening infections seemed to be of no value for improvement of his pancytopenia and for sequential severe infections. He died from asphyxiation in air way bleeding after two months of hospitalization.

The other two patients with classical rheumatoid arthritis experienced sudden catastrophes similar to the condition of sepsis with agranulocytosis. Until the attaks of high fever and acute arthritis, they had been treated with 400mg/day or 200mg/day or 300mg/day of D-penicillamine only for one month with no beneficial effect for their arthritis. They were immediately hospitalized and were found to have leukopenia with little evidence of anemia and thrombocytopenia in their peripheral blood. On the second day in the hospital, agranulocytosis was seen without any changes of platelet and erythrocyte counts and was continued till the sixth day when they died from cerebral bleeding and septic shock respectively.

Our three patients were characterized to possess advanced arthritic lesions, severe infections at the time of fatal blood disturbance and relatively heavy doses of anti-rheumatic drugs including corticosteroids, gold and non-steroidal anti-inflammatory drugs before the start of D-penicillamine. These suggest that our patients had been already suppressed hemopoiesis in bone marrow presumably due to several causes including rheumatoid arthritis itself and medications other than D-penicillamine. In addition, adrenal insufficiency caused by long use of steroid may play a role in sudden onset of severe infections which may result in further consumption of leukocytes. As known to have direct cytotoxic effect on bone marrow or to trigger the immunological reactions toward elimination of leukocytes and other cells, D-penicillamine may further suppress the bone marrow functions enough to be realized by routine blood analysis.

Although our data of three patients are not enough to elucidate the mechanism of marrow suppression or leukopenia by D-penicillamine, learning of rare cases with fatal pancytopenia or agranulocytosis during D-penicillamine therapy may be important for revaluation of the drug and also general clinics of patients with rheumatoid arthritis.

REGULATORY UDATE AND MEDICAL NEWS

Compiled by Dr. Swati Patil
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Clarithromycin: Drug Safety Communication - Potential Increased Risk of Heart Problems or Death in Patients with Heart Disease.

BACKGROUND: Clarithromycin is used to treat many types of infections affecting the skin, ears, sinuses, lungs, and other parts of the body, including Mycobacterium avium complex (MAC) infection, a type of lung infection that often affects people with human immunodeficiency virus (HIV). Clarithromycin is not approved to treat heart disease.

ISSUE: FDA is advising caution before prescribing the antibiotic clarithromycin to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later. FDAs recommendation is based on a review of the results of a 10-year follow-up study of patients with coronary heart disease from a large clinical trial that first observed this safety issue.

The large clinical trial, called the CLARICOR trial, observed an unexpected increase in deaths among patients with coronary heart disease who received a two-week course of clarithromycin that became apparent after patients had been followed for one year or longer. There is no clear explanation for how clarithromycin would lead to more deaths than placebo. Some observational studies also found an increase in deaths or other serious heart-related problems, while others did not. All the studies had limitations in how they were designed. Of the six observational studies published to date in patients with or without coronary artery disease, two found evidence of long-term risks from clarithromycin, and four did not. Overall, results from the prospective, placebo-controlled CLARICOR trial provide the strongest evidence of the increase in risk compared to the observational study results. Based on these studies, FDA is unable to determine why the risk of death is greater for patients with heart disease.

As a result, FDA added a new warning about this increased risk of death in patients with heart disease, and advised prescribers to consider using other antibiotics in such patients. FDA also added the study results to the clarithromycin drug labels. As part of FDA's usual ongoing safety monitoring of drugs, we are continuing to monitor safety reports in patients taking clarithromycin.

RECOMMENDATION: Healthcare professionals should be aware of these significant risks and weigh the benefits and risks of clarithromycin before prescribing it to any patient, particularly in patients with heart disease and even for short periods, and consider using other available antibiotics. Advise patients with heart disease of the signs and symptoms of cardiovascular problems, regardless of the medical condition for which you are treating them with clarithromycin.

Clarithromycin: Drug Safety Communication - Potential Increased Risk of Heart Problems or Death in Patients With Heart Disease. [Internet]. [Cited on April 2018]. Available from https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm597862.htm

Febuxostat: Drug Safety Communication - FDA to Evaluate Increased Risk of Heart-related Death.

ISSUE: FDA is alerting the public that preliminary results from a safety clinical trial show an increased risk of heart-related death with febuxostat.

BACKGROUND: Febuxostat is FDA-approved to treat a type of arthritis called gout in adults. Gout happens when a naturally occurring substance in the body called uric acid builds up and causes sudden attacks of redness, swelling, and pain in one or more joints. Febuxostat works by lowering uric acid levels in the blood.

The febuxostat drug labels already carry a Warning and Precaution about cardiovascular events because the clinical trials conducted before approval showed a higher rate of heart-related problems in patients treated with febuxostat compared to allopurinol. These problems included heart attacks, strokes, and heart-related deaths. As a result, FDA required an additional safety clinical trial after the drug was approved and on the market to better understand these differences, and that trial was finished recently.

The safety trial was conducted in over 6,000 patients with gout treated with either febuxostat or allopurinol. The primary outcome was a combination of heart-related death, non-deadly heart attack, non-deadly stroke, and a condition of inadequate blood supply to the heart requiring urgent surgery. The preliminary results show that overall, febuxostat did not increase the risk of these combined events compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of heart-related deaths and death from all causes.

RECOMMENDATION: Health care professionals should consider this safety information when deciding whether to prescribe or continue patients on febuxostat.

Uloric (febuxostat): Drug Safety Communication - FDA to Evaluate Increased Risk of Heart-related Death. [Internet]. [Cited on April 2018]. Available from https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm585281.htm

MATCH THE FOLLOWING DRUG WITH ITS ADVERSE EFFECT.

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1	Octreotide	a	Peripheral Neuropathy
2	Asparginase	b	Suicidal tendencies
3	Tamsulosin	c	SIADH
4	Rituximab	d	Papilloedema
5	Dipyridamole	e	Increased risk of MI
6	Rimonabant	f	Coronary Steal Phenomenon in elderly
7	Ascorbic acid	g	Gynaecomastia
8	Bortezomib	h	Severe diarrhea
9	Paromomycin	i	Gall stones on longterm
10	Hypervitaminosis	j	Infusion related hypersensitivity
11	Vincristine	k	Constipation
12	Irinotecan	l	Oxalate Stones
13	Rosiglitazone	m	Floppy Iris Syndrome
14	Tricyclic Antidepressants	n	Ototoxicity
15	Cimetidine	o	Haemorrhagic Pancreatitis

Answers : 1 - i; 2 - o; 3 - m; 4 - j; 5 - f; 6 - b; 7 - l; 8 - a; 9 - n; 10 - d; 11 - c; 12 - h; 13 - e; 14 - k; 15 - g

ALPHABET 'R' PUZZLE

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LTMMC & GH, Sion, Mumbai - 22.

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

Clues

1. Being a CYP3A4 inducer, _____lowers the AUC of Indinavir by 90%, and so the combination is contraindicated in HIV patients with tuberculosis.
2. The dose limiting toxicity of this Camptothecin analog is severe diarrhea, which is seen in about 35% of patients.
3. Thrombocytopenia (28%), fatigue (12%), peripheral neuropathy (12%) and neutropenia (11%) are the most common adverse effects seen when this monoclonal antibody is prescribed in patients of multiple myeloma.
4. Gastrointestinal side effects like diarrhea, nausea and abdominal pain occur in upto 50% and gall stones in about 25% patients receiving this somatostatin analog.
5. Besides cessation of antipsychotic treatment and supportive care, administration of _____ or Bromocriptine is the specific treatment for antipsychotic induced neurolept malignant syndrome.
6. Since serious nephrotoxicity results from parenteral use of this antibiotic obtained from the Tracy -I strain of Bacillus subtilis, its current use is restricted to topical application only.
7. The most serious adverse effect during chronic _____ therapy is pulmonary fibrosis, for which, underlying lung disease and doses of 400mg/day appear to be the risk factors.
8. _____ is a rare and reversible side effect of ACE inhibitors, even in absence of hyperglycemia.
9. Elevation of serum transaminases is observed in upto 50% of patients of _____ disease treated with Tacrine.
10. Among all HIV protease inhibitors, _____ causes maximum incidence of skin eruptions (27%).

ALPHABET 'R' PUZZLE: ANSWERS :

1. Rifampicin
2. Irinotecan
3. Bortezomib
4. Octreotide
5. Dantrolene
6. Bacitracin
7. Amiodarone
8. Glycosuria
9. Alzheimer's
10. Amprenavir

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

Please feel free to contact us for the same.

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