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A Review on Pediatric Adverse Effects of First Line Anti-Tubercular Drugs

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ABSTRACT

Tuberculosis is a potentially serious communicable disease caused by mycobacterium tuberculosis. That mainly affects lungs. Tricky mitigation and diagnosis cause the childhood tuberculosis a growing burden for society. Directly Observed Treatment Short course (DOTS) strategy is one of the largest public health programmes found to be beneficial against tuberculosis. Anti-tubercular treatment shows greater level of efficacy high degree of toxicity; however combination treatment, especially during the intensive phase of therapy may produce severe adverse events. First line therapy of Tuberculosis leads to serious adverse effects. Serious adverse effects are less in children receiving drug therapy. Major adverse event associated with anti TB drugs is hepatotoxicity.

Keywords: Tuberculosis, DOTS, isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin

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INTRODUCTION

Tuberculosis is an infection caused by bacteria mycobacterium tuberculosis complex. In 1993 world health organization declared Tuberculosis as a medical emergency. There are two types of tuberculosis TB disease and latent TB infection .TB disease patients have active TB germs. They have symptoms and spread germs to others. Latent TB infection patients are asymptomatic and do not transmit germs to others. [1]

Tuberculosis in children is a one of the major problem. Children can have tuberculosis at any age. Most commonly between 1 and 4 Diagnosis is difficult in childhood tuberculosis .Symptoms are varied and non-specific. DOTS (directly observed treatment short course) is the therapy recommended by WHO for tuberculosis. The duration of therapy is about 6-8 months. It includes therapy with the first line drugs and second line drugs. First lines drugs include isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. [2]

PRINCIPLES OF TUBERCULOSIS TREATMENT IN CHILDREN

Treatment goals of Tuberculosis in children and adults are same.

The important goals are:

1. Patient cure
2. To reduce death from Tuberculosis disease
3. Prevention of relapse of Tuberculosis
4. Prevention of development and spread of drug-resistant Tuberculosis
5. Reduce spread of tuberculosis
6. Achieve all this with minimal toxicity to the patients. [4]

The following are the doses of anti-tubercular drugs used for the treatment of TB in children daily:

10 mg/kg (range 7–15 mg/kg) of Isoniazid (H): A maximum of 300 mg/day

15 mg/kg (range 10–20 mg/kg) of Rifampicin(R): maximum dose of 600 mg/day

35 mg/kg of pyrazinamide (Z) (range 30–40 mg/kg)

20 mg/kg of Ethambutol (E) (range 15–25 mg/kg)

Children who are at a chance to have pulmonary tuberculosis and live in a society with reduced chance to occur HIV and children who are not HIV-positive can be treated first for 2 months with a three-drug regimen (HRZ) ,then for 4 months by a two-drug (HR) regimen at the following doses:

10 mg/kg (range 10–15 mg/kg) of Isoniazid (H): A maximum dose of 300 mg/day

15 mg/kg (range 10–20 mg/kg) of Rifampicin (R): A maximum dose of 600 mg/day

35 mg/kg (30–40 mg/kg) of Pyrazinamide (Z)

In case of children with pulmonary tuberculosis, Streptomycin cannot be used as a first-line drug.[3]

Isoniazid (H)

The major adverse reactions of isoniazid are neurologic and hepatic but both these are less in children. The isoniazid level in the body at any given dose in adults and children is based on the extend of acetylation. Hepatitis is one of serious adverse reaction of isoniazid. Jaundice is also reported in some children. The child may feel sick, constipation, difficulty in passing urine; get tingling or numbness in the hands or feet. [1]

Neurologic side effects are mainly dose related and that includes peripheral neuropathy, ataxia and paraesthesia. The competition of isoniazid with vitamin B6 (pyridoxine) is the reason for neurologic side effects. Children have less chance to cause pyridoxine deficiency with isoniazid when compared to adults. Hypersensitivity reactions include fever, skin eruptions toxic epidermal necrolysis. Haematological reactions include Agranulocytosis, aplastic anemia, thrombocytopenia, and eosinophilia. [1]

Elimination of isoniazid is depending on age. Younger children can eliminate INH faster than older children and adults. This is because; in young children there is larger liver size in proportion to total body weight. [4]

The malnutrition can cause pathophysiological changes in children and which can alter pharmacokinetics, response of drug and may lead to toxicity. [5]

Rifampicin (R)

Rifampicin is a well-tolerated drug. It causes allergic and hepatotoxic side effects. Allergic side effects include fever, eosinophilia, rashes, flu-like syndrome, kidney disease with acute renal insufficiency and haemolytic anaemia. These side effects occur commonly in adults with intermittent, high-dose intake and with increasing age. The occurrence of hepatotoxicity in children using rifampicin alone is found to rare. Using rifampicin and isoniazid for the treatment of TB may develop hepatotoxic reactions. [6]

Children prescribed with 10 mg/kg body weight of Rifampicin have less concentration of drug when compared to adults who receive the same dose of drug. When rifampicin and ethambutol are administered together decreased rifampicin exposure are seen, though it's not significant. Malnutrition in adults reduces the capacity of rifampicin to bind to proteins, and increase the renal elimination and reduce level of drug in adults. [6]

Pyrazinamide (Z)

Most commonly pyrazinamide is used in combination therapy with other drugs. In active TB disease it is used for two months of therapy. The common side effects include gastrointestinal side effects, hepatotoxicity, non-gouty polyarthralgia and gouty arthritis. Other side effects are child's skin may become more sensitive to sun light, stomach upset, and headache, feel dizzy, trouble sleeping. A small raise in plasma concentration of uric acid is also reported in some cases.

It was found that Pyrazinamide and Ethambutol have lower plasma levels of drug and shorter half-lives in children than in adults, and have recommended an increase in the dose for children. Children who are underweight have lower peak concentration of Rifampicin and Pyrazinamide when compared to normal children.[6]

There is no significantl reduction in Pyrazinamide and Ethambutol concentrations in HIV infected children when compared to the uninfected. [7]

Ethambutol (E)

In TB endemic countries Usage of ethambutol in young children is high. The serious adverse effect associated with Ethambutol is retrobulbar neuritis,it can be reversed if identified early. On opthalmoloscopic examination, the fundus appears to be normal because the neuritis is retrobulbar in nature. The marks of toxicity are loss of visual acuity and colour vision. These indications may be slow in young children. Other side effects include stomach upset,cramps, diarrhoea and metallic taste. The child may develop itchiness or rash. Thiacetazone cause severe Stevens–Johnson reactions in HIV-infected adults and children.So,Ethambutol was introduced to replace Thiacetazone. The incidence of eye toxicity depends on dose and duration of therapy. In adults, there is an increased chance for eye toxicity among patients with lower concentrations of Zinc. Tuberculosis infected children, especially having HIV/AIDS are very likely to cause zinc deficiency. There is no evidence on whether HIV infection increases the risk of ethambutol toxicity. Some other rare adverse effect of ethambutol include Blurred vision, pain in the eye, red-green color blindness,loss of vision, fever, joint pain, numbness, tingling, burning pain,weakness in hands or feet, skin rashes.[9]

Streptomycin

Dose related toxic effects are seen in the case of streptomycin and inherent to aminoglycoside antibiotics. The adverse effects are otovestibular toxicity; it can lead to permanent loss of hearing, and nephrotoxicity which is less in case of children. Other adverse effects are stomach upset, nausea, vomiting, loss of appetite, spinning sensation, rash fever, edema etc. Because of serious adverse effect associated with streptomycin its usage in children are limited. Streptomycin produces renal side effects due to their accumulation in the renal tubules. But these are more common in elderly individuals than in children. Immediately after the administration of streptomycin it can cause perioral paraesthesia. This adverse effect is benign. [10]

APROACH TO CONTROL SIDE EFFECTS OF THE MOST COMMON ANTI- TB DRUGS

Side Effects	Causative Drug	Control
Skin rashes	Streptomycin,rifampicin,pyrazinamide,isoniazid	Discontinuation of drugs
Hearing loss	Streptomycin	Discontinuation of drug
Confusion	Most of anti TB drugs	Discontinue the drug
Visual disorders	Ethambutol	Discontinue the drug
Shock, acute kidney disease	Rifampicin	Discontinue rifampicin
Jaundice	Rifampicin, isoniazid and pyrazinamide	Discontinue anti TB drugs
Oliguria	Streptomycin	Discontinue streptomycin

CONCLUSION

Tuberculosis is an infection caused by bacteria mycobacterium tuberculosis complex. . There are two types of tuberculosis TB disease and latent TB infection .Treatment of tuberculosis in children using variety of combination therapy regimens shows that anti-TB drugs are well tolerated at currently prescribed doses. Serious adverse effects are less in children. Major adverse event associated with anti TB drugs is hepatotoxicity. The occurrence of hepatotoxicity in children using rifampicin (R) alone is rare. Because of serious adverse effect associated with streptomycin its usage in children are limited.

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