Single High-Dose Pyridoxine Treatment for Isoniazid Overdose

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• **We treated five isoniazid-overdosed patients each with a single dose of pyridoxine hydrochloride equivalent to the gram amount of isoniazid ingested and compared their outcome with that of 41 patients from the literature who received little or no pyridoxine. Recurrent seizures occurred in 60% of patients who had received no pyridoxine vs 0% in our patients. Metabolic acidosis resolved in our cases but was refractory in the literature cases. In our cases, coma lightened more rapidly and was of shorter duration as compared with that in the literature cases (mean, seven hours vs 24 hours). No adverse effects of pyridoxine were seen in our patients.**

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ISONIAZID is widely used in the treatment of tuberculosis. Cases of intentional and accidental isoniazid overdose continue to be reported, reflecting the drug's extensive use. The principal manifestations of isoniazid overdose (recurrent seizures, metabolic acidosis, and coma)[1,2] are well recognized.

Animal evidence suggests that isoniazid overdose produces a decrease in brain γ-aminobutyric acid (GABA) levels and that this decrease is responsible for the seizure activity that follows.[3] In isoniazid-overdosed animals, pretreatment or concurrent administration of pyridoxine hydrochloride (vitamin B_6) in large doses has prevented a decrease in brain GABA levels,[3] terminated seizures,[3,4] and resulted in decreased mortality.[4]

Based on animal evidence[3,4] and limited human experience,[1,2] doses of pyridoxine equivalent to the amount of isoniazid ingested have been suggested in the treatment of isoniazid overdose in humans. However, the efficacy of such treatment and the optimal means of administration of equivalent doses of pyridoxine have never been established. The majority of cases of isoniazid overdose reported in the literature have received doses of pyridoxine that are less than 10% of the ingested dose of isoniazid. In patients treated with equivalent doses of pyridoxine, the period over which pyridoxine has been administered has varied from 24 hours to five days. Only one documented case exists where a dose of pyridoxine equivalent to the amount of isoniazid ingested was administered over a shorter period (three hours).[5]

We report our experience with five patients treated with pyridoxine, in amounts equivalent to the amount of isoniazid ingested, administered as a single intravenous (IV) dose immediately after ingestion of isoniazid.

METHODS

All ingestions of isoniazid reported to the Massachusetts Poison Control System (Boston) during November 1978 to November 1979 were followed up by at least one of the authors. A uniform treatment protocol was established that included documentation of acid-base status; frequency, duration, and nature of seizures; and grade of coma using the classification of Matthew et al.[6] After estimation, by history, of the amount of isoniazid ingested, an equivalent dose by weight of pyridoxine was administered IV (ie, 1 g of pyridoxine hydrochloride for each gram of isoniazid ingested).

The pyridoxine solution was prepared in a 5% or 10% concentration (W/V) in 5% dextrose and water, filtered through a 0.45-μm filter and infused over 30 to 60 minutes. Clinical status and laboratory values were reassessed after the pyridoxine infusion. Serum isoniazid levels were assayed before and after administration of pyridoxine using the methods described by Maher et al.[7]

Since lack of large numbers of patients with isoniazid overdose precluded a controlled study, we compared our data with data obtained from literature reports of isoniazid overdose.

RESULTS

Prospective Data 'Study Group'

During the study period, five patients with isoniazid overdose were referred to the Massachusetts Poison Control System. The clinical and laboratory findings in each case are summarized in the Table. All five patients had ingested large doses of isoniazid, and all were symptomatic within one hour of ingestion. Cases 1 through 4 exhibited seizures, coma, and acidosis. Case 5 had seizures but was not acidotic or comatose.

Retrospective Data

One hundred ninety-three cases of isoniazid overdose reported in the English and French literature from 1956 to 1980 were reviewed. Forty-one patients from the literature had adequate treatment and

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Characteristics of Study Cases

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, yr/sex	31/M	33/F	2.5/M	31/F	17/F
Dose of isoniazid ingested in grams (mg/kg)	20(286)	25(417)	4(222)	15(310)	5(100)
Other drugs ingested	Alcohol, amitriptyline hydrochloride	Alcohol, cocaine hydrochloride	. . .	Ethambutol hydrochloride	. . .
Time first seen after isoniazid ingestion, hr	<1	<1	1	1	1
Anticonvulsant medication	Phenytoin sodium, diazepam, phenobarbital	Phenytoin	Phenytoin, diazepam, phenobarbital	Phenytoin	. . .
Dose of sodium bicarbonate administered before pyridoxine hydrochloride infusion, total mEq (mEq/kg)	100(1.4)	500(7)	40(2.2)	600(8.6)	. . .
Serum isoniazid levels, μg/mL (hr after ingestion)	109/7	48/3	128/2½	77/1	26/1
	10/12	19/6	20/10½	52/4½	25/2½
	3/37	9/10		8/12	8/5½

outcome data recorded. Their ages ranged from 21 months to 37 years. Twenty-four percent (10 patients) received no pyridoxine; 51% (21 patients) received pyridoxine in a pyridoxine-isoniazid ratio by weight of less than ten percent; 22% (9 patients) in a pyridoxine-isoniazid ratio between 10% to 50%; and one patient[4] had received 100% pyridoxine administered in three doses over three hours of treatment.

Severity, Mortality, Seizures, Coma, and Acidosis

Severity.—In the patients from the literature, the amount of isoniazid ingested ranged from 50 to 545 mg/kg (mean, 204 mg/kg). In the study group, the amount of isoniazid ingested ranged from 100 to 417 mg/kg (mean, 267 mg/kg). Among the patients from the literature, only seven[2] had isoniazid concentrations determined. Six patients had serum concentrations ranging from 20 to 143 μg/mL (mean, 80 μg/mL; therapeutic, 5 to 8 μg/mL). One patient had a concentration of 710 μg/mL. The five patients in the study group had initial serum concentrations ranging from 26 to 128 μg/mL (mean, 78 μg/mL). The two groups are therefore comparable in severity of overdose.

Mortality.—Mortality in the cases from the literature was 7%. All five patients in the study group survived.

Seizures.—All 41 cases from the literature exhibited seizures. In the study group, all five patients experienced grand mal seizures. Four of the five received appropriate doses of phenobarbital, phenytoin sodium, and diazepam without cessation of seizures. After administration of pyridoxine in a pyridoxine-isoniazid ratio of 100%, no further seizure activity occurred in any of the patients (Fig 1). One patient (case 5) received a gram-equivalent amount of pyridoxine and no anticonvulsant medication and experienced no further seizures.

Recurrent seizures (ie, seizures that continued for a three- to four-hour period despite the use of anticonvulsant medication) occurred in 60% of those patients receiving no B_6, in 47% of those receiving less than 10% pyridoxine, and in 11% of those receiving 10% to 50% pyridoxine. Patients receiving 100% pyridoxine experienced no recurrent seizures. The dose-related effect of pyridoxine in preventing recurrent seizures in the literature and study patients is illustrated in Fig 2. A χ^2-square test for trend shows a statistically significant difference between the treatment groups ($P<.004$).

Coma.—All 41 patients from the literature were comatose. A decrease in depth of coma immediately after pyridoxine treatment was not reported. All patients were reported to be breathing spontaneously when first seen. However, in some cases, the large doses of anticonvulsants administered to stop seizures resulted in respiratory depression requiring ventilatory support.

Of the five patients in the study group, 2 were in grade III coma, 2 in grade II coma, and 1 in grade I coma, before pyridoxine treatment. All five patients exhibited a decrease in depth of coma within two hours of pyridoxine administration (Fig 1).

The time, after pyridoxine treatment, for pyridoxine-treated patients from the literature to be fully awake, ranged from 15 minutes to 72 hours (mean, 24 hours). In the study group it ranged from five to nine hours (mean, seven hours). The mean duration of coma is significantly different between the two groups ($P<.01$).

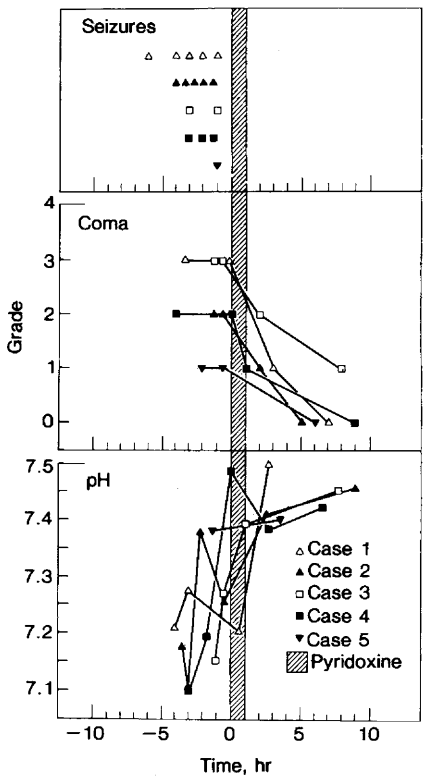

Fig 1.—Outcome of five study cases. Course of seizures, coma, and pH before and after pyridoxine hydrochloride treatment. Time = 0 represents the beginning of the pyridoxine (vitamin B_6) infusion.

Acidosis.—Thirty-six patients from the literature had inadequate acid-base data. Of the remaining, all were acidotic and required large amounts of sodium bicarbonate to correct the acidosis.

In the study group, four of five patients were severely acidotic. All four patients received IV bicarbonate. Only one patient (case 4) responded

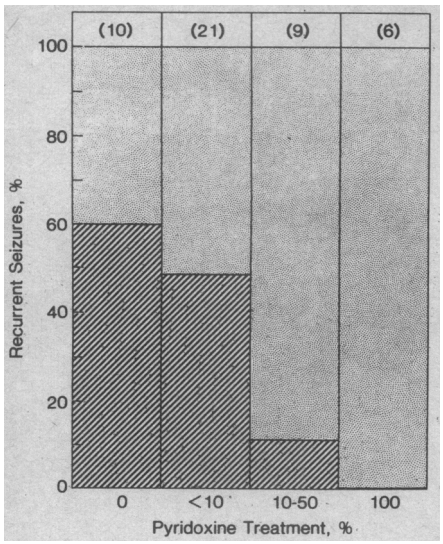

Fig 2.—Dose-related effect of pyridoxine hydrochloride (vitamin B_6) in preventing recurrent seizures. Pyridoxine treatment represented by four treatment groups: 0%, 0% to 10%, 10% to 50%, and 100% (B_6: isoniazid ratio). Percentage of patients who experience recurrent seizures (more than three to four hours of seizures) within each treatment group is illustrated. Number of patients in each treatment group is shown at top of each column. Included in 100% treatment group are five study cases and one patient from the literature who received 100% pyridoxine.

completely to sodium bicarbonate. Cases 1 to 3 remained acidotic despite bicarbonate therapy. Pyridoxine administration effectively corrected the acidosis in the latter three patients (Fig 2). After pyridoxine treatment, none of the five patients required further bicarbonate to maintain a normal pH.

COMMENT

Isoniazid produces toxic effects by inhibiting the activity of brain pyridoxal-5-phosphate, the active form of vitamin B_6.[8] Pyridoxal-5-phosphate is a coenzyme for the enzymes glutamic acid decarboxylase (GAD) and γ-aminobutyric acid transaminase (GABA-T). The GAD and GABA-T are involved in the synthesis and degradation of GABA, respectively. Pyridoxine is thought to prevent the effects of isoniazid on GAD activity and thereby prevent a decrease in brain GABA.[3] Seizure activity in isoniazid overdose is believed to be related to the decrease in brain GABA levels.[9] Acidosis in isoniazid overdose is postulated to be due to lactic acidosis induced by seizure activity.[10] Isoniazid may also interfere with nicotinamide-adenine dinucleotide (NAD) that is necessary for the metabolism of lactate to pyruvate. The principal effect of pyridoxine in correcting acidosis in isoniazid overdose may be related to the prevention of seizures and subsequent lactic acidosis.

Five cases of isoniazid overdose have been presented. All exhibited signs of toxic reactions, and all had serum isoniazid levels in the toxic range. After the IV administration of pyridoxine in a single dose in a gram amount equivalent to that of isoniazid ingested, all five patients demonstrated a cessation of seizure activity, a correction of acidosis, and a decrease in depth of coma within two hours of pyridoxine treatment.

Certain limitations in our data require caution in interpretation. The dose of isoniazid ingested by all of our patients was obtained by history from the patient or relatives. This information is often unreliable, and thus a gram-per-gram equivalency of isoniazid to pyridoxine may be uncertain. Comparison of our cases with historical control subjects also has limitations. However, since numbers of cases of isoniazid overdose are small, and since a controlled trial would be unethical, we compared our data only with those from patients in the literature who had adequate clinical and laboratory data recorded. Four of our five cases, additionally, had received previous anticonvulsant medication, and two had ingested alcohol. Animal data have demonstrated a synergistic effect of diazepam and B_6 in isoniazid overdose.[4] Further, since phenytoin and phenobarbital, like diazepam, increase brain GABA levels, synergy may be expected between these anticonvulsants and pyridoxine. The effects of previous alcohol ingestion in a similar manner are unknown. Only one of our patients was treated with pyridoxine alone (ie, no previous anticonvulsant medication). Although no seizures, acidosis, or coma followed, clinical findings and serum levels indicated she had the least toxic reaction of any of our cases.

Toxic effects of pyridoxine include tachypnea, postural reflex abnormalities, paralysis, and convulsions.[11] The 50% lethal dose of B_6 in dogs is 1 g/kg.[11] Human experience with large doses of pyridoxine is limited. Sievers and Herrier[1] quote a personal communication in which a patient tolerated up to 52 g of IV pyridoxine without adverse effects. No adverse effects of pyridoxine were noted in our five study cases in the doses used (mean, 241 mg/kg; range, 70 to 357 mg/kg).

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