sarcoidlike stromal reactions with granuloma formation may be seen in patients with breast cancer,[15] and there may be an increased incidence of breast cancer in patients with a history of sarcoidosis.[16] Therefore, we took special care to be certain there was no evidence of malignancy in the breast biopsy specimen from our patient. The only abnormalities encountered on careful histologic examination of the biopsy specimen were epithelioid noncaseating granulomata diagnostic of sarcoidosis. To our knowledge, this is only the fourth case of sarcoidosis of the breast to have been reported in the English-language literature since 1978.

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Isoniazid Overdose

Successful Treatment With Pyridoxine and Hemodialysis

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TUBERCULOSIS remains a major public health problem in the developing world. Native Americans, immigrants from the Third World, and immunocompromised patients are the groups in the United States at highest risk. Isoniazid, the hydrazide of isonicotinic acid, is the primary drug prescribed for the treatment of active tuberculosis and the prophylaxis of tuberculosis exposure. Mild, reversible hepatotoxicity is the most common adverse drug reaction associated with therapeutic dosages. Acute neurologic toxicity associated with overdose, however, may be fatal if not recognized and treated promptly. We present a recent case of isoniazid overdose successfully treated with pyridoxine hydrochloride and hemodialysis.

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Report of a Case

The patient, a 16-year-old man, was placed on a regimen of isoniazid prophylaxis in November 1988 after the discovery of a 10-mm reaction to a purified-protein-derivative skin test. He had slashed his wrists twice before and had been treated for drug and alcohol abuse. His medical history was otherwise unremarkable. Eight months later, he ingested between 7,500 and 13,500 mg of isoniazid after a disagreement with his girlfriend. He collapsed 30 minutes later and was rushed to a local community hospital, being comatose on arrival. Three seizures were witnessed in the emergency department, whereupon 8.35 grams of pyridoxine and 8 mg of diazepam were infused. The patient regained consciousness and had no further seizures.

He was transferred by air ambulance to Sioux Valley Hospital in Sioux Falls, South Dakota. On arrival, he was alert and fully oriented. Arterial blood gas determinations showed a pH of 7.42, a Pco_2 of 29 mm of mercury, and a Po_2 of 82 mm of mercury. Other laboratory values included a leukocyte count of 20.1×10^9 per liter (20,100 per μl); hemoglobin 157 grams per liter (15.7 grams per dl); sodium 139, chloride 108, potassium 3.4, and carbon dioxide content 20 mmol per liter; glucose 5.0 mmol per liter (90 mg per dl); creatinine 80 μmol per liter (0.9 mg per dl); blood urea nitrogen 3.2 mmol per liter (9 mg per dl); aspartate aminotransferase (formerly SGOT) 36 units per liter; and alanine aminotransferase (formerly SGPT) 13 units per liter. Isoniazid levels, which were measured by the standard method of Scott and Wright,[1] are shown in Figure 1. Using a femoral vein catheter, hemodialysis was started shortly after admission for several reasons: A Toxline computer search indicated that this patient had ingested nearly double an amount that had previously resulted in death in some patients (80 to 150 mg per kg)[2]; the exact amount ingested was not known, and no charcoal or cathartic mixture had been given to prevent absorption; it was unclear if the initial isoniazid level, which was nearly five times the upper therapeutic level, was a peak or might continue to rise; and he had been symptomatic with the most severe toxic reactions to isoniazid—central nervous system toxicity. No further seizures were noted, and postdialysis isoniazid levels were negligible. He was transferred to a psychiatric facility the following day.

Discussion

Epidemiology

High rates of isoniazid overdose have been reported in Southeast Asian refugee women and Native Americans living on reservations. The government screens all refugees for tuberculosis and treats those with active disease and positive skin tests. The Indian Health Service aggressively identifies contacts of persons with active tuberculosis and provides appropriate treatment.

In Olmsted County, Minnesota, the risk of isoniazid overdose in the Cambodian population is 14 cases per 111 person-years of isoniazid use.[3] Nolan and co-workers estimate that 4.2% of Southeast Asian refugee women between the

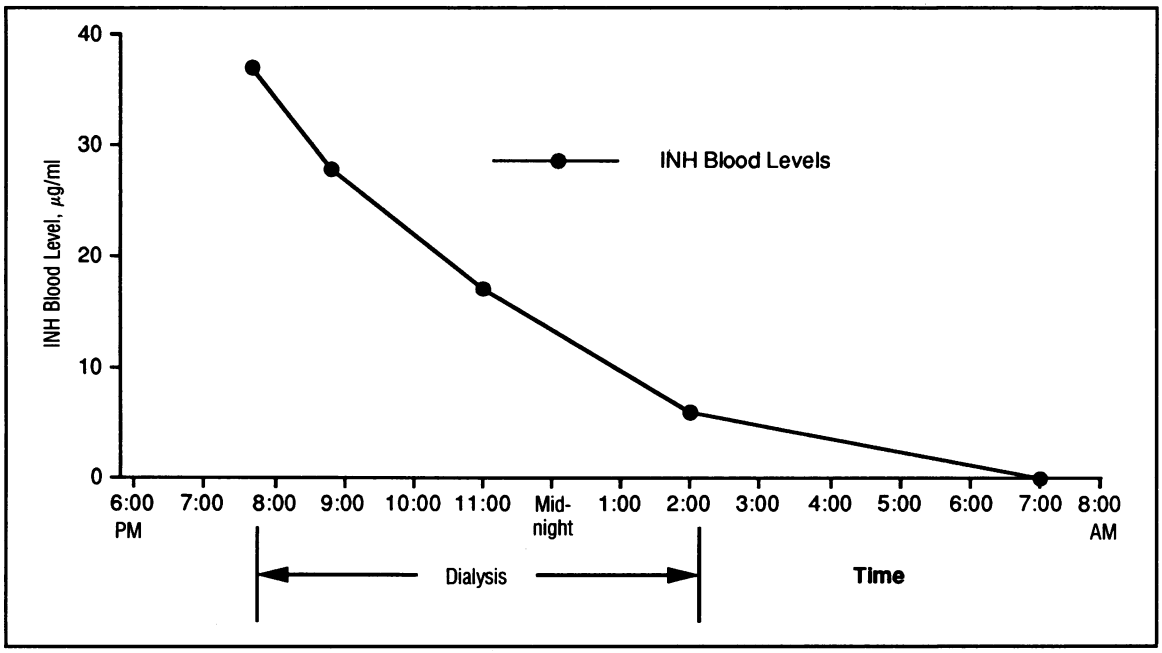

Figure 1.—The graph shows isoniazid (isonicotinic acid hydrazide; INH) levels in blood drawn before, during, and after hemodialysis in a 16-year-old man with seizures.

ages of 25 and 34 overdose on isoniazid while being treated—an extraordinary risk.[4] Depression is the most important risk factor in this group. Many cases, however, are impulsive acts occurring in the context of marital or family problems.

Both suicide and tuberculosis exposure are common in Native Americans.[5] Sievers and colleagues reported that the annual rate of suicide attempts in Arizona Native Americans is 447 per 100,000. Isoniazid was implicated in 8% of suicide attempts and in 17.6% of completed suicides. It was by far the most lethal ingested substance, accounting for 60% of deaths from ingestion. The rate of death from isoniazid overdose was 8.3%, second only to trauma in lethality. Young women were at particular risk for isoniazid overdose. All deaths were associated with ingesting greater than 15 grams of isoniazid and a delay of seeking medical treatment of more than four hours. The rate of isoniazid overdose within a year of starting therapy was 1.2%. The chance of clinical tuberculosis developing was similar to the chance of dying of isoniazid overdose in this group (1/1,400 patient-years versus 1/1,000 patient-years).

Clinical Findings

Ingesting as little as 1.5 grams of isoniazid is toxic in some persons. Consuming 80 mg per kg (sixteen 300-mg tablets in a 60-kg person) or more has a high likelihood of leading to seizures and death if not recognized.[6] Central nervous system effects dominate the clinical symptomatology. The patient may be asymptomatic for as long as two hours. Dizziness, nausea, vomiting, and slurred speech are followed by focal or generalized seizures. Coma may occur at any time. Oliguria and cardiovascular collapse follow in severe cases. Lactic acidosis proportionate to the severity of seizures is common. Severe hepatitis is uncommon. Isoniazid blood levels higher than 10 μg per ml are associated with severe toxicity.[7]

TABLE 1.—*Primary Prevention of Isoniazid Overdose*

Screen patients for suicide risk
Warn parents of the toxicity of isoniazid
See patients frequently to determine compliance
Limit prescriptions to 30 days
Use supervised intermittent therapy in patients at high risk for overdose

Mechanisms of Isoniazid Toxicity

Pyridoxine is an essential cofactor in the production of γ-aminobutyric acid—an important inhibitory neurotransmitter. Isoniazid combines with pyridoxine, forming inactive complexes. This results in a depletion of γ-aminobutyrate levels in the brain, leading to excessive central nervous system stimulation and seizures. The administration of pyridoxine specifically counteracts the neurotoxicity of isoniazid competitively. Studies using dogs[8] show that metabolic acidosis occurs only with major motor seizures and can be prevented by curarization. Correcting the metabolic acidosis does not prevent further seizures. The rate of acetylation (the major route of isoniazid elimination) affects the toxicity of a given dose. Persons in whom acetylation is slow may have greater toxicity at a given dose of the drug.

Primary Prevention of Isoniazid Overdose

Some authors consider isoniazid use to be relatively contraindicated in young female Native Americans[5] and Southeast Asians[4] because of the high risk for suicide and relatively low risk of the activation of tuberculosis. Given the need to eradicate tuberculosis in these groups, however, we propose an alternative approach (Table 1). All patients receiving isoniazid should be screened for depression. Pertinent questions to ask the patient and the family are if the patient's spirits are low or if he or she is losing weight, having difficulty sleeping at night, or has contemplated ending his or her life. Other factors that may increase the suicide risk, such as marital or family problems, school problems, legal problems, the death

of friends or family members, or impulsive behavior, should be excluded. Parents should be warned of the toxicity of isoniazid and should assist in drug administration. All patients should be seen frequently to determine compliance. Weekly visits that include pill counts and blood measurements of isoniazid levels to determine if they are in the therapeutic range are recommended in high-risk patients. Isoniazid prescriptions should be limited to 30 days to reduce the amount of drug available for overdose. Supervised intermittent therapy consisting of 900 mg of isoniazid given twice a week for a year is preferable prophylactic therapy in patients with risk factors for suicide.

Treatment of Isoniazid Overdose

General considerations. Isoniazid overdose can be effectively treated only if suspected. Seizures and coma are due to isoniazid unless proved otherwise in patients with access to the drug. Isoniazid overdose should be a major consideration in patients with status epilepticus poorly responsive to anticonvulsants. Where there is a high concentration of populations at risk for this problem, hospital laboratories should have the capability to measure "stat" isoniazid levels.

Unconscious patients with known or suspected isoniazid overdose should be intubated and lavaged through a large-bore gastric tube to remove any remaining drug from the stomach. Inducing emesis is dangerous in conscious patients because they may seize or become abruptly comatose. The role of activated charcoal slurries and cathartics has not been fully defined.[9] Enough evidence exists, however, to support the administration of 1 gram per kg of activated charcoal immediately after lavage or emesis. Simultaneously, providers should place large-bore intravenous lines immediately and infuse 5% dextrose in a normal saline solution at rates determined by the clinical setting. Vasopressors (dopamine, norepinephrine) are occasionally required. Forced diuresis is not recommended.

Pyridoxine. Pyridoxine is the specific antidote for isoniazid overdose. Physicians should infuse pyridoxine immediately by slow intravenous push (1 gram per minute), even if the patient is fully conscious. The earlier pyridoxine is given, the fewer the complications. The dosage is 1 mg for each milligram of isoniazid ingested. If the amount of isoniazid ingested is unknown or if isoniazid overdose is suspected, infuse 5 grams of pyridoxine. Repeat the initial dose at 5- to 20-minute intervals until the patient becomes stable or the dose of ingested isoniazid is exceeded 1½ times by the dose of pyridoxine.[10]

Seizure control. Pyridoxine alone is effective treatment and prophylaxis of seizures in most patients with isoniazid overdose. If seizures are resistant to pyridoxine, infuse diazepam after adequate airway control is established. Phenobarbital also may be used, but phenytoin is not effective. Seizure control is essential to prevent metabolic acidosis. If the pH drops below 7.2, give sodium bicarbonate. Pyridoxine is acidic and should not be mixed with bicarbonate. All patients should be observed for at least four hours after the last seizure.

Dialysis. Hemodialysis rapidly removes isoniazid from the serum.[7] Its use is not necessary in mild cases of isoniazid overdose but should be considered when coma and seizures are not adequately controlled with pyridoxine or when isoniazid levels are extremely high, as in this case. The most severe toxicity occurs with levels greater than 30 μg per ml.[11] An isoniazid level in this range, unless clearly declining on serial measurements when readily and rapidly available, is a reasonable criterion for considering dialysis.[1,11] Peritoneal dialysis also effectively removes isoniazid but is more cumbersome to do than hemodialysis.

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