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Fomepizole may change indication for hemodialysis in methanol poisoning: prospective study in seven cases

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Key words
antidote – formate – hemodialysis – methanol poisoning

Abstract. Background: Treatment of methanol poisoning includes administration of buffer, antidote and hemodialysis. The role of hemodialysis using the new antidote fomepizole has not been studied. We studied the kinetics of methanol and formate during hemodialysis, and the possibility for delayed hemodialysis in the methanol poisoned patients without severe metabolic acidosis or visual disturbances. Patients and methods: Prospective case series study on methanol, formate and dialysis kinetics in 7 cases of severe methanol poisoning treated with buffer, fomepizole and hemodialysis (average 7 hours, range 5 – 8). Four patients were dialyzed early after diagnosis was obtained, while three were dialyzed "electively" the next day. Results: The median pH upon admission was 6.9 (range 6.6 – 7.5) and median base deficit 20.4 mmol/l (range 5.1 – 30.0). Their median S-methanol was 76.3 mmol/l (range 15.6 – 140.6) and S-formate 13.6 mmol/l (range 3.3 – 21). The median half-life of methanol during fomepizole treatment before dialysis was 71.2 hours (range 69.3 – 77); compared to 2.5 hours (range 1.7 – 3.3) during procedure. The median half-life of formate during dialysis was 1.7 hours (range 1.5 – 1.9). The median dialysis clearance of methanol was 222 ml/min (range 204 – 232) and for formate 225 ml/min (range 220 – 229) at a blood flow of 250 ml/min. One patient died and 2 were discharged with permanent visual and cerebral sequelae, whereas one died one year later. All three patients, in whom "elective" hemodialysis was performed, were discharged without sequelae. Conclusion: The efficacy and side effect profile of fomepizole may change the role of hemodialysis in methanol poisoning. More patients may be stabilized in local hospitals and transferred for "elective" dialysis, if methanol removal is still indicated after correction of metabolic acidosis.

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Introduction

Methanol is metabolized by alcohol dehydrogenase via formaldehyde to formic acid, which is primarily responsible for the toxicity in methanol poisoning [Jacobsen and McMartin 1986]. Metabolism of formate is folate-dependent, and mainly due to a small folate pool in humans, formic acid accumulates [Jacobsen and McMartin 1986, Jacobsen et al. 1990]. Treatment of methanol poisoning consists of rapid and full correction of the metabolic acidosis thereby also reducing formate toxicity [Barceloux et al. 2002, Liesivuori and Savolainen 1991, Roe 1946], inhibition of the metabolism of methanol by inhibiting alcohol dehydrogenase (ADH) with an antidote (ethanol or fomepizole) and hemodialysis [Barceloux et al. 2002]. Fomepizole is a competitive inhibitor of the ADH enzyme, and is gradually replacing ethanol as the antidote of choice [Barceloux et al. 2002, Jacobsen and McMartin 1986, 1997]. Fomepizole is efficient, easier to administer/monitor and without many of the side effects of ethanol [Brent et al. 2001], but it is expensive [Megarbane et al. 2004]. Hemodialysis eliminates methanol and formate, and also helps in correcting metabolic acidosis [Jacobsen et al., Barceloux et al.]. Folinic acid has a potential effect in enhancing the metabolism of formate [Barceloux et al. 2002].

The role of hemodialysis in methanol poisoning is well-established when ethanol is the antidote, but there are few reports and few kinetic data on dialysis when fomepizole is used as an antidote. Although the phase III study leading to the FDA approval of fomepizole in methanol poisoning included dialyzed patients, they were all dialyzed according to

Table 1. Laboratory data on admission.

Patient	Sex/ Age (years)	pH	Base deficit (mM)	pCO_2 (kPa)	HCO_3^- (mM)	S-metOH (mM)	S-formate (mM)	S-ethanol (mM)	Osmolal gap (mOsm/ kgH_2O)	Clinical features	Sequelae
1	M62	6.60	28.0	6.1	4.5	77.5	15.7	0	113	CP, C, RA	VS, CS[3]
2	F46	6.62	ND	4.3	3.0	76.3	13.6	0	94	VD, C	Died
3	M41	6.87	28.9	2.9	3.8	32.5	21.0	0	61	VD, D	VS, CS
4	F54	6.92	30.0	1.9	2.8	15.6	20.4	0	16	CP, VD, D	None
5	M35	7.27	12.7	3.6	12.3	33.8	10.6	19.6[1]	50[2]	VD, D, GP	None
6	M69	7.33	9.2	3.9	15.0	102.8	6.9	0	101	None	None
7	M53	7.50	5.1	4.8	28.0	140.6	3.3	8.7	138[2]	None	None
Median	53	6.92	20.4	3.9	4.5	76.3	13.6	0	94		

[1] Analysis made after treatment with ethanol at local hospital, [2] osmolal contribution from ethanol subtracted, [3] died after one year with massive sequelae, ND = not determined, CP = chest pain, VD = visual disturbances, D = dyspnea (including clinical hyperventilation and insufficient respiration), GP = general paresthesia, C = coma, VS = visual sequelae, CS = cerebral sequelae.

the traditional dialysis indications from the time when ethanol was the only antidote [Barceloux et al. 2002, Brent et al. 2001]. We have previously confirmed other studies demonstrating the efficacy and side effect profile of fomepizole in methanol poisoned patients not undergoing hemodialysis: methanol half-life increased to an average of 52 hours and many patients were stabilized to almost out-patient status within a few hours [Hovda et al. 2004, 2005].

We performed prospective kinetic studies on methanol and formate in seven methanol-poisoned patients treated with fomepizole and hemodialysis in order to evaluate the role of this procedure when using the new antidote and to find a possible new indication for dialysis based on the patient's initial clinical status.

Patients and methods

Patients

Patients were part of an outbreak where illegal spirit consisting of 20% methanol and 80% ethanol were consumed. Except for alcohol abuse, especially in Cases 1 – 3 and 7, they were all previously healthy. Cases 3 and 7 were admitted directly to our university hospital, while the others were transferred after initial admission to local hospitals. The clinical and laboratory data on first admission are given in Table 1 (except Patient 5, where data are from admission to our hospital after initial admission to another hospital). Patients were admitted because of clinical features except Cases 6 and 7, who where admitted on suspicion of methanol poisoning. Patient 2 died despite intensive treatment for 38 hours; organ donation was successfully performed. Patients 1 and 3 were discharged with visual impairment and the typical lesions of the basal ganglia [Server et al. 2003], Patient 1 died one year later with massive sequelae.

Treatment

Six patients were initially given sodium bicarbonate, while Case 1 received trometamol (Tribonat) as a buffer. Patients 5 and 6 were given ethanol intravenously before transferal to our hospital where they all received fomepizole. Fomepizole (Fomepizole, OPi Orphan Pharma international, Paris, France) was given as a bolus dose of 15 mg/kg i.v. diluted in isotonic saline, and then 10 mg/kg every 12 h, all doses given over 30 minutes. From the fifth dose and on, 15 mg/kg were given in order to compensate for increased metabolism. During dialysis, fomepizole was given by 10 mg/kg every 4 hours. The doses are based on clinical studies [Jacobsen et al. 1990] and the META Study [Brent et al. 2001].

Hemodialysis was performed (all patients) for 5 to 8 hours and when terminated, serum methanol was below 10 mmol/l. Pa-

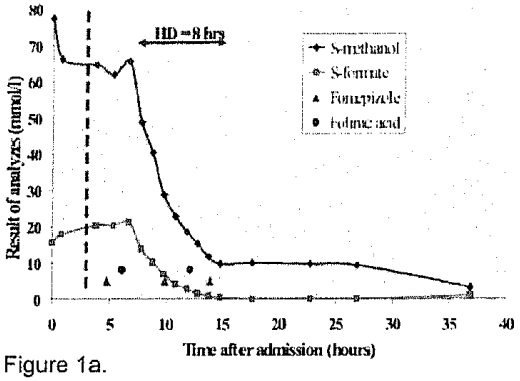

Figure 1a.

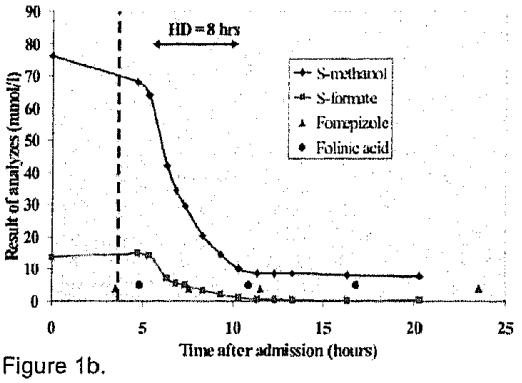

Figure 1b.

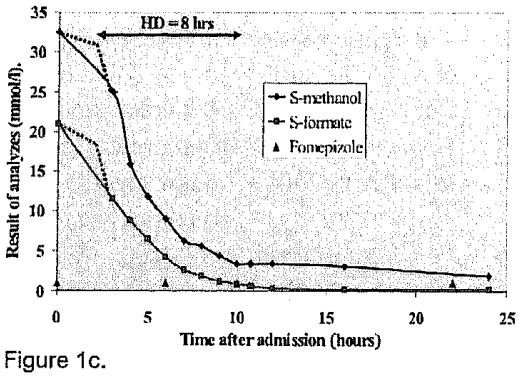

Figure 1c.

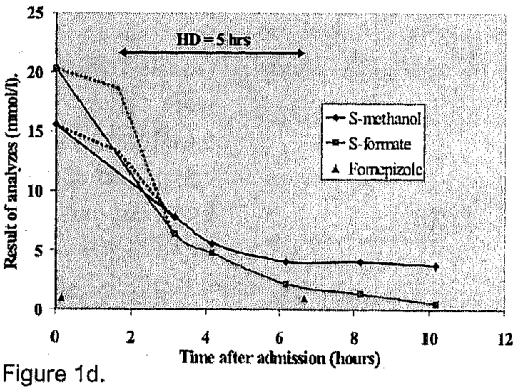

Figure 1d.

Figure 1a,b,c,d. S-methanol and S-formate levels for the patients dialyzed early (patients 1 to 4), including the respective half-lives. OP = observational period and n = number of observations during which time the half-life is calculated. The dotted curved line (Figure 1c,d) represents the assumed S-concentrations when measurements were not taken. The dashed vertical lines (Figure 1a,b) represent the admission to our hospital. The time of dialysis is marked with an arrow (hours).

tients 1, 2, 3 and 4 were dialyzed early after diagnosis was obtained, while cases five, six and seven were dialyzed electively. The decision for early or elective dialysis was done on the basis of the patients' clinical condition; the degree of metabolic acidosis or visual disturbances present which did not disappear with buffer and antidote alone. Patients 1, 2 and 3 also received massive supportive treatment because of their clinical condition: Patients 1 and 3 received antibiotics for sepsis and Cases 1, 2 and 3 were given mechanical ventilation and vasopressors because of respiratory and circulatory failure.

Methods

Methanol in serum was measured by a gas-chromatographic method with flame-ionization detection (GC-FID) and a head-space injector (Fisons GC 8000; 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, Darmstadt, Germany). Formate was measured enzymatically on a Cobas Mira analyzer (Roche Diagnostics, Basle, Switzerland) using formate dehydrogenase (Roche) and nicotinamid adenine dinucleotid (NAD) (Sigma, St. Louis, USA) (sensitivity 0.1 mmol/l, reference range ≤ 0.4 mmol/l, day-to-day coefficient of variation 5%).

Conversion factors from mmol/l to mg/dl for methanol and formic acid are 3.2 and 4.6, respectively.

The dialyzer clearance (D) was calculated from the standard formula

$$D = \frac{Q \times (A - V)}{A}$$

where Q = blood flow (ml/min), A = serum methanol concentration on the inlet side, V = serum methanol concentration on the outlet side of the dialyzer. After blood collection, samples were allowed to equilibrate for 6 hours before spinning, serum separation and storing in freezer (–20 °C) until analyses.

Dialysis was performed using a standard Gambro AK 200 machine (Gambro AB, Stockholm, Sweden) with a Fresenius F8 HPS dialyzer (1.8 m^2) (Fresenius Medical Care,

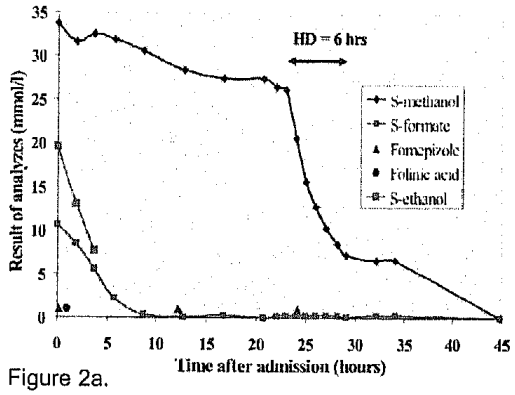

Figure 2a.

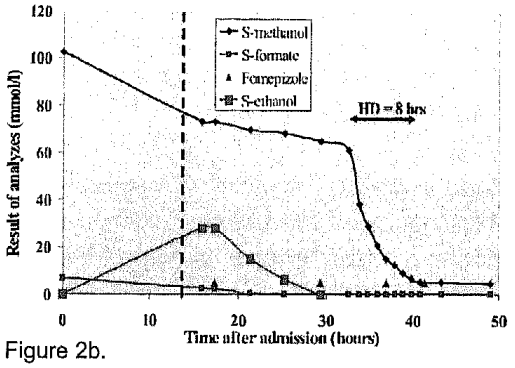

Figure 2b.

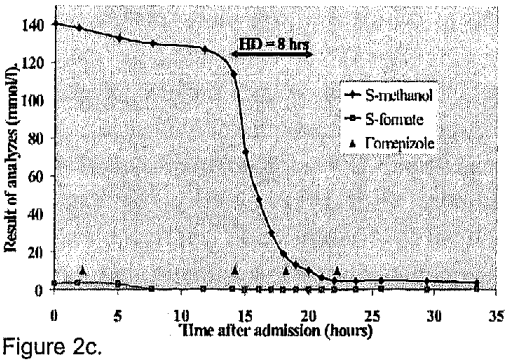

Figure 2c.

Figure 2a,b,c. S-methanol and S-formate levels for the patients dialyzed electively (patients 5 – 7), including the respective half-lives. OP = observational period and n = number of observations during which time the half-life is calculated. The dashed vertical line (Figure 2b), represents the admission to our hospital. The time of dialysis is marked with an arrow (hours).

Bad Homburg, Germany) and a fixed blood flow of 250 ml/min.

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

$$Re = \frac{Ux}{Sx} \times V$$

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

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

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

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

where V_d is the volume of distribution. For methanol, a V_d of 0.7 l/kg (males) and 0.6 l/kg (females) [Jacobsen and McMartin 1986, 1997] was used, and regarding formate, a V_d of 0.5 l/kg was used for both sexes [Jacobsen et al. 1986, 1997].

Results

Elimination kinetics for methanol and formate before, during and after hemodialysis in all 7 patients are shown in Figures 1a,b,c,d and 2a,b,c. The elimination rate of methanol was clearly increased during hemodialysis and apparently followed first order kinetics with a mean R^2 of 0.98 (range 0.96 – 1.00). No rebound effect in serum methanol due to redistribution was observed after terminated dialysis.

The kinetic data during hemodialysis are presented in Table 2. Note that despite similar dialysis clearance, the half-life of formate is shorter than that of methanol, average being 1.7 and 2.5 h, respectively. This is explained by a higher intrinsic elimination of formate (metabolism and a variable renal excretion; Table 3), whereas methanol metabolism is blocked and the renal and pulmonary excretion is small. As such, dialysis represents 83% of the total body clearance of methanol and 68% of the total body clearance of formate in these patients (Table 2). The median dialysis clearance of methanol was 222 ml/min (range 204 – 232, n = 5) and for formate 225 ml/min (range 220 – 229, n = 2) (Table 2). The renal clearance of methanol and formate in Patients 1, 2 and 6 during hemodialysis are presented in Table 3.

Table 2. Essential kinetic data during HD in seven methanol-poisoned patients.

Case	Weight (kg)	D (metOH) (ml/min)	D (form) (ml/min)	$T_{1/2}$ D (metOH) (h)	$T_{1/2}$ D (form) (h)	TBC D (metOH) (ml/min) (1)	TBC D (form) (ml/min) (1)	D/TBC (metOH)	D/TBC (form)
1	100	232 (n = 8, SD ± 10, range 216 – 243)	229 (n = 8 SD ± 18, range 188 – 244)	2.9	1.5	279	424	0.83	0.54
2	70	227 (n = 5, SD ± 8, range 218 – 239)	220 (n = 5, SD ± 14 range 202 – 240	1.9	1.5	255	270	0.89	0.82
3	80	ND	ND	2.5	1.8	259	257	ND	ND
4	70	ND	ND	3.3	1.9	147	213	ND	ND
5	110	219 (n = 6, SD ± 20, range 197 – 250)	ND	3.2	ND	278	ND	0.79	ND
6	63	222 (n = 8, SD ± 19, range 189 – 242)	ND	2.4	ND	212	ND	1.05	ND
7	60	204 (n = 7, SD ± 21, range 168 – 225)	ND	1.7	ND	285	ND	0.72	ND
Median		222	225	2.5	1.7	259	264	0.83	0.68

[1] TBC during HD, blood flow 250 ml/min, metOH = methanol, form = formate, D = mean dialysis clearance, TBC = total body clearance, ND = not determined.

Table 3. Renal clearance (R_c) of methanol and formate during hemodialysis.

Patient	Time (min)	Urine collected (ml)	U metOH (mM)	U form (mM)	Median S-metOH (mM)	Median S-form (mM)	R_c metOH (ml/min)	R_c form (ml/min)
1	480	1 700	46.6	31.6	22	4	7.8	28.0
2	360	350	47.8	9.8	22	4	2.2	2.5
6	480	700	39.7	7.0	15	ND	3.8	ND
Median							3.8	15.3

ND = not determined

Discussion

The severity and outcome of methanol poisoning are correlated to the toxic effects of formate and the degree of metabolic acidosis, and not to the S-methanol, provided start of alkali and antidotal treatment [Barceloux et al. 2005, Bennett et al. 1953, Hammoudeh and Snoudou 1988, Jacobsen et al. 1986, 1997, Liu et al. 1998, Mahieu et al. 1989, Meyer et al. 2000]. This is illustrated in Table 1 where Patients 6 and 7 have by far the highest methanol concentrations, but no clinical features because little methanol is metabolized to formic acid. The early acidosis is due to the production of formic acid whereas lactic acid production occurring in the later stages of poisoning is due to tissue hypoxia

caused by formate uncoupling of cytochrome oxidase [Hovda et al. 2005, Jacobsen and McMartin 1986, 1997, Sejersted et al. 1983]. The potential benefit of dialysis is due to the removal of methanol, the correction of the metabolic acidosis and removal of the toxic metabolite formate. Due to their small molecular weight, small volume of distribution, and lack of protein binding, both methanol and formate are easily dialyzed [Jacobsen et al. 1990].

The efficacy of hemodialysis in removing methanol is undisputable. However, there have been controversies regarding the efficacy of dialysis in removing formate: one study indicates that the endogenous elimination of formate is so rapid that dialysis might hardly represent 40% of its total body elimination – a usual requirement for recommending extracorporeal removal of a drug/toxin from the body [Kerns et al. 2002]. The elimination of formate may be quite variable, and some authors have therefore questioned the conclusion in the former study [Yip and Jacobsen 2003]. Interestingly, in two of our patients dialysis was calculated to represent 54% and 82% of the total body clearance (Table 2). Because the volume of distribution of formate is based on studies in only one patient [Jacobsen et al. 1986, 1997], these calculations are uncertain. The variability of the endogenous elimination of formate may in part be explained by its variable renal excretion as also demonstrated in the same patients (Table 3) and in patients not undergoing dialysis [Hovda et al. 2004, 2005]. We have previously suggested that this variation in the renal handling of formate is pH-dependant; the more acidic the urine becomes, the less formate is excreted. Therefore, the role dialysis has in removing formate most probably becomes more important the more acidotic the patient is because the intrinsic clearance of formate then decreases significantly [Hovda et al. 2004, 2005].

In our 7 patients, there was a high methanol and formate elimination during hemodialysis compared to previous studies [Jacobsen et al. 1986, 1997]. The median half-life of S-methanol was 2.5 hours (range 1.7 – 3.3 h) during hemodialysis. This may best be explained by the larger surface area of the dialyzer and higher blood flow used in our series (1.8 m^2, 250 ml/min) compared to previous studies (1.6 m^2, 200 ml/min) [Jacobsen et al. 1986, 1997]. The present half-life of methanol is significantly shortened compared to the mean half-life of 52 hours reported in 8 patients treated with fomepizole only [Hovda et al. 2004, 2005]. In five of our patients (Figure 1a,b and 2a,b,c), one can easily see how the elimination increases and S-methanol decreases when dialysis is initiated. In Patients 3 and 4 (Figure 1b,d) the effect of hemodialysis on the elimination is best demonstrated by comparing the elimination during this procedure with the slow elimination post dialysis. Because methanol metabolism is blocked by fomepizole and the renal clearance of methanol is low (Table 3), the high methanol elimination caused by hemodialysis is close to its total body clearance as shown in Table 2.

The previous recommendations for hemodialysis using ethanol as an antidote are based on case reports and case series studies, and are as follows: any degree of visual impairment, severe metabolic acidosis (base deficit > 15 mmol/l or anion gap > 30 mmol/l), or blood methanol concentrations above 20 mmol/l (60 mg/dl) [Jacobsen and McMartin 1986, 1997]. Others recommend dialysis even at lower methanol concentrations [Barceloux et al. 2002]. If there are no visual disturbances (or if the visual disturbances are early corrected by bicarbonate and fomepizole only) and no metabolic acidosis, dialysis is only indicated for the removal of methanol per se, and then no cut-off serum methanol may be given. Availability of dialysis must also be taken into consideration. Interestingly, this approach has recently also been suggested in a review paper based on sound theoretical considerations by leading experts [Megarbane et al. 2004]. As demonstrated by the effective block of methanol metabolism by fomepizole in our patients and the clinical improvement after this treatment combined with aggressive correction of acidosis, there is really no longer any recommended serum methanol concentration for discontinuation of dialysis (e.g. 10 mmol/l [Jacobsen and McMartin 1986, 1997]). If methanol analyses are not available, the length of hemodialysis may best be guided by calculations of the osmolal gaps [Hovda et al. 2004, 2005]

The cost of fomepizole is approximately 7800 Euro per patient (3 days treatment, 6 doses), 70 kg patient, average price in Scandi-

navia. Using fomepizole and reducing the need of dialysis, or doing it electively, may therefore be expensive. First, hemodialysis is not available everywhere, and transport to dialysis facilities has economical aspects. Potential adverse effects related to the fact that hemodialysis is an invasive treatment also may have economical aspects. Because the patients are not drunk from ethanol treatment, handling is easier, which further represents an economical benefit. However, our experience that most patients can be treated outside the ICU, or only need a brief stay, is probably most important as also suggested by others [Megarbane et al. 2001, 2004]. None of the three patients treated with elective hemodialysis in the present material needed treatment in the ICU.

Based on our data and theoretical considerations [Megarbane et al. 2001, 2004], the indications for hemodialysis in methanol poisoning using fomepizole as the antidote may therefore be separated into two categories:

- The critically ill patient, with severe metabolic acidosis (base deficit > 20 mM) and/or visual disturbances, should be given buffer, fomepizole and hemodialysis as soon as possible. The main effect of dialysis is then to remove the toxic anion formate and to assist in correcting the metabolic acidosis, thereby also reducing formate toxicity [Barceloux et al. 2002, Liesivuori and Savolainen 1991]. The removal of methanol per se is not life-saving in this setting, because fomepizole prevents further production of formic acid.
- The stable patient, with little to moderate metabolic acidosis and no visual disturbances, should be given buffer and fomepizole. The indication for hemodialysis should then be discussed with an experienced nephrologist and/or clinical toxicologist. The efficacy of fomepizole and the significant different side effect profile from ethanol gives the treating physician the possibility to delay or even drop dialysis in this setting, and thereby change the triage, as patients will not develop more clinical features from methanol poisoning when fomepizole and bicarbonate is given.

This change in triage will be particularly useful in larger methanol outbreaks and in other situations where dialyzing resources are limited. As demonstrated in three of our patients (5 – 7), buffer and fomepizole treatment alone were associated with clinical improvement which resulted in transferral of patients to observational units for elective dialysis the next day.

Conclusions

There is still a role for hemodialysis in methanol poisonings, but it is time to modify indications and triage. The efficient, but expensive fomepizole, is void of the disadvantages of ethanol: no need for monitoring the serum level, no CNS depression, and no drunken patients. This makes treatment with delayed dialysis or even without dialysis an option, and thereby no need for transferral in many cases. Nevertheless, when patients are admitted with severe metabolic acidosis and/or visual disturbances, acute hemodialysis should always be performed. To shorten the treatment period and hence reduce the costs of treatment, dialysis may also be considered when serum methanol exceeds 32 mmol/l (100 mg/dl) unless one is willing to deal with the costs of fomepizole, or the actual setting makes it even more expensive/impractical to dialyze. Since these patients are in general awake and sober, this decision should also be discussed with the patient.

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