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Expert opinion: fomepizole may ameliorate the need for hemodialysis in methanol poisoning

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Fomepizole is now the antidote of choice in methanol poisoning. The use of fomepizole may also change the indications for hemodialysis in these patients. We have addressed this change in a review of articles on methanol poisonings. Review of the literature (through PubMed®) combined with our own experiences from two recent methanol outbreaks in Estonia and Norway. The efficiency of dialysis during fomepizole treatment was reported in only a few reports. One recent study challenged the old indications, suggesting a new approach with delayed or even no hemodialysis. Methanol-poisoned patients on fomepizole treatment may be separated into two categories: 1) The critically ill patient, with severe metabolic acidosis (base deficit >15 mM) and/or visual disturbances should be given buffer, fomepizole and immediate hemodialysis: dialysis removes the toxic anion formate, and assists in correcting the metabolic acidosis, thereby also reducing formate toxicity. The removal of methanol *per se* is not important in this setting because fomepizole prevents further production of formic acid. 2) The stable patient, with less metabolic acidosis and no visual disturbances, should be given buffer and fomepizole. This treatment allows for the possibility to delay, or even drop, dialysis in this setting, because patients will not develop more clinical features from methanol poisoning when fomepizole and bicarbonate is given in adequate doses. Indications and triage for hemodialysis in methanol poisonings should be modified. Delayed hemodialysis or even no hemodialysis may be an option in selected cases.

Key words: antidote; fomepizole; hemodialysis; methanol poisoning

Introduction

Background and purpose of the review

The treatment of methanol-poisoned patients has many facets: Buffer to treat the resulting acidosis, antidote to block the metabolism of methanol to the toxic formic acid, folinic acid to enhance the elimination of formate, and finally hemodialysis to help correct the acidosis and remove the toxic alcohol and its metabolite formate. In recent years, the antidote fomepizole has gradually become the antidote of choice, seemingly reducing morbidity and making the treatment itself easier and more predictable.[1] Although the use of hemodialysis is well established, its efficacy has been questioned regarding the removal of the toxic metabolite formate.[2] Furthermore, the indication for hemodialysis is based on the pre-fomepizole time, when ethanol was the only antidote in use. Therefore, the possible change of indication has been questioned by different authors.[1,3–8]

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The present article evaluates the current literature regarding the indication for hemodialysis in methanol-poisoned patients when fomepizole is the antidote of choice, and suggests a new indication based on the patient's initial clinical status. Although hemodialysis appears to be a relatively safe procedure, it still represents an invasive technique with risk of adverse effects. In addition, dialysis is not universally available, especially in developing countries where these poisonings often occur.[9] Added to that is the mass outbreak aspect, which is regularly seen. This review is focused on the literature on the current topic, and not on methanol poisoning in general.

Methanol poisoning and treatment

Methanol is metabolized by alcohol dehydrogenase (ADH) via formaldehyde to formic acid. The toxicity is a combined effect of the ensuing metabolic acidosis and the anion formate.[3,10] Metabolism of formate is folate dependent, and mainly because of a small folate pool in humans, formate accumulates.[3,11] Treatment of methanol poisoning consists of rapid and full correction of the metabolic acidosis thereby also reducing formate toxicity.[12–14] The metabolism

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of methanol by ADH is inhibited with an antidote (ethanol or fomepizole).[12] Hemodialysis eliminates methanol and formate, and also helps in correcting metabolic acidosis.[12,15,16] In addition, folinic acid has a potential effect in enhancing the metabolism of formate.[12]

The use of antidotes: fomepizole versus ethanol

Ethanol as an antidote in methanol poisoning has been established as a routine for several years[14]: It is readily available and cheap, but it has several side-effects, such as CNS depression and uncooperative patients. Keeping the serum concentration at a constant therapeutic level is also difficult: it requires frequent blood samples and a constant adaptation of the infusion rate. McCoy, *et al.*[17] found a constant level above the therapeutic limit in only 12% of the cases. In another study, Hantson, *et al.*[18] found 22 of 26 patients to experience at least one episode below the suggested therapeutic level of 100 mg/dL, whereas 8 of 26 patients experienced a serum level of ethanol above 200 mg/dL, rendering an increased risk of CNS depression.

Fomepizole, however, is a strong competitive inhibitor of the ADH enzyme gradually replacing ethanol as the antidote of choice.[3,12] Its pharmacokinetics has been extensively studied,[3,19–22] showing that fomepizole is efficient[22–24]: *in vitro*, it has been shown to have approximately 80,000 and 8000 times greater affinity for human ADH than methanol and ethanol, respectively.[25] According to the studies performed, there is no reason to believe that differs much from *in vivo* (see above), and a serum fomepizole level of 10 μmol/L is thought to be sufficient.[25] In addition, fomepizole provides a longer ADH inhibition, and it can be given every 12 h, making it easier to administer. There is no need for monitoring of the S-level, and it is without many of the side-effects of ethanol,[1] but it is expensive.[4,5,26,27] Fomepizole may also be given orally in the same doses as for i.v. administration.[28]

Hemodialysis

Methanol poisoning is one of the few conditions in clinical toxicology where hemodialysis still plays an important role.[29] Hemodialysis or peritoneal dialysis has since 1960 been used to increase the elimination of methanol and formic acid, as well as correcting the metabolic acidosis in methanol poisoning. Later, the superiority of hemodialysis over peritoneal dialysis was accepted,[3,10,30] and the different indications for hemodialysis came into focus. In 1965, Erlanson, *et al.*[31] suggested that patients with obvious toxicity (coma, ocular signs, and acidosis) should receive hemodialysis. Later, in 1978, Gonda, *et al.*[32] suggested hemodialysis when *S*-methanol was above 50 mg/dL. In 1986, Jacobsen and McMartin[10] suggested the following indications for hemodialysis: any degree of visual impairment, severe metabolic acidosis (base deficit >15 mmol/L or anion gap >30 mmol/L), blood methanol concentrations above 20 mmol/L (60 mg/dL), or consumption of more than 40 mL by adults. The latter suggestion has been left relatively unchanged until recently, when fomepizole has become the antidote of choice, and some authors have questioned the proposed indications.[1,3–5]

Methods

Evaluation of the current literature compared with our own experiences from two methanol outbreaks in Norway[33,34] and one in Estonia.[9] The literature search on the topic was done through PubMed®. The search was done for the keywords "methanol poisoning, hemodialysis, antidote." A selection was then drawn based on the authors' reading a summary of these articles, whereas citations from the above articles were searched one by one.

Results

Hemodialysis and methanol

The efficacy of dialysis in removing methanol was reported already in the early sixties by Marc-Aurele, *et al.*[35] and Austin, *et al.*[29] Since then, its efficacy has been documented in several smaller and larger studies.[5,15,32,36] However, except for a few recent studies[1,4,6] and case reports,[37] they have all used ethanol as the antidote. Although the META-study on fomepizole by Brent, *et al.*[1] included dialyzed patients, their treatment protocols were still based on the dialysis indications from the time when ethanol was the only antidote in use.[12] Megarbane, *et al.*[6] have recently raised the question of whether fomepizole obviates the need for hemodialysis, and a later study challenged the triage based on ethanol as the antidote: In the 17 patients studied, there was a high methanol elimination during hemodialysis[5] compared with previous studies.[11,15] The median half-life of *S*-methanol during hemodialysis was 2.5 h (range 1.7–3.3 h). This high elimination rate may best be explained by the larger surface area of the dialyzer and higher blood flow used in that series (1.8 m^2, 250 mL/min) compared with previous studies (1.6 m^2, 200 mL/min)[15]. The half-life of methanol during hemodialysis was significantly shortened compared with the mean

half-life of 52 h reported in eight patients treated with fomepizole only.[27]

Hemodialysis and formate

The role of dialysis has been questioned regarding the elimination of formate. Removal of formate with dialysis as such is an efficient process,[11,38] but questions have been raised regarding the effect of dialysis versus the short endogenous half-life of formate often reported. Kerns, *et al.*[2] claimed that dialysis seems to have a limited role in the acidemic patient with no detectable methanol, based on a non-significant difference in endogenous elimination and elimination during dialysis. Even though they do emphasize an important point, their study has several weaknesses: first, they rely their calculation of half-life before dialysis on only two data points in two of five cases where dialysis was performed, and on three data points (which is usually considered the lowest reliable number) in the three last cases. Second, two of the patients have a longer half-life of formate during dialysis than without dialysis (79 and 94 min vs 149 and 162 min, respectively). This contradicts all earlier findings, and especially the case with the shortest half-life and only two data points on the pre-dialysis calculation, should probably not have been used to calculate the mean values of the whole group as such. As also commented on,[39] there was a variable blood flow during dialysis in two patients that undermines the validity of these kinetic studies. Finally, the fact that dialysis also plays an important role in correcting acidosis is not accounted for in the conclusion.

In four of the seven patients in the recent study from Oslo, the mean half-life of formate during dialysis was calculated to 1.7 h[5] vs 2.6 h without dialysis in three patients in another series of patients.[27] Again, the benefit may seem marginal, but this is a complex issue: first, the patients where formate kinetics was performed *during* dialysis were more severely poisoned. That means they were more acidotic on admission, and hence the endogenous formate half-life in these patients would most probably be significantly longer without dialysis.[27] Therefore, the role of dialysis also in removing formate most probably becomes more important the more acidotic the patient is because the intrinsic clearance of formate then decreases. Second, their clinical condition as a group was worse, as could also be their ability to eliminate formate without dialysis.

The inter-individual variation of formate elimination may also be of a greater variation than earlier thought. Animal studies have shown that formate elimination is slower with time as the liver gradually becomes folate deficient.[40] The half-life of formate in methanol-poisoned patients usually varies between 2.5 and 5 h.[2,27,41] However, a report from 2005 described three patients with half-lives between 7.8 and 12.5 h.[42] 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. Furthermore, 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.[42] In a case report from 1984, a child was found to have a formate half-life about 20 h, but the metabolism of methanol was not completely blocked; hence, formate was still produced and so the half-life was not valid.[43]

The most recent case report found a serum half-life of formate of 77 h, which represents without comparison the longest serum half-life of formate ever reported.[44] 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, *S*-fomepizole levels in this patient were measured and found within the therapeutic range (>10 μmol/L)[1] during the treatment period.[44] Lack of efficiency with therapeutic S-levels has never been described before in any cases of fomepizole use. Furthermore, in this particular patient the metabolism of methanol seemed to be blocked because the elimination half-life of methanol was of the expected magnitude (50 h) and because the elimination of methanol appeared slower after fomepizole administration (Figure 1). In addition, earlier studies have confirmed the efficacy of fomepizole when these recommended doses are given,[1,27] and the fomepizole kinetics are very stable.[1]

Hemodialysis and antidotes

As seen above, 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. Of those few, three were case reports,[7,24,45] one were retrospective and in lack of formic acid analyzes,[4] and although the phase III study leading to the FDA-approval of fomepizole in methanol

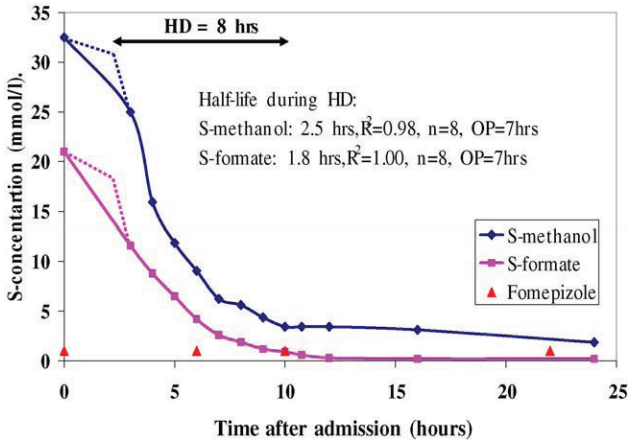

Figure 1 Example of kinetics with early hemodialysis. Reproduced with permission from Hovda, *et al.*[5] The dotted line represents the expected elimination curve (no samples were drawn in the actual time period). HD, hemodialysis; OP, observation period.

poisoning included dialyzed patients, they were all dialyzed according to the traditional dialysis indications from the time when ethanol was the only antidote (*S*-methanol above 50 or 60 mg/dL). Furthermore, this study was designed to evaluate the safety of fomepizole, and not the dialysis indication.[1] The only prospective study performed to evaluate the indication was performed in 2002–2004, and it included seven patients.[5]

Both ethanol [molecular weight (MW) 46][10,31] and fomepizole (MW 82)[46] are small, and hardly protein bound, hence readily eliminated by hemodialysis. Their elimination patterns are, however, different: Although *S*-ethanol varies a great deal with time, both inter- and intra-individually, *S*-fomepizole is more predictable. Increased ethanol administration [16,17] or the addition of 95% ethanol to the dialysate [31,47,48] is necessary to counteract its loss during dialysis. In the study by Hantson, *et al.*,[18] 20 of 26 required hemodialysis, of whom 13 of 20 (65%) had a blood level below the therapeutic limit in *two* consecutive blood samples during hemodialysis. Close monitoring of the *S*-ethanol therefore remains important. Increased doses of fomepizole is also necessary during the procedure,[46] but an increased infusion to 1–1.5 mg/kg/h[49] or dosing fomepizole every 4 h instead of every 12 h is sufficient. There is no need for additional monitoring of the *S*-fomepizole level. Whether antidote is necessary at all during hemodialysis may also be questioned,[1] at least in moderately poisoned patients without visual disturbances.

Administration of antidote should continue for several hours after the cessation of dialysis to protect from potential rebound of the *S*-methanol concentration.[12] Redistribution of 20 mg/dL may occur,[36] although most reports does not describe this phenomenon.[10]

Elective hemodialysis

Most reports and all the guidelines on methanol and hemodialysis are made upon the basis of ethanol as an antidote. However, the efficacy and side-effect profile of fomepizole, in addition to the fact that monitoring of the serum-level of fomepizole is unnecessary, result in an almost outpatient status for many of the patients.[4,6]

Figures 1 and 2[5] illustrate the principles of acute versus delayed hemodialysis. In Figure 1, early dialysis shows a rapidly decreasing serum concentration of both methanol and formate, visualizing the efficacy of the procedure, whereas Figure 2 shows an example of delayed dialysis. Pay attention to the slow elimination of methanol before hemodialysis is initiated, explained by the effective inhibition of the metabolizing ADH enzyme by fomepizole, whereas the elimination increases dramatically with dialysis. Formate, however, is in this patient at an almost endogenous level throughout the whole treatment period, making the patient asymptomatic. That gives the treating physician the option of waiting until there is dialyzing equipment or personnel available, the patient can easily be transported to a different facility, or dialysis can be avoided, provided one is willing to deal with the cost of prolonged fomepizole administration.

The potential benefit of using fomepizole as an antidote during dialysis was addressed in a recent study from Norway,[5] to possibly change indications and triage.

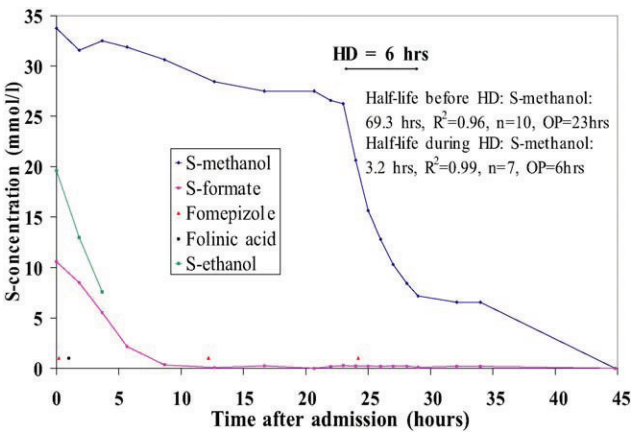

Figure 2 Example of kinetics with delayed hemodialysis. HD, hemodialysis; OP, observation period. Reproduced with permission from Hovda, *et al.*[5]

1) During large outbreaks, there might be *capacity problems*.
2) Because dialysis is an invasive procedure with risk of complications both in adults[50] and children,[51] treatment with dialysis has a *safety aspect*.
3) Change of indication has a *practical consequence* because of the availability of dialyzing facilities.
4) There is an *economical aspect* related to dialysis versus the cost of fomepizole:

   - Hemodialysis is not available everywhere, and transport to dialysis facilities has economical (and safety) implications.
   - HD is not for free; whereas it does not affect the total *calculation* in countries with public health care, the use of HD is charged separately in the countries with private health care, showing the extra cost of the procedure.
   - Fomepizole is also eliminated during dialysis. This makes dosing every fourth hour instead of every twelfth hour necessary during the procedure, increasing the use of fomepizole during the early part of the treatment.
   - Potential adverse effects related to the fact that hemodialysis is an invasive treatment may have economical, and not only medical aspects.
   - Patients are not drunk as they are during the ethanol treatment; patient care is therefore easier and need for extra nursing personnel is less likely, which further represents an economical benefit.
   - Most patients can be treated outside the intensive care unit, or only need a brief stay. This is probably most important as also suggested by others.[6] None of the three patients treated with elective hemodialysis in the series from Norway needed treatment in the intensive care unit.

Comments/discussion

The severity and outcome of methanol poisoning are correlated to the degree of metabolic acidosis and the toxic effects of formate, and not to the *S*-methanol, provided early start of treatment.[12,15,52–56] This is illustrated in one article[27] where two patients have by far the highest methanol concentrations, but no clinical features because little methanol was metabolized to formic acid. The early acidosis is due to the production of formic acid, with lactic acid production occurring in the later stages of poisoning most probably because of tissue hypoxia caused by formate uncoupling of cytochrome oxidase in the mitochondrias.[3,57,58] 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. Because of their small molecular weight, small volume of distribution, and lack of protein binding, both methanol and formate are easily dialyzed.[11,15]

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 toxic agent from the body.[2] The elimination of formate may be quite variable, and some authors have therefore questioned the conclusion in the former study.[39] Interestingly, in two patients dialysis was calculated to represent 54% and 82% of the total body clearance.[27] However, because the magnitude of the volume of distribution of formate is based on studies in only one patient,[11] such calculations are uncertain. The variability of the endogenous elimination of formate may in part be explained by its variable renal excretion as also reported in the same patients[27] and in patients not undergoing dialysis.[27] 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 of dialysis in removing formate most probably becomes more important the more acidotic the patient is because the intrinsic clearance of formate then decreases.[27]

We have recently published a fatal case report of a 63-year-old male presenting with a severe metabolic acidosis following methanol poisoning. Because of profound hypotension, he was not treated with HD before 17 h after admission. In spite of aggressive buffer and antidote treatment, the metabolic acidosis was not corrected before the HD was performed. According to his *S*-methanol half-life, methanol metabolism seemed to be blocked, supported by repeated analyzes of *S*-fomepizole showing therapeutic serum concentrations. In spite of that, he had extremely slow formate elimination with a half-life of 77 h (!).[44] This case report indicates that the individual differences in formate elimination may be of a greater variance than earlier thought, and it pinpoints the difficulty in giving an exact threshold for HD/non-HD regarding the metabolic acidosis. Methanol poisoning is a potentially fatal situation that requires thorough evaluation of each individual patient.

In the seven patients studied closely with the use of dialysis and fomepizole, the established recommendations of early dialysis regardless of clinical condition were challenged.[5] Early hemodialysis was performed in four and later "elective" dialysis in three patients. Two of three from the latter group also had the highest *S*-methanol. The procedure of "elective" dialysis was found safe.[5] On the basis of that data and theoretical considerations,[6] the indications for hemodialysis in methanol poisoning using fomepizole as the antidote may therefore be separated into two categories:

1) The critically ill patient, with severe metabolic acidosis (base deficit >15 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.[12,13] The removal of methanol *per se* is not reducing morbidity or mortality in this setting because fomepizole prevents further production of formic acid.
2) The stable patient, with little to moderate metabolic acidosis (base deficit <15 mM) 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 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 in adequate doses.

There is no study or international consensus on the term severe metabolic acidosis, but in clinical practice a base deficit ranging from 10 to 20 mM is often used. We have based our recommendations for separating the clinical criteria made in this review on experience from two different recent outbreaks of methanol poisonings in Estonia (1) and Norway (2). In these studies, the median base deficit among the patients who survived without sequelae was 21 and 18 mM, respectively. The median base deficit among the patients who died was 29 and 28 mM, and all the patients who died in Norway had a base deficit >22 mM. On the basis of these data, a base deficit below/above 15 mM seems to be a safe threshold for dialysis. Decision on not to dialyze also requires a stable patient, immediate start of other treatment (alkali and fomepizole), and no presence of visual disturbances.

We suggest that patients with a serum methanol level of >32 mM (>100 mg/dL) also should be considered for dialysis from a practical and economical point of view. The serum level is arbitrary, and it has no implication for the prognosis. It is based solely on the long half-life of methanol (50–80 h) and hence a long elimination time (five times the half-life).

Conclusion

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 without severe metabolic acidosis. Nevertheless, when patients are admitted late 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. Because these patients are in general awake and sober, this decision may preferably be discussed with the patient.

References

1 Brent, J, McMartin, K, Phillips, S, Aaron, C, Kulig, K. Methylpyrazole for Toxic Alcohols Study Group. Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 2001; **344**: 424–429.
2 Kerns, W, Tomaszewski, C, McMartin, K, Ford, M, Brent, J. META Study Group. Methylpyrazole for toxic alcohols. Formate kinetics in methanol poisoning. *J Toxicol Clin Toxicol* 2002; **40**: 137–143.
3 Jacobsen, D, McMartin, KE. Antidotes for methanol and ethylene glycol poisoning. *J Toxicol Clin Toxicol* 1997; **35**: 127–143.
4 Megarbane, B, Borron, SW, Trout, H, Hantson, P, Jaeger, A, Krencker, E, *et al*. Treatment of acute methanol poisoning with fomepizole. *Intensive Care Med* 2001; **27**: 1370–1378.
5 Hovda, KE, Froyshov, S, Gudmundsdottir, H, Rudberg, N. Fomepizole may change the indication for HD in methanol poisoning: prospective study in 7 cases. *Clin Nephrol* 2005; **64**: 190–197.

6 Megarbane, B, Borron, SW, Baud, FJ. Current recommendations for treatment of severe toxic alcohol poisonings. *Intensive Care Med* 2005; **31**: 189–195.
7 Bekka, R, Borron, SW, Astier, A, Sandouk, P, Bismuth, C, Baud, FJ. Treatment of methanol and isopropanol poisoning with intravenous fomepizole. *J Toxicol Clin Toxicol* 2001; **39**: 59–67.
8 Mycyk, MB, DesLauriers, C, Metz, J, Wills, B, Mazor, SS. Compliance with poison center fomepizole recommendations is suboptimal in cases of toxic alcohol poisoning. *Am J Ther* 2006; **13**: 485–489.
9 Paasma, R, Hovda, KE, Tikkerberi, A, Jacobsen, D. Methanol mass poisoning in Estonia: outbreak in 154 patients. *Clin Toxicol (Phila)* 2007; **45**: 152–157.
10 Jacobsen, D, McMartin, KE. Methanol and ethylene glycol poisonings. Mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol* 1986; **1**: 309–334.
11 Jacobsen, D, Ovrebo, S, Sejersted, OM. Toxicokinetics of formate during hemodialysis. *Acta Med Scand* 1983; **214**: 409–412.
12 Barceloux, DG, Bond, GR, Krenzelok, EP, Cooper, H, Vale, JA. American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol* 2002; **40**: 415–446.
13 Liesivuori, J, Savolainen, H. Methanol and formic acid toxicity: biochemical mechanisms. *Pharmacol Toxicol* 1991; **69**: 157–163.
14 Roe, O. Methanol poisoning: its clinical course, pathogenesis and treatment. *Acta Med Scand* 1946; **126**: 1–253.
15 Jacobsen, D, Jansen, H, Wiik-Larsen, E, Bredesen, JE. Studies on methanol poisoning. *Acta Med Scand* 1982; **212**: 5–10.
16 Kruse, JA. Methanol poisoning. *Intensive Care Med* 1992; **18**: 391–397.
17 McCoy, HG, Cipolle, RJ, Ehlers, SM, Sawchuk, RJ, Zaske, DE. Severe methanol poisoning. Application of a pharmacokinetic model for ethanol therapy and hemodialysis. *Am J Med* 1979; **67**: 804–807.
18 Hantson, P, Wittebole, X, Haufroid, V. Ethanol therapy for methanol poisoning: duration and problems. *Eur J Emerg Med* 2002; **9**: 278–279.
19 Jacobsen, D, Sebastian, CS, Barron, SK, Carriere, EW, McMartin, KE. Effects of 4-methylpyrazole, methanol/ethylene glycol antidote, in healthy humans. *J Emerg Med* 1990; **8**: 455–461.
20 Jacobsen, D, Barron, SK, Sebastian, CS, Blomstrand, R, McMartin, KE. Non-linear kinetics of 4-methylpyrazole in healthy human subjects. *Eur J Clin Pharmacol* 1989; **37**: 599–604.
21 Jacobsen, D, Sebastian, CS, Blomstrand, R, McMartin, KE. 4-Methylpyrazole: a controlled study of safety in healthy human subjects after single, ascending doses. *Alcohol Clin Exp Res* 1988; **12**: 516–522.
22 McMartin, KE, Hedström, KG, Tolf, BR, Ostling-Wintzell, H, Blomstrand, R. Studies on the metabolic interactions between 4-methylpyrazole and methanol using the monkey as an animal model. *Arch Biochem Biophys* 1980; **199**: 606–614.
23 Blomstrand, R, Ingemansson, SO, Jensen, M, Hedstrom, CG. Normal electroretinogram and no toxicity signs after chronic and acute administration of the alcohol dehydrogenase inhibitor 4-methylpyrazole to the cynomolgus monkey (Macaca fascicularis) – a possible new treatment of methanol poisoning. *Drug Alcohol Depend* 1984; **13**: 9–20.
24 Burns, MJ, Graudins, A, Aaron, CK, McMartin, K, Brent, J. Treatment of methanol poisoning with intravenous 4-methylpyrazole. *Ann Emerg Med* 1997; **30**: 829–832.
25 Pietruszko, R. Human liver alcohol dehydrogenase – inhibition of methanol activity by pyrazole, 4-methylpyrazole, 4-hydroxymethylpyrazole and 4-carboxypyrazole. *Biochem Pharmacol* 1975; **24**: 1603–1607.
26 Wallemacq, PE, Vanbinst, R, Haufroid, V, Di Fazio, V, König, J, Detaille, T, *et al*. Plasma and tissue determination of 4-methylpyrazole for pharmacokinetic analysis in acute adult and pediatric methanol/ethylene glycol poisoning. *Ther Drug Monit* 2004; **26**: 258–262.
27 Hovda, KE, Andersson, KS, Urdal, P, Jacobsen, D. Methanol and formate kinetics during treatment with fomepizole. *Clin Toxicol* 2005; **43**: 221–227.
28 Marraffa, JF, *et al*. Oral administration of fomepizole produces similar blood levels as identical intravenous dose. *Clin Toxicol* 2008; **46**: 181–186.
29 Austin, WH, Lape, CP, Burnham, HN. Treatment of methanol intoxication by hemodialysis. *N Engl J Med* 1961; **265**: 334.
30 Keyvan-Larijarni, H, Tannenberg, AM. Methanol intoxication. Comparison of peritoneal dialysis and hemodialysis treatment. *Arch Intern Med* 1974; **134**: 293–296.
31 Erlanson, P, Fritz, H, Hagstam, KE, Liljenberg, B, Tryding, N, Voigt, G. Severe methanol intoxication. *Acta Med Scand* 1965; **177**: 393–408.
32 Gonda, A, Gault, H, Churchill, D, Hollomby, D. Hemodialysis for methanol intoxication. *Am J Med* 1978; **64**: 749–758.
33 Sejersted, OM, Jacobsen, D, Ovrebo, S. Methanol poisoning. *Lancet* 1981; **2**: 1426.
34 Hovda, KE, Hunderi, OH, Tafjord, A-B, Dunlop, O, Rudberg, N, Jacobsen, D. Methanol outbreak in Norway 2002–2004. Epidemiology, clinical features and prognostic signs. *J Intern Med* 2005; **258**: 181–190.
35 Marc-Aurele, J, Schreiner, GE. The dialysance of ethanol and methanol: a proposed method for the treatment of massive intoxication by ethyl or methyl alcohol. *J Clin Invest* 1960; **39**: 802–807.
36 Swartz, RD, Millman, RP, Billi, JE, Bondar, NP, Migdal, SD, Simonian, SK, *et al*. Epidemic methanol poisoning: clinical and biochemical analysis of a recent episode. *Medicine (Baltimore)* 1981; **60**: 373–382.
37 Lushine, KA, Harris, CR, Holger, JS. Methanol ingestion: prevention of toxic sequelae after massive ingestion. *J Emerg Med* 2003; **24**: 433–436.
38 McMartin, KE, Ambre, JJ, Tephly, TR. Methanol poisoning in human subjects. Role for formic acid accumulation in the metabolic acidosis. *Am J Med* 1980; **68**: 414–418.
39 Yip, L, Jacobsen, D. Endogenous formate elimination and total body clearance during hemodialysis. *J Toxicol Clin Toxicol* 2003; **41**: 257–258.
40 Makar, AB, Tephly, TR. Methanol poisoning in the folate-deficient rat. *Nature* 1976; **261**: 715–716.

41 Moore, DF, Bentley, AM, Dawling, S, Hoare, AM, Henry, JA. Folinic acid and enhanced renal elimination in formic acid intoxication. *J Toxicol Clin Toxicol* 1994; **32**: 199–204.
42 Hantson, P, Haufroid, V, Wallemacq, P. Formate kinetics in methanol poisoning. *Hum Exp Toxicol* 2005; **24**: 55–59.
43 Shahangian, S, Robinson, VL, Jennison, TA. Formate concentrations in a case of methanol ingestion. *Clin Chem* 1984; **30**: 1413–1414.
44 Hovda, KE, Mundal, H, Urdal, P, McMartin, K, Jacobsen, D. Extremely slow formate elimination in severe methanol poisoning: a fatal case report. *Clin Toxicol* 2007; **45**: 516–521.
45 Brown, MJ, Shannon, MW, Woolf, A, Boyer, EW. Childhood methanol ingestion treated with fomepizole and hemodialysis. *Pediatrics* 2001; **108**: E77.
46 Jacobsen, D, Östensen, J, Bredesen, L, Ullstein, E, Mc Martin, KE. 4-Methylpyrazole (4-MP) is effectively removed by haemodialysis in the pig model. *Hum Exp Toxicol* 1996; **15**: 494–496.
47 Chow, MT, Di Silvestro, VA, Yung, CY, Nawab, ZM, Leehey, DJ, Ing, TS. Treatment of acute methanol intoxication with hemodialysis using an ethanol-enriched, bicarbonate-based dialysate. *Am J Kidney Dis* 1997; **30**: 568–570.
48 Doral, M, Pichette, V, Cardinal, J, Geadah, D, Ouimet, D, Leblanc, M. The use of an ethanol- and phosphate-enriched dialysate to maintain stable serum ethanol levels during haemodialysis for methanol intoxication. *Nephrol Dial Transplant* 1999; **14**: 1774–1777.
49 Faessel, H, Houze, P, Baud, FJ, Scherrmann, JM. 4-methylpyrazole monitoring during haemodialysis of ethylene glycol intoxicated patients. *Eur J Clin Pharmacol* 1995; **49**: 211–213.
50 Pond, SM. Extracorporeal techniques in the treatment of poisoned patients. *Med J Aust* 1991; **154**: 617–622.
51 Ellis, EN, Pearson, D, Belsha, CW, Berry, PL. Use of pump-assisted hemofiltration in children with acute renal failure. *Pediatr Nephrol* 1997; **11**: 196–200.
52 Meyer, RJ, Beard, ME, Ardagh, MW, Henderson, S. Methanol poisoning. *N Z Med J* 2000; **113**: 11–13.
53 Liu, JJ, Daya, MR, Carrasquillo, O, Kales, SN. Prognostic factors in patients with methanol poisoning. *J Toxicol Clin Toxicol* 1998; **36**: 175–181.
54 Mahieu, P, Hassoun, A, Lauwerys, R. Predictors of methanol intoxication with unfavourable outcome. *Hum Toxicol* 1989; **8**: 135–137.
55 Bennett, JL, Cary, FH, Mitchell, GL, Cooper, MN. Acute methyl alcohol poisoning: a review based on experiences in an outbreak of 323 cases. *Medicine (Baltimore)* 1953; **32**: 431–463.
56 Hammoudeh, M, Snoudou, H. Methanol poisoning from cologne ingestion. *Saudi Med J* 1988; **9**: 412–415.
57 Sejersted, OM, Jacobsen, D, Ovrebo, S, Jansen, H. Formate concentrations in plasma from patients poisoned with methanol. *Acta Med Scand* 1983; **213**: 105–110.
58 Hovda, KE, Hunderi, OH, Rudberg, N, Froyshov, S, Jacobsen, D. Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. *Intensive Care Med* 2004; **30**: 1842–1846.