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FOREWORD

India has one fifth of world’s tuberculosis (TB) cases. Despite major achievements of Revised National TB Control Programme (RNTCP) like 70% case detection and 85% cure rate, tuberculosis continues to be a major public health problem in India with more than 2 million incident TB cases estimated every year and about 1000 deaths every day. TB control in India is further challenged by emergence of drug resistance, co-infection with HIV and widespread mismanagement of TB in the unorganized, unregulated private health sector, especially in the urban areas which provides treatment to nearly 60% patients outside the purview of the national programme. While default is the major problem in interruption of chemotherapy of tuberculosis, adverse drug reactions hardly accounts for stopping treatment. The adverse drug reactions of first line drugs which occur in minority of patients are completely manageable. Rise in hepatic enzymes with or without nausea and vomiting are commonest side effects of first line drugs like isoniazid and rifampicin. Only rare side effects like thrombocytopenia, haemolytic anemia, acute renal failure due rifampicin, vestibular toxicity due to streptomycin injection, retinoblar neuritis due to ethambutol require permanent stopping of these drugs. Certain anti-TB drug side effects can occur in specific population, for example INH fast acetylators in Japanese and Eskimos are more prone to develop hepatitis and slow acetylators like Scandinavian are likely to develop peripheral neuropathy. The proportion of slow acetylators among Japanese and Eskimos is about 10%; among Chinese about 20%; among Caucasians, Negroes, and South Indians about 60%. Similarly alcoholics are more prone to develop hepatitis, peripheral neuropathy, pellagra due to INH. Thiacetazone causes more adverse skin reaction in HIV patients. Similarly drug interactions can occur between ART agents and Anti-TB drugs. Rifampicin by virtue of hepatic microsomal enzyme induction can increase metabolism of some drugs and render them clinically ineffective. For example Oral Contraceptive failure leading to unwanted pregnancy and difficulty in controlling diabetes with oral hypoglycaemic agents. Certain anti-TB drugs are contraindicated in pregnancy, like ethionamide is teratogenic, streptomycin causes congenital deafness, and fluoroquinolones cause slowing of cartilage growth. However if life of mother is in danger benefit of use must be weighed against risk involved.

The second line anti-TB drugs required to treat multi drug resistant (MDR) TB are more toxic and duration being longer are not tolerated by patients. Therefore constant counselling and reassurance are required. The frequency of adverse effects in few literature are nausea/vomiting 32.8%, diarrhoea 21.1%, arthralgia 16.4%, dizziness/vertigo 14.3%, hearing disturbances 12.0%, headache 11.7%, sleep disturbances 11.6%, electrolyte disturbances 11.5%, abdominal pain 10.8%, anorexia 9.2% and gastritis 8.6%. Apart from this, visual problems may result from ethambutol, cycloserine,
ethionamide etc requiring stopping the drugs for the fear of permanent blindness. When MDR TB patient is put on treatment with second line drugs the patients must be made aware of these adverse drug reaction and need for tolerating in order to survive.

Drugs can be continued with ancillary treatment for some side effects like minor itching with use of antihistaminics; psychosis resulting from isoniazid, cycloserine, ethionamide treated with antipsychotics; peripheral neuropathy from isoniazid with pyridoxine in dosage of 80-100 mg; pyrazinamide induced rise in uric acid with symptoms of gout with anti-inflammatory drugs or allopurinol; hypothyroidism resulting from PAS and ethionamide with Levothyroxine. So majority of drug reactions have some solution. The treatment requires team work of different specialists to tackle menace of ADR. Some require immediate attention and some require more workup in due course.

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ADVERSE EFFECTS OF ANTI-TUBERCULOSIS THERAPY AND ITS MANAGEMENT

Dr Kalpesh Dalvi, Assistant Professor, Department of Pharmacology

Tuberculosis (TB) is considered a “global emergency” by the World Health Organization (WHO). In 2010, there were an estimated 8.8 million incident cases of TB worldwide, equivalent to 128 cases per 100,000 population. Most of the estimated number of cases in 2010 occurred in Asia (59%) and Africa (26%); smaller proportions of cases occurred in the Eastern Mediterranean region (7%), the European region (5%) and the American region (3%). India accounts for an estimated one quarter (26%) of all TB cases worldwide. In 2010, estimated number of TB cases in India were around 2.0 million-2.5 million.\(^1\)

Anti-tuberculosis (TB) chemotherapy regimens have been in use for more than 30 years, however their frequency of severe complications are not well known, probably due to lack of detection, awareness and also under-reporting. The anti-TB therapy includes use of wide spectrum of drugs for a long term depending on the category of TB infection: new cases, re-infection, relapses, failures, MDR-TB or XDR-TB.\(^2,3\)

It is understandable that many patients on anti-TB drugs have adverse reactions which may set hurdles to treatment and also have influence on the treatment outcomes. It is difficult to determine the efficacy or toxicity of each drug among the anti-TB drugs, since it is administered in combination regimens of several drugs.\(^4\) Therefore, close monitoring of patients is essential to ensure that the adverse effects of anti-TB drugs are recognised as soon as possible by healthcare personnel. The ability to monitor patients for adverse effects is one of the main advantage of directly observed treatment (DOT) in comparison with self administration. Therefore, any healthcare provider who is treating a TB patient should assume a public health function that includes not only prescribing an appropriate regimen, but also ensuring patients adherence to the regimen and monitoring side-effects of drugs until treatment is completed.\(^4,5\) This article highlights the most frequent side effects associated with anti-TB drugs, their detection and appropriate management to be taken.

Adverse Effects of Anti-TB Drugs

Anti-TB drugs consist of first-line and second line drug therapy. The first-line therapy is usually used for the treatment of TB patients with susceptible mycobacterium tuberculosis whereas second-line or reserve anti-TB drugs are used for the treatment of multidrug-resistant TB (MDR-TB).\(^4,6\) It is found that second-line anti-TB drugs have many more adverse effects than the first-line anti-TB drugs.\(^7\) The common adverse effects of first- and second-line anti-TB drugs are given in Tables 1 and 2.\(^4,8\)
Table 1: Adverse effects of first-line anti-TB drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main effects</th>
<th>Rare effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Peripheral neuropathy, skin rash, hepatitis, sleepiness and lethargy</td>
<td>Convulsions, psychosis, arthralgia, anaemia</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Abdominal pain, nausea, vomiting, hepatitis, generalised cutaneous reactions, acute renal failure, thrombocytopenic purpura</td>
<td>Osteomalacia, haemolytic anaemia</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Arthralgia, hepatitis, gastrointestinal intolerance</td>
<td>Cutaneous reactions, sideroblastic anaemia</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Retrobulbar neuritis</td>
<td>Generalised cutaneous reactions, arthralgia, peripheral neuropathy hepatitis (very rare)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Vestibular and auditory nerve damage, renal damage, cutaneous hypersensitivity</td>
<td>Pain, rash, induration at injection site, numbness around the mouth and tingling soon after the injection</td>
</tr>
</tbody>
</table>

Table 2: Adverse effects of second-line anti-TB drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main effects</th>
<th>Rare effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin, Amikacin, Capreomycin</td>
<td>Vestibular (vertigo) and auditory nerve damage, nephrotoxicity</td>
<td>Cutaneous hypersensitivity, renal failure</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Gastrointestinal: anorexia, nausea, diarrhoea, abdominal pain, hepatotoxicity</td>
<td>Psychotic reactions including hallucinations and depression, impotence, gynaecomastia, hypothyroidism.</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Gastrointestinal: anorexia, nausea, vomiting</td>
<td>Anxiety, dizziness, headache, convulsions, rupture of the achilles tendon, cartilage damage (with intrauterine exposure)</td>
</tr>
<tr>
<td>Cycloserine hypersensitivity</td>
<td>Dizziness, headache, depression, psychosis, convulsions</td>
<td>Suicidal tendencies, generalised</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>Gastrointestinal: anorexia, nausea, vomiting, hypersensitivity reactions (fever, rash, pruritus)</td>
<td>Hypothyroidism, haematological reactions</td>
</tr>
<tr>
<td>Thioacetazone</td>
<td>Skin rash, sometimes with mucosal involvement</td>
<td>Acute hepatic failure</td>
</tr>
</tbody>
</table>
Majority of patients complete their treatment without any significant adverse effects of drugs. The main adverse effects of anti-TB drugs usually occur during the first two to three weeks of treatment. It is therefore important that patients should be clinically monitored during treatment so that adverse effects can be detected and treated well in time. Healthcare personnel can teach patients how to recognize symptoms of common adverse effects due to anti-TB drugs and to report those if any.

Rapid evaluation, diagnosis and management of adverse effects are very important, even if the adverse reaction is minor and not dangerous. If the adverse effect is minor, the treatment should not be stopped. In such conditions, ancillary drugs may be useful to relieve side effects. Agents can be used for prophylaxis or prevention of side effects of particular anti-TB drugs eg. Vitamin B6 (pyridoxine) should be prescribed to patients receiving isoniazid or cycloserine to prevent neurological adverse effects.

Symptom-based approach to AKT induced adverse effects

Table 3 and 4 gives a brief description on guidelines for management of the most common adverse effects of anti-TB drugs. If a patient develops a major side-effect, the offending drug is generally stopped. Further management depends on the nature of the adverse reaction. Patients with major adverse reactions should be managed in a hospital.

**Table 3: Symptom-based approach to the management of minor adverse effects**

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Drug(s) probably responsible</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia, nausea, abdominal pain</td>
<td>Pyrazinamide, rifampicin, ethionamide, prothionamide, fluoroquinolones, paraaminosalicylic acid,</td>
<td>Give drugs with small meals or last thing at night</td>
</tr>
<tr>
<td>Joint pains/arthralgia</td>
<td>Pyrazinamide, ethambutol, isoniazid, ofloxacin</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Burning sensation in feet</td>
<td>Isoniazid</td>
<td>Add Pyridoxine</td>
</tr>
<tr>
<td>Orange/red urine</td>
<td>Rifampicin</td>
<td>Reassurance.</td>
</tr>
</tbody>
</table>
Table 4: Symptom-based approach for management of major adverse effects.\(^{[4,5,9]}\)

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Drug(s) probably responsible</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness (vertigo and nystagmus)</td>
<td>Streptomycin, kanamycin, amikacin, capreomycin</td>
<td>Stop responsible drug, use alternate drugs</td>
</tr>
<tr>
<td>Deafness (no wax on autoscopy)</td>
<td>Streptomycin, kanamycin, amikacin, capreomycin</td>
<td>Stop responsible drug, use alternate drugs</td>
</tr>
<tr>
<td>Jaundice, hepatitis (other causes excluded)</td>
<td>Pyrazinamide, rifampicin, isoniazid, thioacetazone, ethionamide, prothionamide, para-aminosalicylic acid</td>
<td>Stop anti-TB drugs. Re-introduce drugs grouped serially while monitoring liver function, with most likely agent introduced last, (explained later)</td>
</tr>
<tr>
<td>Visual impairment (other causes excluded)</td>
<td>Ethambutol</td>
<td>Stop ethambutol. Visual examination</td>
</tr>
<tr>
<td>Confusion (suspect drug-induced acute liver failure if jaundice present)</td>
<td>Suspect drug-induced hepatitis</td>
<td>Stop anti-TB drugs. Urgent liver function tests and prothrombin time. If there is jaundice, stop hepatotoxic drugs otherwise suspect INH induced psychosis and seek psychiatric advice</td>
</tr>
<tr>
<td>Itching, skin rash</td>
<td>Thioacetazone, pyrazinamide, rifampicin, isoniazid, streptomycin</td>
<td>Stop responsible drug Antihistamines, steroids, (explained later)</td>
</tr>
<tr>
<td>Shock, purpura, acute renal failure</td>
<td>Rifampicin, streptomycin, kanamycin, amikacin, capreomycin</td>
<td>Stop suspected drug. Use different combinations of drugs</td>
</tr>
</tbody>
</table>

Management of adverse effects of anti-TB drugs:

**Hepatitis**

Hepatotoxicity is consistently the most common serious adverse reaction in patients taking anti-TB drugs. Isoniazid, pyrazinamide and rifampicin which are commonly responsible are stopped and can be replaced with streptomycin and ethambutol. Asymptomatic rise in transaminases are common and if it is less than five times the upper limit of normal withdrawing medication is not needed.\(^{[8,10]}\)

Hepatotoxicity is described in more detail in the following article "Anti tubercular drug induced hepatotoxicity" in this issue.
Gastrointestinal adverse effects

Gastrointestinal (GI) adverse effects like nausea, vomiting, poor appetite, abdominal pain are very common and usually occur in the first few weeks of therapy. Many of the anti-TB drugs can cause gastrointestinal upset. In the presence of gastrointestinal symptoms hepatotoxicity should be ruled out.

The initial approach to gastrointestinal adverse effects is to change the hour of drug administration and/or to administer the drugs with food.[6]

Cutaneous reaction

All drugs used in treating tuberculosis can cause a cutaneous reaction. Management of a cutaneous reaction depends on whether or not the patient is receiving thioacetazone.

If patient’s treatment regimen includes thioacetazone and develops pruritus, with or without a rash, and there is no other obvious cause (e.g. scabies), anti-TB drugs should be stopped immediately. If there is severe rash, or if there is mucosal involvement or hypotension, the patient will need intravenous fluids, and possibly steroids. Treatment is restarted only when the rash has resolved and replacing thioacetazone with ethambutol. A patient must never receive thioacetazone again after any thioacetazone reaction.

If patient’s treatment regimen does not include thioacetazone and develops itching and there is no other obvious cause (e.g. scabies), the recommended approach is to try symptomatic treatment with antihistamines, reassurance and avoiding dry skin, continue TB treatment and observe the patient closely. However, if a skin rash develops all anti-TB drugs must be stopped. Once the reaction has resolved, anti-TB drugs can be reintroduced by systematic rechallenge if the culprit drug is not known.[5] The procedure for rechallenge is explained in detail in the case-report of this issue.

Peripheral Neuropathy[4]

Peripheral neuropathy is primarily caused by isoniazid and to a lesser extent by ethambutol. Peripheral neuropathy due to isoniazid results from inhibition of the formation of the co-enzyme form of vitamin B6, i.e. pyridoxine. Peripheral neuropathy occurs in about 2% of patients if pyridoxine is not given in the recommend doses. Clinical presentation of peripheral neuropathy is prickling, tingling or burning sensation of the fingers and/or toes that usually occurs in a stocking glove distribution. The addition of pyridoxine at a dose of 10mg/day for preventive and 100-120mg/day for therapeutic purposes markedly reduces neurotoxicity. In otherwise healthy people, prescription of pyridoxine is not mandatory. However, it should be routinely
given to those patients who are at greater risk of developing peripheral neuropathy i.e. pregnant women, patients with chronic liver disease, cancer patients, malnourished patients, uremic patients, elderly patient, diabetic patients and chronic alcoholics.

Ocular toxicity (Optic Neuritis)

The main causative agent that decreases visual acuity and may lead to irreversible blindness is ethambutol. It is a dose related side effect. This ADR is not commonly seen with dose less than 25 mg/kg/day during the first 2 months of treatment and 15 mg/kg/day thereafter. At a dose of 15 mg/kg/day for maintenance therapy, ocular toxicity developed in only 1.6% of patients. Advanced age, renal insufficiency, and diabetes can enhance ocular damage.[10]

Ethambutol is a chelating agent and makes zinc unavailable for axoplasmic transport, provoking optic or retrobulbar neuritis. Patients with zinc blood concentrations below 0.7 mg/ml (reference range 0.9-1.0 mg/ml) before the use of ethambutol are at high risk of ocular disturbances.[11]

Clinical presentation includes blurred vision, "spots" present in the patient's field of vision or red/green colour blindness. These signs can happen to one or both eyes. Colour vision and visual acuity should be examined before beginning ethambutol and every 2-4 weeks during treatment. More than 10% visual loss is considered significant. Ethambutol should be permanently discontinued, if decrease in visual acuity is confirmed. Ethambutol is not recommended in children under 5 years old since visual changes are difficult to monitor.[12]

Renal Failure[9]

Nephrotoxicity is one of the serious adverse effects caused by injectable anti-TB drugs (streptomycin, kanamycin, amikacin and capreomycin). This serious complication can be fatal. The suspected anti-TB drugs causing nephrotoxicity should be discontinued. Monthly monitoring of serum creatinine is vital in case of nephrotoxic drug in the regimen. In addition, patients with history of renal disease (including co-morbidities such as HIV and diabetes), advanced age or any other renal symptoms should be monitored more carefully, in particular at the beginning of treatment.

Life threatening adverse effects

Life threatening adverse effects includes anaphylaxis, exfoliative dermatitis, Stevens-Johnson syndrome, severe gastritis with bleeding and severe hepatitis. In such conditions treatment must be stopped. If the offending drug is unknown then all drugs must be discontinued and the patient should be admitted for intensive management.[4]
Conclusion

Adverse effects to Anti-TB drugs generally occur during first 2 to 3 weeks of therapy. If these side effects are not recognised in time and managed properly they can lead to treatment interruption or can even be life-threatening. Therefore, appropriate monitoring has to be carried out during the anti-TB treatment course which includes clinical examination, laboratory tests. Anti-TB treatment adverse effects can be managed by monitoring and early detection of ADR, reducing dosages when it is appropriate, ancillary drugs to treat adverse events, discontinuation of drugs if needed and patient education.

Reference


ANTI-TUBERCULOSIS DRUGS INDUCED HEPATOTOXICITY

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Introduction:

Tuberculosis is widely prevalent in India. According to WHO report 2011, the prevalence of TB in India is 256/1,00,000 population.\textsuperscript{[1]} The adverse effects to tuberculosis treatment diminish its effectiveness, because they significantly contribute to non-adherence, eventually contributing to treatment failure, relapse or the emergence of drug-resistance.\textsuperscript{[2]}

The most frequent adverse effects following the institution of anti-tubercular therapy are hepatitis, dermatological, gastrointestinal and neurological reactions. Anti-tuberculosis drug induced hepatotoxicity (ATDH) is by far the most serious one and although asymptomatic rise in serum transaminase levels are common during anti-tuberculosis treatment; if not recognized early can result in death.

Isotiazid (H), rifampicin (R) and pyrazinamide (Z) are the potentially hepatotoxic drugs among the first line agents, with pyrazinamide being the most toxic.\textsuperscript{[3]} Amongst the second line drugs, ethionamide and para-aminosalicylic acid have greater potential for hepatotoxicity.\textsuperscript{[3]} No/little hepatotoxicity has been reported following ethambutol(E), streptomycin(S) and second line agents like kanamycin, capreomycin, cycloserine and fluoroquinolones.\textsuperscript{[3], [4]}

Definition and incidence:

Drug-induced liver injury (DILI) is ultimately a clinical diagnosis of exclusion. Rechallenge with the suspected offending agent with more than twofold serum alanine aminotransferase (ALT) elevation, and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis.\textsuperscript{[5]}

A common definition of ATDH is a treatment-emergent increase in serum alanine aminotransaminase (ALT) greater than three times the upper limit of normal with symptoms of hepatitis or five times the upper limit of normal without symptoms.\textsuperscript{[6]} The grades of hepatotoxicity have been classified according to the WHO Adverse Drug Reaction Terminology (Table 1).

In general, higher incidences have been reported in India ranging from 8 to 39%.\textsuperscript{[6]} Mild hepatic dysfunction occurs in about 10 to 20% of patients receiving anti-tuberculosis treatment. More serious liver disease induced by anti-TB drugs occurs in 1 to 3% of patients. A study found that the mortality rate was about 2.4% among patients with fulminant ATDH & deaths were related to advanced age, presence of previous hepatotoxicity, and continuation of treatment even after onset of symptoms.\textsuperscript{[7]}
Table 1: WHO definition of hepatotoxicity

<table>
<thead>
<tr>
<th>Grade 1 (mild)</th>
<th>&lt; 2.5 times ULN (ALT 51-125 U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 (mild)</td>
<td>2.5-5 times ULN (ALT 126-250 U/L)</td>
</tr>
<tr>
<td>Grade 3 (moderate)</td>
<td>5-10 times ULN (ALT 251-500 U/L)</td>
</tr>
<tr>
<td>Grade 4 (severe)</td>
<td>&gt;10 times ULN (ALT &gt; 500 U/L)</td>
</tr>
</tbody>
</table>

Since tuberculosis is treated with multiple drugs, the data on incidence with each drug is limited; except for isoniazid being 1-2% when used in prophylactic monotherapy. Incidence of hepatotoxicity for second line agents like ethionamide and para-aminosalicylic acid has been recognized 2% and 0.3% respectively.

**Presentation and Clinical evaluation:**

Anti-tuberculosis DILI has a wide spectrum of presentations, ranging from asymptomatic mild rise in liver biochemical tests to acute hepatitis and acute liver failure. The presentation may be similar to viral hepatitis - jaundice, abdominal pain, nausea, vomiting and asthenia or resembling clinical features of drug allergy in the form of rash, fever and eosinophilia without jaundice.

A feature peculiar to anti-TB drugs is the development of adaptation or tolerance to the drugs. This is defined as elevation of transaminases and or bilirubin, without any symptoms, which resolves with continuation of the drugs. Awareness of the phenomenon of adaptation is critical in tuberculosis to prevent inadvertent discontinuation of anti-tubercular drugs which are critical for successful treatment. Most drug-induced hepatitis occur within the initial 2 months of therapy.

The type of drug induced acute liver injury may be hepatocellular, cholestatic or mixed (Table 2). The liver injury due to isoniazid, rifampin & pyrazinamide is mainly hepatocellular; though conjugated hyperbilirubinemia may be seen with rifampin.

**Table 2: Determining the type of acute liver injury (Ratio (R) of serum activities of ALT/ALP (alkaline phosphatase).**

<table>
<thead>
<tr>
<th>Type</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular</td>
<td>$R \geq 5$, OR (ALT $\geq 2 \times$ ULN and ALP in normal range)</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>$R \leq 2$, OR (ALP $\geq 2 \times$ ULN and ALT in normal range)</td>
</tr>
<tr>
<td>Mixed</td>
<td>$2 &lt; R &lt; 5$ AND (ALT $\geq 2 \times$ ULN and ALP $&gt; \text{ULN}$)</td>
</tr>
</tbody>
</table>
Risk Factors:

**Age & Gender:** Incidence of ATDH is high in adults (about 15%) as compared to children (3-10%).\[^{10}\]** For INH, incidence increases with age.\[^{12}\]** This toxicity is due to decreased clearance of CYP3A4 substrates with advanced age.\[^{13}\]** Risk is more in females as CYP3A activity is more.\[^{11, 13}\]**

**Pre-existing disease:** Many studies have shown that hepatitis B and C co-infection, pre-existing liver disease increase the risk of ATDH.\[^{4}\]** Several studies from India have associated malnutrition and hypoalbuminemia with development of ATDH.\[^{5}\]**

**HIV/AIDS:** HIV-TB co-infection alters oxidative pathway. Combined TB/HIV treatment is often complicated by overlapping toxicities and drug-drug interactions leading to treatment interruption; often delaying Highly Active Anti-Retroviral Therapy (HAART) in HIV-infected TB patients. Rifampicin interacts with antiretroviral drugs raising the plasma levels of these drugs causing hepatotoxicity. Concomitant use of fluconazole is also a risk factor for ATDH.\[^{4}\]**

**Genetic risk factors:** N-acetyltransferase slow acetylator and Glutathione-S-transferase T & M1 null genotypes have higher risk of ATDH.\[^{4,15}\]** Higher CYP2E1 activity increases productions of hepatotoxins. Polymorphisms in pregnane X-receptor (PXR) is involved in CYP3A4 expression; it determines susceptibility to ATDH.\[^{4}\]**

**Alcohol:** Offers a risk of developing hepatitis due to enzyme induction.\[^{4}\]** Risk is higher in alcoholics with malnourishment and glutathione depleted status.

**Dosing schedules:** Daily TB treatment in comparison with thrice-weekly treatment increases the risk of ATDH. However, dosing schedule has only little impact as a risk factor for ATDH in intensive phase.\[^{4}\]**

**Drug interactions:** The incidence of hepatitis with INH increases with co-administration of rifampicin. Concomitant use of ethionamide and para-aminosalicylic acid has shown to increase hepatotoxicity. Allopurinol inhibits enzyme xanthine oxidase which metabolizes pyrazinamide; raised pyrazinamide levels potentiate hepatotoxicity.\[^{5}\]** Loop diuretics increase the serum levels of para-aminosalicylic acid (PAS).\[^{15}\]**

**Mechanism of common drugs causing ATDH:**

**Isoniazid** is metabolized by N Acetyltransferase 2 (NAT2) by acetylation to acetylhydrazine; which is further metabolized to hydrazine. A small amount of INH is directly metabolized by hydrolysis to hydrazine. Recent studies have suggested that hydrazine is the toxic metabolite responsible for irreversible hepatocellular damage; as against the previous hypothesis which held acetylhydrazine as the culprit. Slow acetylators are more often and more severely (two fold) prone to develop hepatitis than fast acetylators as more INH is left for direct hydrolysis to
hydrazine in slow acetylators. TB patients with ATDH have been shown to have lower plasma levels of reduced glutathione and higher malondialdehyde, an oxidative stress marker.[44]

**Rifampicin** causes conjugated hyperbilirubinemia by inhibiting the major bile salt exporter pump.[44] Rifampicin being an enzyme inducer, induces isoniazid hydrolase, thus increasing hydrazine production and may increase chances of ADR. No toxic metabolite has been identified for rifampicin.

**Pyrarizinamide** causes a dose dependent and idiosyncratic hepatotoxicity. Exact mechanism is unknown.[3,5]

**Ethionamide** has a structure similar to Isoniazid.[15] However, mechanism of hepatotoxicity has not been clearly established for ethionamide and para-aminosalicylic acid.

**Prevention and Management of ATDH:**

**Prevention of ATDH:**

Education of the patient and their family members about the risk of TB drugs and the critical need to seek medical attention immediately on development of symptoms should be emphasized. Since old age is a risk factor, a recent study concluded that co-prescription with N-acetylcysteine (NAC) in patients above 60 years prevented ATDH, when compared to those who did not receive NAC.[16]

**Management after diagnosis of DILI:**

Various guidelines for the management of DILI have been propounded by the American Thoracic Society (ATS),[15] British Thoracic Society (BTS)[17] and the World Health Organization (WHO).[18] There are minor variations among these guidelines namely the need for liver biochemical tests and which offending drug to be reintroduced first. BTS recommends reintroduction in the order of isoniazid, rifampicin and pyrazinamide; while WHO and ATS recommend reintroduction of rifampicin with/without ethambutol followed by isoniazid.

As per the WHO guidelines, the management of hepatitis induced by TB treatment depends mainly on[18]:

- Severity of tuberculosis and/or liver disease; and
- Availability of health facility resources.

Anti-TB drugs can be withheld only after all the possible causes of hepatitis have been ruled out. If the patient is severely ill with TB and it is considered unsafe to stop TB treatment, a non-
hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started and continued for 18-24 months.

Once anti-TB drugs are stopped, it is necessary to wait for normalization of ALT levels to < 2 times ULN and resolution of symptoms before reintroducing the drugs. If liver function tests are not available, it is advisable to wait for 2 weeks after resolution of jaundice and upper abdominal tenderness before re-starting the drugs. If the signs and symptoms do not resolve and ATDH is severe, the non-hepatotoxic regimen can be started as mentioned above.

Once ATDH has resolved, reintroduction should be done with one drug at a time (optimal approach). If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped. It is preferable to start rifampicin with/without ethambutol (being less hepatotoxic than isoniazid & pyrazinamide). After 3 days, isoniazid should be reintroduced if above drugs are tolerated. It is advisable to avoid pyrazinamide in severe ATDH as rechallenge with pyrazinamide may be hazardous and the benefit of shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from Pyrazinamide rechallenge. It can be replaced with Streptomycin.

While reintroduction, if any particular drug is implicated in causing hepatitis, alternative regimens excluding the culprit drug have been suggested as follows:

<table>
<thead>
<tr>
<th>Drug implicated</th>
<th>Alternative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol.</td>
</tr>
<tr>
<td>H</td>
<td>6-9 months of rifampicin, pyrazinamide and ethambutol can be considered.</td>
</tr>
<tr>
<td>Z (if stopped in intensive phase)</td>
<td>Isoniazid and rifampicin therapy be extended to 9 months</td>
</tr>
<tr>
<td>H+R</td>
<td>Streptomycin, ethambutol and fluoroquinolone for 18-24 months.</td>
</tr>
</tbody>
</table>

**Conclusion:**

Many comprehensive case series on ATDH continue to increase our awareness about the pathogenesis, clinical pattern and genetic predisposition. The high morbidity and mortality associated necessitates monitoring and early detection of the hepatotoxicity. Hepatic adaptation should be ruled out before stopping the treatment. A reintroduction should be carried out under medical supervision to identify the offending drug and resort to alternative regimens than stop the treatment completely.
References:


EMERGING TREATMENT OPTIONS IN TUBERCULOSIS
Dr Smita Mali*, Dr Manjari Advani**
*Assistant Professor, **Professor (Additional), Department of Pharmacology

Introduction:
Multidrug-resistant tuberculosis (MDR-TB) has emerged worldwide, with an increasing incidence due to failure of implementation of apparently effective first-line anti-tubercular therapy as well as primary infection with drug-resistant strains. There were an estimated 4,40,000 new multi drug resistant tuberculosis cases in 2008, and 150,000 deaths from the disease. It was estimated that 3.3% of all new tuberculosis cases in 2009 were multidrug-resistant. WHO 2010 report classifies Indian tuberculosis profile as high TB and MDR-TB burden. It states that new TB cases with MDR status comprises of 2.1% and with retreatment it grows to 15%. A study conducted in North India showed high level of primary and acquired drug resistance for the first line drugs, in MDR cases. Drug resistance was significantly higher in pulmonary TB cases.

Table 1: WHO Grouping of Anti-tuberculosis drugs:

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: First-line oral anti-TB agents</td>
<td>Isoniazid (H): Rifampicin (R): Ethambutol (E): Pyrazinamide (Z)</td>
</tr>
<tr>
<td>Group 2: Injectable anti-TB agents</td>
<td>Streptomycin (S): Kanamycin (Km): Amikacin (Ain): Capreomycin (Cm): Viomycin (Vm)</td>
</tr>
</tbody>
</table>

Current pharmacotherapy for MDR-TB:
Revised National Tuberculosis Control Program (RNTCP) has introduced a Standardised Treatment Regimen (Cat IV) for the treatment of MDR-TB cases (and those with rifampin
resistance) under the programme. This regimen comprises of 6 drugs- kanamycin, ofloxacin (levofloxacin), ethionamide, pyrazinamide, ethambutol and cycloserine during 6-9 months of the Intensive Phase and 4 drugs- ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine during the 18 months of the Continuation Phase. PAS is included in the regimen as a substitute drug if any bactericidal drug (K, Ofl, Z and Eto) or 2 bacteriostatic (E and Cs) drugs are not tolerated.[4]

Failure of current therapy is attributed to a long duration of treatment leading to non-adherence and irregular therapy, lack of patient education about the disease, poverty, irregular supply by care providers, drug-drug interactions in patients co-infected with human immunodeficiency virus (HIV), inadequate regulations causing marked overlap and irresponsible drug usage in the private sector, and lack of research, with no addition of new drugs in the last four decades. Present standards of care for the treatment of drug susceptible tuberculosis, multidrug-resistant tuberculosis, tuberculosis-HIV co-infection, and latent tuberculosis infection are all unsatisfactory.[5] This scenario warrants active research and development of new drugs in the treatment of tuberculosis.

**Criteria for new anti TB drug:**[6]

The current treatment for tuberculosis is of at least 6 months duration and includes a minimum of four drugs. This may affect compliance of the patient. Hence the search for new drugs and regimens should ideally be in the direction as listed in table 2.

**Table 2: Required properties of new anti-tuberculosis drugs**

<table>
<thead>
<tr>
<th>What a new drug should do?</th>
<th>Characteristics required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplify treatment or reduce treatment duration</td>
<td>Strong early bactericidal and sterilizing activity</td>
</tr>
<tr>
<td></td>
<td>Low pill count, fixed-dose combination</td>
</tr>
<tr>
<td></td>
<td>Allow for intermittent therapy</td>
</tr>
<tr>
<td>Have an acceptable toxicity profile</td>
<td>Low incidence of treatment-limiting adverse events</td>
</tr>
<tr>
<td></td>
<td>No overlapping toxicity profile with other TB drugs</td>
</tr>
<tr>
<td>Be active against MDR-TB/XDR-TB</td>
<td>No cross resistance with first-line drugs</td>
</tr>
<tr>
<td>Be useful in HIV-infected patients with TB</td>
<td>Minimal interactions with antiretroviral drugs</td>
</tr>
<tr>
<td></td>
<td>No overlapping toxicity profile with antiretrovirals</td>
</tr>
<tr>
<td>Be active against latent TB</td>
<td>Active against dormant bacilli</td>
</tr>
<tr>
<td></td>
<td>Favorable toxicity profile</td>
</tr>
</tbody>
</table>

*HIV: human immunodeficiency virus; MDR-TB: multi-drug resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.*
New drugs under evaluation: \[7\]

The key agents currently in clinical testing for TB are organized for discussion into three categories:

i. Present first-line TB drugs being re-evaluated to optimize their efficacy (rifampin, rifapentine)

ii. Currently licensed drugs for other indications and 'next-generation' compounds of the same chemical class being repurposed for TB (gatifloxacin and moxifloxacin; linezolid, PNU100480; metronidazole, OPC-67683 and PA-824).


i. Present first-line TB drugs being re-evaluated to optimize their efficacy:

Higher doses of the rifamycins, especially rifapentine, have the potential to further shorten the duration of TB treatment as studied in mouse models of TB as well as in humans. Therefore, there is renewed interest in establishing the maximally tolerated dose of these drugs, and a number of clinical trials are planned or underway to examine the safety, pharmacokinetics and efficacy of higher than standard doses of rifampin or rifapentine in first-line TB treatment. \[5\]

1. High dose Rifampin:

Rifampin is considered to be the cornerstone in the current treatment of TB. Its standard dose in TB treatment is 10 mg/kg of body weight, corresponding to 600 mg in most populations. More recently, the pharmacokinetics of daily rifampin at 13 mg/kg have been compared with 10 mg/kg in 50 Indonesian patients with pulmonary TB who were treated with the standard regimen (2 months of RHZE followed by 4 months of rifampin and isoniazid [2RHZE/4RH]). Increasing the dose by 30% increased the peak concentration of rifampin in plasma (Cmax) by 49%; the area under the plasma concentration-time curve (AUC) increased by 65%. AUC is an important parameter for concentration-dependent killers such as the rifamycins. It indicates total exposure to the drug over a certain time period. Rifampin is cheap and widely available, and physicians have experience with this drug. If increasing the dose of rifampin proves to be safe and effective, this intervention could be implemented broadly and quickly. Drawbacks of rifampin are its inductive effect on the CYP450 enzyme system, which is involved in the metabolism of many other drugs, and the increasing rate of mycobacterial resistance to rifampin. A higher dose of rifampin is not likely to affect the pharmacokinetics of other anti-TB drugs and antiretroviral drugs more strongly than the standard dose, as rifampin's inductive effect on the cytochrome P450 (CYP450) enzyme system appears to be maximal at a daily dose of 300 mg. \[7,4\]
2. **Rifapentine:**

It is a cyclopentyl rifamycin that, like other rifamycins, inhibits mycobacterial RNA synthesis by binding to the β-subunit of DNA-dependent RNA polymerase. The use of rifapentine once weekly has been restricted to HIV-negative pulmonary TB patients without cavitation and with a negative sputum culture after the intensive phase of treatment. The International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB) is currently conducting the RIFAQUIN clinical trial with moxifloxacin (400 mg) instead of isoniazid (300 mg) in the standard regimen and with rifapentine once weekly (20 mg/kg for 4 months) or twice weekly (15 mg/kg for 2 months) in the continuation phase, the results of which are awaited. Rifapentine is also a candidate drug for latent TB infection (LTBI).[6,8]

ii. **Currently licensed drugs for other indications and 'next-generation' compounds of the same chemical class being repurposed for TB**

1. **Fluoroquinolones:**

All fluoroquinolones share a common mechanism of action: they inhibit the DNA gyrase of M. tuberculosis. Neither gatifloxacin nor moxifloxacin is a strong inhibitor or inducer of the CYP enzyme system and neither undergoes significant metabolism by this system, rendering them relatively free of clinically significant drug-drug interactions.

The Gatifloxacin for TB Study Team (OFLOTUB) performed a phase II clinical trial in which ethambutol in the standard regimen was replaced by gatifloxacin, moxifloxacin, or ofloxacin. The regimen with moxifloxacin caused the fastest decrease in Colony forming units (CFUs) during the early phase of a biexponential fall whereas both moxifloxacin and gatifloxacin accelerated bacillary elimination significantly in the late phase. In a double-blind randomized controlled trial in which isoniazid in the standard regimen was replaced with moxifloxacin, sputum culture conversion rates was achieved in 60% of patients treated with the moxifloxacin-containing regimen and in 55% of patients using isoniazid in two months. A multicenter three-armed REMoxTB trial in which the standard regimen is compared to (i) a regimen of 2RHZM/2RHM and (ii) a regimen of 2RMZE/2RM has recently started.

Potential toxicities of these drugs are mostly class effects but gatifloxacin has been reported to cause dysglycaemia in diabetic and elderly individuals, an issue not evident with moxifloxacin. Moxifloxacin has a greater propensity than most other currently marketed fluoroquinolones to cause cardiac corrected QT interval prolongation. If the phase III trials demonstrate safety and efficacy, a 4-month, fluoroquinolone-based treatment for drug sensitive tuberculosis (DS-TB) could be registered for use by 2015.[7]
2. **Nitroimidazoles**: Metronidazole, OPC-67683, a nitroimidazo-oxazole & PA-824, a nitroimidazo-oxazine

A small study was reported from India in which metronidazole or placebo was added to a regimen of streptomycin, isoniazid and rifampin in the first 2 months of treatment, with improvement reported in clinical, radiological and sputum reduction in the metronidazole-containing arm. Two 'next generation' members of the nitroimidazole class (summarized in Table 3) are currently under development for both DS-TB (Drug Sensitive) and MDR-TB patients' treatment.\(^5\)

3. **Oxazolidinone**: Linezolid

The oxazolidinones are protein synthesis inhibitors and represent a unique mechanism of action relative to the current first- and second line TB drugs. Linezolid has demonstrated good in vitro potency against M. tuberculosis and excellent efficacy in a mouse model. Its use in TB has been limited primarily by safety issues, particularly myelo-suppression and intractable painful peripheral neuropathy or optic neuropathy typically associated with administration for 2 weeks or longer, but it has been used off-label to treat MDR-TB and extensively drug resistant tuberculosis (XDR TB).\(^7\) XDR-TB strains are resistant to at least isoniazid, rifampin, any fluoroquinolone and one of three second-line injectable drugs like amikacin, kanamycin or capreomycin.\(^8\) Linezolid is currently being studied in two clinical trials at 600 mg once daily dose in combination with other TB drugs in MDR-TB and XDR-TB patients. Other authors have suggested comparable efficacy and decreased toxicity can be achieved by halving the dose of linezolid in MDR-TB treatment to 300mg daily, but only limited clinical data are available to date with this regimen.

PNU 100480, analog of linezolid and AZD 5847, an oxazolidinone are being developed for treatment of tuberculosis. Currently both are in Phase I trial for their pharmacokinetic, safety and tolerability evaluation.\(^7\)

### iii. Novel drugs\(^{5,6,7,8}\)

Development of resistance and long duration of treatment of MDR-TB have prompted research into evaluation of novel drugs. These drugs have a unique mechanism of action against M. Tuberculosis which could address the problem of development of resistance. Some of them in early studies have demonstrated post antibiotic effect which would assist in shortening the duration of treatment.\(^9\) A few of these new agents which have already shown their worth in preclinical research and are being evaluated in clinical trials are summarized in Table 3. Some important features of drugs in nascent phase of evaluation are summarized in Table 4.
### Table 3: Overview of anti-tuberculosis (TB) drugs in the clinical pipeline

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial phase</th>
<th>Potential to shorten treatment</th>
<th>Active against MDR-TB</th>
<th>Useful in HIV-Infected patients with TB</th>
<th>Active against latent TB (LTBI)</th>
<th>Interaction with rifampin</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose rifampin</td>
<td>II</td>
<td>Yes</td>
<td>Limited</td>
<td>Yes but not with protease inhibitors</td>
<td>Yes, but not first Choice</td>
<td>--</td>
<td>Effect on pH of other anti-TB &amp; anti-HIV drugs similar to standard dose</td>
</tr>
<tr>
<td>High-dose rifapentine</td>
<td>II</td>
<td>Yes</td>
<td>Limited</td>
<td>To be established</td>
<td>Yes</td>
<td>--</td>
<td>Better sterilizing activity &amp; faster bacillus eradication</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>III</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Reduced AIC of moxifloxacin by 30%</td>
<td>Accelerated bacillary elimination during the early and late phase of growth. *Banned in India[10]</td>
</tr>
<tr>
<td>Catifloxacin*</td>
<td>III</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Possible</td>
<td>Highly selective inhibitor against F0 subunit of the mycobacterial adenine triphosphate (ATP) synthase proton pump.</td>
</tr>
<tr>
<td>Diarylquinoline TMC207</td>
<td>II</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Reduced TMC207 concentration by 30%</td>
<td>No cross-resistance with standard anti-TB drugs.</td>
</tr>
<tr>
<td>(Nitroimidazole derivatives): PA-824 OPC-67683</td>
<td>I/II</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Synergism in vitro</td>
<td>Inhibits mycobacterial cell wall synthesis by acting on &gt;2 targets, development of resistance low.</td>
</tr>
<tr>
<td>Diamine: SQ 109 (Rifabutin analogue)</td>
<td>I/II</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Synergism in vitro</td>
<td>Early &amp; extended early bactericidal activity and pharmacokinetics under evaluation.</td>
</tr>
<tr>
<td>Pyrrole : LL3858 (Sudoterb)</td>
<td>IIa</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Synergism in vitro</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Overview of anti-tuberculosis (TB) drugs in the preclinical/experimental studies:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isothiazoloquinolone: ACH-702</td>
<td>Effective against fluoroquinolone-resistant isolates of M. tuberculosis.</td>
</tr>
<tr>
<td>Dipiperidines: SQ609</td>
<td>Inhibits mycobacterial cell wall biosynthesis with high specificity &amp; ability to prolong the therapeutic effect after withdrawal of drugs during therapy in mice</td>
</tr>
<tr>
<td>Capuramycin: SQ641</td>
<td>Rapid killing activity against M. tuberculosis (MDR strains, atypical mycobacteria including M. Avium complex) with long post-antibiotic effect.</td>
</tr>
</tbody>
</table>
Caprazene nucleosides: CPZEN-45 | Active against both replicating and non-replicating M. tuberculosis (drug-sensitive & extensively drug-resistant) in vitro, suggesting it could be efficacious against latent organisms in vivo.

Thiolactomycin | Targets KasA and KasB enzymes that involved in the fatty acid and mycolic acid biosynthesis. Active against MDR-TB clinical isolate.

**Conclusion:**

The reviewed information related to newer anti-TB drugs and regimens illustrates that higher doses of the rifamycins are promising and are currently being evaluated in regimens of shorter duration. Moxifloxacin and gatifloxacin might shorten tuberculosis treatment as well, possibly in combination with rifapentine, while SQ109 could enhance the activity of rifampin-containing regimens. Co-administration of moxifloxacin and PA-824 could be active against latent tuberculosis, whereas linezolid, PA-824 and TMC207 are candidates for a rifampin-free regimen in MDR-TB and XDR-TB. Unfortunately, these short duration regimens and newer drug combinations are likely to take at least a few years to be fully developed and implemented in clinical practice.

**References:**

# Bulletin on Adverse Drug Reactions

(December 2011-February 2012)

## List of Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Adverse Drug Reaction</th>
<th>Suspected Drugs</th>
<th>Causality Assessment</th>
<th>Literature Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eosinophilia &amp; Leukocytosis</td>
<td>Thalidomide</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>2</td>
<td>Rash</td>
<td>Rifampicin</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>3</td>
<td>Hepatotoxicity</td>
<td>Rifampicin, Dapsone, Clofazimine, Prednisolone</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>4</td>
<td>Hematomesia</td>
<td>Prednisolone, Clofazimine</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>5</td>
<td>Gastrointestinal bleeding</td>
<td>Warfarin</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>6</td>
<td>Rash</td>
<td>Doxycycline</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>7</td>
<td>Digoxin Toxicity</td>
<td>Digoxin</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>8</td>
<td>Hepatotoxicity</td>
<td>Isoniazid, Rifampicin, Pyrazinamide</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>9</td>
<td>Rash</td>
<td>Indomethacin, Hydroxychloroquine</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>10</td>
<td>Rash</td>
<td>Piperacillin-Tazobactam</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>11</td>
<td>Stevens-Johnson syndrome</td>
<td>Rifampicin</td>
<td>Certain</td>
<td>Well documented</td>
</tr>
<tr>
<td>12</td>
<td>Hypersensitivity</td>
<td>Iron-solute</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>13</td>
<td>Rash</td>
<td>Cisplatin, Gemcitabine, Ondansetron, Ranitidine</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>14</td>
<td>Hemolytic Reaction</td>
<td>Ceftriaxone</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>15</td>
<td>Angioedema</td>
<td>Amoxicillin, Diclofenac, Metronidazole, Ranitidine</td>
<td>Amoxicillin, Diclofenac, Metronidazole- Possible Ranitidine-Unlikely</td>
<td>Well documented</td>
</tr>
<tr>
<td>16</td>
<td>Rash</td>
<td>Mannitol</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>17</td>
<td>G.I. Bleeding</td>
<td>Warfarin, Aspirin, Clopidogrel</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>18</td>
<td>Hepatotoxicity</td>
<td>Glibenclamide, Metformin</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>19</td>
<td>Seizures</td>
<td>Ceftriaxone, Ondansetron, Artesunate, Pantoprazole</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>20</td>
<td>Hematuria</td>
<td>Warfarin, Clopidogrel, Efavirenz</td>
<td>Possible</td>
<td>Drug interaction Well documented</td>
</tr>
<tr>
<td>21</td>
<td>G.I. Bleeding</td>
<td>Heparin, Clopidogrel, Aspirin</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>22</td>
<td>Hematuria</td>
<td>Heparin, Clopidogrel, Aspirin</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>23</td>
<td>Rash</td>
<td>Piperacillin-Tazobactam</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>24</td>
<td>Anaphylactoid Reaction</td>
<td>Iohexol</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>25</td>
<td>Drug Eruption</td>
<td>Ceftriaxime, Metronidazole, Paracetamol</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>Sr. No.</td>
<td>Adverse Drug Reaction</td>
<td>Suspected Drugs</td>
<td>Causality Assessment</td>
<td>Literature Documentation</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------</td>
<td>------------------------------------------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>26</td>
<td>Hematemesis</td>
<td>Ferrous Sulfate</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>27</td>
<td>Urticaria</td>
<td>Furosemide, Acebrophylline, Cefixime</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>28</td>
<td>Rash</td>
<td>Ceftriazone, Clindamycin Artesunate, Pantoprazole, Ondansetron, Paracetamol</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>29</td>
<td>Rash</td>
<td>Amoxicillin-Clavulanic Acid</td>
<td>Probable</td>
<td>Well documented</td>
</tr>
<tr>
<td>30</td>
<td>Nausea &amp; vomiting</td>
<td>Rifampicin, Pyrazinamide Isoniazid, Ethambutol</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>31</td>
<td>Urticaria</td>
<td>Ceftriazone-sulbactum, Clarithromycin,Artesunate, Ondansetron, Pantoprazole</td>
<td>Possible</td>
<td>Well documented</td>
</tr>
<tr>
<td>32</td>
<td>Hemolysis</td>
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<td>Thrombocytopenia</td>
<td>Zidovudine, Ceftriazone, Isoniazid Rifampicin,Pyrazinamide, Ethambutol, Co-trimoxazole</td>
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<td>Aminophylline, Ceftriazone*</td>
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<td>Well documented</td>
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<td>Anaphylactic Reaction</td>
<td>Cefotaxim, Pantoprazole</td>
<td>Possible</td>
<td>Well documented</td>
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EVALUATION OF CASE FROM LTMMC AND LTMGH

Case of Anti-tuberculosis therapy induced Cutaneous Adverse Reaction

Dr. Madhubala Ohol*, Dr. Satkar Rajbhjo**, Dr Nilkanth Awad*, Dr. Sudhir Pawar**

* 1st yr resident, Department of Pharmacology, ** 3rd yr resident, Department of Pharmacology,
#Professor and Head, Department of Respiratory Medicine,
##Professor and Head, Department of Pharmacology

Case Report

A 26yrs old female was diagnosed with pulmonary tuberculosis by a private practitioner and was started anti-Kochs therapy (AKT: HRZES) since 13 September 2011. After 15 days of starting AKT, patient developed redness, itching and maculopapular rash over both the upper limbs, anterior aspect of chest and abdomen. She also developed rash with excoriation over lips, neck and face. Patient stopped AKT on her own after which the reaction subsided.

After 15 days of this episode, patient was restarted on AKT for right pleural effusion in a private hospital. Immediately on starting AKT, she developed similar reaction as described above. She was then treated with Inj. Avil (Pheniramine maleate) i.v. 2cc and Inj. Effcorlin (Hydrocortisone) i.v. 100 mg; however there was no significant improvement in her condition.

Patient was then referred to our hospital for further management on 18th October 2011. On admission, she was diagnosed with AKT induced cutaneous reaction and was given symptomatic treatment. Based on patient's history of occurrence of adverse reaction and time of AKT administration, ethambutol was least suspected to cause the adverse reaction. Hence all the antitubercular drugs were stopped except Tab. Ethambutol 800 mg OD. The rash resolved in about 4 days. It was then decided to give rechallenge with AKT with proper protocol to identify the culprit drugs.

Patient was explained about the rechallenge procedure and consent taken. On the first day of rechallenge, she was given Tab. Isoniazid 75 mg OD along with Tab. Ethambutol 800mg OD. Since low dose Isoniazid was well tolerated, the dose of Isoniazid was escalated to 300mg OD on the next day which too was well tolerated.

On the next day, Tab. Pyrazinamide 250 mg OD was added to the treatment and patient developed itching and angioedema for which she was given symptomatic treatment. Pyrazinamide was discontinued after this reaction and the rash subsided in about 4 days.

On 31th October 2011, Rifampicin rechallenge test was done. Syrup Rifampicin at a dose of 50 mg was given to the patient and 20 minutes later she complained of severe itching all over the
body and was treated for the same. Rifampicin was also discontinued from the AKT regimen for this patient.

On 1st November 2011, Streptomycin rechallenge test dose was planned but unfortunately patient took discharge against medical advice. She was however admitted at later date and Streptomycin rechallenge was performed without any adverse reaction.

Discussion

Major adverse reactions to antituberculosis drugs can cause significant morbidity and compromises treatment regimens for tuberculosis. Modification or discontinuation of therapy is mainly dependent on resolution of adverse reaction on dechallenge or recurrence of adverse reaction after rechallenge.\[1\]

Cutaneous adverse drug reactions (CADR) are one of the commonly observed adverse effects of first line antitubercular therapy being reported in 5.7% of tubercular patients. CADR associated with antitubercular treatment include morbilliform rash, erythema multiforme syndrome, urticaria, lichenoid eruption and other more serious ones like Stevens-Johnson syndrome and exfoliative dermatitis. In a large tertiary care centre study on CADR with antitubercular drugs, pyrazinamide was the commonest offending drug (2.38%), followed by streptomycin (1.45%), ethambutol (1.44%), rifampicin (1.23%) and isoniazid (0.98%).\[2\]

Severe hypersensitivity reactions to standard anti-tubercular drugs are rare but they may be fatal. They usually commence after four to six weeks of therapy and must be recognized early to reduce associated morbidity and mortality. Human Immunodeficiency Virus (HIV) infection, polypharmacy, advanced age, autoimmune disorders, and pre-existing renal or liver impairment were common predisposing conditions for developing cutaneous hypersensitivity reactions to antitubercular treatment.

If the cutaneous reaction is not serious, rechallenge can be attempted, but in case of serious reactions, reinstitution of drug should not be attempted.\[3\] Rechallenge is defined as the readministration of a drug suspected to be a possible cause of an adverse reaction, and which has been subsequently discontinued. Rechallenge will be said to be positive if there is recurrence of the same signs or symptoms as those which previously entailed discontinuation of treatment.\[3\]

As per the literature, the management consists of discontinuation of all drugs until the reaction resolves and identification of the causative drug by rechallenging (restarting) each drug sequentially.

The following short description explains the rechallenge procedure as described in the WHO guidelines for AKT.
The idea of drug rechallenging is to identify the drug responsible for the reaction. Drug rechallenge starts with low dose of a drug and with the anti-TB drug least likely to be responsible for the reaction (i.e. isoniazid).

The reason of starting with a small rechallenge dose is that if a reaction occurs to a small rechallenge dose, it will not be such a bad reaction as to a full dose. If the initial cutaneous reaction was severe, smaller initial rechallenge doses should be given (approximately 1/10th of the doses shown for day 1).

The dose is gradually increased over 3 days. The procedure is repeated, adding in one drug at a time. A reaction after adding in a particular drug identifies that drug as the one responsible for the reaction. There is no evidence that this challenge process performed over 3 days period gives rise to drug resistance.[4]

If the drug responsible for the reaction is pyrazinamide, ethambutol, or streptomycin, anti-TB treatment is resumed without the offending drug. If possible, the offending drug is replaced with another drug. It may be necessary to extend the treatment regimen. The start of the resumed regimen is then considered as a new start of treatment. This prolongs the total time of TB treatment, but decreases the risk of recurrence.[4]

If a reaction occurs during drug rechallenge and the causative drug cannot be discontinued (eg INH and RIF), drug desensitization will be necessary. Drug desensitization should not be attempted with severe skin reactions or those involving the mouth or mucous membranes (e.g. exfoliative dermatitis and Stevens - Johnson syndrome).[5,6,7]

The result of rechallenge procedure performed in this case is depicted in table 1.

**Table 1: Appearance of reaction on rechallenge done in the present case**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose of drug</th>
<th>Reaction reappeared</th>
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<tr>
<td>Isoniazid</td>
<td>300 mg</td>
<td>✗</td>
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<tr>
<td>Ethambutol</td>
<td>800 mg</td>
<td>✗</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>250 mg</td>
<td>✓</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>50 mg</td>
<td>✓</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1 gm</td>
<td>✗</td>
</tr>
</tbody>
</table>

In the above case the ADR disappeared on stopping AKT and reappeared on re-administration of a test dose of Pyrazinamide and Rifampicin, indicating that rechallenge was positive. Rechallenge was negative with Isoniazid, Ethambutol and Streptomycin.
As mentioned above, amongst the AKT, cutaneous ADR is least evident with Isoniazid and more common with Pyrazinamide which is also confirmed in the present case. Serious cutaneous reactions to Rifampicin are not uncommon and have been described in the literature.

On evaluating the above, based on the causality assessment scale, the association of the adverse drug reactions was 'Certain' with Rifampicin and Pyrazinamide.

Finally, it is known that the frequency of adverse reactions due to anti-tuberculosis drugs is high compared to that of other drugs due to combination of drugs used and longer duration of therapy. Due to the combination of drugs used, and overlapping ADRs caused by drugs, it may not be possible to always pinpoint the culprit drug. With the help of rechallenge procedure the causative agent for an ADR can be identified and stopped and the remaining drugs can be reinstituted.

References:


PUBLISHED CASE REPORTS ON AKT INDUCED ADVERSE REACTIONS

Dr. Jaisen Lokhande, Assistant Professor, Department of Pharmacology

Pyrazinamide-induced phototoxicity: a case report and review of literature.  
Katiyar SK, Bihari S, Prakash S.

Abstract

A 40-year-old male presented with a fresh case of pulmonary tuberculosis and itchy oozing rashes distributed characteristically over the sun exposed areas of the skin. These rashes had developed since six days following 10 days of start of antitubercular drugs (streptomycin, isoniazid, rifampicin, pyrazinamide and ethambutol at standard dosages). A possibility of drug-induced reaction was entertained and all the antitubercular drugs were discontinued; subsequently they were reintroduced in a sequential manner starting with small dosages, gradually increasing them to their normal dose. The rashes reappeared after introduction of pyrazinamide. We tried to desensitize this very important antitubercular drug but were not successful as the rashes reappeared. The patient was labeled as having pyrazinamide-induced phototoxicity and was started on a regimen containing streptomycin, isoniazid, rifampicin, ethambutol. Five months following treatment, the patient is now sputum negative for AFB. Pyrazinamide forms the integral part of most of the short course regimens, included in all the three categories of DOTS and with increasing coverage of DOTS therapy these rare cases may well be frequently encountered.

A rare case of streptomycin-induced toxic epidermal necrolysis in a patient with tuberculosis: a therapeutic dilemma.  

Abstract

Objective: To report a case of streptomycin-induced toxic epidermal necrolysis (TEN).  
Case Summary: A 55-year-old woman was admitted for treatment of active pulmonary tuberculosis (TB). She was given standard oral anti-TB chemotherapy including isoniazid, rifampin, pyrazinamide, and streptomycin. On the fourth day of therapy, she experienced high fever at 39 degrees C, chills, vomiting, pruritus, and diffuse erythema, followed by extensive bullae formation and skin denudation. Diagnosis of TEN was considered, and all anti-TB drugs were discontinued. Skin biopsy disclosed complete epidermal necrosis with dermal-epidermal cleavage and absence of inflammatory infiltrate, highly suggestive of TEN. The patient was transferred to the intensive care unit. Her general condition and skin lesions improved. A staged-fashion exposure test to the 4 anti-TB drugs allowed the incrimination of streptomycin as the offending agent.  
Discussion: Anti-TB drugs, mainly rifampin, ethambutol, and isoniazid, have been incriminated in TEN. Streptomycin-induced TEN remains an extremely rare event. However, minor allergic skin reactions (rash, urticaria) have been described with this drug. Our patient presents a rare case of streptomycin-related TEN. Even though dangerous, a step-wise exposure test was
necessary to allow safe treatment of active pulmonary TB. It also provided a strong argument of a cause-effect relationship between TEN and streptomycin. An objective causality assessment using the Naranjo rating scale revealed that the adverse drug event was highly probable. **Conclusions:** Streptomycin should be added to the list of drugs that induce TEN.

**Cutaneous leukocytoclastic vasculitis due to anti-tuberculosis medications, rifampin and pyrazinamide**
Kim JH, Moon JI, Kim JE, Choi GS, Park HS, Ye YM, Yim H.

**Abstract**
Anti-tuberculosis drugs frequently result in cutaneous adverse reactions, including pruritus, maculopapular exanths, and urticaria. However, anti-tuberculosis drug-associated cutaneous leukocytoclastic vasculitis (CLV) has been rarely reported. We describe a case of CLV induced by rifampin and pyrazinamide. A 38-year-old male had been diagnosed with pulmonary tuberculosis two months ago and then he started standard anti-tuberculosis therapy with isoniazid, rifampin, ethambutol, and pyrazinamide. Purpuric lesions developed in the extremities after 1.5 months of anti-tuberculosis medication; the lesions progressively spread over the entire body. Histopathology of the purpuric skin lesion was consistent with leukocytoclastic vasculitis. The skin lesion improved after cessation of anti-tuberculosis medications and treatment with oral corticosteroids and antihistamines. Anti-tuberculosis drugs were rechallenged one at a time over 3 days. Purpura recurred on the right forearm and forehead after taking 300 mg of rifampin. The skin lesion disappeared after taking oral prednisolone. Finally, 1,500 mg of pyrazinamide was readministrated, and then purpuric lesions recurred on both forearms. This report describes a case of leukocytoclastic vasculitis secondary to rifampin and pyrazinamide therapy.

**Ethambutol-induced toxic epidermal necrolysis.**
Pegram PS Jr, Mountz JD, O’Bar PR.

**Abstract**
Toxic epidermal necrolysis (TEN) is a severe cutaneous reaction that most commonly is related to drug exposure and that clinically can be confused with other bullous dermatoses, particularly staphylococcal scaled skin syndrome (SSSS) and erythema multiforme major (the Stevens-Johnson syndrome). We report the first case, to our knowledge, of TEN associated with ethambutol hydrochloride administration. Toxic epidermal necrolysis can be partially differentiated from other bullous dermatoses by history and clinical presentation. Microbiological results (eg, the isolation of Staphylococcus aureus in SSSS) and immunological studies (eg, the demonstration of immune complexes in the Stevens-Johnson syndrome) may aid in differentiation, but ultimately the diagnosis depends on histopathological examination of involved skin.
REGULATORY UPDATE

Dr Jaisen Lokhande, Assistant Professor, Department of Pharmacology

EMA Recommends First-Line Anti-TB Drugs for Children

February 22, 2012 - The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) agrees with the World Health Organization (WHO) dosing recommendations for ethambutol, isoniazid, pyrazinamide, and rifampicin as first-line antituberculosis medicines used in children, according to new EMA dosing guidelines released February 17.

Tuberculosis is most prevalent in developing countries, but still occurs in some European Union member states, with the average notification rate for tuberculosis in 2008 being 16.7 per 100,000 population in the European Union and European Economic Area region. In 2008, the WHO recommended changes to pediatric dosing, which the French medicines agency then reviewed in 2011. This review did not include multidrug-resistant tuberculosis. Pharmacokinetic data had shown that weight-based dosing regimens for use of antituberculosis medicines in children might lead to suboptimal exposure if based on corresponding adult weight.

In light of limited evidence to date and various other considerations, the CHMP acknowledged that the pediatric dosing regimen of first-line antituberculosis agents is difficult to define. This is particularly true for infants younger than 3 months because specific data are lacking.

Nonetheless, the CHMP agreed with WHO dosing recommendations for children older than 3 months, as follows:

- ethambutol: 20 mg/kg (range, 15 - 25 mg/kg),
- isoniazid: 10 mg/kg (range, 10 - 15 mg/kg),
- pyrazinamide: 35 mg/kg (range, 30 - 40 mg/kg), and
- rifampicin: 15 mg/kg (range, 10 - 20 mg/kg).

"The review aims at optimising therapeutic management of the disease in the European Union and harmonising dosing in order to encourage the development of fixed dose combinations (FDC) by pharmaceutical companies," the news release states. "FDCs are important as they can improve how well a patient is able to follow medical advice in terms of taking medicine at the right time and taking the correct number and combination of tablets. This can be especially challenging with children."

The CHMP intends to share its opinion statement regarding dosing recommendations with the European Union member states, so that they can implement appropriate policies at the national level.

Recommendations for Human Immunodeficiency Virus (HIV) Screening in Tuberculosis (TB) Clinics

In revised recommendations from 2006, CDC recommends HIV screening for all TB patients after the patient is notified that testing will be performed, unless the patient declines (i.e., opt-out screening). Routine HIV testing is also recommended for persons suspected of having TB disease and contacts to TB patients. Persons at high risk for HIV infection should be screened for HIV at least annually. Prevention counseling and separate written consent for HIV testing should no longer be required.

Why does CDC recommend that TB clinics screen their patients for HIV infection?

HIV infection is the most important known risk factor for progression from latent TB infection to TB disease. Progression to TB disease is often rapid among HIV-infected persons and can be deadly. In addition, TB outbreaks can rapidly expand in HIV-infected patient groups.

Targeted HIV testing based on provider assessment of patient risk behaviors fails to identify a substantial number of persons who are HIV infected. This is because many individuals may not perceive themselves to be at risk for HIV or do not disclose their risks. Routine HIV testing also reduces the stigma associated with testing.

When HIV is diagnosed early, appropriately timed interventions can lead to improved health outcomes, including slower progression and reduced mortality. Identifying TB patients, suspects, and contacts who are HIV infected allows for optimal TB testing of these groups and provides opportunities to prevent TB in those without disease.

Who should be tested for HIV in TB clinics?

All patients in TB clinics should be tested for HIV. This includes TB suspects, patients, and contacts.

Can rapid HIV tests be used to screen TB patients and their contacts?

Yes. Rapid HIV tests, using fingerprick or oral specimens, can be used. Results are available in about 20 minutes. Although the rapid HIV test kits cost about $10 more per test than standard lab assays, they have been shown to be cost-effective and to increase patients' acceptance of HIV testing. Another option is to collect oral swab specimens and use standard lab assays.

WORLD TB DAY 2012

Stop TB In My Lifetime

Dr Jaisen Lokhande, Assistant Professor, Department of Pharmacology

On March 24, 1882, Dr. Robert Koch announced the discovery of Mycobacterium tuberculosis, the bacteria that cause tuberculosis (TB).

During this time, TB killed one out of every seven people living in the United States and Europe. Even today, among the infectious diseases, TB remains the second leading killer of adults in the world, with more than 2 million TB-related deaths each year.

In 1982, a century after Dr. Koch's announcement of the discovery of Mycobacterium tuberculosis, the first World TB Day was sponsored by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD). The event was intended to educate the public about the devastating health and economic consequences of TB, its effect on developing countries, and its continued tragic impact on global health.

WHO is working to cut TB prevalence rates and deaths by half by 2015. Today, World TB Day is commemorated across the globe with activities as diverse as the locations in which they are held. It is a valuable opportunity to educate the public about the devastation TB can spread and how it can be stopped.

This year, CDC joins the global Stop TB partnership in adopting the slogan "Stop TB in my lifetime" that goes with the theme of calling for a world free of TB. The slogan and theme encourage people all over the world, from the youngest to the oldest, to make an individual call for the elimination of TB, and say what changes they expect to take place in their lifetimes.

World TB Day provides an opportunity to raise awareness about TB-related problems and solutions, and to support worldwide TB-control efforts.

The following few were the earlier themes for World TB day

- 2011: On the move against TB: Transforming the fight towards elimination
- 2010: On the move against TB: Innovate towards action
- 2009: I am stopping TB
- 2008: I am stopping TB
- 2007: TB anywhere is TB everywhere
- 2006: Actions for life - Towards a world free of TB
- 2005: Frontline TB care providers: Heroes in the fight against TB
- 2004: Every breath counts - Stop TB now!
- 2003: DOTS cured me - it will cure you too!
- 2002: Stop TB, fight poverty
- 2001: DOTS: TB cure for all
- 2000: Forging new partnerships to Stop TB
CROSSWORD I

Alphabet 'A' Puzzle

Dr Sharmada Nerlekar;* Dr Abhilasha Rashmi;** Dr Girish Joshi***

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

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1. While using cycloserine the patient must be warned against the habit of ---------.
2. -------- group of drugs are one of the treatments of choice against MAC in AIDS patients.
3. Drug resistance to Ethambutol occurs due to point mutations in the emb B gene that encodes the ----- transferase enzyme involved in mycobacterial cell wall synthesis.
4. Resistance to ------ in most cases is due to mutations between codons 507 and 533 of the polymerase rpo B gene involved in RNA biosynthesis.
5. Gastrointestinal problems including anorexia, nausea and ------- pain are predominant in patients taking PAS.
6. Highest incidence of MDR tuberculosis is seen in ------ countries.
7. TMC- 207 an anti-tuberculosis drug in the pipeline is unique as it is rapidly cidal against mycobacteria that show ------ to all existing lines of drug therapy.
8. Mechanism of toxicity to INH is that it induces autoantibody production against the myelo------ present in Mycobacterium tuberculosis.
9. Ethambutol is known to produce ------- scotomata.
10. Pyrazinamide is associated with ------ and hyperuricemia.

ANSWERS:

CROSSWORD II

Dr Abhilasha Rashmi,* Dr Sharmada Nerlekar,** Dr Girish Joshi***

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

Across
1. Pyridoxine 100mg/day is administered to patients to treat ___ toxicity of Cycloserine.(3).
2. This ADR of INH is rare in children, but more common in elderly & alcoholics.(9).
3. Renal failure with Rifampicin is associated with light chain proteinuria,either kappa or ___.(6).
4. Maximum incidence of QT prolongation is seen with ___floxacin among fluoroquinolones, and is also having maximum activity against mycobacteria.(4).
5. Neuropathy due to INH is more frequent in individuals with diabetes mellitus, poor nutrition & ___.(6).
6. Hyperuricemia due to this AKT drug is enhanced by INH & Pyridoxine.(10).
7. ___mycin is a polypeptide antibiotic used as a reserve AKT drug which can cause electrolyte abnormalities.(6).

Down
8. Risk of seizures is highest with ___floxacin when given with NSAIDs.(3).
9. Hepatotoxicity due to INH is likely to be due to its metabolite ___hydrazine.(6).
10. The untoward effects of INH include arthritic symptoms including the ? "Syndrome.(12).
11. Macrolides used in high doses as lifelong therapy to treat ___ infection in AIDS patients, are known to cause a triad of tinnitus, dizziness & reversible hearing loss.(3).
12. Patient compliance with this second line anti TB drug is always poor due to GIT intolerance & hypersensitivity reactions.(3).
13. ADRs like bone marrow suppression & peripheral neuropathy are seen less with Linezolid in cases of TB because it is given 600mg ___which is half of the usual dose.(2).
14. Gout due to inhibition of ___ acid excretion from kidney is seen with Pyrazinamide & Ethambutol.(4).
15. Drug interaction between Rifampicin & ___ class of drugs used in HIV patients, may result in therapeutic failure due to the enzyme inducing property of Rifampicin.(2).
16. Because of its high lipophilicity, ___ cycline is the only Tetracycline active against mycobacteria.(4).
17. Drug interactions with ___ butin is less than Rifampicin because it is a weak enzyme inducer.(4).
18. AKT combinations with Rifampicin can be administered twice or thrice weekly because Rifampicin synergistically prolongs the ___ of other anti TB drugs.(3).
19. Symptomatic treatment with ___ is usually sufficient without discontinuation of therapy for Pyrazinamide induced clinical manifestations of Gout.(7).

ANSWERS

9. ___ hydrazine
16. ___ cycline
18. ___ butin
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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<tr>
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<th>E-mail</th>
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<tbody>
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