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DETECTION OF ISOPROPANOL IN ACETONEMIC PATIENTS NOT EXPOSED TO ISOPROPANOL

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ABSTRACT

Isopropanol has been identified in five acetonemic patients not exposed to this compound. Serum concentrations ranged up to 297 mg/L for IPA and up to 321 mg/L for acetone. Concentration ratios (isopropanol:acetone) ranged up to 5.12. All five patients had Type I diabetes mellitus and were insulin-dependent. At the time isopropanol was detected each patient was hyperglycemic, and four patients were acidotic. These findings tend to corroborate clinically some earlier autopsy reports that acetone may be converted to isopropanol in physiological conditions in which reduced nicotinamide adenine dinucleotide is elevated. The conversion of acetone to isopropanol in vivo has significant clinical and forensic toxicological implications.

INTRODUCTION

Isopropanol (IPA) has for many years been implicated in numerous poisonings, both fatal and nonfatal (1-3). The compound is rapidly metabolized to acetone (ACET) via alcohol dehydrogenase, eighty percent of an absorbed dose undergoing renal excretion as this metabolite (2).

The presence of IPA in biological fluids has traditionally been considered to indicate exposure to this alcohol via oral ingestion, transdermal absorption, or inhalation (2). However, having observed IPA in the blood, milk, and rumen contents of cows suffering from acetonemia, Robertson, Thin, and Stirling (4) speculated that ACET may be converted to IPA. Lewis and coworkers (5) subsequently detected IPA and ACET in autopsy blood samples obtained from decedents who had not been exposed to IPA. These authors conjectured that ACET might be reduced to IPA and, in fact, demonstrated the production of IPA in rats that had been given acetone (5). Davis and associates (6) also reported the finding of IPA and ACET in the blood and tissues of decedents not exposed to IPA. These workers documented the in vitro production of IPA from ACET in the presence of alcohol dehydrogenase and reduced beta-nicotinamide adenine dinucleotide (b-NADH), and they hypothesized that a shunt mechanism for the conversion may prevail in the presence of elevated $NADH/NAD^+$ ratios (6).

Since these previous isolated reports dealt with autopsy cases, the present study was performed in attempt to detect IPA in cases of nonfatal acetonemia in individuals not exposed to IPA.

MATERIALS AND METHODS

Case Finding

By review of computerized laboratory records during the period December 1989 through April 1990, patients in whom ketones had been detected in the serum were identified.

Samples for Analysis

Blood from each of these patients had been drawn for routine diagnostic clinical chemistry analyses ordered by their physician, and the serum had been refrigerated (4°C) by the laboratory immediately after the analyses. All residual serum was gleaned for the study within seven days

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after blood collection, and the samples were maintained at 4°C until the time of analysis for alcohols and ACET. Whole blood specimens anticoagulated with potassium oxalate and preserved with sodium fluoride (the traditional blood sample for alcohol analysis) were not available.

Isopropanol and Acetone Analysis

The serum samples gleaned as above were analyzed within seven days for both IPA and ACET by a modification of the direct-injection gas-liquid chromatographic procedure of Jain (7) using n-propanol as internal standard (8). Concentrations were calculated using peak-height ratios (analyze: internal standard) relative to those obtained with reference calibrators of known concentration. As little as 10 mg/L of IPA and of ACET can be detected by this method. Patients in whom ethanol was also detected were excluded from the study since it was not possible to determine with certainty that these individuals had not ingested IPA concurrently with ethanol.

Clinical and Demographic Information

Clinical and demographic information as well as additional laboratory data were found by review of the medical record of each patient in whom IPA was detected. Exposure to IPA was excluded by review of the medical record.

RESULTS

During the period December 1989 through April 1990, IPA was detected in five acetonemic patients who had no history of IPA exposure according to the medical record. All patients had Type I diabetes mellitus and were insulin-dependent. Serum concentrations of IPA ranged up to 297 mg/L and of ACET, up to 321 mg/L. The IPA: ACET concentration ratios were as high as 5.12 (Table 1).

One patient (# 2) developed isopropanolemia after admission. Other pertinent admission laboratory findings for these five patients are shown in Table 2.

TABLE 1

Detection of Isopropanol in Acetonemic Patients Not Exposed to Isopropanol

Patient #	Age/Sex	Month/Year	Time	Serum (mg/L) IPA*	ACET‡	IPA:ACET
1	26/M	12/89	ADM§	58	321	0.18
			1.0 hr	28	279	0.10
			5.5 hrs	NMA‖	94	0.00
			9.0 hrs	NMA	79	0.00
2	34/F	12/89	ADM	NMA	NMA	—
			25.5 hrs	297	58	5.12
			62.5 hrs	NMA	72	0.00
3	39/F	2/90	ADM	51	108	0.47
			2.0 hrs	NMA	135	0.00
			6.0 hrs	NMA	88	0.00
4	30/M	2/90	ADM	73	301	0.24
			28.5 hrs	NMA	68	0.00
			36.5 hrs	NMA	NMA	—
5	35/F	3/90	ADM	20	69	0.29

IPA* = Isopropanol; ACET‡ = Acetone
ADM§ = Time of Admission; NMA‖ = No Measurable Amount

TABLE 2

Additional Admission Laboratory Findings

Patient #	1	2	3	4	5
Arterial pH	7.28	7.32	7.34	7.28	---
Plasma Glucose (mg/L)	4,300	2,210	5,700	4,440	5,210
Serum Osmolality (mOsm/Kg)	324	---	---	330	---
Serum Bicarbonate (mMol/L)	12	15	17	10	22

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During the process of finding patients for this study, an additional 131 serial serum samples from 32 ketotic patients were analyzed. All of these samples were found to be ACET-positive and IPA-negative. Concentrations of ACET in these samples ranged up to 844 mg/L. Two of the 32 patients were admitted twice, making a total of 34 ACET-positive, IPA-negative cases. The diagnoses for these 34 cases were as follows: diabetic ketoacidosis - 19; followup of diabetes mellitus - 8; intrauterine pregnancy - 4; cellulitis - 1; congestive heart failure - 1; and steroid-induced hyperglycemia - 1. Two of the 32 patients during subsequent admissions were both ACET- and IPA-positive without a history of exposure to IPA and were included in the study as patients #1 and #4 (Tables 1 and 2).

DISCUSSION

Since this study was a retrospective one it was not possible to control the type of specimen available. Hence, all analyses were performed on previously analyzed serum samples instead of on whole blood specimens preserved with sodium fluoride (the more commonly utilized specimen for alcohol analysis). However, all the serum used for this study had been separated from the specimens immediately after arrival in the laboratory and, following routine chemical analysis ordered by the physician, the serum for study had been stored under refrigeration (4°C) in stoppered tubes. Hence, deterioration of the specimen should have been minimal, if it occurred at all. Since alcohols do not cross the erythrocyte membrane to any appreciable extent, serum alcohol concentrations are higher than the more conventional whole blood concentrations (by about 25% to 33% in our experience). Nonetheless, some laboratories do routinely measure alcohols in serum. In addition, ACET is traditionally measured in serum. Finally, since residual serum samples were utilized in this study, it is most likely that IPA was utilized as an antiseptic agent in preparing the venipuncture site. Despite this probability, however, it is standard practice to allow IPA to evaporate prior to the venipuncture. Attempts to introduce IPA into samples by performing venipuncture immediately after swabbing the site with IPA have

not, in our personal experience, introduced measurable amounts of the compound into samples. In addition, during the five-month study of acetonemic patients, 131 ACET-positive but IPA-negative samples were identified, indicating lack of contamination of these samples with IPA. Only six samples from acetonemic patients (two from patient #1 and one each from #2, #3, #4, and #5) had detectable amounts of IPA (Table 1). For patient #1, the serum concentration of IPA declined with time. If in vitro contamination with IPA had occurred, it would have had to have occurred in both serial samples. The degree of contamination would have had to have decreased with time as well. Furthermore, in patient #2 who was admitted with neither isopropanolemia nor acetonemia, IPA and ACET were detected together 25.5 hours after admission (Table 1). In vitro contamination of the specimen with IPA during subsequent venipuncture after admission would not have led to the concurrent detection of ACET in this patient.

Serum concentrations of IPA in the five patients, while low, were indeed measurable and ranged up to 297 mg/L (Table 1). If detected during a conventional alcohol analysis in our institution, these findings would likely have led to the conclusion that IPA had been ingested. The concentrations were similar to those reported for the autopsy cases (5, 6). The IPA:ACET ratios were also similar.

A substantial number of the published autopsy cases involved individuals known to have diabetes mellitus. All five patients in the present study had Type I diabetes mellitus, and all were hyperglycemic upon admission (Table 2). Four patients (#1, #2, #3, and #4) were also acidotic, as evidenced by low arterial pH and low serum bicarbonate (Table 2). Interestingly, two of these patients (#1 and #4) had been admitted previously in diabetic ketoacidosis, and at that time their serum samples demonstrated ACET alone.

In diabetics, particularly those in ketoacidosis, elevated $NADH/NAD^+$ ratios frequently exist (6). In the study of Davis and associates (6) NADH was shown to convert ACET to IPA in the presence of alcohol dehydrogenase, leading to the hypothesis that a shunt mechanism

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may be responsible for metabolism of excessive quantities of ACET in conditions in which NADH is elevated. Importantly, chronic alcoholism is also known to produce elevated NADH concentrations as a direct consequence of the metabolism of ethanol (9). Hence, it is conceivable that alcoholics who develop acetonemia (e.g. through starvation ketosis) may produce detectable concentrations of IPA by the proposed metabolic route. In this study, cases involving ethanol in addition to IPA were excluded since it was not possible to determine with certainty that these individuals had not also ingested IPA. Nevertheless, it is tempting to speculate that some cases of suspected IPA ingestion by chronic alcoholics may, in fact, be due to in vivo conversion of acetone to this compound. This possibility should be considered by both clinical and forensic toxicologists when evaluating the finding of IPA in alcoholics, and it warrants further investigation through prospective studies.

ACKNOWLEDGMENTS

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