

## Hydrazine, Cancer, the Internet, Isoniazid, and the Liver

**T**he ready availability of medical information on the Internet, the burgeoning role of complementary and alternative therapies in present-day health care, and the failure of government to regulate such therapies combine to make the report by Hainer and coworkers in this issue (1) a timely warning. The authors describe a 55-year-old man with squamous-cell carcinoma of the maxillary sinus who accessed an Internet Web site that proclaimed benefits from hydrazine sulfate for people with cancer. He purchased the chemical from a source identified by the Web site and, forsaking medical supervision, took it for 4 months before presenting with evidence of combined renal and liver toxicity. The patient ultimately died of these complications.

Liability issues are intriguing but are not the focus of this editorial. It is mildly reassuring, however, that the U.S. Federal Trade Commission and the U.S. Food and Drug Administration have jointly launched a campaign known as “Operation Cure” in an attempt to lessen the fallout from unsubstantiated claims on the Internet. According to one report (2), “Operation Cure” has identified more than 400 Web sites that make questionable claims about using certain products to treat serious diseases.

Both some reassurance and some cause for alarm can be found in the identity of the compound responsible for liver and kidney failure in the report by Hainer and coworkers. Hydrazine sulfate, although of uncertain benefit in the management of the type of cancer described in the case report, does at least have some support in the literature for its use by patients with cancer (3–5). Furthermore, hydrazine sulfate has garnered a highly vocal advocacy group that has challenged the “establishment” (including the National Cancer Institute) regarding its value in the treatment of cancer. There seems to be little evidence to support its ability to shrink tumors or cure cancer, but by virtue of its inhibition of gluconeogenesis (through inhibition of the enzyme phosphoenolpyruvate kinase), it has been suggested as an effective therapy for cancer cachexia. Although some randomized, placebo-controlled studies have shown some benefit in non-small-cell lung cancer (2, 3), not all investigators have come to this conclusion (6), and no benefit has been shown in other forms of cancer, such as colorectal cancer or leukemia (7).

Despite these seemingly well-conducted studies, which

are at best ambivalent about hydrazine sulfate’s efficacy, charges of a “government conspiracy” against use of the drug have appeared in a popular magazine (8) and in full-page advertisements in *The Washington Post* and *The New York Times*. The data have also spawned contentious debate in prestigious medical journals (9), making use of hydrazine sulfate in cancer management a surprisingly controversial subject. It appears unlikely that the arguments for and against the drug will be resolved any time soon.

A curious aspect of the previously described investigations is the infrequent recognition of important side effects. In these studies, patients took hydrazine sulfate in an escalating regimen, achieving a maintenance dosage of 180 mg/d (the same dosage taken by Hainer and coworkers’ patient). However, although the patients experienced some nausea and vomiting as well as lightheadedness, neither liver nor kidney effects were recognized. This is certainly surprising, given the perception (based on animal data) that hydrazine is highly toxic to both organs and is considered to be hepatocarcinogenic (10). Nevertheless, reports of hydrazine toxicity to the liver and kidney in humans are few. Sotaniemi and coworkers (11), while noting this, reported the case of a 59-year-old machinist who was exposed to hydrazine in the workplace for 6 months before presenting with eventually fatal kidney, liver, and lung disease. The encyclopedic *Poisoning & Toxicology Compendium* lists “fatty degeneration of the liver” associated with hydrazine sulfate, along with adverse effects on the cardiovascular system, the central nervous system, the skin, and the gastrointestinal system—but not the kidney.

It has long been suspected that hydrazine formation is the critical step in isoniazid hepatotoxicity. In fact, the case report by Hainer and coworkers may actually be most useful in helping us explore the possible mechanisms of isoniazid toxicity. Hydrazine and acetylhydrazine are formed during the metabolism of isoniazid, and it has been hypothesized that they play a role in causing liver injury during isoniazid therapy. It is appropriate to reexamine this hypothesis in light of the foregoing. Isoniazid is commonly used in the management and treatment of tuberculosis, which continues to exact a toll in terms of severe and occasionally fulminant liver failure (12, 13). Although the causative role of isoniazid in cases of severe hepatic injury was definitively established in the context of a nationwide

population study in the early 1970s (14), uncertainties regarding its pathogenesis have persisted. Attention has been focused on its metabolic pathways because clinical, laboratory, and histopathologic features of isoniazid hepatotoxicity favor a metabolite-mediated process rather than an immunologically based mechanism (15). Early claims that rapid acetylators are more susceptible to hepatotoxicity (16) have generally been refuted. Independent of the acetylation process, interest has long been directed at the step beyond acetylation, which leads to formation of acetylhydrazine. Because of the long-standing laboratory recognition of hydrazine hepatotoxicity, much attention has been directed at hydrazine and acetylhydrazine as possible candidates for the proximate toxic metabolite that mediates isoniazid hepatotoxicity (17). Acetylhydrazine is formed by hydrolysis of acetylisoniazid, the product of the acetylation process. It has been shown to be capable of undergoing oxidation by human liver microsomes to generate electrophilic intermediates (17), which may become covalently bound to hepatic macromolecules (18). Increased serum concentrations of hydrazine have been noted in a single patient with isoniazid hepatotoxicity (19). One group of investigators (20) was able to show greater *in vitro* toxicity with hydrazine than with acetylhydrazine. Despite these suggestive observations, however, a role for either metabolite in the mediation of isoniazid hepatotoxicity remains speculative.

Examination of the clinical syndrome experienced by Hainer and coworkers' patient demonstrates some similarities to isoniazid hepatotoxicity (such as extensive liver necrosis leading to death), but also some major differences. For example, an early feature of the patient's clinical presentation was evidence of kidney involvement, which does not occur in isoniazid hepatotoxicity but was reported by Sotaniemi and colleagues (11) in another patient who developed hydrazine poisoning. However, renal toxicity is not a constant feature of hydrazine toxicity; it was not observed in another patient who experienced liver injury after accidental ingestion of hydrazine (21). In contrast to the report by Hainer and coworkers, the presence of a skin rash is uncommon in patients with isoniazid toxicity. Finally, although many patients with cancer have probably been taking hydrazine in quantities greatly exceeding that generated in the metabolism of isoniazid, no other cases of hydrazine-related liver injury have previously been recognized. This also weighs against an important involvement of hydrazine in isoniazid hepatotoxicity.

In summary, although hydrazine sulfate has a track record of broad-ranging hepatotoxicity in experimental animal studies, it seems to be much less toxic in humans, and its role in causation of hepatotoxicity during isoniazid therapy appears much less compelling than it did 25 or more years ago. The report by Hainer and coworkers, which describes the unusual case of a patient who developed fatal hepatic necrosis after taking hydrazine sulfate, serves more to remind us of the drug's relative innocuousness than of its intrinsic toxicity. However, while it seems likely that this case will do little to dampen the ardor of hydrazine enthusiasts, there seems to be little justification for the drug's easy availability and unsupervised use. One hopes that it will attract the interest of "Operation Cure."

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