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Acute methanol poisonings: Folates administration and visual sequelae

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ABSTRACT

During the outbreak of methanol poisonings in the Czech Republic 2012, we studied the clinical effectiveness of folate therapy in preventing visual damage. Data were obtained from a combined prospective and retrospective study on 79 patients: folinic acid was administered in 28, folic acid in 35; 16 patients received no folates. The groups were comparable by age, time to treatment, laboratory findings, symptoms, and treatment. The number of patients with visual sequelae differed neither between the groups treated with folinic/folic acid, nor between the groups with/without folate administration. The patients with visual sequelae were more acidotic and differed in pH, HCO_3^-, base deficit, anion gap, but not in methanol, ethanol, osmolal gap, formate, and pCO_2. Serum lactate, but not formate differed significantly. The higher serum glucose on admission was in the patients with visual sequelae. Regardless the rationale for folate administration in acute methanol poisoning, its clinical effectiveness in preventing visual damage was not demonstrated in our study. The detoxifying effect of the pathway of tetrahydrofolate-mediated formate conversion is secondary to the formate elimination by haemodialysis. The results of our study cannot promote folinic acid as more efficient than folic acid, but also cannot discount the possible utility of adjunct folate therapy.

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Introduction

Methanol poisoning is a medical emergency where rapid blocking of alcohol dehydrogenase is important because of the toxic effects of its metabolite, formic acid, on the retina, optic nerve and central nervous system (Jacobsen and McMartin, 1986; Megarbane et al., 2005; Kraut and Kurtz, 2008; Sanaei-Zadeh et al., 2011a). Formate anions as the products of methanol metabolism have a strong cytotoxic effect by inhibition of mitochondrial cytochrome c oxidase activity causing histotoxic hypoxia (Liesivuori and Savolainen, 1991; Hovda et al., 2004). The accumulation of formic acid results in metabolic acidosis, damage of basal ganglia and visual impairment, especially when its concentration rises to 0.9–1.1 mmol/L (McMartin et al., 1980; Sejersted et al., 1983; Osterloh et al., 1986; Sanaei-Zadeh et al., 2011b).

The neurons of the optic nerve are selectively vulnerable to histotoxic hypoxia as its fibres and their myelin sheaths have fewer mitochondria and low reserves of cytochrome oxidase due to their low metabolic requirements (Sharpe et al., 1982; Kavet and Nauss, 1990; Desai et al., 2013). The biochemical and morphologic changes caused by formate toxicity were observed in retinal photoreceptors, Müller cells (retinal glial cells), and in cells of the underlying retinal pigment epithelium (Garner et al., 1995; Seme et al., 1999; Treichel et al., 2003).

The role of folates in the metabolism of formic acid is well-established. Folates enhance formate metabolism converting it to 10-formyl tetrahydrofolate by the activity of 10-formyl tetrahydrofolate synthase followed by its oxidation to carbon dioxide catalyzed by 10-formyltetrahydrofolate dehydrogenase (McMartin et al., 1977; Johlin et al., 1987; Martinasevic et al., 1996). The presence of a folate derivative enhances formate oxidation by preventing the development of enzyme catalyst deficient metabolic pathways (Black et al., 1985).

Based on this rationale and several experimental studies, the folic or folinic acid administration to the methanol-poisoned patients is routinely recommended (Noker et al., 1980; Billings et al., 1981; Barceloux et al., 2002; Kerns et al., 2002). Although folinic acid is preferred to folic acid since it does not require metabolic reduction, folic acid is considered a suitable alternative.

Although there is sufficient evidence in a non-human primate model of methanol toxicity that folate therapy is efficacious (Noker et al., 1980), there have been no clinical studies of the effectiveness of folates in the treatment of acute methanol poisoning in humans (Ghosh and Boyd, 2003). From the ethical point of view it is impossible to plan and fulfil the prospective randomized case–control study, so only retrospective case series studies with sufficient laboratory and clinical data can be used to compare the visual outcome of acute methanol poisonings after the treatment with and without folates.

In this study we report the data based on the recent methanol mass poisoning in the Czech Republic in 2012 (Zakharov et al., 2013). We performed a retrospective study in 79 methanol-poisoned patients treated with buffers, antidotes, folates, and enhanced elimination methods, in order to compare the short-term visual outcomes in the groups of patients with and without the administration of folinic or folic acid.

Materials and methods

Patients and procedures

The study was designed as a combined prospective and retrospective case series study. A total of 121 cases of methanol poisoning occurred during the period from the 3rd of September 2012 until January 2013. One hundred and one patients were treated in hospitals. There were 21 fatalities in hospital (hospital mortality 20.8%), other 20 patients died at home or before reaching hospital, giving a total mortality of 34%.

All 80 patients with acute methanol poisoning confirmed by toxicological analysis (methanol in blood serum), who survived and were discharged from hospitals, were included to the study. One patient was further excluded due to the incomplete information on admission laboratory data and clinical symptoms The protocols for the prospective collection of information on diagnosis and treatment established during the Norwegian methanol outbreak have been used (Hovda et al., 2005), and discharge reports of all hospitalized patients with confirmed diagnosis and results of neurological and ophthalmological examinations on admission, during hospitalization, and on discharge were collected and analyzed in the Czech Toxicological information center. A detailed record of history of poisoning, including information on the onset and character of development of signs and symptoms of ocular and systemic toxicity, was obtained either directly from the patients or from relatives of critically ill patients, on admission.

Laboratory investigations on admission included serum methanol, ethanol, formate, lactate, electrolytes, anion and osmolal gaps, glucose, complete renal and hepatic tests, complete haemogram, haematocrit level and serum proteins. The urine was tested qualitatively for the presence of methanol and its metabolites. Diagnosis was made when (1) a history of recent ingestion of illicit liquor was available and serum methanol concentration greater than 3 mmol/L, and/or an osmolal gap of greater than 15 mOsm/kg was noted, or (2) there was a history/clinical suspicion of methanol poisoning, serum methanol detectable with at least two of the following: pH less than 7.3, serum bicarbonate less 20 mmol/L, and anion gap greater than 19 mmol/L.

The clinical examination protocol included complete ocular examination and standard ophthalmic tests (visual acuity and perimeter measurement, colour vision, contrast sensibility, fundoscopy). The patients were considered having visual sequelae of acute methanol poisonings if pathologic findings on fundus and retina with loss of visual acuity, pathologic perimeter, colour vision, and contrast sensitivity were present on demission. Other causes of visual damage like diabetes mellitus, arterial hypertension, and chronic alcoholism were taken into consideration within the estimation of causal relationship.

The patients were retrospectively divided into four groups: group I, 35 patients treated with folic acid; group II, 28 patients