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Acute methanol poisonings: Folates administration and visual sequelae

Sergey Zakharov [a,*], *Olga Nurieva* [a], *Tomas Navratil* [b,c], *Pavel Diblik* [d], *Pavel Kuthan* [d], *Daniela Pelclova* [a]

[a] *Toxicological Information Center, Department of Occupational Medicine, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague 2, Czech Republic*

[b] *Department of Biophysical Chemistry, J. Heyrovský Institute of Physical Chemistry of the AS CR, v.v.i., Prague 8, Czech Republic*

[c] *Institute of Medical Biochemistry and Laboratory Medicine, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague 2, Czech Republic*

[d] *Department of Ophthalmology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague 2, Czech Republic*

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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.

* *Corresponding author at*: Toxicological Information Center, Department of Occupational Medicine, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Na Bojisti 1, 12000 Prague 2, Czech Republic. Tel.: +420 224 964155; fax: +420 224 964325.

E-mail addresses: Sergey.Zakharov@vfn.cz, zakharnik@seznam.cz (S. Zakharov).

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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

treated with folinic acid; group III, combining the former two groups with total 63 patients treated with folates (folinic or folic acid), and group IV, 16 patients treated without folates.

The further subgroup analysis of treatment outcomes was performed in 30 patients with visual disturbances on admission (group I*, $n = 11$; group II*, $n = 13$; group III*, $n = 24$; group IV*, $n = 6$), and in 49 patients without visual disturbances on admission (group I**, $n = 24$; group II**, $n = 15$; group III**, $n = 39$; group IV**, $n = 10$). The patients were considered having visual disturbances on admission, if hyperaemia of the optic nerve head, oedema of the disc margin and adjacent retina were found on fundoscopy during first 24 h after hospitalization, and/or symptoms of blurry or cloudy vision, central scotomata, alterations in light, colour and depth perception, progressing to total vision loss with absent pupillary response were documented in admission report.

Finally, two groups of patients, with and without visual sequelae, were compared to identify the significant differences in laboratory data on admission.

Treatment

Alkalization treatment with sodium hydrogen carbonate was given as a buffer to the patients with metabolic acidosis (pH < 7.3). Ethanol, fomepizole or the combination of ethanol and fomepizole, e.g. start of therapy with fomepizole followed by ethanol administration, were given as antidotes. Because the availability of fomepizole was limited, it was only recommended for the most severely poisoned subjects with methanol level above 15.7 mmol/L or formic acid above 8.7 mmol/L or pH ≤ 7.0. Fomepizole (Fomepizole EUSA, EUSA Pharma, France) was given as a bolus dose of 15 mg/kg i.v. diluted in isotonic saline, followed by 10 mg/kg every 12 h. From the fifth dose and on, the dose was elevated to 15 mg/kg in order to compensate for increased metabolism (Jacobsen et al., 1990). During the haemodialysis, 10 mg/kg of fomepizole was given every 4 h. Enhanced elimination methods were applied in 56 cases. Intermittent haemodialysis (IHD) was performed in 25 and continuous veno-venous haemodialysis/haemodiafiltration (CVVHD/HDF) in 31 patients.

Folates were administered in 63 patients: folic acid (Acidum folicum Léčiva, tbl. 10 mg, Zentiva, Czech Republic) in 35, and folinic acid (Calcium folinate Hospira, amp. 20 ml, 10 mg/ml Hospira UK Limited, Great Britain) in 28 subjects. The dose of folinic acid was 1 mg/kg/body weight, up to a total dose of 50 mg, administered intravenously, every 4–6 h until methanol and formate have been eliminated. Folinic acid was diluted in 5% glucose in water and administered over 30–60 min. If folinic acid was not available, 50 mg of folic acid was administered orally in every 3–4 h. The corticosteroids were not administered to the patients with visual disturbances.

Statistical analyses

The laboratory data on admission in four groups of patients treated with and without folates (Table 1) and in two groups of patients with and without visual sequelae (Table 7) have been compared using *t*-test: two-sample assuming equal variances, two-sample assuming unequal variances (equal means), two-sample *F*-test for variances, and two-sample

Table 1 – Laboratory data on admission in 79 patients treated with and without folates (medians with ranges).

Group of patients	Age (years)	S-Methanol (mmol/L)	S-Ethanol (mmol/L)	S-Formate (mmol/L)	S-Lactate (mmol/L)	pH	pCO_2 (kPa)	HCO_3^- (mmol/L)	BD (mmol/L)	AG (mmol/L)	OG (mOsm/kgH_2O)
I ($n = 35$) Me	58	30.7	2.6	15.7	3.1	7.21	4.3	13	13	25	50
R	23–74	2.7–228.1	0–96.8	0–22.5	0.5–12.8	6.67–7.46	1.5–5.7	3–27	0–38	11–55	3–235
II ($n = 28$) Me	48	25.8	0	10.1	2.5	7.24	3.6	11	17	28	41
R	23–73	2.7–128	0–96.6	0–31.1	0.9–16.3	6.65–7.46	1.0–6.6	2–26	1–36	11–49	4–132
III ($n = 63$) Me	52	26.70	0.2	13.9	3.7	7.25	4.0	12	14	27	52
R	23–74	2.7–228.1	0–96.8	0–31.1	0.5–16.3	6.65–7.46	1.0–6.6	2–27	0–38	11–55	3–235
IV ($n = 16$) Me	54	15.6	8.1	9.1	2.1	7.30	4.5	18	10	23	41
R	27–69	1.8–108.6	0–57.3	0–17.8	0.7–7.8	6.86–7.46	2.5–6.4	4–25	0–30	15–35	4–120
$P_{I–II}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$P_{I–IV}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	*	n.s.
$P_{II–IV}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$P_{III–IV}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	*	n.s.

Note: Groups I–III – patients treated with folates (I – folic acid, II – folinic acid, III – groups I + II); group IV – patients not treated with folates.
S, serum; BD, base deficit; AG, anion gap; OG, osmolal gap; Me, median; R, range; n.s., not significant.
* Statistically significant.

Table 2 – Clinical symptoms on admission in 79 patients treated with and without folates.

	Asymptomatic	VD	GI	D	CP	C	RA	Time to treatment (h), median (range)
I (n = 35)	10 (28.6%)	11 (31.4%)	17 (48.6%)	11 (31.4%)	2 (5.7%)	8 (22.9%)	1 (2.9%)	48 (7–96)
II (n = 28)	10 (35.7%)	13 (46.4%)	13 (46.4%)	8 (28.6%)	3 (10.7%)	3 (10.7%)	0 (0.0%)	36 (8–60)
III (n = 63)	20 (31.7%)	24 (38.1%)	30 (47.6%)	19 (30.2%)	5 (7.9%)	11 (17.5%)	1 (1.6%)	48 (7–96)
IV (n = 16)	6 (37.5%)	6 (37.5%)	8 (50%)	2 (12.5%)	0 (0.0%)	2 (12.5%)	1 (6.3%)	48 (12–72)
$P_{I–II}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$P_{I–IV}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$P_{II–IV}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
$P_{III–IV}$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Note: Groups I–III – patients treated with folates (I – folic acid, II – folinic acid, III – groups I + II); group IV – patients not treated with folates.
VD, visual disturbances; D, dyspnoea; CP, chest pain; GI, gastrointestinal symptoms; C, coma; RA, respiratory arrest; n.s., not significant.

Table 3 – Treatment measures in 79 patients treated with and without folates.

	Alkalization	Ethanol	Fomepizole	E + F	CVVHD/HDF	IHD
I (n = 35)	17 (48.6%)	27 (77.1%)	0 (0.0%)	5 (14.3%)	16 (45.7%)	9 (25.7%)
II (n = 28)	16 (57.1%)	21 (75.0%)	3 (10.7%)	4 (14.3%)	14 (50%)	9 (32.1%)
III (n = 63)	33 (52.4%)	48 (76.2%)	3 (4.8%)	9 (14.3%)	30 (47.6%)	18 (28.6%)
IV (n = 16)	6 (37.5%)	11 (68.8%)	1 (6.3%)	2 (12.5%)	1 (6.3%)	7 (43.7%)
$P_{I–II}$	n.s.	n.s.	*	n.s.	n.s.	n.s.
$P_{I–IV}$	n.s.	n.s.	n.s.	n.s.	*	n.s.
$P_{II–IV}$	n.s.	n.s.	n.s.	n.s.	*	n.s.
$P_{III–IV}$	n.s.	n.s.	n.s.	n.s.	*	n.s.

Note: Groups I–III – patients treated with folates (I – folic acid, II – folinic acid, III – groups I + II); group IV – patients not treated with folates.
E, ethanol; F, fomepizole; IHD, intermittent haemodialysis; CVVHD/HDF, continuous veno-venous haemodialysis/haemodiafiltration; n.s., not significant.
* Statistically significant.

Kolmogorov–Smirnov test. The clinical symptoms on admission (Table 2), treatment measures (Table 3), and visual sequelae (Tables 4–6) were analyzed using Chi^2 test. The normality of data distribution was characterized using skewness and kurtosis tests. Data are expressed as medians with either range or confidence interval, as appropriate. All statistical calculations were carried out on level of significance $2\alpha = 0.05$. The calculations were performed using Excel 2003 (Microsoft, USA) and QC Expert software 3.1 (Trilobyte, Pardubice, Czech Republic).

Table 4 – Visual sequelae in 79 patients treated with and without folates.

	NONE	VS	Total (n = 79)
I	26 (74.3%)	9 (25.7%)	35
II	21 (75%)	7 (25%)	28
III	47 (74.6%)	16 (25.4%)	63
IV	10 (62.5%)	6 (37.5%)	16
$P_{I–II}$	n.s.	n.s.	
$P_{I–IV}$	n.s.	n.s.	
$P_{II–IV}$	n.s.	n.s.	
$P_{III–IV}$	n.s.	n.s.	

Note: Groups I–III – patients treated with folates (I – folic acid, II – folinic acid, III – groups I + II); group IV – patients not treated with folates.
VS, visual sequelae, n.s., not significant.

Table 5 – Visual sequelae in 30 patients with visual disturbances on admission treated with and without folates.

	None – 15 (50%)	VS – 15 (50%)	Total (n = 30)
I*	6 (54.5%)	5 (45.5%)	11
II*	7 (53.8%)	6 (46.2%)	13
III*	13 (54.2%)	11 (45.8%)	24
IV*	2 (33.3%)	4 (66.7%)	6
$P_{I–II}$	n.s.	n.s.	
$P_{I–IV}$	n.s.	n.s.	
$P_{II–IV}$	n.s.	n.s.	
$P_{III–IV}$	n.s.	n.s.	

Note: Subgroups I*–III* – patients treated with folates (I* – folic acid, II* – folinic acid, III* – groups I* + II*); group IV* – patients not treated with folates.
VS, visual sequelae; n.s., not significant.

Ethics

The study was approved by the General University Hospital Ethics Committee in Prague, Czech Republic.

Results

Among the patients treated with folic acid, there were 29 (83%) males, median age 58 (range 23–74) years, and 6 (17%) females, median age 59 (range 35–69) years. The patients treated with

Table 6 – Visual sequelae in 49 patients without visual disturbances on admission treated with and without folates.

	None – 42 (85.7%)	VS – 7 (14.3%)	Total (n = 49)
I**	20 (83.3%)	4 (16.7%)	24
II**	14 (93.3%)	1 (6.7%)	15
III**	34 (87.2%)	5 (12.8%)	39
IV**	8 (80%)	2 (20%)	10
$P_{I–II}$	n.s.	n.s.	
$P_{I–IV}$	n.s.	n.s.	
$P_{II–IV}$	n.s.	n.s.	
$P_{III–IV}$	n.s.	n.s.	

Note: Subgroups I**–III** – patients treated with folates (I** – folic acid, II** – folinic acid, III** – groups I** + II**); group IV** – patients not treated with folates.
VS, visual sequelae; n.s., not significant.

folinic acid were males in 24 (86%) cases with median age 48 (range 28–73) years, and females in 4 (14%) cases with median age 38 (range 23–66) years. Finally, the group of patients treated without folate administration included 12 (75%) males, median age 49 (range 27–69) years, and 4 (25%) females, median age 60 (range 58–62) years.

The type of alcohol was known in 67/79 patients, and the approximate quantity in 40/79 cases. Twenty subjects drank other alcoholic beverages (wine, beer, whisky, home-made spirits) in addition. Thirty-two patients had detectable ethanol before further antidote treatment was given, with a median concentration of 14 mmol/L (range 0–96.8 mmol/L). In addition, 4 patients were not analyzed for serum ethanol before ethanol treatment was given. There were 48% daily alcohol users.

Admission data

Laboratory data in the subjects, divided into the four groups are given in Table 1. The differences in laboratory data on admission among the groups were not significant (all $P > 0.05$) with one exception only (anion gap between the groups I–IV, III–IV). All collected laboratory data in four groups exhibited normal distribution (with following exceptions: groups I, II, III: methanol, ethanol, osmolal gap; group II: lactate; group III: pH and pCO_2; group IV: lactate).

Clinical symptoms

Among the symptomatic patients, the most frequent symptoms were visual and gastrointestinal disturbances; followed by dyspnoea, coma and chest pain. Further symptoms in all groups involved fatigue, headache, dizziness, hangover, somnolence, anxiety, tremor, seizures, alcoholic delirium, and cardiac arrest.

The clinical symptoms in the subjects, divided into four groups are presented in Table 2.

Treatment

The treatments in the subjects, divided into four groups, are given in Table 3. The differences in treatment between all the groups were not significant (all $P > 0.05$) with two exceptions only: (a) more patients treated with folates underwent CVVHD compared to those without folates, the last ones were treated more often with IHD (but the difference for IHD frequency was not significant between two groups); (b) fomepizole application between the groups I and II. The other treatment measures (bicarbonate, antidote administration) were also applied slightly more often in the folate-treated patients than in those without folate therapy (though the difference did not reach statistical significance).

Outcomes

The visual outcomes of treatment in the subjects, divided into four groups are presented in Tables 4–6. The differences in the number of patients with and without visual sequelae between all four groups were not significant (all $P > 0.05$). The results of subgroup analysis in the patients admitted with visual disturbances, and in the patients admitted without visual disturbances, showed no significant differences between all the groups too (all $P > 0.05$).

The patients with visual sequelae differed significantly from the patients without visual sequelae in pH, HCO_3^-, base deficit, anion gap, serum lactate, and glucose (all $P < 0.05$), and did not differ in serum methanol, ethanol, osmolal gap, formate, and pCO_2 (Table 7).

From 30 patients with visual disturbances on admission, 15 (50%) improved with treatment (Table 5). From 49 patients without visual disturbances on admission, 7 (14%) had visual sequelae on discharge (Table 6). Most of the patients (24/30) with visual symptoms on admission had blurred vision, ''black-and-white vision'', snowflakes, photophobia, ''twilight'' or ''grey'' vision. These symptoms resolved in 13/24 (54%) cases: in 10 cases with folate administration, and in 3 cases without folate therapy. In remaining 11 cases folates were administered to 9 patients. Severe to deep blindness was present in 6/30 (20%) patients. This condition resolved in 2/6 (33%) cases: in one case folates were administered, in the other case were not administered.

Discussion

The study had some principal limitations, because it was neither a randomized controlled trial, nor a cohort trial, which precluded any direct, head-to-head comparisons. It was a combined prospective and retrospective case series study, in which the patients were not uniform, reporting of ingestions might not be accurate, and timing and quality of interventions were not documented in real time. Other factors may confound the result, such as a co-ingestion of different types and quantities of concomitant alcoholic beverages, different temporal patterns of toxic alcohol ingestion, the co-morbidity, etc.

Despite the limitations and confounders, the study is the largest one all around the world, where the effect of folate therapy on visual outcomes of patients poisoned during one mass methanol outbreak was systematically observed, the analyzed groups of patients were comparable by age, circumstances of poisoning and time to treatment; most of the collected data exhibited normal distribution; for all

Table 7 – Laboratory data on admission in the patients with and without visual sequelae (medians with ranges).

Group of patients	Age (years)	S-Methanol (mmol/L)	S-Ethanol (mmol/L)	S-Formate (mmol/L)	S-Lactate (mmol/L)	pH	pCO_2 (kPa)	HCO_3^- (mmol/L)	BD (mmol/L)	AG (mmol/L)	OG (mOsm/kgH_2O)	Glucose (mmol/L)
A (n = 22) Me	56	43.1	0	15.4	5.9	7.10	3.2	6	21	33	53	9.6
R	30–73	5–218.5	0–49.5	0.3–21.2	0.5–16.3	6.65–7.39	1.9–6.1	3–22	2–38	17–55	4–235	5.5–19.8
B (n = 57) Me	52	21.5	3	10.6	2.2	7.30	4.4	18	6	22	28	6.4
R	23–74	0–228.1	0–96.8	0–31.1	0–12.8	6.67–7.46	1.0–6.6	2–27	0.1–34	11–46	3–173	4.4–24.5
P	n.s.	n.s.	n.s.	n.s.	*	*	n.s.	*	*	*	n.s.	*

Note: Group A – patients with visual sequelae; group B – patients without visual sequelae.
S, serum; BD, base deficit; AG, anion gap; OG, osmolal gap; Me, median, R, range; n.s., not significant.
* Statistically significant.

practical means there was sufficient information on laboratory data and clinical symptoms on admission, treatment measures other than folate administration, and short-term outcomes for the statistical analyses in all compared groups. The study was not designed as a randomized trial, because the choice of the mode of treatment in each case was conditioned by different factors, giving the possibility of inherent bias. Nevertheless, this study was not conceived as a study looking at defining the best modality of treatment, rather describing the differences in visual outcomes in methanol-poisoned patients.

Methanol poisoning has a high mortality and incidence of long-term sequelae in spite of complex and resource-consuming treatment (Barceloux et al., 2002; Sanaei-Zadeh et al., 2011b). Administration of folates is a routine treatment to prevent visual sequelae caused by toxic effect of formic acid (Moore et al., 1994; Kerns et al., 2002). However, the clinical effectiveness of folate administration is still under the question.

In our study we aimed to characterize the laboratory and clinical features, treatment measures and visual outcomes in the patients with acute methanol poisoning treated with and without folic/folinic acid administration. The individual groups of patients were comparable by age, circumstances of intoxication (all poisonings occurred within five months of mass methanol outbreak by spirits containing mixture of methanol and ethanol in proportion from 20/80 to 50/50 in strong alcoholic beverages with an alcohol content of around 40% ABV (alcohol by volume), and time to diagnosis. The differences in laboratory data on admission between the groups were tested in serum methanol, formate, pH, pCO_2, HCO_3^-, base deficit, lactic acid, and osmolal gap, and shown to be not significant (all $P > 0.05$). Most of collected laboratory data exhibited normal distribution. The standard deviations were equivalent in all investigated parameters in all groups.

The role of methanol concentration on admission as a prognostic factor of visual sequelae was not defined till now. Some studies showed that the correlation with poor outcome was present (Swartz et al., 1981; Liu et al., 1998; Paasma et al., 2007; Desai et al., 2013), while others indicate that the differences were not significant (Naraqi et al., 1979; Lushine et al., 2003; Brent, 2010). In our study the correlation between serum methanol, osmolal gap, and visual sequelae was not found.

Laboratory data showed that visual sequelae correlated to the degree of metabolic acidosis (significant difference in pH, HCO_3^-, base deficit, anion gap) on admission. Lactate accumulation plays a significant role in the acidosis alongside with the amount of formate (Smith et al., 1981). In this study the difference in lactate level between the subgroups with and without visual sequelae was significant, unlike the difference in formate level. Higher lactate level causes deeper inhibition of citrate acid cycle and disturbances in the glycolysis process. Consequently, higher level of lactate results in deeper deteriorating metabolic acidosis, enabling greater diffusion of dissociated formic acid into retinal nerve fibres and neurons of optical nerve, which worsens the visual outcome of poisoning.

The new interesting finding was the significantly higher glucose level on admission in the patients with visual sequelae

($P = 0.01$). The mechanism suggestive of the increased blood glucose can be stress-induced hyperglycaemia usually seen in the critically ill patients. Earlier it was found that hyperglycaemia can be a prognostic factor of lethality in methanol poisoning (Sanaei-Zadeh et al., 2011a). Further studies are necessary to confirm this correlation, explain its biochemical and physiological mechanism, and test its clinical significance as a prognostic sign, and the target of possible therapeutical intervention.

Analysis of the clinical symptoms on admission showed that the differences in proportion of asymptomatic patients, patients with visual disturbances, gastrointestinal disturbances, dyspnoea, and coma among the groups were not significant. The treatment measures differed only in the mode of enhanced elimination with lower frequency of CVVHD/HDF application in the group IV.

The differences in visual outcomes between all groups were not significant (all $P > 0.05$). Interestingly, the differences were not significant among both the subgroups of patients with visual disturbances, and the subgroups without visual symptoms on admission. However, the data suggest that folates tended to be administered to the patients that were more severely affected (generally with slightly higher anion gap, serum lactate, and lower serum bicarbonate). So, the fact that more acidotic patients being treated with folates did not have more frequent visual sequelae can imply a certain degree of its efficacy.

In our earlier study of formate kinetics during different modes of enhanced elimination we did not find any difference in formate elimination half-lives in the patients with and without folate therapy (Zakharov et al., 2014). In the present study 76% of the patients with folic/folinic acid administration and 50% without folate therapy were treated with haemodialysis. The mean elimination half-life of formate is 3.6 h on CVVHD/HDF, and 1.6 h only on IHD (Zakharov et al., 2014). It is significantly shorter than the reported endogenous elimination half-life of formate: 5–6 h (Moore et al., 1994; Kerns et al., 2002; Hantson et al., 2005), and 20 h (Shahangian et al., 1984) and even 77 h (Hovda et al., 2007) in two further case reports. Apparently, haemodialysis enhances formate elimination to such an extent, that the elimination by the slower pathway of tetrahydrofolate-mediated formate conversion is less significant. In 23 cases where enhanced elimination was not used, the formate level was higher than 200 mg/L in four patients only with two of them discharged with visual sequelae (one treated with folic acid, another one without folates administration).

Our study confirms the earlier results (Sanaei-Zadeh et al., 2011b), that in methanol-poisoned patients symptoms of blurred or snowfield vision would be resolved as a result of adequate primary treatment measures aimed at correction of metabolic acidosis, blocking of methanol metabolism, and rapid elimination of methanol and formate by haemodialysis, with or without the specific treatment with folates.

In our study we did not demonstrate persuasively the positive effects of folate administration, i.e., that folates provided additional efficacy over standard treatment regimens. On the other hand we also could not prove the negative hypothesis, that the treatment with folates was actually not effective. The main reason is the complex character of the issue: multiple patients being treated at different times after ingestion, in different stages of poisoning, with different other modalities of treatments, etc. The further reason is related to the fact that folate administration is the adjunct therapy, with the primary treatment measures being the ADH blocking/inhibition with antidote (ethanol or fomepizole), correction of metabolic acidosis with bicarbonate, and extracorporeal elimination of methanol and formate. Success or failure in preventing visual sequelae is more likely to be tied in with the efficacy of these primary treatment measures. The evidence of it was that the only parameters correlating with visual sequelae in our study were the acidosis-related ones, so the metabolic acidosis has to be mostly counter-acted as fast as possible by the primary treatment measures.

Conclusions

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. Thus, we agree with the conclusion of Ghosh and Boyd, that till now ''there is no direct evidence of the usefulness of folates in methanol poisoning in humans'' (Ghosh and Boyd, 2003). The results of our study cannot promote folinic acid as more efficient than folic acid. Although we could find no evidence of efficacy of folates in our study, there was also no evidence against their use as adjunct agents in the treatment of methanol poisoning.

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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