Case Report

Continuous haemodiafiltration compared with intermittent haemodialysis in the treatment of methanol poisoning

George Kan1, Ian Jenkins2, Gopala Rangan1,3, Andrew Woodroffe1, Helen Rhodes1 and David Joyce3

1Renal Department and 2Intensive Care Unit, Fremantle Hospital, Perth and 3School of Medicine and Pharmacology, University of Western Australia and Western Australian Centre for Pathology and Medical Research, Perth, Australia

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Introduction

Methanol (MeOH) is a toxic alcohol present in many solvents and antifreeze solutions. Ingested MeOH undergoes enzymatic oxidation to toxic formic acid, resulting in acidosis, neurotoxicity and death in severe poisoning. Treatment relies on antidote administration (fomepizole or ethanol) to antagonize MeOH oxidation, folic acid to facilitate the catabolism of formic acid, correction of acidosis and dialysis to accelerate MeOH elimination [1]. Intermittent haemodialysis (HD) is used conventionally [1]. Continuous veno-venous haemodiafiltration (CVVHDF) has not been formally evaluated against this standard.

Here we compare the relative efficiencies of HD and CVVHDF in accelerating MeOH elimination and correcting metabolic abnormalities in three severely poisoned patients, seen simultaneously in two tertiary referral hospitals. At that time, only CVVHDF was available in the Intensive Care Department of the hospital that treated two patients. The third patient received HD. Toxicokinetics and clinical outcomes of CVVHDF and HD treated patients were compared.

Cases

Patients A, B and C were males aged 44, 25 and 43 years old, respectively. The poisonings occurred at sea, ~1 day before presentation. The ingested solution was analysed to contain 54% MeOH and no ethanol. Both patients A and C had endotracheal tubes placed for airway protection. Patient A had earlier experienced central chest pain. Patient C had experienced epileptiform seizures. Table 1 summarizes the initial biochemical and clinical data and outcomes. Patients A and C were severely acidic, obtunded and had Kussmaul’s respiration. All three patients were haemodynamically stable. Intravenous ethanol infusions (rate 10 g/h after bolus, doubled during dialysis) were commenced and serum ethanol levels were maintained above 100 mg/dl. Folic acid was administered.

Veno-venous blood access was achieved with Vas-cath central venous catheters. CVVHDF was performed for 37 h on patient A using an Asahi APS-650 dialyser (1.3 m²) and the Kimal Hygieia Plus dialysis machine. CVVHDF was performed for 27 h on patient B using a Prisma M60 filter (0.6 m²) and the Prisma CFM dialysis machine. For both patients, the blood flow rates were maintained at 150 ml/min, dialysate flow rate at 16.7 ml/min and replacement fluid (bicarbonate based) flow rate at 33.3 ml/min (‘predilutional’). Patient C initially received 4 h of HD using a Fresenius F8 dialyser (1.8 m²), after which blood MeOH concentration was 40 mg/dl. The blood flow rate on HD was 375 ml/min and the dialysate flow rate was set at 500 ml/min. Dialysis was then continued with 6 h of CVVHDF using a Prisma M100 filter.

Serum and dialysate MeOH concentrations were collected and measured by a gas chromatographic method. The serum half-life of MeOH \( t_{1/2} \) for each stage in management was estimated by the relationship, \( t_{1/2} = 0.693/k_{(el)} \), where \( k_{(el)} \) is the elimination rate constant. The value of \( k_{(el)} \) is derived by fitting the serum MeOH concentrations to an exponential decay function of the form \( C = C_0e^{-k_{(el)}t} \), where \( C_0 \) is the concentration at the beginning of the phase, \( C \) describes subsequent concentrations and \( t \) is the time between the first and subsequent measurements [2]. Total body clearances (ClTB) were estimated using the relationship, \( Cl_{TB} = k_{(el)}/V_d \), where \( V_d \) is the distribution volume for MeOH. Clearances due to CVVHDF \( Cl_{CVVHDF} \) were derived using the relationship, \( Cl_{CVVHDF} = D/AUC \), where \( D \) (dose)
is the measured amount of MeOH in dialysate (concentration × volume) and AUC is the area under the serum concentration–time curve for MeOH, estimated by integrating the monoexponential function that describes the serum concentrations during CVVHDF for each patient [2]. Dialysate MeOH concentrations were not available for patient C.

Figure 1 displays the measured serum MeOH concentration over time from presentation. The elimination of MeOH closely followed first-order kinetics during CVVHDF. The serum MeOH declined slowly during post-HD CVVHDF in patient C, presumably reflecting redistribution of tissue MeOH into the circulation. We therefore do not have a valid estimate of ClCVVHDF for patient C.

Table 1 displays the toxicokinetic results. Aggregating the data, the $T_{1/2M}$ were 19–30 h predialysis, 10–12 h on CVVHDF and 2 h on HD. The MeOH clearances on CVVHDF with patients A and B were 45 (83% of ClTB) and 48 ml/min (96% of ClTB), respectively. For patient A, CVVHDF increased the ClTB 3-fold compared to without dialysis. Comparing the dialysis clearances between patients and dialysis modalities (patient C on HD vs patients A and B on CVVHDF), the ClHD was ~5-fold greater than ClCVVHDF. For patient C, HD increased the ClTB 10-fold compared to no dialysis. The duration of dialysis required for the bicarbonate concentration to normalize was 24 h for patients A and B, and within 12 h for patient C.

Patient A died from severe neurological toxicity and the MRI demonstrated extensive subcortical and putaminal necrosis associated with haemorrhages. No clinically detectable neurological deficits occurred with

<table>
<thead>
<tr>
<th>Patient</th>
<th>MeOH (mg/dl)</th>
<th>GCS</th>
<th>Serum pH</th>
<th>Dialysis mode</th>
<th>$t_{1/2}$ (h)</th>
<th>ClTB (ml/min)</th>
<th>ClD</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Predialysis</td>
<td>Dialysis</td>
<td>Predialysis</td>
<td>Dialysis</td>
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</tr>
<tr>
<td>A</td>
<td>210</td>
<td>30</td>
<td>10</td>
<td>CVVHDF</td>
<td>18</td>
<td>54</td>
<td>45^a</td>
<td>Death</td>
</tr>
<tr>
<td>B</td>
<td>163</td>
<td>**</td>
<td>12</td>
<td>CVVHDF</td>
<td>**</td>
<td>50</td>
<td>48^a</td>
<td>No deficits</td>
</tr>
<tr>
<td>C</td>
<td>170</td>
<td>19</td>
<td>2</td>
<td>HD</td>
<td>28</td>
<td>265</td>
<td>237</td>
<td>Higher cortical; visual deficits</td>
</tr>
</tbody>
</table>

MeOH, serum MeOH concentration; GCS, Glasgow Coma Scale; CVVHDF, continuous haemodiafiltration; HD, haemodialysis; $T_{1/2M}$, half-life of MeOH; ClTB, total body clearance; ClD, clearance from dialysis; **, commenced dialysis on presentation.

^aClCVVHDF calculated from dialysate MeOH (see text).

Derived from ClTB dialysis – ClTB predialysis. This may be an underestimate because predialysis ClTB was measured before ethanol administration.

Fig. 1. Serum MeOH concentrations for patients A, B and C over time from presentation (0 h). The time points of commencement (HD or CVVHDF) and cessation (OFF) of dialysis, and commencement of ethanol infusion (arrows) are indicated.
patient B who was treated with CVVHDF. Patient C sustained intellectual deficits resulting in impulsiveness and memory loss associated with decreased visual acuity. The MRI demonstrated severe ischaemic hypoxic injury involving the ‘water-shed’ distributions of the cerebral and cerebellar arteries and these were most pronounced in the peripheral putamen and external capsules.

Discussion

These three patients presented with severe MeOH poisoning, as evidenced by clinical and metabolic abnormalities and by persisting or lethal, neurological damage in two. Toxicokinetic analyses confirm the superiority of HD over CVVHDF in clearing MeOH, reaching target serum MeOH concentrations and correcting metabolic derangement. Similar HD clearances of MeOH have been reported previously [3,4].

MeOH clearance during HD in patient C was 5-fold higher than during CVVHDF in the other two patients. Nonetheless, CVVHDF still increased $Cl_{TB}$ 3-fold above the pre-dialysis clearance and, judging from the 3-fold reduction in $MeOH_{t_{1/2}}$, would have substantially reduced the time to safe serum MeOH concentration and to correction of metabolic derangement. The pre-dialysis estimates themselves probably exceed endogenous clearance during dialysis, because endogenous clearance would have been nearly completely blocked by ethanol during dialysis. This accords with our observation that nearly all the cleared MeOH could be accounted for in dialysate during CVVHDF.

We did not examine the effects of HD or CVVHDF on formic acid toxicokinetics in these patients. Serum formic acid levels and the degree of acidosis on presentation strongly influence outcome in MeOH poisoning [3,5–7]. Formic acid levels correlate with serum pH [8] and there is a latent period of 12–24 h from MeOH ingestion before symptoms of toxicity occur [1]. HD clears formic acid [9,10] but this may not be clinically important because formic acid has a high endogenous clearance. Its half life is $\sim$3.4 h [10].

In summary, we conclude that CVVHDF accelerates MeOH elimination usefully, shortens the time to target serum MeOH concentrations and likely shortens the period of metabolic derangement and blockade of neural tissue energy metabolism. However, it is materially slower than HD in reaching important treatment endpoints and is not a substitute for HD. It may have limited application in less severely poisoned cases if HD is unavailable or not feasible, for example, because of haemodynamic instability. It remains important to characterize the efficiency of CVVHDF in removing formic acid.

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References


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