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ARTICLE

Methanol and Formate Kinetics During Treatment with Fomepizole

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Objective. **Methanol is metabolized by a1cohol dehydrogenase to formaldehyde, and further to formic acid, which is responsible for the toxicity in methanol poisoning. Fomepizole (4-methylpyrazole) is a potent competitive inhibitor of a1cohol dehydrogenase and is used as an antidote to treat methanol poisonings. We report serum methanol kinetics in eight patients treated with bicarbonate and fomepizole only.** ***Methods.*** **Prospective case series study of eight patients with methanol poisoning, who were selected to fomepizole and bicarbonate treatment only, because of moderate metabolic acidosis. Three of the patients were later dialyzed, because of high serum methanol concentrations and very slow methanol elimination.** ***Results.*** **Upon admission the median pH was 7.27 (range 7.12–7.50), median base deficit was 15 mmol/L (5–22 mmol/L) and median serum methanol was 20.4 mmol/L (65 mg/dL) (range 8.4–140.6 mmol/L). The kinetics of methanol during fomepizole treatment in six patients was best described by a first-order elimination one-compartment model. The mean correlation coefficient (R^2) describing the first-order elimination model in all eight patients was 0.95 (range 0.90–0.99). The mean plasma half-life ($t_{1/2}$) of methanol during fomepizole treatment was 52 h (range 22–87); the higher the serum methanol, the longer the $T_{1/2}$. Mean half-life of serum formate was 2.6 h, when methanol metabolism was assumed blocked by fomepizole and no folinic acid was given. This rapid formate elimination in nonacidotic patients may be explained by high renal excretion of formate.** ***Conclusion.*** **Based on our data, methanol-poisoned patients with moderate metabolic acidosis and methanol levels up to 19 mmol/L (60 mg/L) may safely be treated with bicarbonate and fomepizole only, without dialysis.**

Keywords Methanol poisoning; Formate; Kinetics; Fomepizole

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INTRODUCTION

Methanol is metabolized by alcohol dehydrogenase to formaldehyde and then to formic acid, which is primarily responsible for the toxicity in methanol poisoning (1). This toxicity results from a combination of the metabolic acidosis (H^+-production) and an intrinsic toxicity of the anion formate (2). Metabolism and hence elimination of formate is folate dependent. Due to a small folate pool in humans, formate accumulates (2,3). Treatment of methanol poisoning consists of rapid and full correction of metabolic acidosis (2,4,5), prevention of the production of formic acid by inhibiting alcohol dehydrogenase (ADH), and increased elimination of methanol and formate by hemodialysis (6–8). Until recently, ADH inhibition has been performed by the use of ethanol, but during the last few years the antidote fomepizole has come into use (2,7,9). Fomepizole is a potent competitive inhibitor of ADH and most probably a better alternative to the use of ethanol, which itself has several disadvantages (8). Because of low hepatic folate in humans, folic acid or its active derivative folinic acid may enhance formate metabolism (10). It is therefore recommended in treatment (8), but there are no clinical trials in humans to confirm this.

In the late 2002/early 2003, there was an epidemic of methanol poisonings in Norway. We selected eight of these patients for treatment with bicarbonate and fomepizole only, according to a prospective protocol in order to study methanol and formate kinetics without the influence of dialysis. These results add further documentation toward a simpler way of treating these patients.

PATIENTS AND METHODS

Patients

Eight males with methanol poisonings were studied, with laboratory data and clinical features upon admission given in

TABLE 1
Clinical and laboratory data upon admission

Patient	Age (yrs)	pH	pCO_2 (kPa)	HCO_3 (mM)	Base deficit (mM)	AG (mM)	OG (mOsm/ kgH_2O)	S-methanol (mM)	S-ethanol (mM)	S-formate (mM)	Clinical features	Sequelae
1	53	7.50	4.8	28	5	23	138	140.6	8.7	3.3	none	–
2	69	7.33	3.9	15	9	24	101	102.8	0	6.9	none	–
3	35	7.27	3.6	12	13	25	50	33.8	19.6*	10.6	VD, D, GP	–
4	70	7.12	2.4	6	22	30	24	21.9	13.0*	11.1**	VD, GI	–
5	46	7.23	1.9	6	19	39	25	18.8	0	ND	VD, D, CP, GI	–
6	52	7.38	2.7	12	11	27	28	15.6	6.5*	ND	VD	–
7	48	7.25	2.3	7	17	30	29	12.5	0	ND	VD, D, GI	–
8	35	7.26	2.5	8	17	28	24	8.4	8.7*	11.7	VD, D, CP	visual
Median	50	7.27	2.6	10	15	28	29	20.4	8.7	10.6	–	–

AG=anion gap, OG=osmolal gap, ND=not determined.

Clinical features: VD=visual disturbances, D=dyspnoea, GI=GI-symptoms, CP=Chest pain, GP=general paresthesia.

The conversion factor for pCO_2 from kPa to mmHg is 7.5.

*Blood sample drawn after treatment with ethanol at local hospital.

**Blood sample drawn 5 h after admission.

Table 1. Three of the patients were admitted directly to our hospital, while five were transferred after initial admission to other hospitals. The basis for selection of patients for bicarbonate and fomepizole treatment without hemodialysis was mild to moderate metabolic acidosis upon admission, and no visual disturbances after rapid and full correction of metabolic acidosis in the emergency department. The present patients were the only ones to meet these criteria. Fomepizole (Fomepizole®, OPi Orphan Pharma international, Paris, France) was given as a bolus dose of 15 mg/kg IV diluted in isotonic saline, and then 10 mg/kg was given IV every 12 h. Five of the patients had detectable S-ethanol concentrations upon admission (median 8.7 mmol/L, range 6.5–19.6), in four because of treatment with ethanol before transferal to our hospital. Three patients (1, 2, and 3) were dialyzed after 14, 23, and 32 h, because of the very slow elimination of the S-methanol related to their high initial S-methanol levels. Only data from the predialysis period of these patients are presented. Five (four upon admission) of the patients were also analyzed for S-formate and in two cases urine was also collected (patients 2 and 3). The urine was analyzed for formate and methanol. One of the patients (patient 6) was also

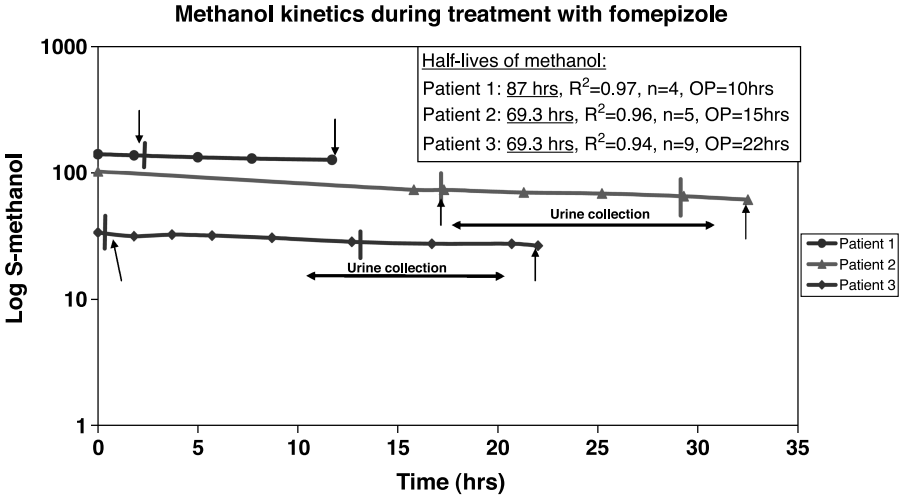

FIG. 1. Methanol kinetics during treatment with fomepizole, patients 1–3. Vertical bars represent dosing of fomepizole, vertical arrows (↑ or ↓) indicate time of half-life calculations. OP=observation period.

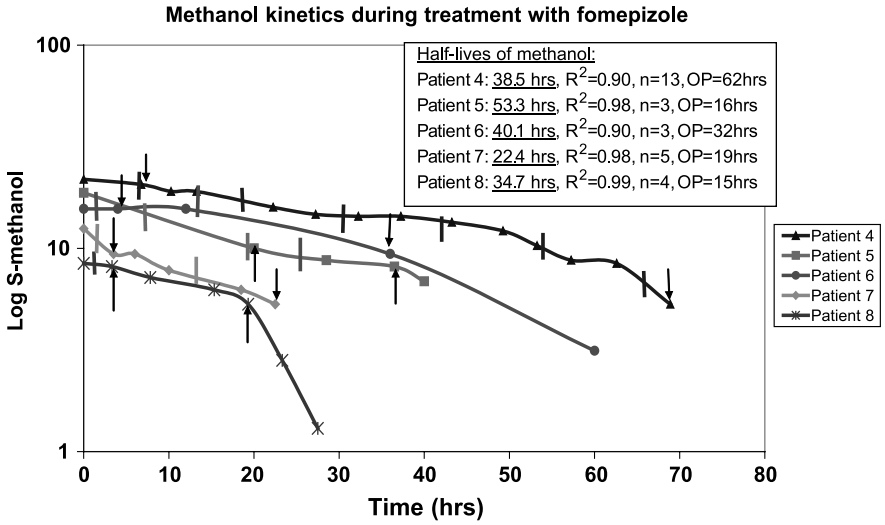

FIG. 2. Methanol kinetics during treatment with fomepizole, patients 4–8. Vertical bars represent dosing of fomepizole, vertical arrows (↑ or ↓) indicate time of half-life calculations. OP = observation period.

treated three times with folinic acid (50 mg IV every 6 h) while S-formate was measured. Most of the patients in this material were admitted early in the accident, and there was no routine for giving folinic acid at this time. Patient 1 was not given folinic acid because of his low initial formate (3.3 mmol/L). The visual disturbances in six patients rapidly disappeared in five of them upon treatment on admission. Due to language problems, persistence of slight visual impairment in one eye in patient 8 was not discovered until later.

METHODS

Methanol in serum was determined by gas chromatography using a headspace injector (Fisons GC 8000; Carlos Erba Instruments, Rodano, Italy) (sensitivity 1.3 mmol/L and day-to-day coefficient of variation 5%). Calibrators and controls were made by dilution of 100% methanol (Merck, Damstadt, Germany). Formate was measured enzymatically on a Cobas Mira analyzer (Roche Diagnostics, Basle, Switzerland) using formate dehydrogenase (Roche) and nicotinamide adenine dinucleotide (NAD) (Sigma, St. Louis, USA) (reference range $\leq$0.4 mmol/L, day-to-day coefficient of variation 5%).

Elimination half-life was calculated from the relationship of methanol or formate concentrations vs. time, respectively. Linear regression analysis determined K_e, the elimination constant, from the slope of the natural log of methanol or formate concentration vs. time. The elimination half-life was then calculated from the relationship $t_{1/2} = 0.693/K_e$.

Renal clearance (RC) of methanol and formate was calculated from the formula

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

where U_x and S_x are urine and mean serum concentrations of methanol and formate, respectively, and V is the average urine volume excreted per time in the urine collection period (mL/min). The mean S-concentration used was the S-concentration on the elimination curve in the middle of the urine collection period (Fig. 1).

The total body clearance (TBC) (mL/min) was calculated from the formula

$$TBC = \frac{V_d \times 0,693}{T_{1/2}}$$

where V_d is the volume of distribution of methanol, which is approximately 0.7 L/kg for males (1). Most likely, the

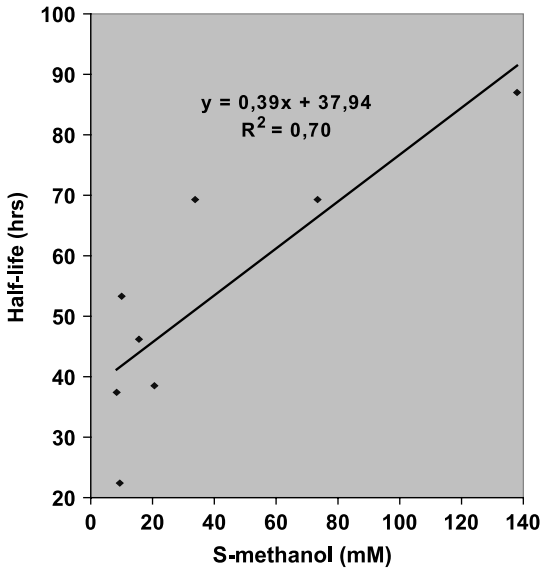

FIG. 3. Correlation between S-methanol half-lives during fomepizole treatment and S-methanol concentrations upon admission in all 8 patients.

TABLE 2
Kinetic data in blood and urine for patients 2 and 3 (see Fig. 1)

Patient	Time (min)	Urine collected (mL)	U-meth (mM)	U-form (mM)	Mean S-meth (mM)	Mean S-form (mM)	R_c meth (mL/min)	R_c form (mL/min)	TBC meth (mL/min)
2	840	1100	66	28.4	69	0.2	1.2	183	7.4
3	600	800	35	65	28	0.2	1.7	423	12.8
Mean							1.45	252	10.1

R_c=renal clearance, TBC=total body clearance.

difference between TBC and RC is the pulmonary clearance, but other minor pathways could be involved. We have assumed that these are practically negligible, and therefore calculated the pulmonary clearance (PC) (mL/min) of methanol during fomepizole treatment using the formula

$$PC = TBC - RC$$

Anion and osmolal gaps were calculated by standard equations with reference ranges of 4–20 mmol/L and $\leq$19 mOsm/kgH_2O, respectively (1,11,12). Conversion factors from mmol/L to mg/dL for methanol and formate are 3.2 and 4.6, respectively.

RESULTS

During fomepizole treatment, the elimination of methanol apparently followed first-order kinetics, as illustrated in Figs. 1 and 2. Interestingly, a shift from first-order (linear) to zero-order (nonlinear) kinetics was observed in one patient (no. 8, Fig. 2) when the effect of fomepizole decreased (elimination rate approximately 20 mg/dL/hr, using the three last data points obtained). He received only one dose of fomepizole, because of his low S-methanol concentrations. His acid/base-status and anion gap remained normal.

The mean S-methanol half-life during fomepizole treatment was 52 h (range 22–87 h). The three longest half-lives were measured in the patients with the highest S-methanol, and there was a significantly increasing half-life with higher S-methanol levels for all eight patients (Spearman's r_s=0.874, p=0.005) (Fig. 3). In the two patients studied, total body clearances for methanol during fomepizole treatment were 7.4 and 12.8 mL/min (Table 2). Analyses of urine in two patients showed a mean renal clearance of methanol of 1.2 and 1.7 mL/min and of formate of 183 and 423 mL/min, respectively (Table 2). Note the high renal clearance of formate compared to that of methanol in these two nonacidotic patients. The

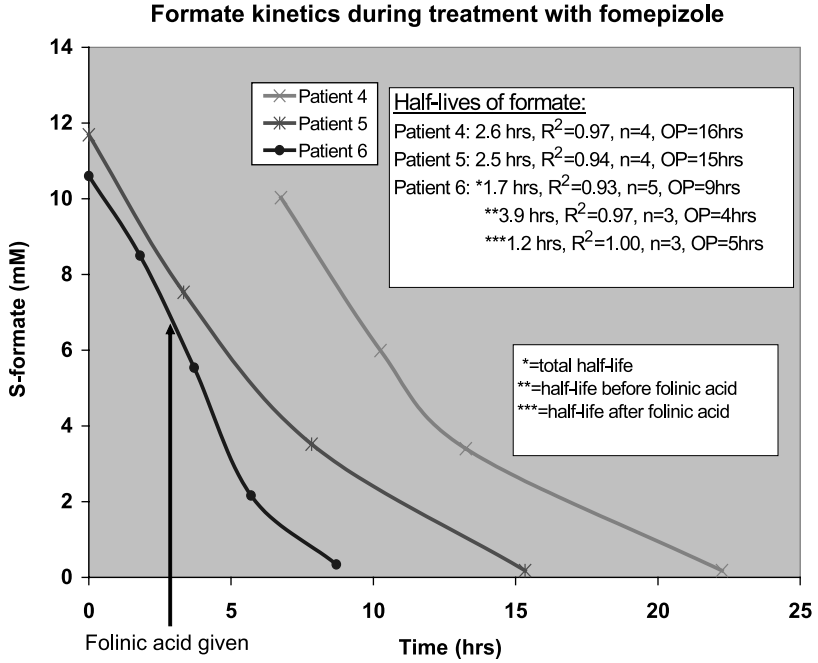

FIG. 4. Formate kinetics during treatment with fomepizole in patients 4, 5, and 6. (Given R^2-values refers to a semilogarithmic plot.)

pulmonary clearances of methanol in these cases were 6.2 and 11.1 mL/min, respectively.

The elimination of formate in the three studied patients followed first-order kinetics until levels reached reference values of $\leq$0.4 mmol/l (Fig. 4). The mean formate half-life was 2.3 h (range 1.7 to 2.6 h). Interestingly, the shortest S-formate half-life (1.7 h) was measured in patient 3 treated with folinic acid three times. In the two patients not given folinic acid, the mean formate half-life was 2.6 h.

DISCUSSION

Methanol half-life in our patients was long (mean $T_{1/2}$ 52 h) when ADH was assumed blocked by fomepizole treatment. This corresponds well to earlier published material (8,9,11). During ADH inhibition, there is no formation of formic acid and hence no further acid-/base-disturbances develop. There was a good correlation (R^2) to first-order elimination kinetics in six of our patients (Figs. 1 and 2) supporting the assumption that ADH was blocked. The elimination of methanol in patients 4 and 6 did not fit as well with first-order kinetics (R^2=0.90 in both). We have no explanation for this, but interestingly, patient 4 was treated the longest with fomepizole. Since fomepizole induces its own metabolism over time, induction of metabolism resulting in subtherapeutic concentrations cannot be ruled out (13). Although antidote levels were not monitored, the curving of the elimination line at its end may support this. The fact that the first three analyses in patient 6 had values of the same magnitude is also unusual. There was no clinical or laboratory evidence in this patient suggesting either respiratory or renal insufficiency.

There is a limitation in our data regarding the length of the observational period vs. the apparent half-life of methanol. However, because the mean half-life of methanol was 52 h,

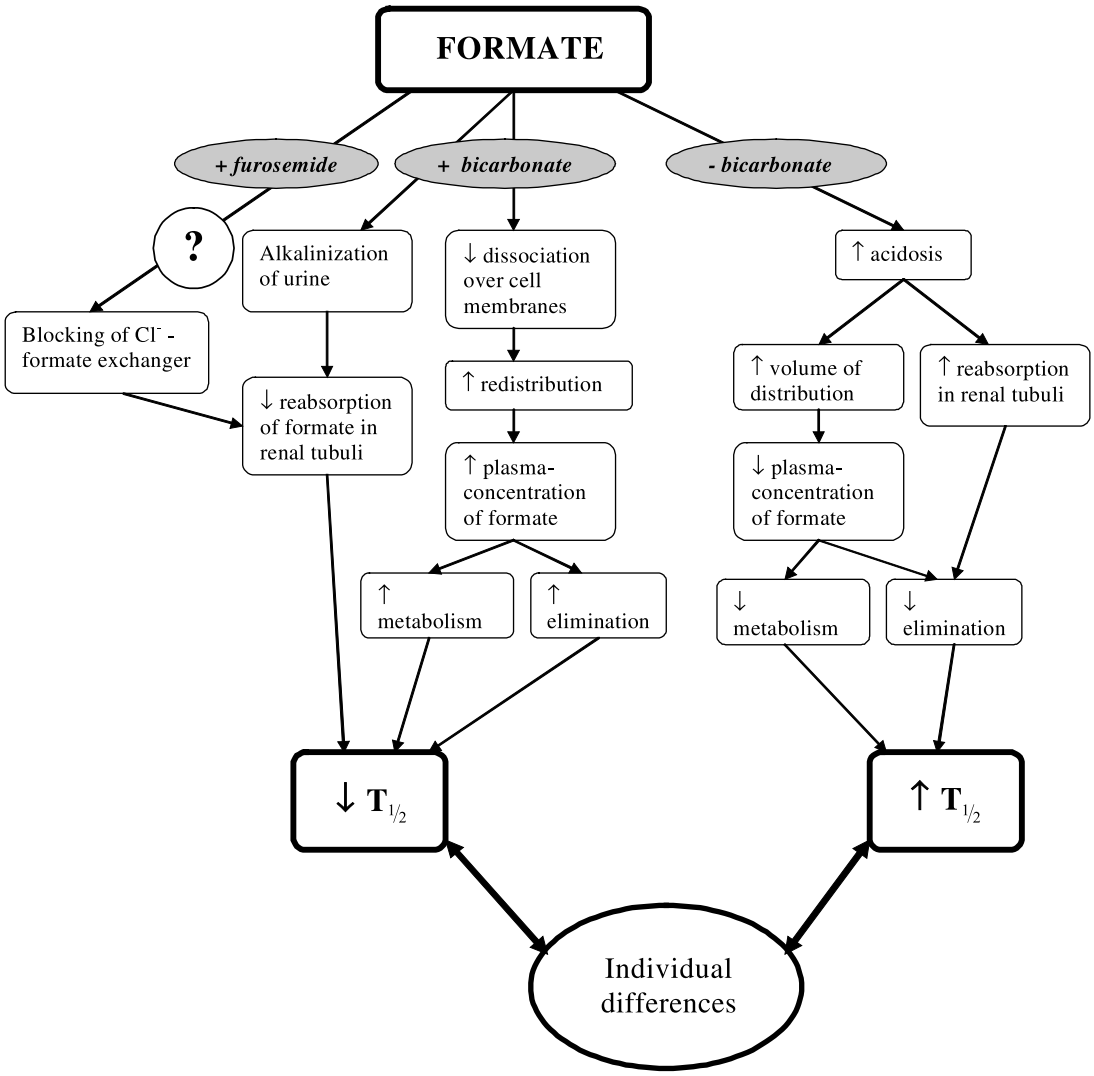

FIG. 5. Different mechanisms for variability in formate elimination half-life.

it was difficult to make the observational period three times the half-life. There is also a limitation in the number of representative data points in a few of the patients, but the data extracted are within the time-span of metabolic inhibition by the antidote.

There was a significant longer half-life for the higher initial methanol concentrations, as also indicated by Megarbane et al. in their retrospective study in five patients (7). Our larger group of patients with a wider range of S-methanol concentrations seems to confirm this tendency (Fig. 3). This may be explained by a concentration-dependent and saturable pulmonary and renal elimination of methanol when ADH is blocked (7). Another explanation could be lesser inhibition of ADH at lower S-methanol concentrations. The latter explanation seems very unlikely according to Michaelis Menten kinetics.

The pulmonary clearances of methanol during fomepizole treatment in two of the patients (Table 2), is another interesting observation. Assuming the pulmonary clearance is the only nonrenal clearance, this would make the pulmonary elimination of methanol in these two cases to be 84 and 87% of the total body clearance, respectively. This corresponds to an earlier observation in another patient, also without hyperventilation, which may increase the pulmonary clearance (11).

The half-life of serum formate in most cases is reported to be 2.5–5 h (14,15), although in one patient, 20 h is reported (16). The elimination demonstrated in this specific case, however, showed that no first-order elimination was present, i.e., no half-life could be correctly calculated. A critical question is how the anion formate can accumulate in methanol-poisoned patients with the short elimination half-lives found in our patients (mean 2.6 h without folinic acid)? First, there seem to be significant interindividual differences in the uninhibited metabolism rate of methanol—and thereby formate production. The only published case reports an elimination rate of 8 mg/dL/h (17). In our case 8 (Fig. 2), the elimination rate seems to be 20 mg/dL/hr after discontinuation of antidote treatment. Confounders in our case are the limited number of analyses (n=3), short observational period (8 h), and low S-methanol (<6 mmol/L). Second, different levels of folate in the liver, due to nutritional status or prior alcohol consumption, probably contribute to interindividual variations in formate elimination (18). Third, formic acid is reabsorbed in the renal proximal tubuli by different pH-dependent mechanisms (see later and Figs. 5 and 6). Reabsorption increases with lower urinary pH, thus the actual serum half-life might be significantly longer *after* metabolic acidosis is present and *before* buffer treatment starts (Fig. 5). Finally, the first-order kinetics of formate elimination during antidotal treatment could not be extrapolated to estimate formate kinetics prior to this treatment, because of continuous metabolism of methanol to formate.

There are few studies on renal clearance of formate found in the literature, but it is reported to be an unexpectedly slow process (8,19), with substantial intraindividual and interindividual variations in urine formate concentrations. However, there is little experimental or clinical evidence for these statements (20). In our study, renal formate excretion was high compared to that of methanol and there was a 2 to 3-fold difference in the renal clearance of formate between the two patients (Table 2). In addition to interindividual differences, there can be different explanations for this: analytical errors (not likely, because the samples were analyzed twice) or incomplete emptying of the bladder before collection of urine (but differences in Rc of methanol were small, suggesting this was not likely). Further, chloride/formate exchange across the epithelial membranes in the kidneys is dependent on the pH (Figs. 5 and 6), whether regarding the nonionic diffusion of formic acid (pKa of formic acid is 3.7), a H^+/formate cotransport, or an indirect coupling of formic acid transport to Na^+/H^+ exchange (21,22) (Fig. 6). The result at low pH can be a continuous recycling of formate in the proximal tubules, an increased reabsorption, and hence a reduced elimination of formate. Therefore, the most probable explanation for the variation in renal formate excretion would be differences in urinary pH, which was unfortunately not measured.

The discussion further supports the importance of buffer treatment in methanol poisoning: In addition to decreasing metabolic acidosis and hence formate toxicity by reducing access of formate to the central nervous system (5,23), alkalinization of urine would most probably increase the renal excretion of formate (Figs. 5 and 6). In his thesis on methanol poisonings in which he studied the effect of alkali treatment and proposed ethanol as an antidote, Roe noted effects both

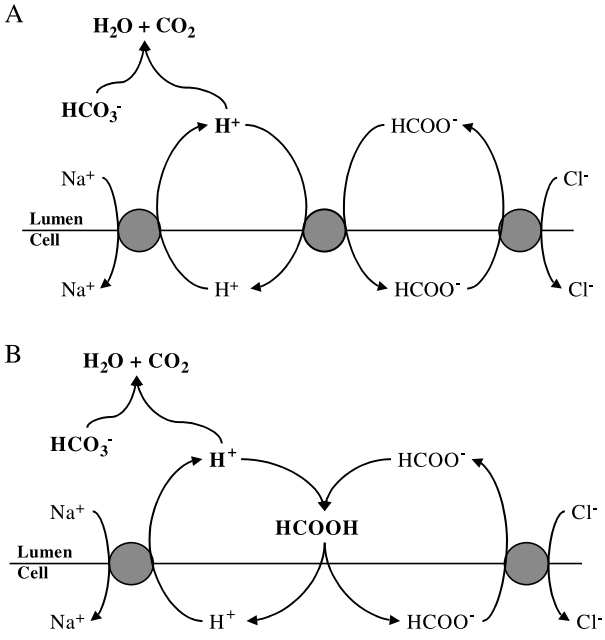

FIG. 6. Mechanisms of reabsorption of formic acid in the renal proximal tubule. A: H^+/formate cotransport. B: Nonionic diffusion of formic acid and indirect coupling of formic acid to Na^+/H^+ exchange [modified from Ref. (18)].

on visual acuity and general clinical condition from alkali treatment alone (4,24,25). Such a theory might challenge the importance of the hitherto most recommended regimen for enhancing formate elimination in methanol poisoned patients: to give folinic acid to increase formate metabolism (8,18,26). Such a challenge, however, does not mean that folinic acid should not be given. One of our patients received folinic acid (patient 3), but there were too few analyses to draw definite conclusions. Interestingly, however, the half-life of formate before and after folinic acid treatment was 3.9 (Fig. 3, first three data points) and 1.2 h (Fig. 3, last three data points), respectively.

Visual impairment in methanol poisoning is considered difficult to treat (7,9). In our study, six patients presented with assumed mild visual disturbances and only one was discharged with visual sequelae. Due to language difficulties his visual impairment was not recognized upon admission to our hospital. If this had been realized, this patient (no. 8) would have been dialyzed according to our treatment protocol. In all other patients, visual impairment rapidly disappeared and they therefore stayed within the treatment protocol of bicarbonate and fomepizole only.

Based upon our data, it appears that methanol-poisoned patients with moderate metabolic acidosis (pH>7.10 and base deficit $\leq$ 22 mmol/L) and visual disturbances that are reversed by the initial bicarbonate administration may safely be treated with fomepizole only. However, dialysis shortens the period of hospitalization when the S-methanol is high (>19 mmol/L or 60 mg/dL), and elimination half-lives are as long as presented here.

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