OPEN

Intermittent hemodialysis is superior to continuous veno-venous hemodialysis/hemodiafiltration to eliminate methanol and formate during treatment for methanol poisoning

Sergey Zakharov[1], Daniela Pelclova[1], Tomas Navratil[2], Jaromir Belacek[3], Ivana Kurcova[4], Ondrej Komzak[4], Tomas Salek[5], Jiri Latta[6], Radovan Turek[7], Robert Bocek[8], Cyril Kucera[9], Jaroslav A. Hubacek[10], Zdenka Fenclova[1], Vit Petrik[1], Martin Cermak[11] and Knut Erik Hovda[12]

[1]Department of Occupational Medicine, Toxicological Information Center, General University Hospital and First Faculty of Medicine of Charles University in Prague, Prague, Czech Republic; [2]J. Heyrovský Institute of Physical Chemistry of the AS CR, v.v.i., Prague, Czech Republic; [3]Institute of Biophysics and Informatics of First Faculty of Medicine of Charles University in Prague, General University Hospital, Prague, Czech Republic; [4]Department of Toxicology, Institute of Forensic Medicine and Toxicology, General University Hospital in Prague and of the First Faculty of Medicine of Charles University in Prague, Prague, Czech Republic; [5]Department of Clinical Biochemistry, Tomas Bata Regional Hospital in Zlin, Zlin, Czech Republic; [6]Department of Internal Medicine, Tomas Bata Regional Hospital in Zlin, Zlin, Czech Republic; [7]Department of Anesthesiology and Resuscitation, Tomas Bata Regional Hospital in Zlin, Zlin, Czech Republic; [8]Department of Anesthesiology and Intensive Care, Hospital Havirov, Havirov, Czech Republic; [9]Department of Anesthesiology and Resuscitation, City Hospital Ostrava, Ostrava, Czech Republic; [10]Centre for Experimental Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [11]Department of Anesthesiology and Intensive Care, Regional Hospital Pribram, Pribram, Czech Republic and [12]Department of Acute Medicine, The Norwegian Center for NBC Medicine, Oslo University Hospital, Ullevaal, Norway

During an outbreak of methanol poisonings in the Czech Republic in 2012, we were able to study methanol and formate elimination half-lives during intermittent hemodialysis (IHD) and continuous veno-venous hemodialysis/hemodiafiltration (CVVHD/HDF) and the relative impact of dialysate and blood flow rates on elimination. Data were obtained from 11 IHD and 13 CVVHD/HDF patients. Serum methanol and formate concentrations were measured by gas chromatography and an enzymatic method. The groups were relatively comparable, but the CVVHD/HDF group was significantly more acidotic (mean pH 6.9 vs. 7.1 IHD). The mean elimination half-life of methanol was 3.7 and formate 1.6 h with IHD, versus 8.1 and 3.6 h, respectively, with CVVHD/HDF (both significant). The 54% greater reduction in methanol and 56% reduction in formate elimination half-life during IHD resulted from the higher blood and dialysate flow rates. Increased blood and dialysate flow on the CVVHD/HDF also increased elimination significantly. Thus, IHD is superior to CVVHD/HDF for more rapid methanol and formate elimination, and if CVVHD/HDF is the only treatment available then elimination is greater with greater blood and dialysate flow rates.

Kidney International advance online publication, 12 March 2014; doi:10.1038/ki.2014.60

KEYWORDS: continuous veno-venous hemodialysis; elimination half-life; formate kinetics; intermittent hemodialysis; methanol kinetics; methanol poisoning

Methanol poisoning is a medical emergency where rapid elimination of the toxin and its metabolite is crucial for recovery. This is because the accumulation of the toxic metabolite formic acid/formate is cytotoxic through the inhibition of mitochondrial respiration.[1–4] In addition, the accumulation of formic acid results in a metabolic acidosis, visual impairment, and damage of the basal ganglia, especially when its concentration rises to 9–11 mmol/l.[5–8]

The role of hemodialysis in methanol poisoning is well established.[9,10] Hemodialysis eliminates both methanol and formate, and helps to correct metabolic acidosis. Both intermittent and continuous modalities of hemodialysis are commonly used in the treatment of poisonings; however, comparative studies are scarce for methanol kinetics and nonexistent for formate kinetics.

Given the fact that ~80% of all dialysis sessions in 2006 were performed in the developed world,[11] whereas

Correspondence: *Sergey Zakharov, Department of Occupational Medicine, Toxicological Information Center, General University Hospital and First Faculty of Medicine of Charles University in Prague, Na Bojisti 1, 12000, Prague 2, Prague, Czech Republic. E-mail: Sergey.Zakharov@vfn.cz*

Received 27 August 2013; revised 23 December 2013; accepted 2 January 2014

the majority of methanol poisoning outbreaks occur in underdeveloped countries where resources are scarce; a thorough evaluation of the efficacy and limitations of the various modalities of treatment should be carried out. In addition, challenges regarding the availability of antidotes in some countries (for example, the general lack of fomepizole in the developing world, and cultural limitations regarding the medicinal use of ethanol in some Islamic countries) further emphasize the importance of extracorporeal elimination techniques in the treatment of patients with methanol toxicity.

In addition to the availability of different dialysis equipments, the choice of modality may be governed by the patient's clinical condition, especially with regard to the circulatory status. The risk of performing a dialysis session with a high dialysate and blood flow rate in a patient with a very low blood pressure has to be weighed against the benefits of the increased elimination rate of the toxic substances and correction of the acidosis. We therefore also wanted to study the relative impact of the blood and dialysate flow on the elimination of both methanol and formate to see whether this could add to the recommendations for the treatment.

The above questions were addressed in a prospective observational study on methanol and formate elimination in 24 methanol-poisoned patients treated with antidotes and two different methods of enhanced elimination in order to compare the elimination half-lives of methanol and formate. All patients were treated during the recent outbreak of mass methanol poisoning in the Czech Republic in 2012, where 121 cases of poisoning were admitted and a total of 41 patients died (of whom 21 died in hospital). The epidemiological description of the outbreak is presented elsewhere.[12]

RESULTS

The clinical features, laboratory data, and patient outcomes are presented in Table 1. Among the 24 patients, 11 were treated with intermittent hemodialysis (IHD), whereas 13 were treated with a continuous modality (eight with continuous veno-venous hemodialysis (CVVHD) and five with continuous veno-venous hemodiafiltration (CVVHDF)). In two patients (patients nos. 8 and 11, Table 1), ethanol infusion was started before the initial blood sample was drawn, explaining why they were acidotic in spite of their serum ethanol concentration.

The two groups of patients treated with different modes of enhanced elimination were comparable by age, time to diagnosis/treatment, and number of patients. The mean time to diagnosis and treatment after the toxic alcohol consumption was 37 h in the CVVHD/HDF group and 48 h in the IHD group. All collected data were normally distributed with two exceptions: (a) serum ethanol in both groups of patients, and (b) serum methanol in the CVVHD/HDF group. There were no statistical differences between the two groups in admission data with respect to serum methanol, formate, pCO_2, HCO_3^-, base deficit, anion gap, and osmolal gap (all $P>0.05$). The patients treated with CVVHD/HDF were more acidotic than those treated with IHD (mean pH 6.9 ± 0.1 vs. 7.1 ± 0.1, respectively), with higher lactate levels (both $P=0.04$).

Data on formate and methanol elimination in 11 patients treated with IHD and 13 patients treated with CVVHD/HDF are presented in Tables 2 and 3, respectively.

The mean methanol elimination half-life in our study was 3.7 ± 1.4 h for IHD and 8.1 ± 1.2 h for CVVHD/HDF. The mean formate elimination half-life was 1.6 ± 0.4 h during IHD and 3.6 ± 1.0 h during CVVHD/HDF. The elimination half-lives of both formate and methanol on IHD were significantly shorter than on CVVHD/HDF (both $P<0.001$).

Regardless of the mode of dialysis, the elimination half-lives of methanol (Figure 1) and formate (Figure 2) were shorter when the blood flow rates were higher (both $P<0.001$).

In the CVVHD/HDF group, the elimination half-lives were shorter when the dialysate flow rate was higher ($P=0.015$, Figure 3) and when the dialyzer membrane surface was larger (both $P<0.05$). In IHD, only one dialysate flow rate and only two sizes of membrane were used (Table 2), yet a significant correlation was found between the dialyzer membrane surface and the elimination half-life of methanol ($P=0.015$, Figure 4).

No significant correlation was present between the elimination half-lives of methanol and formate and the predialysis serum concentrations of methanol, formate, ethanol, bicarbonates, and lactate (all $P>0.05$). However, a significant correlation was present between the elimination half-life of formate and arterial blood pH; the longer half-life of formate was present in more acidotic patients ($P=0.038$).

No significant correlations of methanol and formate elimination half-lives were found with the folate substitution (treatment with either folic or folinic acid, or without folates) and with the specific antidote (ethanol or fomepizole) administration (all $P>0.05$). As regards the outcome, the patients with visual and CNS sequelae of methanol poisoning had significantly longer elimination half-lives of formate than those without sequelae ($P=0.005$). The differences in mortality ($P=0.36$) and morbidity (survivals with sequelae, $P=0.19$) between IHD and CVVHD/HDF groups were not significant.

The results of the multivariate regression analysis of variables influencing the elimination half-lives of formate and methanol based on all 24 cases are shown in Tables 4 and 5. Five independent variables included in the model explained 82.8% of the formate elimination half-life variation. The most significant factor was the blood flow rate. The dialysate flow rate ($P=0.013$) was based on the CVVHD/HDF cases only; however, it was still contributing significantly to the model. The 'dialyzer membrane surface' was grouped together as interchangeable with 'dialysate temperature', explaining why 'other dialyzer properties' is given as the term in the model, in spite of the linear correlation between both the methanol and the formate elimination half-lives. The variable 'Clinical features' consists of Glasgow coma scale, mean arterial pressure, and pulse rate. The variable