Book review

How to investigate the use of medicines by consumers

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In developing countries, medicines may account for 30-40% of the health expenditure. Self-medication is common and medicines are often purchased without a prescription. In developing countries availability of medicines is often a problem and medicines are often prescribed, dispensed and sold inappropriately.

The book starts by telling us why we should study the use of medicines by consumers. The common patterns of inappropriate medicines are described. Self-medication with prescription drugs, misuse of antibiotics, overuse of injections, and unsafe use of herbal medicines are a few of the pressing problems. The steps in developing an effective intervention aimed at enhancing rational drug use by consumers has been covered in detail.

The second chapter deals with factors which influences medicines use by consumers. The topic has been covered at the household, community, health institution, national and international levels. Boxes deal with the belief about medicines among villagers and the cultural influences on the selection and use of medicines.

The problems of studying medicines use by consumers forms the basis of the third chapter. Document reviews, semi-structured interviews, focus group discussions, observation techniques, structured interviews, weekly illness recalls are a few of the methods covered. The need for triangulation (using a combination of methods to cross-check information) has been emphasized. The model or specimen forms for key informant interviews, creating an inventory of household medicines, making a family health calendar will be found useful.

Prioritizing and analyzing community medicine use problems forms the basis of the next chapter. The chapter describes the use of the rating matrix to prioritize community medicine use problems with an appropriate example. The chapter proceeds further through a set of interesting activities. The use of a problem analysis diagram to analyze drug use problems in greater detail has been well described.

The fifth chapter deals with sampling methods and the problem of bias in sampling. The sixth chapter deals with data analysis. Processing and analyzing qualitative and quantitative data has been covered. The last chapter deals with monitoring and evaluating rational medicine use interventions in the community. The four types of evaluation designs- the randomized control, the quasi-experimental, time-series and pre-post have been described diagrammatically.

In Nepal studies on drug use in the community and at the health institution level have been carried out. However, the problem of inappropriate use of medicines by consumers exists and studies to delineate the problem and suggest possible interventions are required in various regions. This book will be helpful for people interested in studying the problem of drug (medicines) use by consumers.

The book is well produced and different variations of pink form the main colour theme. The book will be interesting reading for pharmacologists, pharmacists, community health personnel, social scientists, medical anthropologists and all those interested in drug use in the community. The book has been co produced by the World Health Organization, University of Amsterdam and the Royal Tropical Institute, Netherlands.

Literature review

Introduction to DOTS strategy and the safety profile of first line antitubercular drugs- a review of literature

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Background: Tuberculosis (TB), caused by bacteria belonging to the *Mycobacterium tuberculosis* complex, is one of the oldest diseases known to affect humans. Directly observed treatment, short course (DOTS) is a strategy to ensure that every patient starting TB treatment gets the best chance of being cured. DOTS strategy was adopted since the early 1990s by the WHO and was started in Nepal in 1995. First line anti-TB drugs combine the greatest level of efficacy with an acceptable level of toxicity. However, these agents are still capable of causing many adverse drug reactions (ADRs) like peripheral neuropathy, hepatotoxicity, hypersensitivity reactions, ocular toxicity, gastrointestinal effects, etc. Since TB is a common problem in developing countries, the healthcare professionals should focus more on the safety profile of these drugs.

Conclusion: Though the ADRs due to these rugs cannot be prevented totally, a systematic approach can definitely be useful in minimizing the incidence of ADR in TB patients.

Key Words: Mycobacterium tuberculosis, DOTS, Adverse drug reaction (ADR)

Introduction

Tuberculosis (TB) is one of the oldest disease known to affect humans and is caused by bacteria belonging to the *Mycobacterium tuberculosis* complex. The most frequent agent of human disease is *M. tuberculosis* itself. The complex includes *M. bovis* (the bovine tubercle bacillus, cause of a small percentage of cases in developing countries, TB being transmitted by unpasteurized milk) and *M. africanum* (isolated in a small proportion of cases in West and Central Africa).[1] Despite being known for a long time and despite the existence of effective antitubercular drugs for more than 50 years, TB is still a major health problem in most parts of the world. In view of all this, WHO declared TB as a global emergency in 1993.[2]

In the late 1990s, between 3.5 to 4 million new cases of TB, 90% of them from developing countries were reported annually to the WHO and these reports were considered only a fraction of the total because of a low level of case detection and incomplete notifications in many national TB control programs. In 1997, it was estimated that 8 million new cases of TB occur worldwide, 95% of them in developing countries and nearly two million deaths occurred from tuberculosis, 98% of them in developing countries.[1] These figures were estimated to rise to 10.2 million new cases and 3.5 million deaths due to TB by 2000.[3] These days, with the emergence of HIV/AIDS and multi drug resistant (MDR) TB, TB is getting to pose a bigger challenge than ever. Nepal also is not immune from this global threat of TB. About 60% of the economically active Nepalese population is infected with it.

Directly observed treatment, short course (DOTS) strategy: The DOTS strategy was adopted since the early 1990s by the WHO. DOTS essentially is a strategy to ensure that TB patients are cured, in which a person accountable to the health service observes the patient taking their medicine properly and provides him/her with the information and encouragement he/she needs.[4] DOTS is a package of five points: [5,6]

1. Commitment of governments to a national tuberculosis programme,
2. Detection of cases through case finding by sputum smear microscopy examination of patients with

suspected tuberculosis in general health services,

3. Standardized short course chemotherapy with the first line drugs isoniazid, rifampicin, pyrazinamide, ethambutol (and streptomycin) for at least, all smear positive cases of tuberculosis under proper conditions of case management,
4. Regular, uninterrupted supply of all essential antitubercular drugs,
5. A monitoring system for programme supervision and evaluation.

The DOTS strategy was adopted and four DOTS pilot centers were established in 1996. In 2001, there was

Table 1: Category I: New sputum smear positive patients[4]

	Intensive phase Daily during months 1 and 2				Continuation phase Daily during months 3 to 8	
Pretreatment weight of patient	**Isoniazid (H)(mg)**	**Rifampicin (R)(mg)**	**Pyrazinamide (Z)(mg)**	**Ethambutol (E)(mg)**	**Isoniazid (H)(mg)**	**Ethambutol (E)(mg)**
21- 33 kg	300	300	1000	800	300	800
34- 50 kg	300	450	1500	800	300	800
51 kg or more	300	600	2000	1200	300	1200

The different antitubercular drugs with their dosage as used for the treatment of TB for patients in category 1 as per the DOTS strategy in Nepal *(Table 1).*

Table 2: Category II: Retreatment patients[4]

Intensive phase Daily during months1 and 2		Daily during months 1, 2 and 3				Continuation phase Daily during months 4 to 8		
Pre-treatment weight of patient	**Strepto-mycin Inj (gm)(S)**	**Isonia-zid (mg) (H)**	**Rifam-picin (mg) (R)**	**Pyrazinamid (mg) (Z)**	**Ethambutol (mg) (E)**	**Isonia-zid (mg) (H)**	**Rifampicin (mg) (R)**	**Ethambutol (mg) (E)**
21- 33 kg	0.5	300	300	1000	800	300	300	800
34- 50 kg	0.75	300	450	1500	800	300	450	800
51 kg or more	1	300	600	2000	1200	300	600	1200

The dosage of drugs used for the treatment of TB for patients in category 2 as per the DOTS strategy in Nepal *(Table 2).*

Table 3: Category III: New smear negative and extra- pulmonary patient[4]

	Intensive phase Daily during months 1 and 2			Continuation phase Daily during months 3 to 8	
Pretreatment weight of patient	**Isoniazid (mg) (H)**	**Rifimpacin (mg) (R)**	**Pyrazinamide (mg) (Z)**	**Isoniazid (mg) (H)**	**Ethambutol (mg) (E)**
21- 33 kg	300	300	1000	300	800
34- 50 kg	300	450	1500	300	800
51 kg or more	300	600	2000	300	1200

The dosage of drugs used for the treatment of TB for patients in category 3 as per the DOTS strategy in Nepal *(Table 3)*.

Table 4: Short- course antituberculosis therapy (ATT) regimen for children (0-5 years old); Categories 1 and 3

	Intensive phase Daily during months 1 and 2 (HRZ)			Continuation phase Daily during months 3 to 8 (HE)	
Pretreatment weight of patient	**Isoniazid (mg) (H)**	**Rifimpacin (mg) (R)**	**Pyrazinamide (mg) (Z)**	**Isoniazid (mg) (H)**	**Rifimpacin (mg) (R)**
5- 10 kg	50	75	250	50	75
11 – 20 kg	100	150	500	100	150

The short course regimen for chemotherapy of TB in children less than 5 years *(Table 4)*.

Table 5: Doses of first- line anti TB drugs

Drug	Daily (Maximum)	Twice weekly (Maximal)	Thrice weekly (Maximal)
Isoniazid	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
Rifampicin	10 mg/kg (600 mg)	10 mg/kg (600 mg)	10 mg/kg (600 mg)
Ethambutol	15 mg/kg (1600 mg)	45-50 mg/kg (4000 mg)	25-35 mg/kg
Pyrazinamide	25 mg/kg (2000 mg)	40-50 mg/kg (4000 mg)	35 mg/kg (3000 mg)
Rifabutin	5mg/kg (300mg)	5mg/kg (300mg)	5mg/kg (300mg)

expansion of DOTS in 75 districts achieving 69% case finding and 89% treatment success rates, which increased to 70% case finding and 90% treatment success in 2002.[4] In the DOTS policy in Nepal, three categories of treatment regimens exist, viz categories I, II and III.[4]

Anti tubercular drugs[7]: Between the 1890s and 1940s, cure for TB included a variety of diets, drugs and surgeries. Patients often improved spontaneously, and a fourth of them would be 'cured'. The cures were attributed to interventions, but relapses often occurred. Hopes for cure led to the first controlled clinical trial of streptomycin in 1948.[8] Although it was seen to be effective at first, development of resistance soon developed. In 1946, anti-tubercular activity of para-aminosalicylic acid (PAS) was discovered.[9] The idea of combination therapy took shape when it was seen that combination of PAS and streptomycin could really cure TB. Isoniazid (INH) was discovered in 1953.[10] Pyrazinamide, ethambutol, thiacetazone, ethionamide, cycloserine, capreomycin and aminoglycosides were introduced in the late 1950s and 1960s. Rifampicin, though discovered in 1966, came into popular use only in the late 1970s.

By the end of 1960s, standard treatment for TB was two years treatment with INH and ethambutal, later reduced to 18 months. PAS, streptomycin and the other drugs were reserved for resistant disease, difficult cases and special situations like meningitis. In the late 1970s, a series of well performed trials by the British Thoracic society and subsequently other trials showed that pyrazinamide, rifampicin and INH for 6 months was adequate for the treatment of TB. With experience and subsequent studies, a fourth drug, ethambutol was added and these drugs were established as the core of the current treatment for TB. Drugs used for chemotherapy of TB are categorized into first-line and second-line agents.

1. First line anti TB drugs [7]**:** These are the agents that combine the greatest level of efficacy with an acceptable level of toxicity. These are the generally used drugs for treatment of TB in all non drug-resistant strains.

The doses of standard first line anti-TB drugs for adults are given *(Table 6)*.[11,12]

2. Second line anti-TB drugs: These are the agents used in the case of multidrug-resistant tuberculosis that is resistant to at least INH and rifampicin, hence rendering the first line agents much less effective.[13] They are not used as primary agents because of the toxicity of these agents.

Some of the drugs and dosage of the same used as second line anti TB agents are given *(Table 7)*.[11,12]

Table 7: Second line anti-TB drugs

Drug	Daily (Maximum)	Twice weekly (Maximal)	Thrice weekly (Maximal)
Streptomycin[a]	15 mg/kg(1000 mg)	15 mg/kg(1000 mg)	15 mg/kg(1000 mg)
Levofloxacin[b]	(500 mg)	-	-
Moxifloxacin[b]	(400 mg)	-	-
Gatifloxacin[b]	(400 mg)	-	-
Capreomycin[a]	15 mg/kg(1000 mg)	15 mg/kg(1000 mg)	15 mg/kg(1000 mg)
Rifapentine	10 mg/kgOnce or twice weekly(600 mg)	-	-
Amikacin[a]	15 mg/kg(1000 mg)	15 mg/kg(1000 mg)	15 mg/kg(1000 mg)
Kanamycin[a]	15 mg/kg(1000 mg)	15 mg/kg(1000 mg)	15 mg/kg(1000 mg)
Ethionamide[b]	15-20 mg/kg(500- 700 mg)	-	-
PAS[b]	(8-12 g in 3 doses)	-	-

Table 6: Common side effect profile of first line anti TB drugs

Efefcts	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol	Streptomycin
CNS effects	Peripheral neuropathy, ataxia, muscle weakness, paralysis, focal seizures, euphoria, impairment of memory, psychosis	Drowsiness, headache, dizziness, ataxia, generalized numbness, muscular weakness, pain in the extremities, delusion, disorientation, hallucination, agitation etc	-	Peripheral neuropathy	Neuromuscular blockade
CVS effects	-	Shock	Acute symptomatic hypertension (rarely)	-	-
GI effects	Epigastric distress, Gastric burning, dry mouth, nausea	Nausea, vomiting, epigastric pain, diarrhea, loss of appetite, abdominal cramps		Nausea, vomiting, epigastric pain	
Hepatic effects	Increase in AST, ALT, bilirubin	Transient increases in AST, ALT, bilirubin, alkaline phosphatase, fulminant hepatic reaction with INH	May range from asymptomatic alterations of liver function tests to clinical jaundice	Jaundice, non-icteric liver disease	Altered liver function tests
Renal effects	Nephrotoxicity (rare)	Increased BUN and serum uric acid concentrations	-	-	Acute tubular necrosis or gradually evolving nonoliguric renal failure.
Special senses	Optic neuritis in combination with ethambutol	-	-	Optic neuritis	Hearing loss and vestibular damage
Skin reactions	Morbiliform, maculopapular, Purpuric and urticarial rashes	-	Urticarial and maculopapular rashes	Rashes, SJS, TEN	-
Other effects	Cushing's syndrome, gynecomastia, amenorrhea, hyperglycemia, arthritic symptoms, back pain, acute pancreatitis, agranulocytosis, thrombocytopenia. eosinophilia, hemolytic anemia	Rashes, fever, flu-like illness.	Hyperuricaemia, acute gout, arthralgia, pellagra	Endocrine, metabolic: Increased blood urate concentration.	Exanthematous skin reactions, Stevens Johnson syndrome. Severe hearing loss and deficient vestibular function in children when administered to mother during pregnancy, hypomag-nesaemia.

Dose and interval depends upon efficacy of companion drugs and mycobacterial burden. Reduce dose to 750 or 500 mg for the elderly. Start or move to twice or thrice weekly soon.

Intermittent dose not established.

Adverse effects caused by first line anti-TB drugs:[14,15,16] The different types of ADRs caused by the commonly used first- line antiTB agents are mentioned below:

1. INH: It is generally well tolerated at currently recommended doses. Commonly encountered and reported adverse effect pattern of isoniazid are as follows:

i. Nervous system effects: Peripheral neuropathy is a well recognized adverse effect of INH. It is usually preceded by paresthesia of feet and hands. Numbness or tingling of the extremities in the 'glove and stocking' distribution can occur early during treatment. This seems to occur most frequently in alcoholics, malnourished, diabetic and uremic patients and seems to result from interference with pyridoxine metabolism. Symptoms generally consists of hyperesthesia, reduced vibratory and position sense, and exaggerated or reduced tendon reflexes, but ataxia, muscle weakness, and even paralysis can develop.[17] Other neurological adverse effects include: seizures, toxic encephalopathy, muscle twitching, ataxia, stupor, tinnitus, euphoria, memory impairment, separation of ideas and reality, loss of self control, dizziness and toxic psychosis. Neurotoxic effects may be prevented or relieved by administration of 10-50 mg of pyridoxine hydrochloride daily during treatment with isoniazid. Pyridoxine should be routinely administered in malnourished patients, pregnant women and those predisposed to neuritis, e.g., HIV infected individuals.

ii. Hepatic effects: Abnormal liver function is the most commonly described adverse reaction of isoniazid. Mild hepatic dysfunction, as seen by transient increases in serum aspartate transaminase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT), alanine transaminase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT), and bilirubin concentrations has occurred in approximately 10-20% of patients, usually during the first 4-6 months of therapy but return to pretreatment values despite continued treatment. Rarely, progressive liver dysfunction, bilirubinuria, jaundice and severe and sometimes fatal hepatitis have occurred.[15] In severe cases, the characteristic pathological damage was centrilobular necrosis. The mechanism responsible for this toxicity remains undetermined. A metabolite of INH, acetylhydrazine, causes hepatic damage and may play a role.

The risk factors for severe hepatotoxicity are alcoholism, malnutrition, diabetes, previous liver damage, renal insufficiency, and drug abuse. Age is another risk factor. Hepatic damage seems to be rare under the age of 20 years; incidence is 0.3% in age group 20-34 years, 1.2% in age 34-49 years and 2.3% over the age of 50 years.[21] If signs and symptoms suggestive of hepatic damage (e.g., persisting fatigue, weakness or fever exceeding 3 days, malaise, nausea, vomiting, unexplained anorexia, darkening of urine) occur during INH therapy, the drug should be discontinued promptly.

iii. Hypersensitivity reactions: These occur infrequently and include skin eruptions (morbiliform, maculopapular, purpuric, and urticarial rashes) with or without fever, vasculitis, lymphadenopathy and rarely hypotension. At the first sign of hypersensitivity, all drugs should be stopped. If INH is reinstituted, it should be done only after symptoms have cleared and should be restarted in small and gradually increasing doses. If there is any indication of recurrence of hypersensitivity, INH should be discontinued at once.

iv. Endocrine, metabolic effects: Cushing's syndrome, gynecomastia, amenorrhea, and precocious puberty is thought to occur due to the enzyme–inhibiting activity of INH, which results in derangement of hepatic hormone metabolism. Hyperglycemia and metabolic acidosis can occur, strict control of glucose metabolism is necessary in diabetics.

v. Hematological effects: Agranulocytosis, thrombocytopenia, hemolytic anemia, sideroblastic anemia, pure red cell aplasia, methemoglobinemia, and eosinophilia can occur exceptionally during isoniazid treatment.

vi. Respiratory effects: Symptoms suggesting bronchial obstruction occur very rarely during INH treatment.

vii. Pancreatic effects: Acute pancreatitis has recently been attributed to INH.[18]

viii. Gastrointestinal effects: GI symptoms are limited to epigastric distress, gastric burning, dry mouth and nausea. Symptoms occur particularly if the drug is taken before food or in combination with other antituberculous drugs.

ix. Urinary system: Urinary retention is a rarely seen complication. Nephrotoxicity is rare, but may occur in combined therapy with rifampicin and streptomycin or in patients who develop hypersensitivity reactions.

x. Special senses: Optic neuritis and atrophy have occurred in patients taking INH.

xi. Musculoskeletal system: Arthritic symptoms, with back pain, bilateral proximal interphalangeal joint involvement, arthralgia of the knees, elbows and wrist can occur.

2. Pyrazinamide: Most of the adverse effects of pyrazinamide seem to be toxic rather than allergic.

i. Hepatic effects: Liver damage is the most common adverse effect of pyrazinamide. It varies from an asymptomatic alteration of liver function detectable only by laboratory tests, through a mild syndrome characterized by fever, anorexia, malaise, liver tenderness, hepatomegaly and spleenomegaly, to more serious reactions with clinical jaundice and finally the rare form with acute yellow atrophy and death. Pyrazinamide should be avoided in patients with liver disease and porphyria. As most patients take a combined regimen of pyrazinamide with isoniazid and rifampicin, it is difficult to determine which of the three drugs causes the hepatotoxicity; it could even be due to a combined effect. During treatment with pyrazinamide, hepatic function should initially be monitored every few weeks.

ii. Endocrine, metabolic effects: Hyperuricemia and acute episodes of gout or arthralgia can occur as pyrazinamide inhibits renal excretion of urate. It should be used with extreme caution in patients with history of gout, especially in the elderly, in whom urinary urate stones can cause renal failure. Arthralgia responds better to NSAIDs than to uricosuric drugs.[19] Pyrazinamide can also cause pellagra. However, prophylactic nicotinamide is not recommended; in cases of pellagra, a dose of 300 mg/day should be used for treatment.

iii. Cardiovascular effects: There has been a report of acute symptomatic hypertension following administration of pyrazinamide.[20]

iv. Skin and appendages: Urticaria and maculopapular rashes can occur. Hypersensitivity reactions have not been reported.

3. Rifampicin: Rifampicin given in usual doses (i.e. 10 mg/kg/day**)** is well tolerated and causes ADRs in only about 4% of patients. As a potent microsomal enzyme inducer, rifampicin shortens the half- lives of many other drugs. This effect occurs after about 7 days and persists for a few days after withdrawal.

i. Gastrointestinal: Nausea, vomiting, epigastric pain, diarrhea, loss of appetite, abdominal cramps, and meteorism are often restricted to the beginning of rifampicin therapy. These effects can be lessened by taking the drug after meals. Recently, there have been reports of cases of histologically confirmed pseudomembranous colitis with bacteriology showing mainly *Clostridium difficile* resistant to rifampicin and several other antibiotics. In such cases, discontinuation of rifampicin and use of vancomycin has been helpful.[21]

ii. Hepatic effects: Rifampicin has caused transient increases in serum concentrations of AST, ALT, bilirubin and alkaline phosphatase. The risk of hepatotoxicity appears to be low in patients with normal liver function. When given with INH, rifampicin can cause a fulminant liver reaction. This may be due to enhancement of isoniazid hepatotoxicity as a result of enzyme induction by rifampicin. Transaminase activities and other liver function tests should be measured weekly in patients with liver dysfunction and every 4 weeks in patients with no known liver disease.

iii. Respiratory effects: Respiratory symptoms are very rare. There may be part of flu-like illness with bronchial obstruction.

iv. Nervous system effects: These include drowsiness, headache, dizziness, ataxia, generalized numbness, pain in the extremities, muscular weakness, confusion, inability to concentrate, delusions, disorientation, hallucinations and agitation.[22]

v. Cardiovascular effects: Shock and a flu- like illness (fever, chills, bone pain, shortness of breathe, myalgia) have been observed most often in patients taking intermittent therapy, dosages over 1000 mg/day, or on restarting treatment.

vi. Urinary system effects: Increased blood urea nitrogen (BUN) and serum uric acid concentrations, light chain proteinuria, hematuria, renal insufficiency, interstitial nephritis, acute tubular necrosis, and acute renal failure have occurred infrequently with rifampicin. Acute renal failure is rare during continuous treatment but may occur after restarting treatment or during intermittent therapy. Early symptoms of renal failure are oliguria and anuria, hematuria, or hemoglobinuria often preceded by hemolysis or a flu-like illness.

vii. Endocrine and metabolic effects: Rifampicin has been associated with precipitation of adrenocortical insufficiency in patients with compromised adrenal function, possibly due to increased cortisol metabolism secondary to hepatic microsomal enzyme induction by rifampicin. Patients taking corticosteroids for Addison's disease may need to increase corticosteroid dosage. The combination of rifampicin and INH reduces the serum concentrations of 25-hydroxycholecalciferol (the major circulating metabolite of vitamin D). Rifampicin acts by induction of an enzyme that promotes conversion of 25- hydroxycholecalciferol to an inactive metabolite and isoniazid acts by inhibiting 25-hydroxylation and 1- hydroxylation. Menstrual disturbances have also been reported.

viii. Hematological effects: Thrombocytopenia, leukopenia, purpura, hemolysis, hemolytic anemia, hemoglobinuria, and

decreased hemoglobin concentrations have occurred with rifampicin. Acute hemolytic anemia has generally occurred only with intermittent therapy. Thrombocytopenia has been reported after high dose intermittent therapy but has also been reported rarely when rifampicin therapy was discontinued and restarted. Thrombocytopenia is generally reversible if rifampicin therapy is discontinued as soon as purpura occurs; cerebral hemorrhage and fatalities have been reported when rifampicin therapy was continued or resumed after the appearance of purpura. Rarely, disseminated intravascular coagulation has also been reported in patients receiving rifampicin.[23]

ix. Hypersensitivity and dermatological effects: Anaphylaxis has been reported rarely. Hypersensitivity reactions characterized by a flu-like syndrome with episodes of fever, chills and sometimes with headache, dizziness and bone pain have occurred. Edema of the face and extremities, decrease in blood pressure and shock has also been reported. Occasionally pruritus, rashes, urticaria, acneiform eruptions, pemphigoid reactions, erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, eosinophilia, sore mouth, sore tongue, exfoliative dermatitis, and exudative conjunctivitis have also occurred.

x. Local effects: Extravasations during IV infusion has caused local irritation and inflammation; if it occurs, the infusion should be discontinued and restarted at another site.

xi. Immunological effects: A drug- induced lupus like syndrome consisting principally of malaise, myalgias, arthritis and peripheral edema accompanied by positive antinuclear antibody (ANA) test has been reported in patients receiving rifampicin or rifabutin. Manifestations of the syndrome disappeared within 1-10 weeks following discontinuation of rifamycin therapy despite continuation of other antimicrobial therapy. All patients were receiving concomitant therapy with clarithromycin and/or ciprofloxacin which are known inhibitors of cytochrome P-450 enzyme system, and which could have increased the serum concentration of the rifamycins.[24]

xii. Miscellaneous: Fever, headache, malaise and bone pain shortly after the administration of rifampicin usually occurs with higher doses given weekly or twice weekly. The usual procedure is to reduce the dose or increase the frequency of treatment. Antipyretic drugs can also be used for symptomatic relief.

4. Rifabutin: It is a generally well tolerated drug in clinical trials. The most common ADRs, including those resulting in discontinuation of the drug are rash, GI intolerance and neutropenia.

i. Gastrointestinal effects: Nausea, vomiting, abdominal pain, taste disturbance, diarrhea, dyspepsia, and eructation have occurred in patients receiving the drug in controlled clinical trials. In patients prone to GI effects of rifabutine, the drug may be administered after food and the total daily dose may be given as two divided doses. Rifabutine induced diarrhea and pseudomembranous colitis caused by overgrowth of toxin producing clostridia like *C. difficile* have been reported rarely.

ii. Nervous system effects: Headache, fever, asthenia, and nonspecific complaints of pain occurred in patients with severe HIV infections receiving rifabutin in controlled clinical trials. Although a casual relationship to rifabutin has not been established, seizures, paresthesia, aphasia, and confusion have also been reported in patients receiving the drug.

iii. Musculoskeletal effects: Myalgia, arthralgia and myositis have occurred in patients taking the drug. Risk of rifabutin-induced arthralgia appears to be highest in patients receiving a dosage of 1050 mg daily or higher. The arthralgia usually involves small joints of hands and involves many joints; in some patients, periarticular swelling or joint tenderness may be present. The arthralgia was reversible after discontinuation of the drug.

iv. Ocular effects: Uveitis, which may be unilateral or bilateral and which is characterized by pain, redness and possible temporary or permanent loss of vision, may occur occasionally in patients receiving rifabutin 300-900 mg daily in combination with other agents, particularly clarithromycin and/or fluconazole. They inhibit cytochrome P450 drug metabolism leading to increased blood concentrations of rifabutin. If rifabutin is combined with clarithromycin 1 g/ day the dose of rifabutin should be limited to 300 mg/day, an advice endorsed by the UK Medicines Control Agency.[25] Rifabutin is less likely to caus uveitis when it is used in combination with azithromycin 500 mg/day than with clarithromycin.

v. Hepatic effects: Increased serum concentrations of ALT (SGPT), and AST (SGOT) were reported in 9% and 7% respectively of patients with sever HIV infection in controlled clinical trials. Increased serum alkaline phosphatase concentrations occurred in less than 1% of patients and hepatitis was reported in less than 1% of patients receiving the drug.

5. Ethambutol: The adverse effects of ethambutal are mainly seen in patients taking very high doses, i.e. over 25 mg/kg/ day, doses below 20 mg/kg/day are therefore recommended.

i. Ocular effects: The most important effect of ethambutal

is optic neuritis with decreases in visual acuity, constriction of visual fields, central and peripheral scotomas, and loss of red-green color discrimination. One or both eyes may be affected. The extent of ocular effect appears to be related to the dose and duration of ethambutol therapy. Doses not over 25 mg/kg/day during the first two months and 15 mg/kg/day thereafter are generally acceptable. Rarely, such toxicity has also been reported only a few days after starting therapy and may represent an idiosyncratic reaction. Tests for visual acuity should be performed using a Snellen eye chart prior to and periodically during ethambutol therapy. Changes in visual acuity may be unilateral or bilateral, so each eye must be tested separately and both eyes tested together. In diabetics with retinopathy, monthly monitoring of the fundus and visual acuity are mandatory.

When ocular toxicity is detected early and ethambutol is discontinued promptly, the visual effects are generally reversible over a period of weeks or months then therapy has been restarted without recurrence of ocular toxicity. Rarely, depending on the degree of impairment, recovery may be delayed for up to one year or more or the effect may be irreversible.

ii. Endocrine and metabolic effects: Blood urate concentrations increases due to reduced excretion of uric acid.

iii. Hepatic effects: Transient impairment of liver function as indicated by abnormal liver function test has occurred. Cholestatic jaundice which appeared to have been caused by ethambutol has also been reported.

iv. Gastrointestinal effects: GI upset, abdominal pain, nausea, vomiting and anorexia have been reported during ethambutol therapy.

v. Other adverse effects: Dermatitis, pruritus, headache, malaise, dizziness, fever, mental confusion, disorientation, possible hallucinations, and rarely anaphylactoid reactions.

6. Streptomycin: Since the advent of less toxic oral antituberculous drugs, the use of streptomycin has diminished considerably. However, for good reason, there are still countries, including Nepal, where streptomycin is still an important standard drug in programs for the treatment of tuberculosis.

i. Nervous system effects: Neuromuscular blockade with respiratory depression can occur, especially after intrapleural or intraperitoneal use. Peripheral neuritis is rare but a disturbance of vision has been observed in some cases. Occasionally, intrathecal administration was followed by radiculitis, myelitis and other neurological problems.[26]

ii. Effects on special senses: Streptomycin can cause ototoxicity, which tends to affect the vestibular apparatus. It is generally accepted that in patients with normal kidney function, the main factors involved in the ototoxicity are the daily dose and the total amount received over a certain period. In the absence of renal insufficiency, amounts up to 30 g have been reported as being safe in old literatures. However, vestibular damage has occurred after administration of no more than 5-30 g in dosages of 1 g/day. A familial incidence of damage to the inner ear after even smaller doses is presumably due to hereditary susceptibility. Toxicity from small doses of streptomycin has occurred in patients with otitis media or with a history of otitis media.

Complete or partial anosmia has been reported after treatment with streptomycin over prolonged periods.

iii. Immunological and hypersensitivity reactions: Exanthematous skin reactions and Stevens- Johnson syndrome caused by streptomycin have been reported. People who regularly handle streptomycin (nurses, pharmaceutical employees) often develop hypersensitivity to streptomycin due to skin contact or inhalation. In such people, skin tests can be dangerous and can precipitate an anaphylactic or anaphylactoid reaction.

iv. Second generation effects: Severe hearing loss and deficient vestibular function has been reported in children after the use of streptomycin in pregnancy.

Need for ADR monitoring in TB: Despite the availability of cost effective tools that can cure the disease, tuberculosis still remains the primary killer of adults in most developing countries. Since the emergence of HIV/AIDS in the 1980s, the TB is once again emerging as a major health problem even in the developed countries. Even in the presence of HIV, TB can be effectively cured if treated with appropriate agents for a suitable length of time.[27] However, these agents used for the treatment of TB can cause many serious adverse effects like peripheral neuropathy, optic neuritis, hepatotoxicity, ototoxicity, nephrotoxicity, etc. which can be serious enough to result in permanent disability or even be fatal if not detected and treated on time. [5] In addition, in the context of Nepal, several problems related to drug use exist like remote rural population, poor pharmacy practice, poverty, illiteracy, etc. due to which people have no sense of risk in taking drugs.[28] Hence, monitoring of ADR due to anti TB drugs can be of tremendous help in better control of the disease and to minimize the risk of serious adverse effects. The summary of ADRs caused by first line anti-TB drugs are listed in Table 6.

Reports /studies on ADR monitoring of TB drugs in Nepal: A few studies carried out in Nepal regarding the ADR monitoring of antitubercular drugs were reported. A brief

outline of these studies is mentioned below.

In studies carried out by *Shakya et al* [29,30] with the aim of studying the incidence and management of antituberculosis drug-induced hepatotoxicity, reintroduction procedure and assessment of risk factors for the same. In the prospective cohort study carried out in 50 patients from Dec 2001 to Oct 2002, 4 patients had developed anti-TB drug induced hepatotoxicity. Younger age, female gender, and nutritional status were considered the predisposing factors. In all four cases, the patients tolerated the anti- TB drugs well after reintroduction without recurrence of hepatotoxicity.

In another study carried out by *Koju et al* [31] in urban Nepalese population under DOTS treatment, 80% of the total patients reported at least one type of side effects and 34.29% experienced major side effects. Female gender, alcoholics and sputum smear positive patients were associated with an increased occurrence of major side effects.[31]

Strategies to prevent the occurrence of ADRs due to first line ATT drugs: Different strategies can be adopted to prevent or minimize the occurrence of ADRs due to ATT drugs. Some of them are as follows:

1. Counsel the patients regarding the disease, drugs and possible adverse effects as well as methods to detect and prevent them.
2. Include pyridoxine in the standard treatment regimen for population of lower socioeconomic status or malnourished individuals.
3. Determine the dosage of the ATT drugs based on weight of patient.

Conclusion

Although effective anti tubercular drugs have been available for decades, they are still capable of causing significant ADRs, some of which can be fatal. As TB is still a global problem and the number of patients undergoing ATT is significant, monitoring for ADRs due to antitubercular drugs is very important. Timely detection and prevention of ADRs can reduce morbidity and mortality as well as improve patient compliance, hence ensuring success of the program.

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