

Online Supplement

Influence of ECTR on the elimination of formate

A potential benefit of ECTR is enhanced elimination of formate with the aim of decreasing end-organ damage. However, the effect of ECTR for enhancing the elimination of formate is less convincing than that of methanol. The mean half-life of formate during ECTR is 2-3 hours, range 0.6-10.3 hours, Table 3 (1-11). A recent study noted that the elimination half-life during intermittent hemodialysis (IHD) was significantly shorter than continuous modalities (median 1.6 vs 3.6 hours, $P < 0.001$) (12). The endogenous apparent elimination half-life of formate is 1.2-12.5 hours, commonly < 5.0 hours. However, endogenous elimination may be saturable or influenced by various factors, including blood pH, adequacy of ADH inhibition, availability of folic/folinic acid and potentially kidney function (1-3, 13-15). For example, in a fatal case the apparent elimination half-life of formate was 77 hours without ECTR or ethanol (16). Given inter-individual variability in the endogenous elimination of formate, the contribution of an extracorporeal therapy may not be significantly shorter than the endogenous half-life noted in many cases (2) so the overall benefit may be limited.

Economic considerations with the use of ECTR in asymptomatic methanol poisoning

The use of ECTR for the treatment of asymptomatic methanol poisoning may be economically favorable and practical (17), which is discussed further in the Online Supplement. This is because the duration of medical treatment using ethanol (or fomepizole) is proportional to the initial methanol concentration. Given the prolonged half-life of methanol in the context of ADH blockade, this may require treatment for several days in the absence of ECTR, as demonstrated in online supplement, Figure S2. This relationship was confirmed in a clinical study where a therapeutic ethanol concentration was required for more than 10 days in some patients without significant acidemia

who did not receive ECTR (18). ECTR decreases the apparent half-life of methanol to approximately 3 hours, thereby shortening the duration of admission and antidote therapy and its associated costs and risks, as illustrated in online supplement, Figure S3.

The relationships shown in online Supplement Figures S2 and S3 are likely to oversimplify the clinical reality given inter-individual differences in the toxicokinetics of methanol and formate. Although the mean apparent elimination half-life of methanol is 54 hours (13, 19, 20), it may vary between 9 and 87 hours (4, 13, 15, 19-28). This variability may reflect any or a combination of dose-dependency (13, 23, 29), uncharacterized inter-individual variability in toxicokinetics (30), prolonged or variable absorption, or inaccuracies based on calculations from two blood samples. Therefore, treatment decisions may be supported by quantifying the apparent elimination half-life of methanol in an individual patient prior to commencing ECTR. This may provide a better estimate of the anticipated duration of therapy if ECTR is not used. For example, in the first instance methanol concentrations can be collected daily and the rate of decline can be determined.

EXTRIP definition of impaired kidney function

From the perspective of poison clearance, EXTRIP defines impaired kidney function to include:

- Advanced stage 3, 4 or 5 chronic kidney disease (i.e. $eGFR < 45 \text{ mL/min/1.73 m}^2$), or
- KDIGO Stage 2 (doubling of creatinine from baseline within 7 days) or 3 acute kidney injury, or
- In the absence of a baseline serum creatinine, 2 mg/dL (176 $\mu\text{mol/L}$) in adults, or 1.5 mg/dL (132 $\mu\text{mol/L}$) in elderly patients or those with low muscle mass, or
- In children with no baseline creatinine, a serum creatinine greater than twice the upper limit of normal for age and gender, or

- The presence of oligo/anuria should raise awareness of impaired kidney function, regardless of serum creatinine concentration.

Effect of differing types of extracorporeal methods on methanol clearance

Intermittent hemodialysis (IHD) is associated with higher methanol clearances compared to continuous modalities, and in particular compared to peritoneal dialysis where clearance (based on the half-life during therapy) was highly variable, see Table 3. Methanol and formate were initially dialyzable by sorbent hemoperfusion in a single case (9), but this was non-sustained and did not correct acidemia, so it is not recommended by EXTRIP.

Other methods such as therapeutic plasma exchange, exchange transfusion or peritoneal dialysis are not recommended for the treatment of methanol poisoning (all Grade 1D; plasmapheresis: median=1, UIQ=1, DI=0; exchange transfusion: median=1, UIQ=2, DI=0.02; peritoneal dialysis: median=1, UIQ=2, DI=0.13). Although peritoneal dialysis may allow a high clearance or short plasma half-life of methanol, this is technically demanding and may not be tolerated (31). For example, peritoneal dialysate must be exchanged at 6 L/hour to achieve a plasma half-life of 3 hours (similar to that achieved by IHD), while a 2-2.5 L/hour exchange produces a half-life of 8 hours which is comparable to that from continuous modalities (31).

Solute clearance varies with components of the extracorporeal modality, including blood and dialysate/filtrate flows, and the filter size and duration (32). This explains differences in methanol elimination between IHD and continuous modalities (table 3), but also within a modality (12). Therefore, it is possible that elimination of methanol achieved by these extracorporeal modalities may change as these technical components are varied, or with new technology.

Predicting the required duration of ECTR based on the admission methanol concentration

The duration of ECTR may be predicted by determining the admission methanol concentration (if available) and calculating the time required to reach the <200 mg/L (6.2 mmol/L) target concentration using an elimination half-life of 3 hours (in the case of intermittent hemodialysis, Table 3). Other methods for estimating the duration of ECTR are also described (33-35).

Voting items for which consensus was not obtained

Voting was neutral for the use of intracerebral hemorrhage (ICH) on imaging (Grade 3D; median=5.5) as an indication or contraindication. Reasons expressed included the inability of ECTR to reverse this complication, the potential for the bleeding to progress if anticoagulation is used, and concerns about whether this is a marker of severe neurological injury from which recovery is unlikely regardless of the treatment. Further, it is not known if ECTR itself increases the occurrence of ICH because the literature is biased by indication, where ICH is a marker of severe poisoning and ECTR is frequently performed in such cases. Some authors consider the presence of ICH to be a contraindication to ECTR (36). An ICH can expand during ECTR, although less so if continuous modalities are used or if the IHD technical prescription is adjusted to involve shorter and more frequent treatments, slower blood and dialysate flow rates and a higher sodium concentration in the dialysate (37).

No agreement was reached on whether lethargy, ataxia and dysarthria were indications for ECTR because they were not sufficiently reliable features of significant methanol poisoning and they are not life-threatening.

Future research questions

No studies were located in which determination of the merits of monitoring for resolution of acidemia following antidote therapy and sodium bicarbonate prior to commencing ECTR, compared to prompt initiation of ECTR. Therefore, criteria for when ECTR offers benefits over administration of bicarbonate or other buffers are not defined. Although ECTR is a convenient, practical and safe option in many contexts, this may not always be the case; for example, if it requires transfer to another treatment center. In the unfortunate event of an epidemic, there are often more patients with poisoning than there are ECTR resources, so the triage of patients on the basis of likely benefit is necessary. The response to bicarbonate was an indication for ECTR in the META study, as follows: a decrease in the arterial pH of more than 0.05 unit, if pH cannot be kept above 7.3, or a decrease in the serum bicarbonate concentration of more than 5 mmol/L, despite bicarbonate supplementation (20). This specific indication has not been validated, but this approach is appealing due to its simplicity so further research is warranted to determine whether the response to bicarbonate therapy can differentiate patients requiring urgent ECTR from others. It is also necessary to determine the dose of bicarbonate that will maximize effects without inducing adverse reactions such as pulmonary edema and hypernatremia. This approach to triage and therapy may also have economic and practical implications.

According to a single small study, hemodialysis did not significantly increase the clearance of formate in patients with methanol poisoning (2). However, there was controversy regarding this conclusion (14) and there is marked variability in formate kinetics, as already discussed. It would be useful if future observational studies could confirm this observation, or determine circumstances when ECTR will significantly increase the clearance of formate. Similarly, data regarding clearance using continuous or hybrid ECTR modalities (for example, sustained low-efficiency dialysis) are

extremely limited so this information is also required. Future studies should also explore the effect of these various forms of ECTR on methanol clearance as data regarding the influence on clearance of the dialysis prescription (eg. changes in blood flow, ultrafiltration and dialysate flow), are also limited (see table 3).

We have referred to the difficulty with determining the duration of ECTR in the absence of methods to estimate the concentration of methanol (or an OG, which has other limitations). Research exploring decisions based around the concentration of formate, or a surrogate measure such as base excess, would be useful (38). This may guide decisions for starting and stopping ECTR, and also for the occurrence of rebound toxicity with subtherapeutic ADH blockade.

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											CNS toxicity
Renal failure				Oliguria							
Visual symptoms											
Osmolal gap		"very high"			10			If HAGMA			
Other end organ dysfunction											
Progressive deterioration											Despite supportive measures
Exposure				20-40 mL					>30 mL		
[Methanol]	500 mg/L if no	500 mg/L	500 mg/L	500 mg/L	500 mg/L	500 mg/L if no	500 mg/L		200 mg/L	500 mg/L	500 mg/L

	fomepizole					fomepizole					
[Formate]		"Very high"		200 mg/L							
Other											Severe electrolyte imbalance; a desire to shorten the duration of the poisoning

BE, base excess; AG, anion gap; HCO₃, bicarbonate; CNS, central nervous system; AACT, American Association of Clinical Toxicology; HAGMA, high anion gap metabolic acidosis

Black = recommended; grey = relative indication

Table S2. Role of ECTR in the treatment of a patient with methanol poisoning, including summary statistics of the votes.

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|---|
| <p>1) Severe methanol poisoning (Grade 1D; Median=9, LIQ=8, DI=0), including any of:</p> <ul style="list-style-type: none">a) Coma (Grade 1D; median=8, LIQ=7, DI=0.3)b) Seizures (Grade 1D; median=8, LIQ=7, DI=0.3)c) New vision deficits (Grade 1D; median=9, LIQ=8, DI=0.1)d) Metabolic acidosis from methanol poisoning<ul style="list-style-type: none">i) Blood pH ≤ 7.15 (Grade 1D; median=8, LIQ=7, DI=0.16)ii) Persistent metabolic acidosis despite adequate supportive measures and antidotes (Grade 1D; median=9, LIQ=8, DI=0.1)e) Serum anion gap higher than 24 mmol/L (Grade 1D; median=9, LIQ=7, DI=0.29); calculated by serum $[\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$. |
| <p>2) Serum methanol concentration</p> <ul style="list-style-type: none">a) Greater than 700 mg/L or 21.8 mmol/L in the context of fomepizole therapy (Grade 1D; median=7.5, LIQ=7, DI=0.29)b) Greater than 600 mg/L or 18.7 mmol/L in the context of ethanol treatment (Grade 1D; median=8, LIQ=7, DI=0.29)c) Greater than 500 mg/L or 15.6 mmol/L in the absence of an ADH blocker (Grade 1D; median=9, LIQ=7.25, DI=0.13)d) In the absence of a methanol concentration, the osmolal/osmolar gap may be informative (Grade 1D) |

3) In context of impaired kidney function (Grade 1D; median=8, LIQ=7, DI=0.3)

To optimize the outcomes from ECTR, we recommend:

- 4) Intermittent hemodialysis is the modality of choice in methanol poisoning (Grade 1D; median=9, LIQ=9, DI=0). Continuous modalities are acceptable alternatives if intermittent hemodialysis is not available (Grade 1D; median=7, LIQ=7, DI=0.13).
- 5) ADH inhibitors are to be continued during ECTR for methanol poisoning (Grade 1D; median=9, LIQ=8, DI=0.13); as well as folic acid.
- 6) ECTR can be terminated when the methanol concentration is <200 mg/L or 6.2 mmol/L and a clinical improvement is observed (Grade 1D; median=7, LIQ=7, DI=0.16).

Table S3. Non-randomized controlled clinical studies *

Study	N= (I,C)	Exposure	ECTR	Allocation method	Baseline	Outcomes
Keyvan-Lariyami 1973, USA (43)	3,3	Acute misuse	HD,PD	Cohort (simultaneous ingestion); hospital of presentation	HD: pH 7.17; meth 1530 mg/L; VD 2 PD: pH 7.09; meth 1850 mg/L; VD: 1, 2 unk	HD: all recovered PD: 1 death (infection, AKI); VD 1
Puka 1973, Poland (44)	12,22	22 misuse, 12 DSP	PD	Retrospective, biased by indication: Meth concentration, severity of poisoning.		4 deaths, 1 VD
Swartz 1981, USA (26)	13,33	Acute, misuse	HD	Retrospective, biased by indication: meth >500 mg/L, severe acidosis, &/or clinically unstable		3 deaths, 8 VD. Resolution of vision signs or symptoms in 15 patients
Fadnes 1985, Sweden (27)	5,4	Accidental	HD	Retrospective, biased by indication (clinical features &/or acidosis)		1 death

Phang 1988, Canada (45)	41,4	Acute, misuse or DSP	HD	Retrospective, biased by indication: severe acidosis, meth > 500 mg/L, coma		18 deaths, 4 residual neuronal injury (vision or cognition)
Nolla-Salas 1995, Spain (46)	12,4	Acute, DSP, misuse	11 HD, 1 PD	Retrospective, biased by indication: pronounced acidosis, meth >500 mg/L, coma		5 deaths, 5 VD, 2 parkinsonism, 1 dementia. Resolution of visual signs or symptoms in 10 patients
Meyer 2000, New Zealand (18)	7, 19 (5 pts presented > once)	Acute, misuse	HD 2, CH 5	Retrospective, biased by indication: acidemia. CH was utilised in patients with hemodynamic instability	3 pts with acidemia did not receive HD: 7.29 (asym), 7.28 (asym), 7.14 (nausea)	4 deaths, 1 'severe neurological deficit'. Resolution of VD in 1 patient
Brent 2001, USA (20)	7, 4	Acute, misuse	HD	Prospective, biased by indication: acidosis, meth >500 mg/L, VD, slow meth elimination		2 deaths. Resolution of VD in 3 patients
Megarbane 2001, France (23)	4, 10	DSP, misuse	HD	Retrospective, biased by indication: VD		4 persistent VDs

Hantson 2005, Belgium (3)	15, 3	DSP	HD	Retrospective, biased by indication: meth >500 mg/L, metabolic acidosis, VD		4 deaths, 5 residual VDs
Hovda 2005, Norway (47)	37, 14	Accidental	HD	Retrospective. Unclear indications, ?acidosis. Two asympt received HD for meth 109 & 147 mmol/L		9 deaths, 5 VDs, 4 cerebral sequelae. VD resolved in 19 pts with HD and 4 pts without HD
Brahmi 2007, Tunisia (48)	11, 5	Misuse	HD	Retrospective, biased by indication: VD, metabolic acidosis		3 deaths, 2 VDs. Resolution of VDs in 5 pts
Hassanian 2007, Iran (49)	12, 13	Misuse, accidental	HD	Retrospective, biased by indication: HD withheld due to CV instability		12 deaths, 3 VDs
Paasma 2007, Estonia (36)	79, 32	Accidental	HD & CH	Retrospective, biased by indication (clinical features & acidosis) & availability		25 deaths (MOF,CNS), 18 VDs, 3 cerebral deficits
Unsal 2011, Turkey (50)	25, 5	Accidental	HD	Retrospective, biased by indication (clinical features &/or acidosis)		7 deaths, 5 VDs

HD, hemodialysis; PD, peritoneal dialysis; VD, vision deficit; unk, unknown; AKI, acute kidney injury; I, intervention group; C, control group; DSP, deliberate self-poisoning; asym, asymptomatic; CH, continuous venovenous hemodiafiltration; CV, cardiovascular

*Routine care included supportive care, sodium bicarbonate, folic or folinic acid and either alcohol or fomepizole.

Figure S1. Process used to reach consensus on voting statements, utilizing the Delphi method (two rounds) and scoring tools.

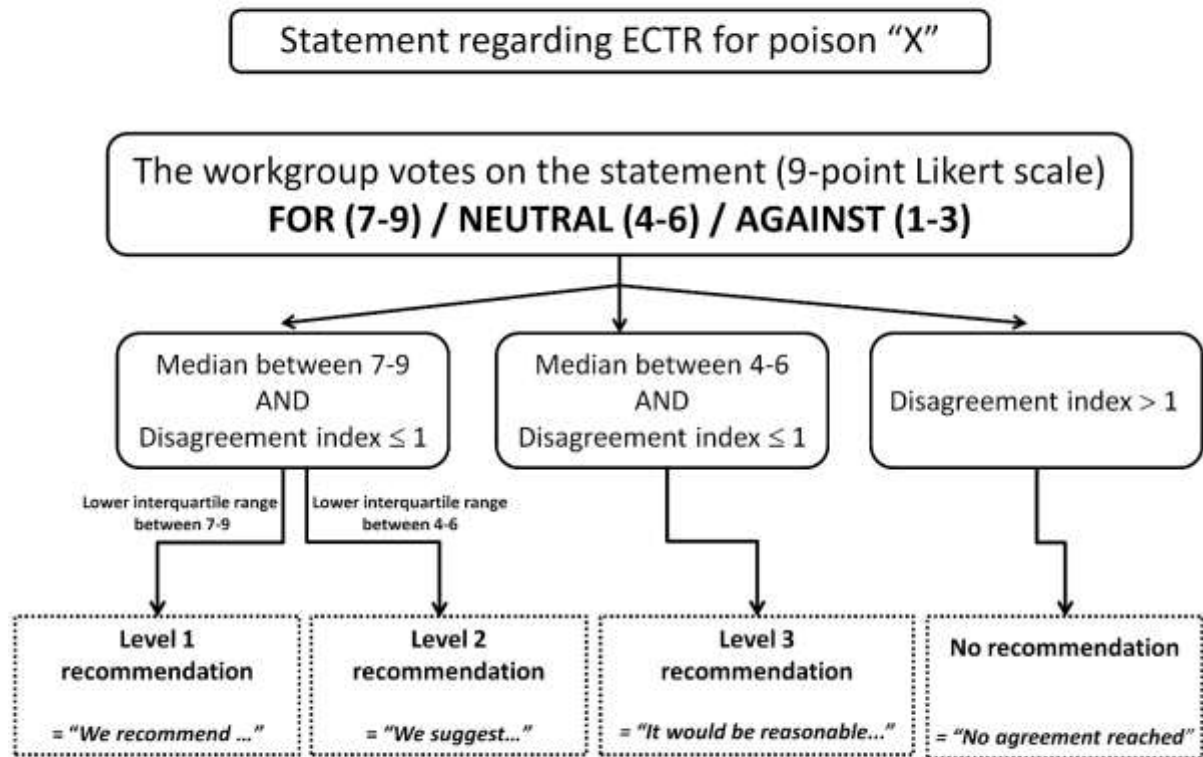


Figure S2. Simulation showing the influence of the initial methanol concentration on the time taken for the concentration to decrease to 200 mg/L (6.24 mmol/L), based on an apparent elimination half-life of 54 hours.

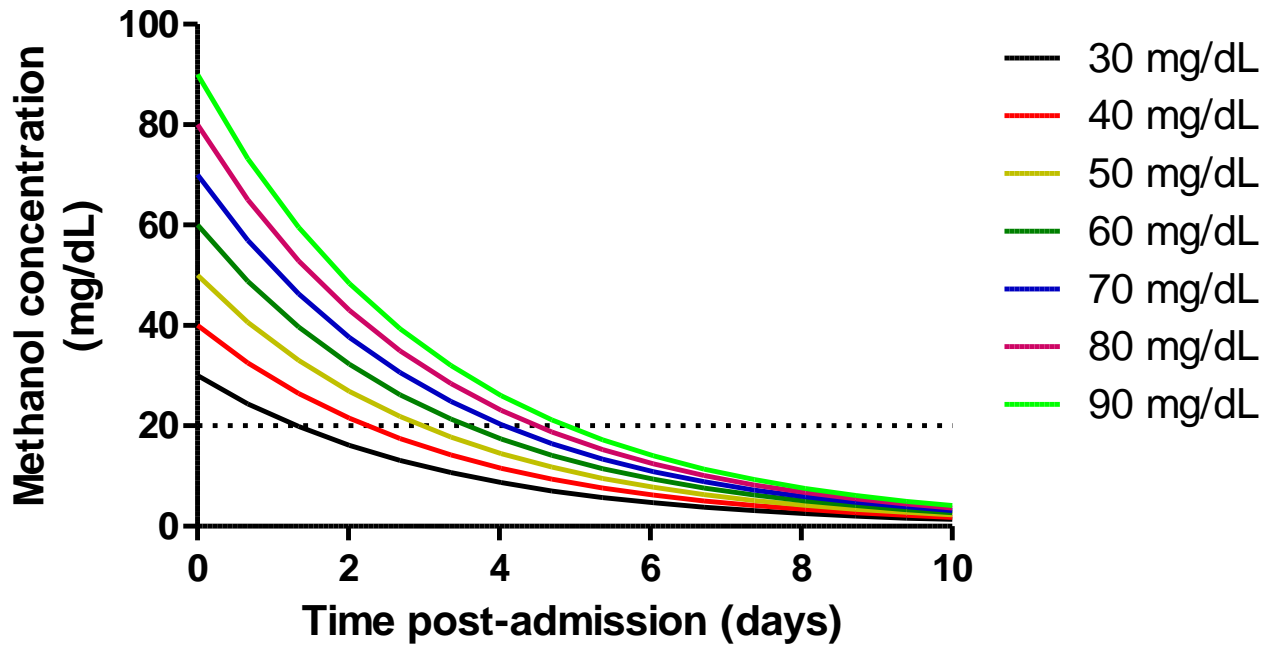
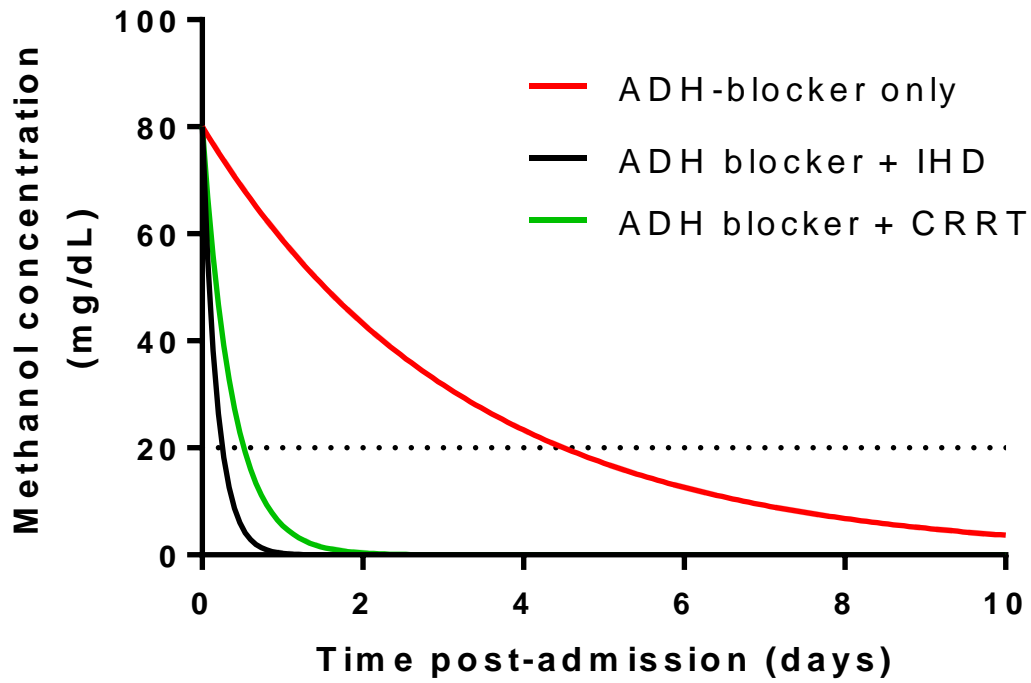


Figure S3. Simulation showing the influence of ECTR on the plasma concentration-time profile of methanol following an identical exposure (based on methanol half-life of 54 hours without ECTR, 3 hours with intermittent hemodialysis (IHD), and 8 hours with continuous renal replacement therapy (CRRT))



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