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Is Supplementation of Pyridoxine A Necessary Adjunct with Daily First Line TB Chemotherapy Regimen for Indian Patients?

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ABSTRACT

Prophylactic pyridoxine is routinely prescribed to patients on TB chemotherapy to prevent Isoniazid induced neuropathy. The study aimed to determine the incidence of peripheral neuropathy in Indian patients on daily TB chemotherapy without prophylactic pyridoxine and whether they really needed therapeutic doses of pyridoxine, if it occurred. 559 patients on TB chemotherapy as per WHO categorization without prophylactic pyridoxine were followed throughout the course of treatment. Patients with proven or suspected drug resistance, those with existing peripheral neuropathy or those suffering from a condition predisposing to neuropathy such as diabetes were excluded. Patients reporting with symptoms of peripheral neuropathy were followed. Other causes of neuropathy were ruled out. They were given daily vitamin B-complex for one week. 100 mg daily pyridoxine was given only if there was no adequate response. A total of 26/559 patients (4.65%) developed neuropathy symptoms. 19/26 (73.07%) patients responded to one week course of B-complex and never had recurrence of symptoms. 7/559 (1.25%) patients needed 100 mg of pyridoxine to relieve their symptoms. This study indicates very low incidence of peripheral neuropathy in patients on daily TB chemotherapy without use of prophylactic pyridoxine, in Indian scenario. Not all patients developing neuropathy need high dose pyridoxine.

Keywords: INH, Isoniazid, neuropathy, pyridoxine, Vitamin B6

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INTRODUCTION

Daily TB chemotherapy is a standard practice all over the world. Since the introduction of guidelines by WHO, categorization of TB chemotherapy regimens became a standard practice in most countries including India. [1] The Revised National TB Control Programme (RNTCP) has adopted intermittent regimens. [2] However, most private practitioners in India prescribe daily regimens, as there are concerns over possible inferiority of intermittent regimens. [3][4] Although, the drug combinations and duration as per WHO categorization are usually followed by most.

Giving pyridoxine 6-10 mg daily along with TB chemotherapy had been a recommendation for long time and has been adopted by textbooks on TB. [5]

In our experience however, the incidence of neuropathy due to INH is very uncommon in Indian patients with daily TB chemotherapy regimens.

RATIONALE:

The TB treatment regimens recommended by WHO are as follows: New sputum positive pulmonary TB case is treated with 2HREZ/4HR, New sputum negative pulmonary TB or an extra-pulmonary TB case is treated with 2HRZ/4HR and a retreatment case is treated with 2SHREZ/1HREZ/5HRE regimen. [1]

Pyridoxine i.e. vitamin B6 is routinely given as an adjunctive treatment with TB chemotherapy. The rationale of this adjunctive therapy had been the increased incidence of neuropathy that occurs on TB chemotherapy due to INH. Many studies have proven efficacy of pyridoxine as a preventive treatment. [6]

In India, the only brands of pyridoxine available are of 40 mg and 100 mg. The practicing doctors therefore tend to use these, leading to overdosing of pyridoxine. This can be detrimental to the TB treatment itself since the receptors on mycobacterial cell wall that uptake INH are competitively inhibited by pyridoxine. It has also been documented that pyridoxine reverses the inhibitory effect of INH on mycobacterial catalase and a complex is formed involving pyridoxal, cupric ions, and INH. [7] This can be dangerous as high intake of pyridoxine can easily lead to suboptimal levels of INH in mycobacterium, thus predisposing to drug resistance. [8]

We have been analyzing data of adverse events of first line anti-TB drugs and found that the incidence of neuropathy in Indian patients is very low. We therefore thought that routine pyridoxine supplementation is probably unnecessary.

Intermittent paresthesias are not uncommon in society. Most incidences get abolished with multivitamin or B-complex preparations that typically contain 3 mg of pyridoxine. If the

patient is incidentally also on INH therapy, it may be incorrect to assume that the neuropathy symptoms are due to INH.

The study was thus designed around these three questions: Is neuropathy common on INH therapy in Indian patients? Is it correct to relate all neuropathy symptoms to INH therapy? And is it necessary to add pyridoxine as an adjunct to TB chemotherapy daily regimen?

SUBJECTS AND METHODS

Patients on daily TB chemotherapy regimens were studied. The patients were on standard WHO defined regimens. The dosages were adjusted as per the weight bands. Patients with proven or suspected drug resistance were excluded from the study. Patients with pre-existing peripheral neuropathy or those suffering from a condition predisposing to neuropathy such as diabetes were also excluded. The patients who defaulted the anti-TB treatment or those who were lost to follow up were excluded from the analysis. Dietary advice was given to all patients, which included daily inclusion of leafy vegetables or fruits in the diet. No patient was treated with prophylactic pyridoxine.

Patients reporting with symptoms of peripheral neuropathy such as tingling, numbness and other paresthesias; any times during the TB chemotherapy were followed. Other causes of neuropathy were ruled out by detailed clinical examination and necessary investigations, which included minimum blood sugar assessment. They were given daily vitamin B-complex (containing pyridoxine 3 mg) one tablet thrice a day for one week. They were given 100 mg pyridoxine daily only if there was no significant clinical response within one week.

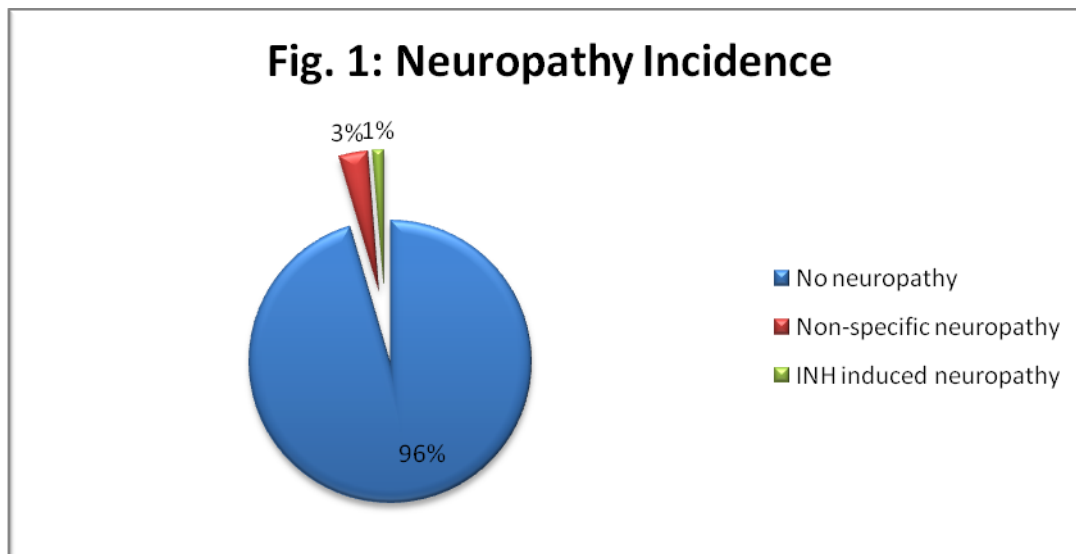
RESULTS

A data of 559 patients was analyzed. A longitudinal data of follow up records of these patients throughout their entire duration of TB treatment was evaluated.

Presence of tingling, hyperesthesia or numbness of hands and feet was taken as suggestive of peripheral neuropathy. Presence of neuralgia type radiating pains was carefully evaluated to rule out a compressing pathology at vertebral level. A total of 26/559 patients (4.65%) developed typical peripheral neuropathy symptoms.

19/26 (73.07%) patients responded to a significant extent, with a one week course of B-complex supplementation. The neuropathy gradually resolved over next 2 weeks and they never had recurrence of symptoms. 7/26 (26.92%) patients had persistent symptoms without any relief in spite of 1 week course of B-complex. The neuropathy of these patients was then attributed to INH after ruling out all other possible causes and after confirming the neuropathy by nerve conduction study in few. They were prescribed 100 mg of pyridoxine daily. Thus only 7/559 (1.25%) of the patients on anti-TB treatment had significant INH induced neuropathy and

needed pyridoxine to relieve their symptoms. The relief came gradually and took 5-6 weeks to disappear completely. (Refer to Fig.1)



DISCUSSION

Although recommended by WHO and adapted by RNTCP, most physicians believe that intermittent regimens are inferior to daily regimens in curing TB. There is a recent meta-analysis of randomized trials to support this view. [9]

Adverse effects of anti-TB drugs are more on daily regimens compared to intermittent regimens. INH is the usual culprit for TB chemotherapy induced neuropathy. In vivo, pyridoxine is converted into coenzymes which play an essential role in the metabolism of brain amines. INH apparently competitively inhibits the action of pyridoxine in these metabolic functions of the nerve cells. [10] Vitamin B-complex is overall essential for normal neurological function. [11] Deficiency of adequate pyridoxine or B-complex vitamins, available for the nerve cells makes them susceptible to malfunction. Plenty of studies done in 1960s suggested that INH can cause neuropathy. [12] It was proposed that this results from a deficiency of biologically active pyridoxine. The deficiency was also believed to be caused by the combination of INH and pyridoxine to form a hydrazone which is excreted in the urine. Dietary deficiency of pyridoxine thus can make patients more susceptible to develop peripheral neuropathy on Isoniazid treatment. The researchers therefore recommended Vitamin B6 as prophylactic treatment. [13] Pyridoxine deficiency, severe enough to manifest with clinical symptoms, is more common in malnourished individuals, alcoholics, patients with chronic renal failure, alcoholism, chronic liver disease, pregnant women and HIV co-infected individuals. [14][15] The risk in HIV patients further increases with co-administration of anti-retroviral treatment, especially stavudine. [16] Also, it can rarely occur early in the treatment. [17] It may be incorrect to assume that all TB patients are malnourished and have pyridoxine deficiency. Recently, WHO has also supported this and now recommends pyridoxine only to patients in above mentioned categories and the

recommended dose is 10 mg per day. The dose recommended for treatment of INH induced neuropathy is 75-100 mg per day. [18]

Prescribing B-complex vitamin preparations is a standard practice for treatment of peripheral neuropathy and hence this policy was adopted in the protocol. However, a recent Cochrane review of randomized trials failed to clearly demonstrate the efficacy of such treatment. [19]

Our study suggests that the incidence of peripheral neuropathy in Indian patients on daily TB chemotherapy on first line drugs is low. A good dietary advice, which is usually given to all TB patients, may be enough. Textbooks on TB have mentioned a standard dose of 6-10 mg pyridoxine to prevent INH neuropathy and have also commented that a dose of more than 50 mg may reduce the efficacy of INH. [5] Regular preventive treatment with pyridoxine seems to be un-necessary for Indian patients because the incidence of INH neuropathy is low enough so as to not warrant prophylaxis for every patient. As per WHO guidelines, this may be offered only to a selected subgroup of patients. Some recent studies have suggested that occurrence of INH neuropathy should prompt the checking of acetylator status and dose of INH may be reduced. [20-22]

None of the patients in our study required discontinuation of INH. Data suggests that such discontinuation is probably justifiable only with central neurological adverse events such as convulsions. [23] Similar studies from India on childhood Tuberculosis suggest that routine B6 supplementation is not necessary. [24]

The possibility of developing INH resistance due to poor uptake of INH in Mycobacteria by receptors that are over competed by pyridoxine seems to be a real risk. It is logically not worth to prevent neuropathy in 1.25% of patients and risk the failure of treatment in all. It will be interesting to see if this risk is hypothetical or real. This has not been assessed in the present study due to its limitations. Another limitation of the study was that the incidence of neuropathy was not correlated with the acetylator status of the individuals, as this testing facility is not routinely available. A prospective study to assess and compare the cure rate in patients on pyridoxine 100 mg daily supplementation vs. patients who are not on any pyridoxine supplementation will be interesting but probably unethical in the light of present study's results. However an observational analysis will still be possible as co-prescription of 100 mg pyridoxine along with TB chemotherapy is very common in the private practice settings of India. To complicate the matter further, there has been a published case report of worsening of peripheral neuropathy due to Pyridoxine administration. [25]

CONCLUSION

The incidence of INH neuropathy on daily TB chemotherapy with first line drugs appears to be low. Addition of pyridoxine to the regimen is not warranted. Not all patients developing peripheral neuropathy on TB chemotherapy need high dose pyridoxine. Rather, a high dose of

pyridoxine may be dangerous as it may interfere with INH efficacy and this need to be evaluated by a randomized trial.

Abbreviations: TB = Tuberculosis, H = Isoniazid = INH, R = Rifampicin, E = Ethambutol, Z = Pyrazinamide

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