Pharmacokinetic Analysis of a Case of Isopropanol Intoxication

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A comatose 46-year-old woman, admitted to the emergency room, had isopropanol and acetone concentrations of 2000 and 120 mg/L, respectively, in her serum. She had no known history of acute isopropanol intoxication and was otherwise physically healthy. Pharmacokinetic analysis showed that the elimination of both isopropanol and its major metabolite acetone obeyed apparent first-order kinetics with half-lives of 6.4 and 22.4 h, respectively. These data contrast with the commonly held view that isopropanol is slowly metabolized. Concentrations of these analytes in cerebrospinal fluid 6 h after admission were similar to those in serum. This is the first report of the pharmacokinetics of both agents in a nonalcoholic person, and it gives the first data on concentrations of these substances in cerebrospinal fluid.

Additional Keyphrases: acetone • toxicology • cerebrospinal fluid

Intoxication with isopropanol is a common, potentially lethal toxicologic emergency. Most standard textbooks of toxicology state that isopropanol is metabolized and eliminated much more slowly than ethanol, presumably accounting for the longer duration of its toxic effects (1). Isopropanol is metabolized to acetone (1, 2), a process probably catalyzed by alcohol dehydrogenase (EC 1.1.1.1) (1, 3). However, little is known regarding the pharmacokinetics of either isopropanol or its metabolite in humans. Of the few such studies (4, 5), only one (4) included successive simultaneous analyses for both isopropanol and acetone. In addition, these few studies all contained pharmacokinetic data derived from alcoholic patients, some of whom had biopsy-documented liver disease. A history of alcoholism or liver disease is a significant consideration in evaluating a pharmacokinetic analysis; either may profoundly affect the metabolism of drugs, especially if the drug is detoxified in the liver. On the basis of previous work, therefore, we could not a priori predict the metabolic fate of isopropanol or acetone in normal individuals. Furthermore, we are unaware of any information regarding the disposition of either drug in the cerebrospinal fluid after toxic overdose. We present here clinical and pharmacokinetic data on the metabolism of isopropanol and acetone in a physically healthy, nonalcoholic woman, and report the concentrations of these agents in her cerebrospinal fluid.

Case Report

A comatose 46-year-old black woman without a known medical history was brought to the emergency room. Her rectal temperature was 35 °C, pulse rate 100 per minute, respiratory rate 24 per minute, and blood pressure 100/80 mmHg. She did not regain consciousness after being intravenously administered 50 mL of a 500 g/L solution of dextrose and seven 1-mL (400 μg/mL) ampules of naloxone, but she vomited large amounts of clear vomitus. At this time she was in Grade V coma. Intubation was followed by gastric lavage and the administration of activated charcoal and magnesium citrate.

The patient's breath had a fruity odor. There were no signs of trauma. Neurological examination revealed equal, slowly reactive 2-mm-diameter pupils, flaccid extremities, no response to pain, symmetrically diminished deep tendon reflexes, and flexed toes. Chest examination revealed coarse rhonchi. Results of cardiovascular examination were unremarkable, as were all other aspects of the patient's physical examination.

She was transferred to the intensive-care unit, where her systolic blood pressure of 80 mmHg responded to administration of intravenous fluids.

Her laboratory values at the time of admission were: arterial blood (room air) pH = 7.35, pO2 = 99 mmHg (13.2 kPa), pCO2 = 41 mmHg (5.5 kPa); leukocyte count 11,800/mm3 (49% polymorphonuclear leukocytes and 49% lymphocytes); hematocrit 41%; serum Na+ 140 mmol/L, K+ 3.7 mmol/L, Cl− 106 mmol/L, HCO3− 24 mmol/L, urea nitrogen 80 mg/L; creatinine 10 mg/L, and glucose 1.41 g/L. Serum ketones were negative by the "Acetest" tablet procedure (Ames, Division of Miles Laboratories, Elkhart, IN).

A chest roentgenogram showed plate-like atelectasis at the lung bases. Electrocardiographic findings were normal. A computerized tomography of the head showed no abnormalities. Cerebrospinal fluid (lumbar puncture) showed leukocytes and erythrocytes, two each per cubic millimeter; protein, 340 mg/L; and glucose, 1.16 g/L.

At the time of admission, the concentrations of isopropanol, ethanol, and acetone in serum were 2000, 130, and 120 mg/L, respectively. Pharmacokinetic data are presented in Figure 1. Nicotine and diphenhydramine were detected in the patient's urine, but not quantified. No other drugs were detected in either urine or serum.

The patient was managed supportively. The next day, she gradually awakened and showed spontaneous movement of all four extremities, but she did not obey commands or
rubbing respond to deep pain. Two days after admission the patient was alert and responsive, at which time she was identified as a chronic schizophrenic who was being treated with diphenhydramine, fluphenazine hydrochloride, and thiothixene. She admitted ingesting an unknown amount of rubbing alcohol (isopropanol). The patient had missed her last dose of antipsychotic medications.

Materials and Methods

We determined alcohols and acetone by flame-ionization gas chromatography, using a head-space analysis technique (6) with a Model 3920B gas chromatograph and an HS-6 head-space module (both from Perkin-Elmer Corp., Norwalk, CT). We used a 180 cm \times 2 mm (i.d.) Carbopack B/5% Carbowax 20M column (Supelco, Bellefonte, PA) isothermally at 85 °C, with nitrogen carrier gas at a flow rate of 45 mL/min. n-Propanol was the internal standard. We quantified results by determining peak-height ratios. We calculated drug half-lives by nonlinear least-squares regression analysis of the elimination-phase data points (7). Urine was screened for drugs with "Toxi-Lab" (Marion Labs.) and "EMIT" (Syva) kits (8, 9).

Discussion

Isopropanol. Since the first description of isopropanol intoxication in 1948 (10) many additional cases have been reported, and recently comprehensively reviewed (11). Despite this accumulation of clinical information, there is little on the metabolism of isopropanol or acetone after isopropanol intoxication. Isopropanol is generally believed to be metabolized and eliminated much more slowly than ethanol (1), but we found that this healthy, non-alcoholic individual metabolized isopropanol, present in her bloodstream at toxic concentrations, with apparent first-order kinetics and a biological half-life in blood of approximately 6.4 h (Figure 1). In a recent report of two cases of acute isopropanol intoxication in alcoholic persons, the kinetic pattern was similar and the isopropanol half-life was approximately 3 h (4). Data from another case report also support first-order elimination kinetics and a half-life of approximately 4 h (11). The differences in half-lives may reflect the effects of various therapeutic maneuvers, induction of drug-metabolizing activities secondary to alcoholism, the concomitant presence of ethanol, or possibly genetic variations in alcohol dehydrogenase (12). Increased metabolism of ethanol is reported in chronic abusers of ethanol (13), and some investigators suggest that such abusers may have a cross tolerance to isopropanol (1, 4). Despite the lack of controlled studies of this issue, our data and those cited clearly establish that isopropanol is metabolized much faster than is commonly believed. In addition, recent studies have shown apparent first-order elimination kinetics in several cases with very high concentrations of blood ethanol and ethanol half-lives of 4 to 5 h (13, 14). Interestingly, in cases of toxic overdoses of either alcohol, both the kinetic pattern of decay and the biological half-lives in blood are very similar.

Acetone. In contrast to the two above-mentioned studies, we obtained detailed pharmacokinetic data for acetone after isopropanol intoxication and observed apparent first-order elimination kinetics, with a half-life in serum of 22.4 h (Figure 1). Data from another case report show similar kinetics (15). These data also agree with the first-order elimination kinetics and a 31-h half-life reported in a case of acute acetone intoxication (5). Although that patient had biopsy-proven cirrhosis, the authors surmised that pulmonary clearance and not hepatic metabolism was probably of primary importance in the elimination of acetone, in view of the low acetone concentrations at which metabolism is saturated in persons with normal livers (5). Our data, derived from a patient whose liver function was normal, support this conclusion.

Finally, results of analysis for both isopropanol and acetone in the single CSF specimen (Figure 1) agree well with measured values for serum and establish for the first time that these agents equilibrate between these body fluids. We saw no increase in CSF protein in the cerebrospinal fluid, in contrast to an earlier report emphasizing this finding (16).

References


Fig. 1. Isopropanol and acetone concentrations in serum after an acute overdose of isopropanol
Closed and open circles indicate serum isopropanol and acetone concentrations, respectively. Isopropanol and acetone concentrations in spinal fluid are indicated by closed and open triangles, respectively.

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8. Toxi-lab drug detection system instruction manual. Analytical
10. McCord WM, Switzer PK, Brill HH. Isopropyl alcohol intoxica-
alcohol intoxication: Diagnosis and management. Am J Med 75,
12. Bosron WF, Li T-K. Alcohol dehydrogenase. In Enzymatic Basis
13. O’Neill S, Tipton K, Prichard J, Quinlan A. Survival after high
blood alcohol levels: Association with first-order elimination kinet-
14. Hammond KB, Rumack BH, Rodgerson DO. Blood ethanol: A
report of unusually high levels in a living patient. J Am Med Assoc
15. Hawley PC, Falko JM. "Pseudo" renal failure after isopropyl
protein following isopropyl alcohol intoxication. NY State J Med 71,
887–888 (1971).