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Administration

Cost-effectiveness of hospital treatment and outcomes of acute methanol poisoning during the Czech Republic mass poisoning outbreak[☆]



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ABSTRACT

Purpose: During an outbreak of mass methanol poisoning in the Czech Republic in 2012–2014, we compared the total hospital costs and one-year medical costs in the patients treated with different antidotes (fomepizole versus ethanol) and modalities of hemodialysis (intermittent hemodialysis, IHD, versus continuous renal replacement therapy, CRRT).

Methods: Cross-sectional study in 106 patients with confirmed diagnosis treated in 30 ICU settings. For each patient, the following data were analyzed: admission laboratory data, GCS, PSS, ICU length of stay, organ failures, treatment, outcome, and total hospital costs. Of 83 survivors, in 54 (65%) patients the follow-up examination, quality of life measurement with SF36 questionnaire two years after discharge, and one-year medical costs analysis were performed.

Results: The median total hospital costs were 7200 (IQR 1500–10,900) euros and the median one-year medical costs were 1447 (IQR 133–1163) euros in the study population. The total hospital costs were higher in the patients treated with fomepizole comparing to ethanol: 12,890 (IQR 6910–16,210) versus 5590 (IQR 1430–6940) euros ($p < 0.001$). The hospital costs in the patients treated with IHD were 5400 (IQR 1520–6910) versus 12,410 (IQR 5380–16,960) euros in the patients with CRRT ($p = 0.317$).

The geometric mean ratio for increased hospital costs in the patients treated with fomepizole versus ethanol adjusted for the severity of poisoning was 3.30 (1.70–3.80 CI 95%), $p < 0.001$, and in the patients treated with IHD versus CRRT - 0.70 (0.60–0.99 CI 95%), $p = 0.047$.

The patients with visual sequelae had higher total hospital costs than those without sequelae: 10,419 (IQR 2984–14,355) versus 4605 (IQR 1303–4505) euros ($p = 0.009$). The patients with GCS ≤ 13 on admission had higher one-year medical costs as well ($p < 0.001$). No difference was found in physical and mental condition scores in the patients treated with different antidotes and modalities of hemodialysis two years after discharge (both $p > 0.05$).

Conclusion: The total hospital costs in the patients with acute methanol poisoning were more than three times higher in the patients treated with fomepizole than in the patients treated with ethanol after adjustment for the severity of poisoning. The dialysis modality did not affect the total hospital costs, but the trend to lower costs was present in IHD-group.

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1. Introduction

1.1. Background

The outbreaks of mass or cluster methanol poisoning as a result of its use as a cheap substitute for ethanol present a number of challenges the health systems face worldwide. Delayed presentation and diagnosis, non-specific clinical signs and features at admission, limited availability of diagnostics and treatment resources in the hospitals, insufficient

evidence of comparative clinical effectiveness and safety of therapeutic measures, complications during the treatment, high mortality rate and prevalence of long-term health damage in the survivors are the main ones [1–3].

During 2000–2012, >50 methanol mass poisoning outbreaks with about 5000 poisoned subjects and >2000 fatalities had occurred worldwide [4]. Most of the events occurred in the developing countries, where the resources were limited and the epidemiological, laboratory and clinical data were insufficient for an adequate analysis. Nevertheless, recent mass methanol poisoning outbreaks in Estonia with >150 cases of poisoning [5], in Norway with >50 cases [6], and in the Czech Republic [7] provide clear evidence of this public health emergency for the health systems of developed European countries as well.

The treatment of acute methanol poisoning is highly specific and resource-consuming, requiring hospitalization on ICU unit, administration of antidote to block alcohol dehydrogenase (ADH), correction of acidemia with bicarbonate, folate substitution, and enhanced elimination methods [8–10]. If specific interventions are inadequate or delayed, mortality exceeding 40% as well as serious health sequelae in survivors may occur [11–16].

1.2. Importance

The role of ethanol in the treatment of acute methanol poisoning has been well established since the 1940s [17–19]. Ethanol has approximately ten times higher affinity for ADH than methanol, and a serum concentration of 100–150 mg/dL (22–33 mmol/L) is sufficient to block the metabolism of methanol to formate [20–22]. Fomepizole (4-methylpyrazole) is another effective antidote with affinity to ADH several thousand times higher than methanol [23,24]. It was first approved for use in the US for the treatment of ethylene glycol toxicity in 1997, and for the treatment of methanol toxicity in 2000 [25,26]. In Europe, it has been approved as an antidote for poisoning with ethylene glycol since 2002 [27]. The antidote fomepizole was recently (2014) added to the WHO Essential Medicines List, but its availability is still limited. As a rule, higher cost and limited availability of fomepizole in Central and Eastern European regions, as well as in the underdeveloped countries, render the issue of ethanol administration as a cheaper and more widely available antidote, especially during the outbreaks of mass methanol poisonings.

Evidence exists regarding the superiority of fomepizole over ethanol antidote due to more predictable pharmacokinetics, safer side-effect profile, and decreased need for hemodialysis [28–31]. We found no difference in clinical effectiveness of two antidotes in our previously published study [32]. Based on the most comprehensive modern systematic assessment of the literature on the problem, Beatty et al. (2013) called for further research into the relative benefits of fomepizole in the management of toxic alcohol ingestions [25].

Intermittent and continuous modalities of hemodialysis are used in the treatment of methanol poisoning. Despite an established consensus regarding the role of hemodialysis in the treatment of methanol poisoning, specific indications and the modalities of choice for its use, no data on comparative cost-effectiveness of different modalities have been published [8]. Given the fact that approximately 80% of all dialysis sessions in 2006 were performed in the developed world [33], whereas the majority of methanol poisoning outbreaks occur in underdeveloped countries where resources are scarce, and even in developed countries the extracorporeal treatments may be a limited resource during mass methanol poisoning outbreak [8,34], a thorough evaluation of the efficacy and limitations of the various modalities of extracorporeal treatment is needed.

1.3. Goals of this investigation

Close collaboration between the Ministry of Health, Toxicological Information Center (TIC), medical insurance companies, and national

hospitals allowed us to address the question of the cost-effectiveness of hospital treatment of acute methanol poisoning during a recent methanol mass poisoning in the Czech Republic [7]. The primary outcome of this study was the cost of hospital treatment in the patients treated with two different antidotes (fomepizole versus ethanol) and two modalities of extracorporeal treatment (intermittent hemodialysis, IHD versus continuous renal replacement therapy, CRRT). The secondary outcomes were one-year medical costs following discharge from hospital and the quality of life of the survivors measured by SF36 questionnaire two years after discharge from hospital.

2. Materials and methods

2.1. Study design and setting

This was a prospective, observational cross-sectional study of patients with acute methanol poisoning treated in hospital during the Czech Republic mass methanol poisoning outbreak from the 3rd of September 2012 until the 31st of August 2014 [7]. To identify the cases, mandatory reporting to the Ministry of Health and the Czech Toxicological Information Center (TIC) on all cases of hospital admission with laboratory-confirmed methanol poisoning and nationwide daily monitoring of the situation in all hospitals started on September 6, 2012, 3 days after admission of the first 3 patients with acute methanol poisoning. The admission data were collected prospectively by the treating providers using a standardized data collection form and sent to the TIC on the day following each admission to a hospital. A protocol for collection of data based on experience from a methanol outbreak in Norway in 2002–2004 was used [6]. The data on hospital treatment and outcome were collected and reviewed retrospectively from the hospital discharge reports.

The study was performed in 30 hospitals in 11 regions of the Czech Republic, where the poisoned patients were treated. These hospitals were located in the regional city-centers, had intensive care units and toxicological laboratories, and were equipped with hemodialysis and gas chromatography facilities.

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

2.2. Patient population

During the Czech mass methanol outbreak, 137 patients were poisoned and 106 of them were treated in hospitals; 83 patients survived. A detailed history of the poisoning, and of the onset and dynamics of ocular and systemic toxicity, was obtained in a prospective manner. The data on the patients admitted before distribution of the protocol were collected retrospectively. On admission, the laboratory investigations included serum concentrations of methanol, ethanol, formate, lactate, electrolytes, and bicarbonate, arterial blood gases, anion and osmolal gaps, glucose, renal- and hepatic analysis, complete blood count, hematocrit, coagulation profile, and serum proteins. Diagnosis was established when (i) a history of recent ingestion of illicit spirits was available and serum methanol was higher than 6.2 mmol/L (20 mg/dL), or (ii) there was a history/clinical suspicion of methanol poisoning, and serum methanol was above the limit of detection with at least two of the following: pH < 7.3, serum bicarbonate < 20 mmol/L (20 mEq/L), and anion gap (AG) \geq 20 mmol/L [24,28].

Hemodialysis was performed if the patients met any of the following criteria: serum methanol higher than 15.6 mmol/L (50 mg/dL), metabolic acidosis with a pH < 7.30, or visual disturbances [1,24,28]. The mode of dialysis, 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 a patient on admission, or the severity of poisoning, and availability of dialysis equipment [35]. The patients with low mean arterial blood pressure and coma on admission were treated prevalently on

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