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Metabolism of Acetone to Isopropyl Alcohol in Rats and Humans

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ABSTRACT: Isopropyl alcohol and acetone have been detected in autopsy blood samples of individuals not previously exposed to these compounds. Since some of these individuals had a history of diabetes mellitus, it has been suggested that in these cases, reduction of acetone to isopropyl alcohol might be a metabolic pathway for its production. This hypothesis was investigated in a study of normal and diabetic rats. Acute administration of acetone resulted in measureable levels of isopropyl alcohol in blood. Metabolism of acetone to isopropyl alcohol was different in normal and diabetic animals. Blood levels of isopropanol reached a maximum at the second highest dose in normal rats, but there was a two-phase response in diabetic rats. In a second series of experiments, acetone was administered on alternate days for a week. In spite of this chronic administration (and persistence of high blood acetone), there was no enhancement of acetone metabolism to isopropyl alcohol. These experiments indicate that high levels of blood acetone could result in transformation to isopropyl alcohol.

KEYWORDS: pathology and biology, diabetes mellitus, acetone, isopropyl alcohol

Toxicology analyses for volatile substances performed on autopsy cases at the Southwestern Institute of Forensic Sciences have revealed isopropyl alcohol in blood samples from a number of cases (see Table 1). This finding, when not associated with isopropyl alcohol ingestion, has usually been considered insignificant. It is well established that liver alcohol dehydrogenase (ADH) is a relatively nonspecific enzyme capable of using nicotinamide adenine dinucleotide (NAD) to reversibly convert primary, secondary, aromatic, and other alcohols and their corresponding aldehydes and ketones [*1,2*]. Because diabetes or diabetic ketoacidosis was reported as the cause of death in several of the cases with isopropyl alcohol in the blood, it was suspected that ADH may form isopropyl alcohol from acetone present in the blood.

A clinical feature of diabetes, besides elevated blood glucose, is the presence of high concentrations of ketone bodies, namely acetoacetate, β-hydroxy-butyrate, and acetone, in plasma [*3-5*]. Acetoacetate results from the fatty acid oxidation occurring to provide energy in the absence of available glucose, and can be reduced to β-hydroxy-butyrate depending on the cellular NADH/NAD ratio [*4,6*]. Acetoacetate can also undergo spontaneous decarboxyl-

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TABLE 1—*Blood concentrations of acetone and isopropyl alcohol in autopsy cases.*

Cause of Death[a]	Acetone,[b] g/L	Isopropyl Alcohol,[b] g/L	Ratio[c]
Liver disease (11)	0.24	<0.10	<0.4
	0.25	<0.10	<0.4
	0.17	<0.10	<0.6
	0.32	0.16	0.5
	0.23	<0.10	<0.4
	0.34	0.12	0.4
	<0.10	<0.10	<0.1
	0.19	0.44	2.3
	0.20	<0.10	<0.5
	<0.10	<0.10	<0.1
	0.24	<0.10	<0.4
Diabetes (4)	0.56	0.14	0.25
	0.44	0.20	0.5
	0.46	0.28	0.6
	0.20	0.10	0.5
Liver disease plus diabetes (2)	0.17	<0.10	<0.6
	0.10	0.20	2.0
Unrelated[d] (10)	0.17	<0.10	<0.6
	0.35	<0.10	<0.3
	0.10	<0.10	<1.0
	0.17	0.27	1.2
	0.51	<0.10	<0.2
	0.16	0.14	0.9
	0.10	0.10	1.0
	0.13	<0.10	<0.8
	0.10	<0.10	<0.8
	0.10	<0.10	<0.1

[a] As reported by individual medical examiners, Dallas County. Number of cases in parentheses.
[b] From toxicology screens, Southwestern Institute of Forensic Sciences. Approximate limit of method for quantitation is 0.10 g/L.
[c] Ratio of isopropyl alcohol levels to acetone levels.
[d] Cardiovascular disease, drug overdose, and so on.

ation to form acetone and carbon dioxide [*3,6*]. At low blood concentrations (150 mg/L or less), metabolism of acetone accounts for approximately 60% of its disappearance, whereas at high concentrations (1000 mg/L or greater), more than 75% of the acetone is excreted unchanged [*7*]. Respiratory excretion is the major route of elimination, although some is excreted in the urine [*6,8,9*]. A small amount of acetone is slowly metabolized. It can be metabolized to a two-carbon acetyl and a one-carbon formyl fragment, to pyruvate, or directly to glucose [*3,5,10,11*]. Products of acetone metabolism have been found in cholesterol, glycogen, fatty acids, urea, and several amino acids [*12*].

To our knowledge, isopropyl alcohol has not heretofore been identified as a metabolic product of acetone. The presence of this alcohol has been reported in patients with ketonuria or those recovering from ketoacidosis, but it was uncertain whether this was a precursor or metabolite of acetone [*5*]. Several laboratories have reported the presence of a variety of volatile urinary metabolites in persons with diabetes mellitus [*13-15*], although the metabolic origins of these metabolites, including isopropyl alcohol, were not discussed. The conversion of acetone to isopropyl alcohol was therefore investigated. An acute study was performed in which different doses of acetone were administered to fasted normal and fasted dibetic rats. A subacute study, in which one dose of acetone was given on alternate days for a week, was also performed to determine if the enzyme was affected by pretreatment with acetone. To elevate

ketone levels, and because acetone is metabolized at a higher rate by rats in a fasted condition [7], food was withheld from animals in both experiments until the time of sacrifice.

Materials and Methods

Human Cases

Twenty-seven cases were collected from records of the Dallas County Medical Examiners Office from 1975 to 1979 (Table 1). The cases were selected for the presence of isopropyl alcohol in the blood. They were segregated by recorded cause of death into four groups: liver disease, diabetes, combination of liver and diabetes, and unrelated causes—for example, cardiovascular disease.

Acute Study in Rats

Forty six-week-old male Sprague-Dawley rats with an average weight of 191 g were randomly divided into eight groups. Alloxan (Eastman Kodak Co., Rochester, NY 14650) was dissolved in sodium phosphate, monobasic buffer (0.2 mol/L) and administered intravenously (60 mg/kg) in the dorsal tail veins of rats in four of the groups. All eight groups were then fasted for 48 h. Three different doses of acetone (Fisher Scientific Co., Fair Lawn, NJ 07410, 99.5% pure, containing less than 0.01% isopropyl alcohol) were prepared with distilled water as the vehicle and administered per os. Three groups of diabetic and three groups of normal animals each received acetone in a dose of either 1, 2, or 4 g/kg following the fast. They were killed 6 h after the dose was given. The remaining two groups, one normal and one diabetic, were not treated with acetone but were fasted 48 h and then killed.

Subacute Study in Rats

Fifteen male Sprague-Dawley rats with an average weight of 500 g were randomly divided into three groups. Five control animals were fasted for 48 h and then killed. Five rats received 2 g/kg acetone orally every other day, for a total of four doses over a seven-day period. They were then fasted for 48 h and killed. The remaining five animals received the same treatment, but were given a fifth dose of acetone after the 48-h fast (Day 9) and then sacrificed 6 h later.

All rats were killed by cervical dislocation. Approximately 1.5 mL of blood was drawn by cardiac puncture into B-D Vacutainer tubes containing 1 mL of heparin, which were then refrigerated.

Analytical Method

A Hewlett-Packard gas chromatograph, Model 5710A (Avondale, PA 19311) with flame ionization detector and a 180-cm by 2-mm inside diameter glass column packed with 5% Carbowax 20M on 60-80 mesh Carbopack B (Supelco, Inc., Bellefonte, PA 16823) was used to analyze the blood samples for acetone and isopropyl alcohol. The oven temperature was 150°C, the detector temperature 200°C, and the injector port temperature 250°C. The carrier gas was nitrogen at a flow rate of 30 mL/min. Samples were prepared and injected by using the direct blood injection method of Jain [16]. Peak height ratios of the samples were determined with *n*-propanol (1.58 g/L) serving as the internal standard; these ratios were then compared with those for acetone and isopropyl alcohol standards prepared in the same manner. Each sample was run in triplicate and the average used as the value for each rat.

Statistical analyses include determination of the means and standard error of the mean (S.E.M.) and two sample student *t* tests for comparisons between groups.

Results

Table 1 summarizes the human autopsy cases in which isopropyl alcohol was found and was believed unrelated to ingestion of this alcohol. The causes of death were obtained from the medical examiner's conclusions, as given, along with acetone and isopropyl alcohol blood concentrations and the ratios of isopropyl alcohol to acetone levels. Six of these cases had confirmed or suspected diabetes mellitus and thirteen had some form of liver disease.

Alloxan was administered intravenously to induce diabetes in rats within 24 to 48 h [*17*]. Although the blood sugar levels were not measured, the presence of higher acetone concentrations in fasted diabetic rats as compared to fasted controls was taken as an indication that a diabetic state had been induced. In human diabetic ketoacidosis, blood acetone concentrations range from 0.1 to 0.7 g/L [*6,8*]. The blood acetone levels of the diabetic controls and the animals given the lower doses of acetone fell within this range.

Oral administration of three different doses of acetone resulted in increased levels of blood acetone in all groups. In nondiabetic rats, the group given 1 g/kg acetone had ten times higher acetone levels compared to untreated controls, and the group given 2-g/kg acetone had approximately 20 times higher levels than untreated controls. These differences were significant ($P < .05$). Administration of higher doses (4 g/kg), however, did not result in significantly higher blood levels of acetone than the 2-g/kg dose ($P < .10$). Comparisons between the groups of diabetic rats showed significant differences ($P < .05$) only between the group that received 2-g/kg acetone and the one that received 4 g/kg. There was only a slight difference in acetone levels between untreated diabetic rats and controls ($P < .10$), and no difference between untreated diabetic rats and diabetic rats given 1-g/kg acetone or between diabetic rats given 1-g/kg and those given 2-g/kg acetone. The groups of diabetic animals did not have significantly higher acetone levels than the corresponding groups of nondiabetic animals. However, the nondiabetic rats that received 2-g/kg acetone had significantly higher ($P < .05$) blood levels of acetone than the diabetic group given the same dose. These data are shown in Table 2.

Animals that did not receive acetone had no detectable levels of isopropyl alcohol, whereas all animals treated with acetone had measurable levels of isopropyl alcohol. In nondiabetic rats, there was a sixfold increase (significant at the 0.10 level) in blood levels of isopropyl alcohol when the acetone dose was doubled from 1 to 2 g/kg, but no difference between animals given 2- and 4-g/kg acetone (Fig. 1). In contrast, in the diabetic animals there was a fivefold increase ($P < .05$) in the isopropyl alcohol levels between the group given 2-g/kg acetone and the one given 4 g/kg, but no difference between the groups that received 1- and 2-g/kg acetone (Fig. 2). Thus in diabetic animals, isopropyl alcohol production increased significantly only at the highest acetone dose given; in nondiabetic rats, this production reached a plateau regardless of further increases in acetone dose.

With the exception of nondiabetic rats that received 1-g/kg acetone, the ratios of blood isopropyl alcohol to acetone were relatively uniform. The aforementioned group had a low ratio (0.008), whereas the other groups had ratios that ranged from 0.016 to 0.027.

In the subacute study, oral administration of 2-g/kg acetone on alternate days before the 48-h fast did not cause higher levels of blood acetone than the 48-h fast alone. No isopropyl alcohol was produced with either treatment. However, if the animals received an additional dose of acetone following the fast, the blood levels of acetone increased markedly and isopropyl alcohol could be detected in the blood. The ratio of isopropyl alcohol to acetone levels in this last group was 0.033, the highest observed in either study. These data are given in Table 3.

Discussion

The significance of the detection of isopropyl alcohol in the blood of persons that reportedly did not ingest this compound has, in the past, been unresolved. Several of the people in whom this was found either had a history of, or died of, complications caused by diabetes mellitus.

TABLE 2—*Blood concentrations of acetone and isopropyl alcohol in normal and diabetic rats treated with acetone.*[a]

	Concentration, g/L									
	Normal					Diabetic				
	Acetone		Isopropyl Alcohol			Acetone		Isopropyl Alcohol		
Treatment	Mean	S.E.M.	Mean	S.E.M.	Ratio[b]	Mean	S.E.M.	Mean	S.E.M.	Ratio[b]
Control	0.048	0.010	0	0	0	0.290	0.105	0	0	0
1-g/kg acetone	0.445	0.017	0.004	0.002	0.008	0.511	0.030	0.009	0.004	0.017
2-g/kg acetone	0.983	0.120	0.022	0.007	0.023	0.612	0.052	0.010	0.004	0.016
4-g/kg acetone	1.542	0.217	0.024	0.005	0.016	1.678	0.285	0.046	0.012	0.027

[a] For all groups $n = 5$.
[b] Ratio of isopropyl alcohol levels to acetone levels.

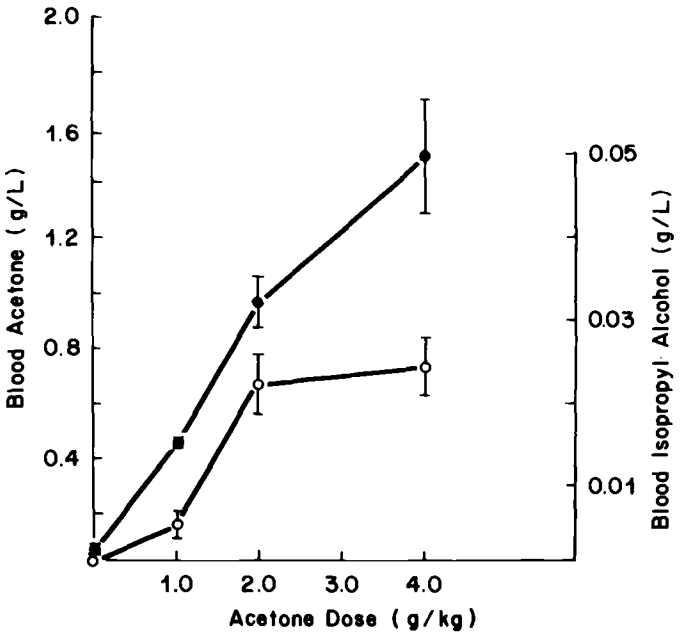

FIG. 1—*Blood concentrations of acetone (●——●) and isopropyl alcohol (○——○) in fasted normal rats.*

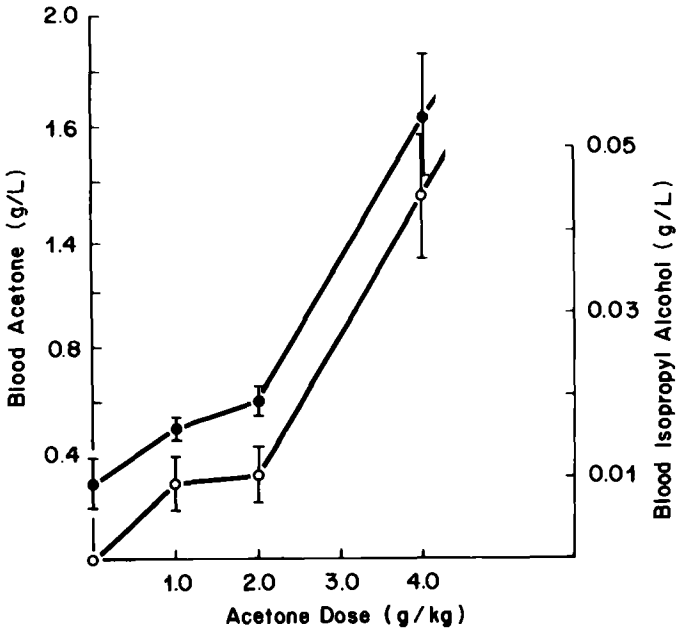

FIG. 2—*Blood concentrations of acetone (●——●) and isopropyl alcohol (○——○) in fasted diabetic rats.*

TABLE 3—*Blood concentrations of acetone and isopropyl alcohol in rats (subacute study).*[a]

Treatment	Concentration, g/L				
	Acetone		Isopropyl Alcohol		
	Mean	S.E.M.	Mean	S.E.M.	Ratio[b]
48-h fast	0.041	0.002	0	0	0
2-g/kg acetone every other day for seven days (four doses), 48-h fast	0.050	0.010	0	0	0
2-g/kg acetone every other day for seven days (four doses), 48-h fast, 2-g/kg acetone	1.174	0.190	0.039	0.009	0.033

[a] For all groups, $n = 5$.
[b] Ratio of isopropyl alcohol levels to acetone levels.

The presence of isopropyl alcohol in the blood in these cases, and the fact that high plasma concentrations of acetone are found in diabetic and starvation ketosis [*3,4*], suggested the possibility that alcohol dehydrogenase reduces acetone to isopropyl alcohol in certain clinical disease syndromes. This enzyme can interconvert many alcohols and their aldehydes or ketones [*1,2*].

There are apparent differences between the diabetic and nondiabetic animals in the attainment of blood concentrations of acetone and in metabolism of acetone to isopropyl alcohol. In nondiabetic rats, administration of increasing doses of acetone resulted in respectively higher blood acetone concentrations, as expected. An increase in isopropyl alcohol concentrations coincided with the increase in blood acetone but leveled off at a concentration of about 0.02 g/L. Thus, the conversion of acetone to isopropyl alcohol does not appear to be concentration-dependent. This might indicate that in the nondiabetic rats, there is limited metabolism of acetone by this pathway, or that isopropyl alcohol is converted back to acetone. In diabetic rats, blood acetone concentrations did not increase consistently with an increasing dose of acetone. Instead, there was only a slight increase until the highest dose of acetone was given. Isopropyl alcohol concentrations were parallel to those of acetone. Thus, the most remarkable difference between control and diabetic groups occurred in blood isopropyl alcohol concentrations at the highest concentrations of blood acetone.

There is evidence that acetone is metabolized to products that enter gluconeogenic pathways [*3,10,11*]. It is possible that in diabetic rats, acetone and NADH, both needed for isopropyl alcohol production from acetone, are diverted to these pathways to meet the animals' need for glucose, resulting in the short plateau seen in acetone and isopropyl alcohol concentrations. The subsequent rise in the concentrations of both compounds might be due to several events. First, the animals received a large dose of acetone, which is a substrate for ADH. Second, there is probably limited utilization of acetone for gluconeogenesis. The fatty acid oxidation that provides energy when glucose is unavailable (that is, in diabetes) generates NADH which, in the presence of rising acetone concentrations, could reduce acetone to isopropyl alcohol. The resultant NAD would then be available to reenter this oxidative pathway with further production of ketone bodies and generation of NADH. These events could explain the increases in both blood acetone and isopropyl alcohol following a short plateau. In nondiabetic rats, this excess NADH generation probably does not occur. Thus the leveling off in isopropyl alcohol, but not in acetone concentrations, might reflect the different metabolic and redox states of the nondiabetic animals. The lower redox state (that is, low NADH/NAD ratio) in these animals would not favor isopropyl production from acetone.

Because human diabetes is not an acute condition, a subacute study was also performed

with rats to determine if this enzyme was influenced by pretreatment with acetone. Administration of acetone on alternate days and a subsequent 48-h fast did not elevate blood acetone sufficiently to case isopropyl alcohol production. The additional dose of acetone administered after the fast was necessary for isopropyl alcohol production to occur.

Acetone concentrations in the human cases were not as high as those produced in animals (diabetic or normal) by administration of acetone, yet the human isopropyl alcohol levels were considerably higher than any seen in the rats. This is clearly reflected by the differences in the ratios of isopropyl alcohol to acetone levels. Ratios in the experimental animals were small, the highest being 0.027. In humans, most of the ratios were around 0.5, although in three cases the ratios were greater than one. Ingestion of isopropyl alcohol could explain this observation, although in such cases much higher levels of both products are usually observed [*18*].

A difference in the enzyme systems of the two species may account for these findings. Human ADH may be a higher capacity enzyme or have a higher affinity for acetone, since less acetone was needed to produce greater amounts of isopropyl alcohol as compared to the rat enzyme. Many of the individuals were chronic alcoholics and this condition may also account for the differences. It has been reported that chronic alcoholics develop ketonemia [*19*], which could elevate blood acetone levels. Chronic ingestion of ethanol can also increase its own metabolism, probably by inducing ADH [*20,21*]. These events together—higher acetone levels and induction of ADH—might explain the high isopropyl alcohol concentrations observed in some of the human cases in this study. In experimental animals, the acute administration of actone coupled with short-term starvation did not appar to induce ADH. Thus, an explanation of the different ratios in rats could be the activity of ADH. Alternatively, other enzymes in rats could influence the removal of isopropyl alcohol.

It is evident that this area is open to much speculation and is in need of more research. Nonetheless, we now have confirmed that conversion of acetone to isopropyl alcohol can occur in rats, providing a possible explanation, other than ingestion, for the presence of this alcohol in humans.

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