Formaldehyde Poisoning

Rapid Metabolism to Formic Acid

Janis Thane Eells, MS; Kenneth E. McMartin, PhD; Kurt Black; Viravan Virayotha, MS; Ronald H. Tisdell; Thomas R. Tephly, MD, PhD

THERE has been a great deal of current interest in the toxicity of formaldehyde, and most of the recent concern has centered on the release of formaldehyde into the environment from urea-formaldehyde foam used in insulation products.[1] However, systemic formaldehyde intoxication has not been adequately characterized, and the few reports that exist on human intoxication represent descriptive and pathologic evaluations.[2,3] There is little information available on the extent of formaldehyde absorption in mammals, and to our knowledge, there are no data in the literature concerning its conversion to formic acid and carbon dioxide in humans. We report a case involving the ingestion by one person of 120 mL of formaldehyde solution. Methanol, formaldehyde, and formic acid levels in the blood of the patient are reported following the ingestion of formaldehyde solution. The levels of these substances were monitored for 28 hours after admission of the patient to the hospital. Blood electrolyte values and acid-base balance were also determined over the course of the intoxication. This report demonstrates that formic acid accumulates markedly after the ingestion of formaldehyde and that the conversion from formaldehyde to formic acid is rapid.

Report of a Case

A 41-year-old woman was brought to the emergency room one-half hour after the ingestion of 120 mL of formaldehyde solution. This solution contained 37% w/v formaldehyde, 12.5% v/v methanol, and no formic acid. Immediately after the ingestion of formaldehyde solution, the patient reported severe abdominal pain before becoming unconscious. The patient was admitted to the emergency room in a cyanotic, apneic, and markedly hypotensive state. Rapid intubation and ventilation were initiated. Gastric lavage was performed and an obvious odor of formaldehyde was noted in the stomach contents. Intravenous (IV) fluid therapy (lactated Ringer's solution later replaced by 5% dextrose in water) was initiated. Epinephrine (1 mL at 1:1,000 dilution) and sodium bicarbonate (total dose, 132 mEq/L) were administered IV. A catheter was inserted in the urinary bladder. Laboratory data are given in the Table. In addition, the hemoglobin value was 14.3 g/dL, the hematocrit reading was 42.1%, and the WBC count was 8,200/cu mm, with a normal differential cell count.

The patient was transferred to the intensive care unit and her condition was maintained on endotracheal respiration. Blood pressure (BP) was sustained using dopamine hydrochloride therapy. The patient's urine output for the first few hours was adequate; however, she became anuric approximately seven hours after admission. The patient's condition deteriorated over the next day, despite attempts to maintain BP and acid-base balance, and she died 28 hours after admission to the hospital. Blood levels of methanol, formaldehyde, and formate are given in the Figure. Analysis for methanol was performed by the method of Baker et al,[4] and formaldehyde was measured by the method of MacFadyen as described by Tephly et al.[5] Formic acid was measured by the sensitive and specific method of Makar et al[6] using a formate dehydrogenase preparation isolated from *Pseudomonas oxalaticus*.

Comment

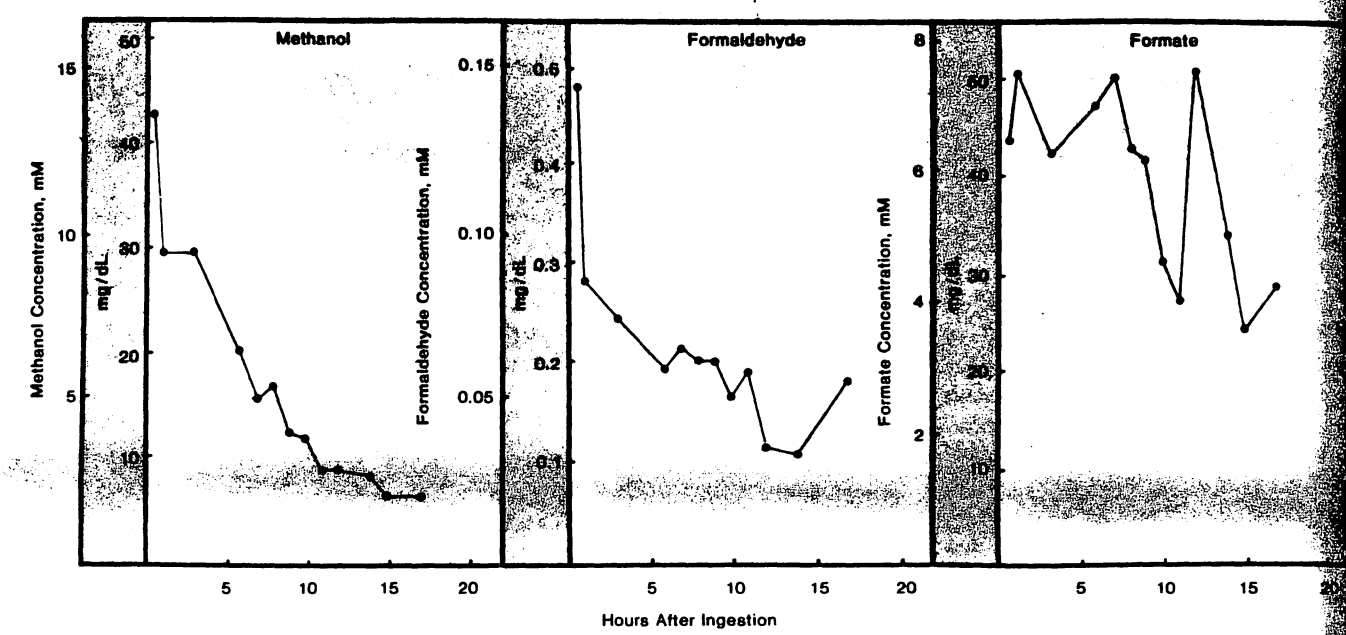
Analysis of blood samples taken from the patient clearly demonstrates that formic acid accumulates rapidly after the ingestion of formaldehyde. The Figure shows that the blood formate level was approximately 7mM at the time of admission to the hospital, which was only 30 minutes after ingestion of the formaldehyde. The patient was clearly in a state of metabolic acidosis at the time of admission, as indicated by a blood pH value of 6.87 and by reduction of the blood bicarbonate value to 3.5 mEq/L. Studies of methanol toxicity in monkeys and humans have shown that formate accumulation is primarily responsible for the metabolic acidosis observed.[7-9] Formate accumulation occurs in a manner reciprocal to the depletion of blood bicarbonate.[7] In the present case of formaldehyde poisoning, the high initial blood level of formate correlates well with the depletion of blood bicarbonate observed.

Laboratory Values Following Formaldehyde Ingestion

Value	Hours After Ingestion		
	0.5	1	25
Sodium, mEq/L	145	144	92
Potassium, mEq/L	5.1	3.5	5.3
Chloride, mEq/L	109	96	60
Bicarbonate ion, mEq/L	3.5	19	10
Calcium, mg/dL	8.2	. . .	3.7
Serum creatinine, mg/dL	1.3	. . .	2.9
BUN, mg/dL	8.0	. . .	12.0
Dextrose, mg/dL	307	. . .	1,700
Lactic dehydrogenase, units/dL	425	. . .	1,830
SGOT, units/dL	317	. . .	1,520
Blood pH	6.87	7.41	7.09
Blood P_{CO_2}, mm Hg	20	30	35
Blood P_{O_2}, mm Hg	83	109	54

From the Toxicology Center, Department of Pharmacology, University of Iowa, Iowa City (Ms Eells, Drs McMartin and Tephly, Mr Black, and Ms Virayotha); and the Texas State Poison Center, University of Texas Medical Branch, Galveston (Dr Tisdell).

Reprint requests to the Toxicology Center, Department of Pharmacology, University of Iowa, Iowa City, IA 52242 (Dr Tephly).



Blood levels of methanol, formaldehyde, and formate in human subject with formaldehyde poisoning. Blood samples were obtained from patient and analyzed for methanol, formaldehyde, and formate concentration. Time frame is in reference to hours after ingestion of formaldehyde solution.

It could be suggested that the formate seen in the blood of this patient was derived solely from the metabolism of methanol present in the formaldehyde solution. Indeed, methanol has been shown to be metabolized to formic acid, presumably with formaldehyde as a metabolic intermediate in humans.[9] However, all of the methanol present in the formaldehyde solution can be accounted for unchanged in the patient at the time of admission. The amount of methanol consumed by the patient corresponds to a dose of 209 mg/kg of body weight. Methanol distributes to total body water,[10] and the methanol blood level of 40 mg/dL (Figure) is consistent with the amount of methanol ingested distributing to about 70% of the body water in the 60-kg patient. Since there was no formic acid present in the formaldehyde solution ingested and the methanol present in the solution could not have been metabolized to a significant extent to formate, most of the formic acid in the patient at the time of admission must have been derived from formaldehyde. It has been postulated that formaldehyde is rapidly metabolized to formate, since, in cases of methanol poisoning, no significant formaldehyde levels have been reported in body fluids. However, because of the extreme reactivity of formaldehyde with many cellular constituents and physiologic metabolites, the role of formaldehyde in methanol poisoning has been difficult to assess adequately.

We have conducted experiments in rats in which a dose of formaldehyde solution equivalent to that consumed by the patient was administered orally. Formic acid accumulated in the blood of these animals to concentrations of 5.6±0.4mM within the first hour after ingestion (J.T.E. and T.R.T., unpublished observations). This concentration of formate is similar to that seen in the patient on admission. ^{14}C-formaldehyde conversion to $^{14}CO_2$ accounted for 10% of the administered dose within one hour after the administration of the formaldehyde solution to the rats. Necropsies performed on these animals revealed gastric lesions similar to those reported in human poisoning.[2,3] Thus, although formaldehyde may produce extensive pathologic changes in the gastrointestinal tract, sufficient formaldehyde is apparently absorbed and metabolized rapidly to formic acid, and this accounts at least in part for the profound metabolic acidosis seen.

Because formic acid accumulates rapidly following ingestion of formaldehyde, serious consideration should be given to dialysis procedures (either hemodialysis or peritoneal dialysis) in patients who have ingested formaldehyde. Dialysis is effective in removing formic acid from the blood of humans,[9] and removal of formic a may be effective in combating metabolic acidosis that may occur systemic formaldehyde poisoning.

Nonproprietary Name and Trademark of Drug

Dopamine hydrochloride—*Intropin.*

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