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CASE REPORT

Extremely slow formate elimination in severe methanol poisoning: A fatal case report

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Methanol poisoning is a potentially fatal medical emergency because of its metabolism to formic acid. The half-life of formate has been reported in the range of 2.5–12.5 hours, but the degree of inter-individual variation is not known. We studied methanol and formate kinetics in a case of late diagnosed methanol poisoning with persisting metabolic acidosis and circulatory failure. *Case Report*. A 63-year-old man was referred to our hospital with a tentative diagnosis of stroke. He was awake on admission, but he soon deteriorated in the emergency department and a metabolic acidosis was revealed. Methanol poisoning was then suspected approximately five hours after admission but in spite of intensive treatment he died after six days. *Results*. The S-methanol half-lives during treatment with fomepizole before and during hemodialysis were 49.5 and 4.1 hours, respectively, while the similar half-lives of S-formate were 77.0 and 2.9 hours. S-fomepizole was measured and found to be within the therapeutic range during treatment. *Discussion*. The patient was treated with the established dosing regimen for fomepizole and the measured S-fomepizole levels throughout the treatment were adequate; the S-methanol elimination also suggests that methanol metabolism was blocked. Hence, other explanations for this exceptionally long formate half-life include slow formate metabolism, due to small hepatic folate stores or to genetic deficiencies in formate-metabolizing enzymes, or slow formate excretion, due to renal tubular acidosis, to a non-oliguric renal failure, or to genetic deficiencies in the renal formate transporters. *Conclusion*. This case report indicates that the half-life of S-formate may have greater inter-individual variation than earlier expected, being by far the longest half-life reported in the medical literature. These results support the use of hemodialysis in the treatment of such patients.

Keywords Methanol poisoning; Formate; Half-life; Kinetics; Fomepizole; Hemodialysis

Introduction

Methanol poisoning is a potentially fatal medical emergency because of the accumulation of its toxic metabolite, formic acid. Knowledge of the kinetics of formate has special interest and implication for the evaluation of the need for hemodialysis in methanol poisoning. In patients, the half-life of formate elimination has usually been reported in the range of 2.5–5 hours (1–3). Because the endogenous half-life of formate can be very short, the indication for hemodialysis solely based on the formate level, independent of the patient's condition and the methanol level, has been questioned (1,2). However, there might be a greater individual difference in formate elimination than the above mentioned 2.5–5 hours half-life (3). In 2005, Hantson et al. reported half-lives between 7.5 and 12.5 hours in three individual subjects (4).

Also, the reported inter-individual differences in sensitivity to methanol (5) may in part be explained by different elimination of formate. We present a case of late diagnosed methanol poisoning, with a prolonged metabolic acidosis, very slow formate elimination, and a fatal outcome. Potential explanations for these very unusual findings are discussed, as well as a discussion of methanol and formate kinetics.

The patient was one of approximately 50 patients admitted to the hospital during a large methanol outbreak in Norway. The spirit consumed consisted of approximately 20% methanol and 80% ethanol (6).

Case report

A 63-year-old male presented to our hospital with a history of increasing headache, vomiting, reduced visual acuity, and dizziness. He was referred to our hospital with stroke as a tentative diagnosis. Upon admission he was awake and oriented, dysphonic, but in a stable circulatory condition. The initial clinical exam revealed normal status of heart, lungs,

and abdomen. His blood pressure was 179/90 mmHg and his heart rate was regular at 80 beats/min. His pupillary responses were reported to be normal and his ECG was found normal.

In the emergency department, he became increasingly dyspnoeic and pale and he developed seizures with dilated pupils. He was given mechanical ventilation and vasopressors. Cerebral, abdominal, and thoracic CT were performed and all were found to be without pathology. Arterial blood-gas revealed a metabolic acidosis: pH 7.13, pCO_2 2.0 kPa (15 mmHg), HCO_3^- 4.9 mmol/L, base deficit 24.4 mmol/L, and pO_2 16.0 kPa (120 mmHg).

Based on his clinical condition, the osmolal gap was analyzed from the admission sample and found to be 56 mOsm/kgH₂O. S-ethanol on admission was 0, and the anion gap was found to be 32 mmol/L at 5.5 hours after admission. Methanol poisoning was then suspected, and the patient was given a loading dose of fomepizole of 15 mg/kg IV approximately 5.5 hours after admission. S-methanol from the admission sample was analyzed and found to be 23.4 mmol/L (75 mg/dL). Because of circulatory instability in spite of large doses of buffer and vasopressors he was not treated with hemodialysis before the next morning, when his circulatory condition improved (Fig. 1). His metabolic acidosis persisted until hemodialysis was performed. He was also given one dose of 50 mg folinic acid IV (Fig. 1), and he received antibiotics for suspected aspiration pneumonia.

Regarding his renal function, his creatinine was 110–185 µmol/L, his urea (BUN) was 7.5–8.4 mmol/L, and his urine production was high. In spite of that, he had severe hypotension and was dependent on vasopressors, consistent with a mild non-oliguric renal failure. He gradually developed cerebral edema. At six days after admission, loss of cerebral perfusion

was demonstrated. His organs were successfully donated post mortem.

The most relevant lab data are given in Table 1. Note the deterioration of the patient between 1.8 and 5.7 hours, when he became hypotensive and in need of vasopressors and mechanical ventilation.

Methods

Methanol was measured by gas chromatography and formate by enzymatic analysis in serum and urine as previously described (3,7,8).

Serum samples were prepared for fomepizole analysis using solid phase extraction with Bond-Elut-SCX columns (Varian, Inc., Palo Alto, CA) (9). Fomepizole was measured by high pressure liquid chromatography using a reverse phase column, Prodigy 5 ODS-3 (Phenomenex, Torrance, CA) (10). The detectability limit of the assay was 5 µmol/L, with a day-to-day coefficient of variation of 5.6 and 1.5% at 25 and 200 µmol/L, respectively. Assessment of the elimination rate of fomepizole was based on an assumption of Michelis-Menten kinetics (11), and calculated from the slope of the plasma concentration versus time disappearance curve (Fig. 2).

Conversion factors from mmol/L to mg/dL for methanol and formic acid are 3.2 and 4.6, respectively. Dialysis was performed using a standard Gambro AK 200 dialyzer (Gambro AB, Stockholm, Sweden) with a Fresenius F8 HPS cartridge (1.8 m²) (Fresenius Medical Care, Bad Homburg, Germany) and a fixed blood flow of 250 mL/min.

The renal clearance (R_c) during dialysis was calculated from the formula

$$R_c = \frac{U_x}{S_x} \times V$$

where U_x and S_x are urine and serum concentrations of methanol and formate (mmol/L), respectively, and V = vol/time (mL/min).

Results

The methanol half-life during treatment with fomepizole and prior to hemodialysis was 49.5 hours (n = 10, R^2 = 0.45, observational period = 9 hours), while formate half-life was calculated to be 77.0 hours (n = 9, R^2 = 0.84, observational period = 9 hours) (Fig. 1). The average zero order elimination rate for formate calculated from the same data was 0.25 mmol/L/h, R^2 = 0.85. The methanol half-life during hemodialysis was 4.1 hours (n = 4, R^2 = 0.99, observational period = 3 hours) and formate half-life was 2.9 hours (n = 4, R^2 = 0.99, observational period = 3 hours). Methanol elimination before antidote was given was apparently of zero order with an elimination rate of 2 mg/dL/h (0.02 g/L/h).
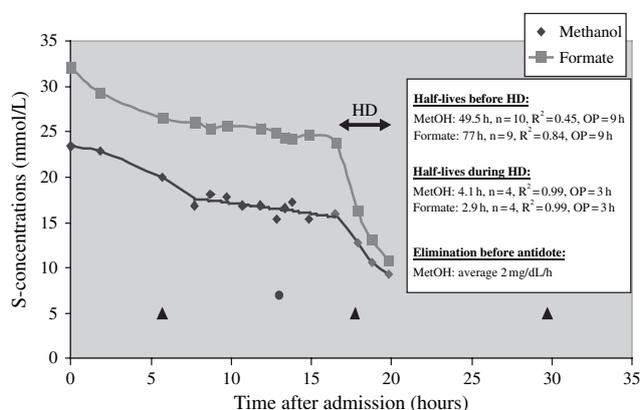
Fig. 1. S-methanol and S-formate levels during the time-course after admission to hospital, including the respective half-lives. Time of treatment with fomepizole (▲) and folinic acid (●) is indicated. HD = hemodialysis, OP = observational period, and n = number of observations during which the time the half-life is calculated; R^2 is based on the semi-logarithmic plot (not shown).

Table 1. Relevant lab data

Time (hrs)	0	1.8	5.7	7.7	8.7	9.7	10.7	11.8	12.8	13.3	13.8	14.8	16.5	17.9	18.8	19.8
S-methanol (mmol/L)	23.4	22.8	20.0	16.9	18.1	17.8	16.9	16.9	15.3	16.6	17.2	15.3	15.9	12.8	10.6	9.4
S-formate (mmol/L)	32.1	29.3	26.5	26.0	25.4	25.7	–	25.4	24.9	24.4	24.2	24.7	23.8	16.2	13.1	10.8
S-lactate (mmol/L)			6.4	6.2	5.9		5.2		4.2							
pH		7.13	6.77	6.86	6.94		7.03		7.13		7.19		7.31	7.34		7.38
pCO_2 (kPa)		2.0	9.3	9.6	9.6		9.6		8.0		6.97		6.23	6.29		5.8
HCO_3 (mmol/L)		4.9	9.5	12.2	14.6		17.9		19.4		19.3		22.8	24.9		25.1
Base deficit (mmol/L)		24	28	24	20		15		10		9		3	1		0
pO_2 (kPa)		16.0	12.1	10.3	11.3		9.5		8.8		8.7		7.3	7.5		8.2
Anion gap (mmol/L)			32	28	27		11		22							
Osmolal gap (mOsm/ kgH$_2$O)	56						63									
ASAT (U/L)	121						91									158
ALAT (U/L)	111						66									66
CK (U/L)	104						88									1079
GT (U/L)	374						234									234
ALP (U/L)	104															66
INR (ratio)	1.0						1.3									1.3
S-fomepizole (μmol/L)				229	201	184	180	157	137	136	114					
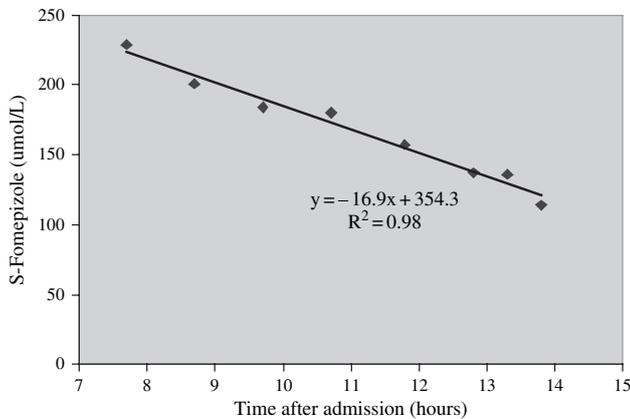
Fig. 2. Elimination of S-fomepizole after admission to hospital before hemodialysis was initiated.

In figure:

$$y = -16.9x + 354.3$$
$$R^2 = 0.98$$

Table 2. Renal clearance of methanol and formate

Sample	1	2	3	4	5
HD	No	No	No	Yes	*
U-pH	5.61	5.68	5.86	6.29	5.82
Volume (mL)	1370	2000	1410	200	2350
Urinary output (mL/min)	2.9	11.1	11.3	3.6	1.4
U-metOH (mM)	19.1	19.1	18.1	16.9	11.9
U-form (mM)	26.5	25.8	25.9	30.0	18.9
Median S-metOH (mM)	16.9	16.6	15.6	11.7	N.A.
Median S-form (mM)	26.0	24.2	20.0	12.0	N.A.
R_c metOH (mL/min)	3.2	12.8	13.1	5.3	N.A.
R_c form (mL/min)	2.9	11.9	14.6	9.1	N.A.
Time period collected (hours from admission)	4–12	12–15	15–17	17–18	18–47

*120 min of HD, 180 min without HD.
HD = hemodialysis, metOH = methanol, form = formate, and N.A. = not applicable.

S-fomepizole was analyzed in eight different samples between eight and 15 hours after admission (i.e., when the pre-dialysis half-life was measured) and found to be within the therapeutic range (from 114 μmol/L to 229 μmol/L). The rate of elimination of S-fomepizole was found to be 16.9 μmol/L/h ($n = 8$, $R^2 = 0.98$) (Fig. 2).

S-folate was measured in three different samples: two before (4.6 and 4.5 nmol/L, reference range 6.0–24)) and one after (>50 nmol/L) folinic acid was given.

During the first two days, five urine samples were collected and measured for methanol, formate, and pH. Neither formate nor methanol were concentrated in the urine compared to their serum concentrations. (Table 2).

Discussion

The half-life of both methanol and formate may be quite variable during antidote treatment (3,4,12–14). When appropriately studied, the half-life of methanol during fomepizole treatment has been reported in the range of 50–87 hours (3,13,14). In these studies, methanol metabolism was sufficiently inhibited, as indicated by the lack of production of formate. Interestingly, two independent research groups have demonstrated that methanol half-life in the presence of fomepizole seems to increase with increasing S-methanol concentration (3,13). Neither study was able to explain this,

indicating that unknown factors may influence methanol elimination at high concentrations during such treatment.

The half-life of formate is difficult to study in non-primate species because of their rapid metabolism of formate. In humans data are scarce, but longer half-lives of formate have been suggested because of the low folate reserve. Animal studies have shown that formate elimination is slower with time as the liver gradually becomes folate deficient (15). The half-life of formate in methanol poisoned patients usually varies between 2.5–5 hours (1,3,16). On the other hand, a report from 2005 described three patients with half-lives between 7.8 and 12.5 hours (4). The authors described a varying S-ethanol in some of the cases, indicating that methanol metabolism may not have been completely blocked, which would explain the long formate half-lives (or more correctly: elimination rate) in these patients. Further, the study was retrospective and based on a "not strictly homogenous" treatment during a period of 14 years. Nonetheless, the study has a high number of cases (n = 18), and it suggests a greater individual variation in the S-formate half-life than earlier expected (4). In a case report from 1984, a child was found to have a formate half-life about 20 hours, but the metabolism of methanol was not completely blocked; hence, formate was still produced and so the half-life was not valid (17).

Whether there was ongoing methanol absorption in this patient at Time 0 is an important question. The patient drank a mixture of 20% methanol and 80% ethanol, and his S-ethanol on admission was 0, suggesting that the ethanol must have been absorbed and metabolized prior to Time 0. Since methanol is also easily absorbed, ongoing methanol absorption is highly unlikely.

One likely explanation for the slow formate elimination could also have been that fomepizole was not inhibiting this particular patient's ADH enzyme, which would imply an ongoing metabolism of methanol, and hence a zero order elimination where a valid half-life could not be calculated. However, this has never been described before in any cases of fomepizole use. Furthermore, in our patient the metabolism of methanol seemed to be blocked, because the elimination half-life of methanol was of the expected magnitude and because the elimination of methanol appeared slower after fomepizole administration (Fig. 1). In addition, earlier studies have confirmed the efficacy of fomepizole when these recommended doses are given (3,18). Compared to the often fluctuating serum levels when ethanol is used as an antidote (4,13,18), fomepizole kinetics are very stable (18). Finally, S-fomepizole levels in this patient were definitely within the therapeutic range (>10 μmol/L) during the treatment period (Table 1) (18).

This case is one of the first reports of fomepizole kinetics in a poisoned patient. We estimated the rate of elimination of fomepizole to be 16.9 μmol/L/h. Interestingly, Michelis-Menten kinetics, which has been demonstrated in healthy humans (11), was also found in this patient (Fig. 2). It is also interesting to compare this rate with the rates determined in 10 healthy subjects by Maraffa et al. (19). After a

single IV dose of 15 mg/kg they found a Vmax for elimination of 18.6 ± 9.6 (SD) μmol/L/h, which compares well to our results.

Whether methanol and formate are actually eliminated by first order kinetics when the ADH enzyme is blocked is another question. Under such conditions, methanol and formate are eliminated by excretory processes, which normally are thought to act via first order kinetics. In this patient, the calculated correlations for both zero and first order elimination of methanol were almost identical. We made similar calculations for methanol in earlier reported cases (3) and found the same results. Based on the fact that this is a single case report, we find no reason to suggest a change in current understanding and literature of methanol kinetics. Regarding formate, there is no real consensus on whether formate is eliminated by first or zero order kinetics when ADH is blocked, although most reports have suggested a first order elimination, and hence reported half-life as such instead of elimination rate as a zero order process. In the lack of such consensus, we have reported both first and zero order elimination data, and found the correlation coefficient to be practically similar. When calculating earlier reported cases, we also found similar correlation for formate in these patients (3).

Our patient's formate half-life of 77 hours was calculated late in the course of this methanol poisoning when he had a severe metabolic acidosis and he was severely deteriorated with hypotension. The critical state of this patient could have reduced his ability to eliminate formate (see below). Alternatively, the data could support the theory of inter-individual variation. A reduced ability to eliminate formate seems highly probable in this patient, by either a reduced metabolism, or a reduced excretion, or both:

1. One possibility is an individual difference in formate metabolic reactions. A genetic variation in the ability to produce functional formate metabolizing enzymes, namely 10-formyl tetrahydrofolate synthetase and 10-formyl tetrahydrofolate dehydrogenase could exist in this patient. This would imply highly reduced formate metabolism, and hence explain alone, or together with other mechanisms, this extremely long formate half-life.

2. A decreased quantity of folate in the liver and hence a low efficiency of formate metabolism is another possible explanation. Serum folate was measured and found to be somewhat decreased (in the lower end of the reference range) in two samples before folinic acid was given. Although the decrease in serum folate is probably not enough to account for the apparent low rate of formate elimination, an uncertain relationship between liver and serum levels of folate should be accounted for. Liver, and not serum, folate stores correlate well with rates of formate metabolism (20), and so represent the key parameter.

3. Increasing formate reabsorption with decreasing pH is a likely feature. In our patient, the acidosis was not corrected

before hemodialysis was applied and the formate half-life was significantly prolonged. He was acidotic, although his urine was not as acidotic as expected (Table 1). An increased reabsorption of formate in the acidotic kidneys must nonetheless be suspected (3,21).

4. The severe acidemia and/or hypotension could impair vital organ perfusion, including the liver, which could disrupt enzyme systems involved in formate metabolism, thus contributing to the very slow formate elimination. However, in the actual time period, fomepizole is significantly decreasing (elimination rate in the expected range, see above). Fomepizole is metabolized by hepatic CYP P450, which strongly suggests a properly perfused and functioning liver.

5. Loss of active formate excretion, either because of renal failure or because of genetic deficiencies in the transporters, could also be an explanation. The adequate diuresis and slightly elevated S-creatinine and S-urea (BUN) levels do not support acute oliguric renal failure in our patient. On the other hand, non-oliguric renal failure may still explain a loss of ability to excrete formate, which correlates well with the lack of concentration of formate in the urine. In studied cases, formate was considerably concentrated in the urine (22), while methanol was not. In Table 2, the U-formate is very similar to the U-methanol, indicating that this patient's kidneys only filtered the formate down a concentration gradient and did not actively secrete formate from the blood, as would usually be seen (23). A genetic deficiency in the transporters could theoretically have the same effect, since an altered number of formate-chloride exchangers or formate-H$^+$ co-transporters would probably have a significant impact on the excretion.

Even if a certain degree of individual variation should be expected, the 15-fold increase in the half-life of formate compared to what has been reported (1,3), or the 6–7 fold increase towards a recent report (4), indicates that there may be some genetic defect in the production of the metabolizing enzymes or in the ability to produce transporters in the kidneys. A reduced renal elimination may contribute to a slower elimination, but would not explain the extraordinary findings in this patient alone.

The elimination rate of methanol, before fomepizole administration, was approximately 2 mg/dL/h, which is slower than reported in two other patients (8.5 mg/dL/h (14) and 20 mg/dL/h (3)). This supports the theory of fewer or sub-optimal working formate-transporters in the kidney. Another interesting feature in this case was that the S-formate seemed to be decreasing faster before, rather than after, fomepizole was given. We have no explanation to this phenomenon other than decreasing liver folate stores over time.

This case study also visualizes the difficulties of diagnosing methanol poisoning (5,7,8,12). Cases like this should also be considered when indications for dialysis are evaluated (23,24). Future studies should focus on estimating S-formate half-life in different subjects with parallel analyzes of pH in both serum and urine. Chronic methanol abusers or patients with a higher threshold for methanol toxicity are of special interest, as the relative ability to concentrate formate in the urine might be higher (U-formate/S-formate), because of potential up-regulation in the number or efficacy of the renal formate transporters in these patients.

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