Pyridoxine and the Isoniazid-Induced Neuropathy*, **

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Soon after isoniazid was employed in the treatment of tuberculosis, several investigators noted the occurrence of peripheral neuropathy in adult patients treated with the drug.1-4 This neuropathy was characterized by symmetrical numbness and tingling of the extremities in the “stocking-glove” distribution. It tended to develop earlier and was more severe in the feet than in the hands. In the early stages sensory manifestations predominated. Later stages were characterized by paresthesia, pain and aching in muscle and bone, hypesthesia, hyperesthesia, diminution of vibratory and position sense, exaggerated or reduced tendon reflexes, ataxia, muscle weakness and muscle paralysis. The neuropathy occurred sooner and was more severe in patients who received a larger amount than the usual isoniazid dose. It tended to regress when isoniazid was stopped, although the longer symptoms were present, the longer it took for them to disappear. In occasional instances the neuropathy was relieved by nicotinic acid, but it was unaffected by thiamin or vitamin B12. A pelagra-like state resulting from isoniazid has been reported5, 6 but the clinical picture of nicotinic acid deficiency does not resemble the isoniazid-induced neurotoxicity nor does the latter usually respond to the administration of nicotinic acid.

With the commonly employed dose of 300 mg. of isoniazid daily the neuropathy occurs in approximately 2 per cent of patients.7 Biehl and Skavlem1 reviewed the incidence of neurotoxicity in 100 patients receiving isoniazid in daily doses of 400 mg. to 1600 mg. Of 65 patients who had not taken isoniazid previously, 11 (17 per cent) developed symptoms or signs of neurotoxicity 24 to 71 days after starting the drug. The remaining 35 patients had received isoniazid immediately previous to the increase in dose and 12 ((33 per cent) developed neurotoxicity as early as six days after this was done. In another study in which 16 patients received isoniazid in amounts ranging from 1100 mg. to 2400 mg. daily, 5 (37 per cent) showed some evidence of peripheral neuropathy. The 30 to 40 per cent incidence of neurotoxicity with high doses of isoniazid was confirmed in a report on the treatment of 116 adult patients.8

Although a deficiency of the vitamin B complex had been suggested as the cause of neuropathy, Biehl and Wilte8, 9 were among the first to relate this to a deficiency in biologically active pyridoxine. These authors measured the 24 hour urinary excretion of pyridoxine and nicotinic acid before, during and after varying dosages of isoniazid. In addition, they determined the amount of xanthurenic acid excreted after a test dose of tryptophane, an increase being evidence of pyridoxine deficiency. They found that the level of pyridoxine increased while the excretion of nico-

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Pyridoxine deficiency resulted from a pyridoxine deficiency. This was the study by Reilly and associates\(^{14}\) on the convulsant effects of unsubstituted hydrazides, isoniazid being one example. Semicarbazide, another example, produced grand mal seizures which could be readily reversed by the administration of pyridoxine. These authors were also aware that patients with both tuberculosis and epilepsy required higher than the normal maintenance doses of anticonvulsant medication when receiving isoniazid.

Peripheral neuropathy is not a serious problem in patients treated with the 300 mg. isoniazid, the commonly employed daily dose. This dose, however, is not sufficient for all tuberculosis patients. One reason for this is that isoniazid is metabolized and altered to derivatives which have little or no antituberculous activity.\(^{15,16}\) The rate of this alteration while constant for any one person varies from one individual to another;\(^{15,17}\) the same dose of isoniazid, therefore, produces different effective antimicrobial levels of the drug in different persons. For this reason, doses greater than 300 mg. daily have been recommended for all tuberculous patients.\(^{18}\) Such doses will result in a higher incidence of peripheral neuropathy if pyridoxine is not given concomitantly.

Biehl and associates found that the daily administration of from 50 to 450 mg. of pyridoxine in conjunction with 1400 mg. of isoniazid effectively prevented the occurrence of peripheral neuropathy.\(^{7,9}\) In their series, no patient given the two drugs developed peripheral neuropathy within ten weeks, whereas the expected incidence would have been 40 per cent. The
prophylactic value of pyridoxine in preventing the isoniazid-induced neuropathy has been confirmed by two other studies.\textsuperscript{19, 20} In one of these,\textsuperscript{19} 25 mg. of pyridoxine with a daily dose of isoniazid of 500 mg. to 600 mg. and 50 mg. with a daily dose of 1100 mg. to 1200 mg. effectively prevented the occurrence of peripheral neuropathy. In the other study,\textsuperscript{20} the daily administration of 100 to 300 mg. of pyridoxine prevented the occurrence of peripheral neuropathy in patients receiving isoniazid in doses of 1000 mg. to 1800 mg. Pyridoxine was effective in some instances in which the neuropathy had already been established. When pyridoxine was given, it was not necessary to interrupt isoniazid therapy in some patients and, in others, it could be resumed at an early date.

The exact dose of pyridoxine needed to prevent the isoniazid-induced neuropathy has not been established but 10 mg. for each 100 mg. of isoniazid appears adequate. This amount should also be sufficient to prevent any possible or potential subclinical deficiency of this vitamin. The prophylactic use of pyridoxine concomitantly with isoniazid does not interfere with its antituberculous action. Several authors have shown in both animal and human studies that the neurotoxic and antituberculous effects of isoniazid are independent of each other.\textsuperscript{21-23}

The complete relationship between isoniazid and pyridoxine is, as yet, not known. One problem is whether isoniazid produces pyridoxine deficiency in children. Employing a relatively insensitive test of pyridoxine deficiency, Morales and Lincoln\textsuperscript{24} found that pyridoxine deficiency did not occur in tuberculous children treated with isoniazid and stated that prophylaxis with pyridoxine was not required.

**SUMMARY**

The isoniazid-induced peripheral neuropathy occurring in adult tuberculous patients results from a deficiency of biologically active pyridoxine. The deficiency is caused by the combination of isoniazid and pyridoxine to form a hydrazone which is excreted in the urine. It can be prevented by administration of pyridoxine whenever isoniazid is given. A 10 mg. dose of pyridoxine for each 100 mg. of isoniazid appears adequate to prevent both clinical and potential subclinical manifestations of pyridoxine deficiency. The administration of pyridoxine does not interfere with the antituberculous action of isoniazid.

**RESUMEN**

La neuropatía periférica producida por la isoniazida en los tuberculosos adultos, es resultado de la deficiencia de piridoxina biológicamente activa. La deficiencia es causada por la combinación de la isoniazida con la piridoxina para formar hidrazona que se excreta en la orina. Puede evitarse administrando piridoxina cuando se dé la isoniazida. La dosis de 10 miligramos por cada 100 mg. de isoniazida parece adecuada para evitar tanto las manifestaciones clínicas como las potenciales subclínicas de la deficiencia piridoxínica.

La administración de la piridoxina no interfere con la acción antituberculosa de la isoniazida.

**RESUME**

L'atteinte du système nerveux périphérique due à l'isoniazide, survenant chez des adultes tuberculeux provient d'une déficience en pyridoxine biologiquement active. La déficience est provoquée par l'association d'isoniazide et de pyridoxine qui forment un hydrazone qui est excrété dans l'urine. On peut l'empêcher par l'administration de pyridoxine même si on donne de l'isoniazide. Une dose de 10 mmgr. de pyridoxine pour 100 mmgr. d'isoniazide semble être la dose suffisante pour empêcher les manifestations cliniques et éventuellement subcliniques de la déficience en pyridoxine. L'administration de pyridoxine n'influence pas l'action antituberculeuse de l'isoniazide.

**ZUSAMMENFASSUNG**

Die durch INH bewirkte periphere Neuropathie, wie sie bei erwachsenen tuberkulösen Patienten auftritt, ist die Folge eines Fehlens von biologisch aktiven Pyri-
doxin. Dieser Mangel hat als Ursache die Verbindung von INH und Pyridoxin zur Bildung eines Hydrazons, das mit dem Urin ausgeschieden wird. Dies kann verhindert werden durch Gaben von Pyrazinamid, jedesmal, wenn INH verordnet wird. Eine 10 mg-Dosierung von Pyridoxin auf je 100 mg INH scheint angemessen zur Ver-
hinderung sowohl von klinisch wie potentiell subklinischen Manifestationen von Pyri-
doxinmangel. Die Verordnung von Pyrazinamid hat keinen störenden Einfluss auf die antituberkulöse Wirkung von INH.

REFERENCES
22 Ungar, J., Tomich, E. G., Parkin, K. R. and Muggleston, P. W.: "Effect of Pyri-
23 Boune, J., Cayze, R. M. and Viallier, J.: "Effect of Vitamin B on the Anti-Tubercu-