Fomepizole in the treatment of acute methanol poisonings: Experience from the Czech mass methanol outbreak 2012-2013

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Objective. During an outbreak of mass methanol poisonings in the Czech Republic in 2012-2013, fomepizole was applied as an alternative antidote to ethanol. We present the laboratory data, clinical features, adverse reactions, and treatment outcomes in all patients treated with fomepizole.
Methods. Combined retrospective and prospective case series study in 25 patients, median age 50 (16-73) years, 18 males and 7 females.
Results. There were 24% fatalities, 36% survivors without health impairment, and 40% survivors with sequelae. All the patients who died were comatose on admission; the mortality was 50% among patients in a coma. The median intensive care unit length of stay was six (2-22) days. The median total dose of fomepizole was 2 (1-9) g. Complications were observed in 7/25 cases: aspiration pneumonia (4), sepsis (2), bleeding (2), malignant arrhythmia (1), delirium tremens (1), and rebound of acidosis (1). The patients who survived without impairment were less acidotic than those who died or survived with sequelae ($P<0.01$). No difference in serum methanol and formate was found between the three groups.
Conclusion. There is no evidence whether fomepizole is a more efficient antidote than ethanol with regards to the hospital mortality. The possibility of delirium tremens in the patients with a history of chronic alcohol abuse has to be taken in consideration. The benefits of fomepizole were indirect: no need to monitor serum ethanol's level during the hemodialysis in severely poisoned patients and less working overload on ICU doctors treating several poisoned patients simultaneously.

Key words: methanol poisoning, fomepizole, ethanol, treatment outcome, visual sequelae, CNS sequelae

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INTRODUCTION

Acute methanol poisoning is a serious cause of outbreaks of mass poisonings resulting in serious health sequelae and high mortality[1,2]. These poisonings generally occur either intentionally through abuse, attempted *suicide* or unintentionally through misuse or accident[3]. It is a medical emergency where rapid administration of antidotes, fomepizole or ethanol, preventing toxic metabolite formic acid formation by blocking alcohol dehydrogenase (ADH) is crucial for successful treatment[4,5]. Formate anions as the products of methanol metabolism have a strong cytotoxic effect by inhibition of mitochondrial respiration[6,7]. The accumulation of formic acid results in metabolic acidosis, lactacidemia, visual impairment and damage to the basal ganglia, especially when the concentration rises to 9-11 mmol/L (approximately 300-400 mg/L) (ref.[8-11]).

The role of ethanol in the treatment of acute methanol poisonings is well-established[12,13]. Ethanol has approximately ten times higher affinity for ADH than methanol. Thus, it effectively blocks the enzyme when its concentration in blood serum is between 1000-1500 mg/L (22-33 mmol/L) (ref.[5,14]). Fomepizole (4-methylpyrazole) is another effective antidote with affinity for ADH several thousand times higher than of methanol[15-18].

There is some evidence for the superiority of fomepizole in the treatment of methanol-poisoning[16-22]. Several authors have reported that fomepizole is pharmacokinetically more predictable than ethanol, has a safer side-effect profile, and reduces the need for hemodialysis[19-23]. However, few clinical studies exist to support or refute these arguments, and the evidence favoring fomepizole over ethanol consists of a few small, non-comparative trials involving a total of 51 patients and none of them was prospective[2,18,22]. Based on the most comprehensive current systematic assessment of the relevant literature, Beatty L. et al. urged further research into the relative benefits of fomepizole in the management of toxic alcohol ingestion[19].

In this study, we report data based on the recent mass methanol poisoning in the Czech Republic in 2012-2013 (ref.[24]). The antidote fomepizole was recently (2013) added to the WHO Essential Medicines List, but its availability is still limited. Until September 2012, fomepizole was not registered in the Czech Republic. On September 12th, one week after the first cases of methanol poisonings emerged, the Czech Toxicological Information Center

(TIC) asked the Ministry of Health for emergency permission to distribute fomepizole to the hospitals treating the poisoned patients. The Ministry issued permission on the same day, and from the following day, fomepizole was supplied to 16 hospitals in 10 regions of the Czech Republic.

We performed a combined retrospective and prospective case series study in 25 methanol-poisoned patients treated with fomepizole in order to present the new data for the laboratory parameters, clinical features, adverse reactions, treatment measures and outcomes, which will be useful for the further meta-analysis studies of the efficacy, safety and cost-effectiveness of treatment of acute methanol poisonings with fomepizole.

MATERIALS AND METHODS

Patients and procedures

The study was designed as a combined retrospective and prospective case series study. A total of 25 cases of confirmed methanol poisonings were treated with fomepizole during the period from 14 September 2012 until 12 July 2013. All these poisonings have been documented using a standardized admission protocol developed after the Norwegian methanol outbreak[2], and the discharge reports of these patients with the results of the neurological and ophthalmologic examinations on admission, during hospitalization, and on discharge have been collected and analyzed in the Czech TIC. A detailed medical record of the history of the poisoning, the onset, and the dynamics of the signs and symptoms of ocular and systemic toxicity were obtained either directly from the patients or from the relatives of critically ill persons on admission, and specified retrospectively in standardized questionnaires.

On admission, the laboratory investigations included serum concentrations of methanol, ethanol, formate, lactate, electrolytes, arterial blood gases, anion and osmolal gaps, glucose, renal- and hepatic tests, complete blood count, hematocrit, and serum proteins. The diagnosis was established if (1) a history of recent ingestion of illicit spirit was available, and serum methanol concentration was more than 6.2 mmol/L (20 mg/dL), and/or an osmolal gap higher than 19 mOsm/(kg H_2O) were noted, or (2) there was a history/clinical suspicion of methanol poisoning, serum methanol detectable, and at least two of the following were present: pH less than 7.3, serum bicarbonate less 20 mmol/L (20 mEq/L), and anion gap more than 19 mmol/L (19 mEq/L).

In 11 patients (58% of survivors), the follow-up examination was fulfilled three to six months after discharge from hospital within the prospective study of long-term visual and CNS sequelae of acute methanol poisonings[25]. The clinical examination protocol included complete ocular examination and standard ophthalmic tests (visual acuity, perimeter, color vision assessment, contrast sensibility, fundus examination), optical coherence tomography (OCT) with retinal nerve fibers layer thickness evaluation, visual evoked potentials (VEP), magnetic resonance imaging of the head, neurological and neuropsychological examinations, biochemical tests (electrolytes, glucose, glycohemoglobin, albumin, pre-albumin, renal and hepatic tests, cholesterol, lipids, thyroid-stimulating hormone (TSH), vitamin B_{12}, carbohydrate deficient transferrin (CDT), complete blood count, hematocrit, ethyl glucuronide in urine), and standardized questionnaire forms (circumstances of poisoning, medical history, comorbidities, etc.).

The patients were retrospectively divided into three groups according to the outcome: group I, the patients who survived without sequelae; group II, the patients who survived with sequelae; group III, the patients who died. Patients were considered to have visual impairment if the symptoms of toxic neuropathy of the optic nerve were documented on admission/during hospitalization, with pathologic findings on visual acuity, visual fields, color vision, and contrast sensitivity, and persisting lesions on fundoscopy, OCT, VEP with other symptoms of visual damage were found on discharge from hospital and/or 3-6 months after discharge. Patients were considered as having impairment of the central nervous system (CNS) with sequelae of poisoning if symmetrical necrosis and hemorrhage of the basal ganglia were present on computed tomogram during the hospital stay and/or magnetic resonance image of the brain 3-6 months after discharge.

Treatment

All patients were treated in accordance to the American Association of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists (AACT/EAPCCT) practice guidelines on the treatment of methanol poisoning[26]. Bicarbonate 8.4% or 4.2% solution was administered intravenously as a buffer to patients with metabolic acidosis. Fomepizole (Fomepizole EUSA, EUSA Pharma, France) was administered as a bolus dose of 15 mg/kg i.v. diluted in isotonic saline, and then 10 mg/kg every 12 h in patients without hemodialysis, and every 4 h during hemodialysis. From the fifth dose and on, 15 mg/kg was administered in order to compensate for increased metabolism[27].

Because there was limited availability of fomepizole, the following antidote-saving approach was used: a) if fomepizole was not available immediately, the standard scheme of ethanol administration to rapidly achieve the protective serum concentration 100-150 mg/dL (21.7-32.6 mmol/L) was initiated as soon as possible; b) fomepizole treatment was prioritized in patients with serum methanol higher than 50 mg/dL (15.6 mmol/L) (or formate higher than 40 mg/dL (8.9 mmol/L)) and pH≤7.0, or methanol higher than 30 mg/dL (9.4 mmol/L) and pH≤7.0 in patients unable to hyperventilate (pCO_2 > 3.07 kPa or 23.0 mmHg); c) treatment with fomepizole was stopped and followed by ethanol administration when methanol concentration decreased below 30 mg/dL (9.4 mmol/L) given a normal pH, or 20 mg/dL (6.2 mmol/L) if metabolic acidosis was not yet corrected. The rationale for this approach was to decrease the risk of incomplete ADH blocking by possible fluctuations of ethanol levels in the

most severely poisoned patients, especially during hemodialysis, and to avoid respiratory depression caused by ethanol in patients hyperventilating to compensate for the acidosis.

Hemodialysis was performed if the patients filled any of the following criteria: serum methanol higher than 50 mg/dL (15.6 mmol/L), metabolic acidosis with a pH<7.30, or had visual toxicity[21]. The mode of dialysis, intermittent hemodialysis (IHD), extended daily dialysis (EDD), or continuous veno-venous hemofiltration/hemodialysis/hemodiafiltration (CVVH/HD/HDF), was based on several factors, such as the hemodynamic stability of the patient on admission, or the severity of poisoning, but availability also played an important role: some smaller hospitals only had CVVH/HD/HDF available in the anesthesiology departments, whereas larger hospitals usually also had EDD/IHD available.

Folates were administered to substitute the inner pool of tetrahydrofolate: folinic acid (Calcium folinate Hospira, amp. 20 mL, 10 mg/mL Hospira UK Limited, Great Britain, and folic acid (Acidum folicum Léčiva, tbl. 10 mg, Zentiva, Czech Republic)). The dose of folinic acid was 50 mg, administered intravenously, every 4-6 h until methanol and formate were eliminated. Folinic acid was diluted 5% glucose in water and administered over 30-60 min. If folinic acid was not available, 50 mg of folic acid in tablets were administered orally every 3-4 h. Corticosteroids were not administered to patients with visual disturbance.

Laboratory investigations

Methanol was measured using gas chromatography with flame ionization detection and a direct injection with internal standard (Gas Chromatograph Chrom 5, Laboratory Instruments Prague, Czech Republic), limit of detection 1.9 mmol/L (60 mg/L) and day-to-day coefficient of variation 2.5-5.4%. Calibrators and controls were made by dilution of methanol p.a. (Penta, Czech Republic).

Formate was measured enzymatically by a Hitachi analyzer (Hitachi 912, Hitachi Science Systems Ltd., Japan) using formate dehydrogenase (Roche, France) and nicotinamide adenine dinucleotide (NAD) (Roche, France), according to a previously published method[28-31]. Pure sodium formate (Sigma-Aldrich, USA) was used to prepare a standard of 1.1 mmol/L phosphate buffer and two control sera. Day-to-day coefficient of variation was 5.6%, and the upper reference limit was 0.4 mmol/L (20 mg/L).

Serum ethanol was analyzed by gas chromatography with flame ionization detection and a direct injection with internal standard (Gas Chromatograph Chrom 5, Laboratory Instruments Prague, Czech Republic). Limit of detection is 0.9 mmol/L (40 mg/L) and day-to-day coefficient of variation 3.8-7.1%. Ethanol standards were purchased from Erba Lachema, Czech Republic. Osmolality was measured by freezing point depression method on a Fiske one-ten osmometer. Reference range for the osmolal gap was -9 - 19 mOsm/(kg H_2O). The osmolal contribution from ethanol was subtracted from the measured osmolality.

Calculations and data analysis

The admission laboratory data, clinical symptoms, treatment measures and outcomes in the separate groups were compared group by group using Two-Sample Assuming Unequal Variances (Equal Means), Two-sample F-Test for Variances, Bias test, and two-sample Kolmogorov-Smirnov test. The normality of data distribution was characterized using skewness and kurtosis tests. Data are expressed as medians and arithmetic means with either range or standard deviation or confidence interval (significance level α=0.05), as appropriate. For comparison of results, common statistical tests were (t-Test: Two-Sample Assuming Equal Variances, t-Test: Two-Sample Assuming Unequal Variances (Equal Means), Two-sample F-Test for Variances, Bias test, ANOVA test, etc.). All statistical calculations were carried out at a level of significance α = 0.05 (ref.[32,33]). The calculations were performed using Excel 2003 (Microsoft, USA) and QC Expert software 3.1 (Trilobyte, Pardubice, Czech Republic).

RESULTS

The discharge reports and standardized admission protocols of all 25 patients, median age 50 (16-73 years), 18 males and 7 females, treated with fomepizole were analyzed in Czech TIC. Six patients (24%) died in hospital and 19 (76%) survived. Eleven of these signed the informed consent and were subjected to clinical examinations three to six months after discharge. The ingested toxic spirits contained approximately 50% methanol and 50% ethanol in different kinds of strong alcoholic beverages (Slivovitz, Rum Tuzemak, Vodka Drak and others) with total alcohol content around 40% ABV (alcohol by volume, v/v). Four subjects consumed other alcoholic beverages (wine, beer, whisky, and home-made spirits) concomitantly. Eight patients had detectable ethanol before hospital treatment with antidote. Only 24% of the patients were admitted within 24 h after the methanol ingestion, 40% within 48 h, and 24% later than 48 h. In 12% of cases, it was impossible to identify reliably the time to diagnosis. A medical history of chronic alcohol abuse was present in 6 cases.

Admission data

The laboratory data in the patients treated with fomepizole on admission are shown in Table 1.

Clinical symptoms

The clinical features on admission are shown in Table 2.

Among the patients treated with fomepizole 3/25, (12%) were asymptomatic on admission; two of them appeared inebriated with measurable ethanol in the blood. Among the symptomatic patients, the most frequent signs

Table 1. Demographics and laboratory data on admission in 25 patients treated with Fomepizole.

No.	Age	G	Alcohol abuse	Time to diagnosis (h)	Dose ingested mL	Coing. EtOH	MetOH mmol/L	EtOH mmol/L	Formate mmol/L	Lactate mmol/L	pH	pCO_2 kPa	HCO_3^- mmol/L	BE mmol/L	AG mmol/L	OG. mmol/ kgH_2O	Glucose mmol/L	Creatinine µmol/L
1.	37	M	No	48-72	ND	Yes	12.5	0.0	14.4	1.1	7.25	ND	13.8	-13.9	24	14	6.1	109
2.	30	M	No	48-72	ND	No	86.7	0.0	19.9	11.4	6.71	ND	4.3	-38.1	55	128	18.4	175
3.	38	M	ND	48-72	100	No	43.1	0.0	ND	8.2	6.69	3.2	2.7	-29.1	33	70	19.8	154
4.	46	M	ND	24	350	Yes	93.6	10.9	ND	1.5	7.37	4.9	20.9	-3.5	24	111	6	84
5.	66	F	ND	11	100	No	22.5	1.7	16.6	ND	7.06	1.5	3.2	-24.7	36	52	5.9	58
6.	46	M	Yes	18	600	No	108.6	5.0*	ND	7.8	6.86	2.6	3.5	-30	28	120	12.7	87
7.	60	M	Yes	60	ND	No	22.5	0.0	12.5	3.5	7.02	1.3	2.5	-26.4	32	41	11.9	127
8.	40	M	ND	30	700	No	49.3	0.0	ND	3.0	7.05	1.0	2	-26.2	36	65	9.3	115
9.	54	M	Yes	36	500	No	47.8	25.6	ND	ND	7.39	3.9	17.2	-6.3	20	51	6.6	101
10.	58	F	No	48	100	No	105.4	5.2*	17.8	2.1	7.11	3.4	7.8	-21	24	91	7	71
11.	73	M	No	24	400	ND	30.9	17.4*	13.5	1.7	7.16	4.0	11.4	-17	29	52	7.7	81
12.	60	M	ND	48	ND	ND	75.5	0.0	12.2	9.3	6.65	7.8	6.3	-31.9	33	104	11.2	188
13.	43	F	ND	ND	ND	No	56.2	0.0	16.4	8.0	6.93	4.9	7.6	-26.9	ND	ND	15.8	105
14.	67	M	ND	52	250	No	13.1	3.0	4.9	3.7	7.18	3.0	10.8	-18.1	ND	ND	5.7	120
15.	50	M	ND	26	750	Yes	27.2	11.7*	8.9	2.6	7.34**	4.7	18.7**	-6.1	20	ND	5.5	84
16.	48	F	ND	ND	ND	ND	56.5	0.0	9.6	9.5	6.65	3.2	3.6	-35.7	43	82	15	102
17.	61	M	Yes	48	250	Yes	21.8	0.0	1.0	ND	7.37	4.2	18	-6	18	ND	6.1	85
18.	36	M	ND	24	1200	No	51.8	0.0	3.8	4.0	6.98	1.5	3.4	-27.2	40	128	6.5	112
19.	62	M	Yes	48-72	ND	ND	41.5	0.0	15.6	12.4	6.65	4.3	3.2	-28.9	45	108	15	178
20.	16	F	No	48	750	No	11.5	0.0	13.4	7.1	6.7	4.1	3.9	-33.6	25	41	12.5	191
21.	56	F	No	ND	ND	ND	67.4	0.0	ND	5.6	6.79	5.3	6	-31	50	ND	11.1	121
22.	32	F	No	30	500	No	10.1	0.0	14.7	6.4	6.99	3.0	5.2	-25.8	25	ND	9.4	110
23.	63	M	Yes	48	ND	ND	123.3	0.0	ND	ND	6.85	3.5	4.6	-28.5	45	ND	13.4	118
24.	50	M	No	48	ND	No	20.3	0.0	ND	ND	7.25	2.7	8.8	-16.7	28	41	6.4	109
25.	33	M	No	48	ND	ND	28.9	0.0	15.4	16.3	6.72	3.2	2.9	-34.6	49	34	19.5	199
Median (range)	50 (16-73)	-	-	48 (11-72)	450 100-1200	-	43.1 10.1-123.2	0.0 0.0-25.6	13.5 1.0-19.9	6.0 1.1-16.3	6.99 6.65-7.39	3.4 1.0-7.9	5.2 2.0-20.9	-26.4 -3.5- -38.1	32.2 18.1-54.8	67.5 14-128	9.4 (5.5-9.8)	110 (58-119)
Mean (95%CI)	49 (±5.8)	-	-	43.6 (±8.3)	470 (±180)	-	49 (±14)	3.2 (±2.7)	12.4 (±2.7)	6.3 (±1.9)	6.99 (±0.10)	3.53 (±0.66)	7.7 (±2.4)	-23.5 (±4.1)	33.2 (±4.6)	74 (±18)	10.6 (±1.9)	119 (±16)

G - gender; M - male; F - female; EtOH - serum ethanol; MetOH - serum methanol; AG - anion gap. BE - base excess; OG - osmolal gap. Me - median. R - range; ND - not determined; CI - confidence interval; Coing. EtOH - coingestion of ethanol in other alcoholic beverages;

*ethanol was administered before the first measurement; **bicarbonate was administered before the measurement. To convert from mg/L to mmol/L divide the concentration in mg/L on the following conversion factors: methanol - 32.05; ethanol - 46.08; formate - 46.03; lactate - 90.09; glucose - 180.18. To convert bicarbonate and base deficit from mmol/L to mEq/L use the conversion factor 1.0. To convert kPa to mmHg (torr) use the conversion factor 7.501.

Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014 Dec; 158(4):641-649.

Table 2. Clinical features on admission, treatment and outcomes in 25 patients treated with Fomepizole.

No.	Clinical features	PSS	GCS	MAP	VP/IN	Intubation	Alkalization	Folate	Hemodialysis (duration hrs.)	Complications	Total dose of Fom (g)	ICU LOS (days)	Control examination	Outcome of poisoning
1.	GI.VD	1	15	85	No	No	No	No	EDD (5)	0	2	2	YES	VS, CS
2.	VD.D.C	3	3	79	No	Yes	Yes	AF	EDD+CVVHD	Pneumonia	5**	7	YES	VS, CS
3.	GI.D.F.C	3	3	83	Yes	Yes	Yes	AF	IHD (8); CVVHD	Ventricular fibrillation, elevation of cardiomarkers, bleeding	2*	10	YES	VS, CS
4.	Ebriety	1	15	93	Yes	No	No	AF	CVVHD (80)	0	5*	6	YES	NONE
5.	GI.VD.D	3	15	88	No	No	Yes	AF	CVVHDF (36)	0	3*	4	YES	NONE
6.	GI.VD.C	3	5	78	No	Yes	Yes	No	CVVHDF (72)	Delirium tremens, sepsis	4.5*	22	YES	VS, CS
7.	CP.D.GI.VD	3	15	47	Yes	Yes	Yes	Leuc	CVVHD	Pneumonia, SIRS, MODS	6	15	NO	NONE
8.	D.GI.VD	3	15	98	No	No	Yes	Leuc	IHD (8)	0	1	2	NO	VS***
9.	Ebriety	1	15	113	No	No	No	Leuc	IHD (8)	0	2	3	NO	NONE
10.	VD.GI	3	15	117	No	No	Yes	No	IHD (4x3)	0	3**	3	NO	NONE
11.	VD.D	2	15	113	No	No	Yes	Leuc	IHD (2x2)	0	2,5*	3	YES	VS
12.	CP.D.RA.C.S	3	3	70	Yes	Yes	Yes	No	IHD(5);CVVHD(11)	0	2,8*	2	NO	died
13.	CP.D.GI.VD.C	3	3	84	Yes	Yes	Yes	AF	IHD (9)	0	6	15	NO	died
14.	D.GI.VD.C	3	3	43	Yes	Yes	No	AF	CVVHD (30)	Pneumonia	2*	14	NO	NONE
15.	GI.D	1	12	92	Yes	Yes	Yes	AF	IHD (3x8)	Sepsis	2*	12	NO	NONE
16.	D.GI.VD.C	3	3	104	No	Yes	Yes	Leuc	CVVHD (20)	0	1*	17	NO	CS, VS
17.	GI	1	15	85	No	No	No	Leuc	IHD (8)	0	1	2	YES	NONE
18.	CP.GI.VD	3	12	127	No	Yes	Yes	Leuc	IHD (8)	0	4,5*	7	YES	CS
19.	C.CP.D.VD	3	3	57	Yes	Yes	Yes	AF	CVVHD (57)	0	9*	6	NO	died
20.	C	3	3	80	Yes	Yes	Yes	Leuc	CVVH	0	3,5	8	NO	died
21.	C	3	3	98	Yes	Yes	Yes	Leuc	CVVH	Pneumonia, hematuria, bleeding, rebound acidosis	2*	17	NO	died
22.	GI.VD.D	3	12	85	Yes	Yes	Yes	No	EDD (9)	0	1*	3	YES	CS
23.	C.RA	3	3	97	Yes	Yes	Yes	Leuc	CVVHD	0	2*	5	NO	died
24.	No	2	15	127	No	No	Yes	Leuc	IHD (8)	0	1*	4	NO	NONE
25.	GI.VD.C	3	5	73	Yes	Yes	Yes	Leuc	CVVHDF (19)	0	2*	15	YES	VS, CS

VD - visual disturbances, GI - gastrointestinal symptoms, D - dyspnea, CP - chest pain, C - coma, RA - respiratory arrest; PSS - Poisoning Severity Score; GCS - Glasgow coma scale; MAP - mean arterial pressure; VP/IN - vasopressors/inotropes administration; Alkalization - administration of 8.4% or 4.2% bicarbonate i.v. to correct metabolic acidosis; AF - acidum folicum; Leuc - Leucovorine (acidum folinicum i.v.); HD - hemodialysis; IHD - intermittent hemodialysis; EDD - extended daily hemodialysis; CVVHD - continuous veno-venous hemodialysis; CVVHDF - continuous veno-venous hemodiafiltration; CVVH - continuous veno-venous hemofiltration; SIRS - systemic inflammatory response syndrome; MODS - multiple organ dysfunction syndrome; ICU LOS - intensive care unit length of stay; Fom - fomepizole; Control examination - examination 3-6 months after discharge from hospitals; VS - long-term visual sequelae; CS - long-term CNS sequelae; *initial dose of ethanol was administered before fomepizole application; **ethanol administration followed the treatment with fomepizole after methanol concentration decreased below 30 mg/dL (9.4 mmol/L); ***symptoms of regressing pseudopapillitis on discharge.

Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014 Dec; 158(4):641-649.

were visual (blurry or cloudy vision, central visual field defects, and alterations in light, color and depth perception) and gastrointestinal disturbance (nausea, upset stomach, vomiting) – both were present in 15/25 patients (68%); dyspnea was found in 13/25 (52%), coma in 12/25 (48%), and chest pain in 5/25 (20%) patients. Altogether 16/25 (64%) of the patients were intubated, 13/25 (52%) were administered vasopressors/inotropes to support hemodynamics, and 18/25 (72%) of the patients had severe grade of Poisoning severity score (PSS 3) on admission.

Treatment

The treatment of patients with fomepizole included alkalization in 80%; initial bolus of ethanol was administered before fomepizole application in 16/25 (64%) of cases, and administration of ethanol followed the treatment with fomepizole after the decrease in methanol concentration under 20 mg/dL (6.2 mmol/L) and correction of metabolic acidosis in 2/25 (8%) cases. The median total dose of fomepizole administered during the course of treatment was 2 g (1-9 g) that is 20 ampules containing 100 mg of the substance. Folates were administered in 20/25 (80%) subjects (folinic acid in 12 patients, folic acid in 8 patients). Continuous modes of hemodialysis were applied in 56% of patients; intermittent hemodialysis was performed in 44%, and extended daily hemodialysis in 12%.

Complications during treatment were found in 7/25 (28%) of cases: the most frequent being aspiration pneumonia (4 cases), followed by sepsis (2 cases), and bleeding due to heparinization during the hemodialysis (2 cases). No cases of seizures, hypoglycemia, or pancreatitis, renal or hepatic failure due to fomepizole administration occurred. One case of malignant arrhythmia (ventricular tachycardia with ventricular fibrillation requiring two series of defibrillation) followed by acute coronary syndrome with significant elevation of cardio markers was observed during the IHD. One case of delirium tremens occurred in a patient with a history of chronic alcohol abuse. Finally, one case of rebound of metabolic acidosis after the discontinuation of CVVH due to bleeding episodes occurred.

Outcomes

The outcomes in the patients treated with fomepizole were the following: 24% fatalities, 36% survivors without health impairment, and 40% survivors with sequelae, of whom solely visual impairment was diagnosed in 2/25 (8%), solely CNS impairment in 2/25 (8%), and both visual and CNS sequelae in 6/25 (24%).

All the patients who died were comatose on admission. Mortality was 50% among patients in a coma on admission. The patients who survived with health impairment were comatose on admission in 50% of cases and had signs of visual toxicity before admission in 90% cases.

Median intensive care unit length of stay (ICU LOS) was six days (range 2-22 days). The median ICU LOS in the patients who survived without impairment was 4 (2-15 days), in those who survived with sequelae 7 (2-22) days, and finally in those who died 7 (2-17) days. One patient with complications during therapy died, three survived with both visual and CNS injury, and other three subjects survived without impairment.

The outcomes of the treatment with fomepizole in three groups of patients are shown in Table 3. Patients who survived without health impairment differed significantly from the other 2 groups in arterial blood pH, bicarbonates, base deficit, anion gap, serum lactate and glucose. The patients who survived with visual/CNS impairment differed from those who died, in serum ethanol on admission and pCO_2, but not in severity of metabolic acidosis. There were no significant differences in serum methanol or formate between the three groups.

DISCUSSION

Methanol poisonings have a high mortality and incidence of long-term health impairment in spite of a complex and resource-consuming treatment[34]. Fomepizole administration as a first-choice antidote is a well-established treatment in patients with acute methanol poisoning[14,34]. However, the relative efficacy of fomepizole is still under discussion[35,36].

In our study, fomepizole was administered to patients hospitalized during the outbreak of mass methanol poisonings in the Czech Republic. However, due to the limited availability of this antidote, ethanol was used more frequently but the severely poisoned patients were mainly treated with fomepizole. More than 70% of these patients had a PSS 3 grade and half of them were comatose on admission. Nevertheless, our data demonstrated that the hospital mortality of the patients treated with fomepizole did not differ significantly from the total hospital mortality of all the patients treated in hospitals with acute methanol poisonings in the Czech Republic (24% (n=6/25) vs. 21% (n=21/101), $P>0.05$)) (ref.[24]). This fact can indirectly suggest that giving fomepizole to the most severely poisoned patients in the resource-limited situation of mass outbreak was justified; the rate of mortality in the most severely poisoned patients treated with fomepizole was no higher than the total hospital mortality rate during the mass methanol outbreak.

The hospital mortality rate in the first mass methanol outbreak in Norway, where fomepizole was used predominantly, did not differ from the hospital mortality rate in our study (7/36, 19% vs. 6/25, 21%; $P>0.05$) (ref.[2]). No other data from mass methanol outbreaks, where fomepizole was used, were found in the literature till now. In Estonia, where solely ethanol was used as an antidote during the outbreak in 2001, reported hospital mortality rate did not differ from the results of our study (23% vs. 21%; $P>0.05$). Therefore, no direct proof of the greater efficacy of fomepizole with regards to the hospital mortality was found.

Nevertheless, we did not design this study as a randomized control trial, as the groups were likely too small, and fomepizole was often given after the initiation of treat-

Table 3. Laboratory data and clinical features on admission in 25 patients treated with Fomepizole divided according to the outcome groups (medians, ranges).

Group	Age	Coma	VD	MetOH mmol/L	EtOH mmol/L	Formate mmol/L	Lactate mmol/L	pH	pCO_2 kPa	HCO_3^- mmol/L	BD mmol/L	AG mmol/L	OG mmol/ kgH_2O	Glucose mmol/L	Creatinine µmol/L
I (n=9)	58 46-67	1	4	22.5 13.1-105.4	3.0 0-25.6	10.7 1.0-17.81	2.6 1.5-3.7	7.25 7.02-7.39	3.4 1.3-4.9	10.8 2.5-20.9	-16.7 -26.4- -3.5	23.7 18.1-36.3	51.6 40.6-111	6.1 5.5-11.9	85 58-127
II (n=10)	38 30-73	5	9	46.2 10.1-108.6	0 0-17.4	14.4 3.8-19.9	7.1 1.1-16.3	6.92 6.65-7.25	3.1 1-4	3.6 2-13.8	-28.2 -38.1- -13.9	34.7 23.9-54.8	70 14-128	11.1 6.1-19.8	111 81-199
III (n=6)	58 16-63	6	2	61.8 11.5-123.3	0 0-0	14.5 12.2-16.4	8 5.6-12.4	6.75 6.65-6.93	4.6 3.5-7.9	5.3 3.2-7.6	-30 -33.6-26.9	45 24.7-50.4	104.1 41.4-108	13 11.1-15.8	149.5 105-191
$P_{I=II}$	0.007**	0.223	0.033*	0.696	0.236	0.451	0.025*	0.002**	0.346	0.024*	0.004**	0.026*	0.563	0.013*	0.062
$P_{I=III}$	0.446	<0.001***	0.667	0.315	0.05*	0.232	0.005**	<0.001***	0.048*	0.025*	0.001**	0.016*	0.465	<0.001***	0.006**
$P_{II=III}$	0.308	0.006**	0.018*	0.439	0.05*	0.652	0.538	0.171	0.009**	0.993	0.414	0.575	0.804	0.721	0.251

EtOH - serum ethanol; MetOH - serum methanol; AG - anion gap. BD - base deficit. OG - osmolal gap. VD - visual disturbances on admission. Me - median. R - range; $P_{I=II,}$ $P_{I=III,}$ $P_{II=III}$ - results of Chi^2 test of difference in laboratory parameters between the Groups I, II, and III (*α≤0.05; ** α≤0.01; ***- α≤0.001 (α- significance level)).

To convert from mg/L to mmol/L divide the concentration in mg/L on the following conversion factors: methanol - 32.05; ethanol - 46.08; formate - 46.03; lactate - 90.09; glucose - 180.18. To convert bicarbonate and base deficit from mmol/L to mEq/L use the conversion factor 1.0. To convert kPa to mmHg (torr) use the conversion factor 7.501.

Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014 Dec; 158(4):641-649.

ment with bolus of ethanol or followed by ethanol infusions after the critical phase of poisoning. The benefits of fomepizole observed in the study were indirect ones: no need to monitor serum ethanol level (each 1-2 hours) during the hemodialysis in severely poisoned patients and less work overload on ICU doctors treating several poisoned patients simultaneously. This allowed for management of the most severely poisoned patients through the most critical phases, including the dialysis sessions where ethanol dosing is especially difficult[37].

The relatively higher prevalence of visual and CNS sequelae in our study compared to the literature, where 18-30% have been reported[26,36], can be explained as an underestimation of the long-term impairment due to the absence of follow-up prospective studies in patients who survived poisonings with complete ocular and neurological examinations, and CT/MRI of brain to detect the subclinical damage to the basal ganglia.

In our study we found no adverse effect directly related to the administration of fomepizole. Most complications during treatment were caused by infectious agents and heparinization during the continuous enhanced elimination. No case of hypoglycemia, seizures, pancreatitis, renal or hepatic damage due to administration of fomepizole was reported. The single case of rebound of metabolic acidosis was related to the early discontinuation of CVVH due to bleeding complications and further inhibition of mitochondrial respiration by the remaining formic acid resulting in further accumulation of lactic acid.

One case of delirium tremens was caused by the abrupt discontinuation of ethanol intake in a patient with a history of chronic ethanol abuse of approximately 1 L of strong alcoholic distillate daily. This case may represent the single condition where fomepizole treatment instead of ethanol has to be considered carefully. As a result of the complication during therapy, this patient was in the ICU for longer than all the other patients.

Finally, the episodes of malignant arrhythmia during the IHD requiring repeated defibrillation in one subject were most probably related to the development of acute coronary syndrome with significant elevation of cardio markers in the severely poisoned patient.

Both the patients who died and the patients who survived with health impairment were significantly more acidotic on admission than those who survived without sequelae; but the difference in severity of metabolic acidosis was not significant between those who died and those who survived with sequelae. In an earlier study of Paasma et al., there was a trend to a "positive" shift in morbidity and mortality (i.e., a better outcome) in the fomepizole group relative to the ethanol group regarding the pH, but this difference was not significant[38]. In our study, the patients treated with fomepizole who survived with visual/CNS injury had a median pH 6.92 (6.65-7.25, n=10), that was lower than the median pH 7.02 (6.65-7.39, n=20) of all the patients surviving methanol poisoning with visual/CNS impairment during the Czech mass methanol outbreak 2012 (ref.[24]), but the difference was not significant (P=0.218). Hence the observation of a "positive" shift in the patients treated with fomepizole from lethal outcome toward survival with sequelae remains unproven.

In conclusion, we have to agree with the statement of Beatty L. et al. based on the results of meta-analysis of all the data available to 2012 on the treatment of toxic alcohols poisoning with fomepizole and ethanol, that "until further evidence on the use of ethanol and fomepizole is available, either antidote may be considered for ADH blockade. Clinicians should consider other factors, including cost, efficiency, resource utilization, patient demographic, availability of antidote, and familiarity with the drug when making decisions on the management of toxic alcohol ingestion[36]".

STRENGTH AND LIMITATIONS

The study has limitations. It is neither a randomized controlled trial nor a cohort trial precluding any direct comparisons. It is a case series, with heterogeneous patients, the reporting of ingestion doses might not be accurate, and timing and quality of interventions were not documented in real time. Other factors may confound the results such as the co-ingestion of different types and quantities of concomitant alcoholic beverages, different temporal patterns of toxic alcohol ingestion, co-morbidities, and so on. Many of these factors could be established with some degree of approximation only.

Despite these limitations, this is to date the most comprehensive data ever presented on the use of fomepizole during a mass methanol outbreak. Most of the essential clinical and laboratory data on admission were collected during the hospitalizations using standardized forms distributed to the hospitals by the TIC during the first weeks of the outbreak. Further, this is the first-ever study to include follow-up examination in almost 60% of the patients who survived the poisoning, 3-6 months after the discharge using advanced technologies to identify and characterize the long-term visual and CNS sequelae of methanol poisonings. All patients were seen within the follow-up examination at the same medical facility, according to a standardized protocol including complete ophthalmologic and neurological examinations, as well as biochemical and toxicological tests to limit the influence of other confounders.

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