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RAIDO PAASMA

Clinical study of methanol poisoning: handling large outbreaks, treatment with antidotes, and long-term outcomes

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Clinical study of methanol poisoning: handling large outbreaks, treatment with antidotes, and long-term outcomes

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LIST OF ORIGINAL PUBLICATIONS

I Paasma R, Hovda KE, Tikkerberi A, Jacobsen D. Methanol mass poisoning in Estonia: outbreak in 154 patients. Clin Toxicol (Phila) 2007; 45: 152–157

II Paasma R, Hovda KE, Hassanian-Moghaddan H, Brahmi N, Afshari R, Sandvik L, Jacobsen D. Risk factors related to poor outcome after methanol poisoning and the relation between outcome and antidotes – a multicenter study. Clin Toxicol 2012, 50: 823–831.

III Paasma R, Hovda KE, Jacobsen D. Methanol poisoning and long term sequelae – a six years follow-up after a large methanol outbreak. BMC Clin Pharmacol 2009; 9:5

My contribution to the articles referred to in the current thesis are as follows:

Ref. I participation in the planning of the study, coordinating the collection of the data, drafting the manuscript.

Ref. II participation in the planning of the study, the collection of the data, drafting the manuscript.

Ref. III participation in the planning of the study, drafting the manuscript, examing the patients, and coordinating the collection of the data.

ABBREVIATIONS

ABG	–	arterial blood gas
ADH	–	alcohol dehydrogenase
AG	–	anion gap
ANOVA	–	analysis of variance
BD	–	base deficit
CNS	–	central nervous system
CO	–	carbon monoxide
CT	–	computed tomography
CVVHD	–	continuous veno-venous haemodialysis
et al.	–	*et alii* – and others
GI	–	gastrointestinal
Gr	–	group
GCS	–	Glasgow Coma Scale
HD	–	haemodialysis
ICU	–	intensive care unit
IPCS	–	International Programme on Chemical Safety
IV	–	intravenous
K	–	potassium
MRI	–	magnetic resonance imaging
MW	–	molecular weight
NI	–	neurological impairment
OG	–	osmolal gap
OR	–	odds ratio
ROC	–	receiver operating characteristic
S	–	(e.g., S-methanol, S-formate) – serum concentration
VD	–	visual disturbance

1. INTRODUCTION

The term "poison" generally refers to any agent that can kill, injure, or impair the normal physiological functions of humans (Shannon *et al*., 1998). As stated by Paracelsus (1493–1541); "Any substance may be a poison – it is just a question of the dose". Poisonings were even described by the Sumerians of Mesopotamia in approximately 1400 BC. In recent times, we remember not only the Tokyo subway attack with sarin in 1995, but also the Minamata Bay mercury poisonings (1932–1968), the methyl isocyanate gas leakage in Bhopal (1984), and the Jonestown mass suicide with Valium and cyanide (1977) (Shannon *et al*., 1998).

Acute poisonings remain a major health problem today. Treatment often requires special knowledge, which is most often provided by national or regional poison information centres.

In Estonia, acute poisonings result in approximately 3,000 ambulance calls, more than 1,000 hospitalisations, and 350–420 deaths every year (EstTox2009 – epidemiologic study of acute poisonings in Estonia. Manuscript in preparation). The main toxic agents are illegal opioids, carbon monoxide (CO), and ethanol (EstTox2009). Alcohol abuse is a serious problem in our society and acute ethanol poisonings are more and more often observed among teenagers. Poisonings and deaths not only from ethanol but also from toxic alcohols, such as methanol, ethylene glycol, and isopropanol, are reported every year. Among these poisonings, methanol is the most frequent cause of death. The successful management of methanol poisonings highly depends on early hospitalisation and diagnosis because treatment is effective only when initiated in a timely fashion.

Methanol has a low toxicity in non-primates in which this substance does not cause the typical formate accumulation and ensuing metabolic acidosis that is observed in human patients. This fact gives methanol a special place among the toxic alcohols because animal experiments are of limited value for elucidating the mechanisms of toxicity and treatment of the poisoned patient. Hence, to increase our knowledge of methanol poisoning and of how to treat poisoned patients, data collection from- and publication of- human cases are important.

Different patterns of methanol poisoning have been historically documented and include mass poisonings (Bennett *et al*., 1953; Swartz *et al*., 1981; Sejersted *et al*., 1981; Krishnamurthi *et al*., 1968; Naraqi *et al*., 1979; Hovda *et al*., 2005a; Ahmad 2000) and individual cases spread over time (Hassanian-Moghaddam *et al*., 2007; Brahmi *et al*., 2007). In the scientific literature, methanol poisonings are regularly reported as case reports or smaller case series, whereas mass poisonings are rare. The poisoning events typically occur in countries with high taxes on alcohol or when methanol is used as a cheap substitute for ethanol. Illegal spirits may contain a mixture of ethanol and methanol, but in certain cases, methanol is the only alcohol distributed on the black market. Methanol can be found in commercial products, such as gasoline,

antifreeze, gasohol, windshield washer fluid, copy machine fluid, and solvents that remove wood finishes. There is also an ongoing discussion of the possible use of methanol as an alternative energy source in combustion engines.

In September 2001, a large outbreak of methanol poisoning occurred in the western part of Estonia. Over the course of nine days, more than 100 patients were hospitalised, and more than 60 died from methanol poisoning. Managing such an outbreak in a rather small hospital was a great challenge. Due to good coordination and cooperation locally and between different hospitals, many lives were saved. Unfortunately, this was not the first methanol poisoning outbreak in Estonia; in 1985, there was a smaller outbreak in the eastern part of Estonia, in which 36 people were poisoned, and 19 died. The first part of the present thesis is based on the 2001 outbreak, during which treatment protocols were rapidly established for data collection and information storage. In the second part of this thesis, our data were included in the largest international multicentre case series ever published on methanol poisoning. Finally, in the third part of this thesis we performed the first prospective long-term follow-up study of methanol poisoning victims to obtain information on their long-term prognosis.

2. LITERATURE REVIEW

2.1. Properties of methanol

Methanol *(*methyl alcohol, CH_3OH, "wood alcohol", "carbinol", or "colonial spirit") is a colourless, volatile liquid at room temperature. Today, nearly all methanol is made synthetically by the catalytic reaction of carbon monoxide (CO) or carbon dioxide in the presence of hydrogen. Methanol has a molecular weight (MW) of 32 g/mol and it boils at 65°C (IPCS 1997). This alcohol is used industrially as a solvent and as a fuel and is found in many commercially available products. After oral administration, methanol absorbs rapidly. Depending on the presence or absence of food, peak absorption occurs within 30–60 minutes. Similar to other organic solvents, methanol is relatively well absorbed through the skin and also by inhalation. It is estimated that the pulmonary absorption fraction is 65–75%. Moreover, methanol is water soluble and has an apparent volume of distribution of 0.6–0.7 L/kg (Jacobsen *et al*., 1982; Jacobsen *et al*., 1997).

2.2. Metabolism of methanol

Methanol itself has a low toxicity, whereas its metabolites are toxic. Methanol is metabolised by alcohol dehydrogenase (ADH) into formaldehyde, which is rapidly converted to formic acid by aldehyde dehydrogenase. Formic acid is mainly responsible for methanol toxicity by causing metabolic acidosis and due to the toxicity of its anion, formate (Barceloux *et al*., 2002; McMartin et *al*., 1980). The enzymes that convert formate into nontoxic carbon dioxide and water are dependent on folate. Because most primates (some apes and humans) have only small pools of folate, formate accumulates after the ingestion of methanol. The majority of other non-primate animals have sufficient stores of folate, so formate is further metabolised and does not accumulate. This makes methanol non-toxic to most animals; therefore, animal studies are of limited value in understanding methanol toxicity in humans. Thus, knowledge must be mainly gathered from human cases of methanol poisoning.

The toxic effect of formate (the anion of formic acid) is two sided: initially, metabolic acidosis is generated because of the metabolism of methanol into formic acid (formic acid $\leftrightarrow H^+ + \text{formate}^-$). The accumulated formate anions then inhibit the mitochondrial cytochrome oxidases, which interrupts the aerobic generation of energy in cells. Early formic acid acidosis is thereby augmented by lactic acidosis in the late stages of methanol poisoning (McMartin *et al*., 1980; Jacobsen *et al*., 1986). This process is the mechanistic background for the common clinical signs (dyspnoea/hyperventilation, visual disturbances (VDs), and abdominal discomfort) in exposed patients.

The slow metabolism of methanol explains why these clinical features develop 12–24 hours or even longer after methanol intake. The simultaneous

consumption of ethanol, which has a higher affinity for ADH and hence inhibits methanol metabolism, further delays the development of metabolic acidosis and clinical features from hours to days, particularly if ethanol is ingested on a regular basis. In this situation, as observed in certain cases in the Norwegian outbreak in 2002–2005 (Hovda *et al*., 2005a), the signs and symptoms of methanol poisoning may first develop when ethanol consumption is stopped and ethanol is metabolised.

2.3. Clinical features of methanol poisoning

The first signs and symptoms of poisoning include the development of VDs, abdominal pain, and dyspnoea/hyperventilation due to respiratory compensation for developing metabolic acidosis. In the late stages of poisoning, acidosis is exaggerated by the increasing production of lactic acid from anaerobic glycolysis. A clinical worsening of VDs (from "double vision" to deep blindness), increasing hyperventilation, and neurological impairment (NI) then develop. The degree of the VDs varies from blurred vision, decreased visual acuity, photophobia, and the "feeling of being in a snow field" to complete blindness. Acidosis may further increase this toxicity by affording the greater diffusion of formic acid into cells. Formic acid specifically targets the optic disc and the retrolaminar section of the optic nerve, causing optic disc oedema, the breakdown of the myelin sheaths, and optic nerve lesions (Martin-Amat *et al*., 1978; Benton *et al*., 1952). Thus, early signs of methanol poisonings are hyperaemia of the optic disc and a reduced papillary response to light. Peripapillary retinal oedema and oedema of the optic disc with loss of physiological cupping develop more slowly. This sign of "pseudopapillitis" (blurred disc margins without any dioptric difference from the retina), which is detected by ophthalmoscopy, is strongly indicative of methanol poisoning (Roe 1955).

The most common neurological signs in mild to moderate methanol poisoning are headache, vertigo, lethargy, and confusion. In severe cases, the presence of coma and convulsions suggests cerebral oedema. The pathological findings related to the neurological features are signs of oedema; necrotic damage to the basal ganglia of the brain, and more specifically to the putamen; and haemorrhages in the subcortical white matter. These findings are observed during autopsy, but are also observable by magnetic resonance imaging (MRI) (Server *et al*., 2003) and computed tomography (CT) (Feany *et al*., 2001; Taheri *et al*., 2010). Damage in this region is most likely due to local cellular oedema, which is related to the failure of the Na-K adenosine triphosphatase pump caused by the inhibition of cytochrome oxidase by formic acid (Deniz *et al*., 2000).

It is not known why the eyes and basal ganglia are the primary target organs in methanol poisoning. The high energy consumption in these brain areas, which require a high number of mitochondria, could be a feasible explanation.

2.4. Diagnosis of methanol poisoning

The initial symptoms of methanol poisoning are often non-specific and may resemble the symptoms of other medical conditions. Specific laboratory analyses are most often not available where the poisonings occur. Biochemically, typical findings during methanol intoxication are metabolic acidosis, increased anion gap (AG) and osmolal gap (OG) (where testing available), increased serum (S)-methanol (seldom available), and increased S-formate (as determined with a new and simple diagnostic approach with (so far) limited, yet increasing, availability) (Hovda *et al.,* 2005b). The measurement of arterial blood gases (ABGs) is thus the most commonly available laboratory analysis that helps to diagnose methanol poisoning.

The OG and AG, together with their correlation with each other, are useful diagnostic tools that may indicate different stages of methanol poisoning (Hovda *et al*., 2004). Each milligram of methanol per decilitre raises the OG by approximately 0.34 mOsm/kg H_2O. However, the OG also increases after the intake of other osmotically active alcohols, such as ethanol, ethylene glycol, and isopropanol (Glaser *et al*., 2006). The maximum OG occurs following the peak absorption of methanol, prior to the start of metabolism. During methanol metabolism into formic acid, the OG decreases, and the AG increases (Sullivan *et al*., 1999; Almaghamsi *et al*., 1997). The generation of formate and, to a certain extent, lactate contributes to the AG during methanol poisoning (McMartin *et al*., 1980). Therefore, in the early stages of methanol poisoning, the OG is elevated, and the AG stays at normal or slightly elevated levels. In the intermediate stages of poisoning, both the OG and the AG are elevated. Finally, in the late stages of poisoning, the OG is decreased, occasionally to normal levels (depending on the initial concentration of methanol), whereas the AG is accordingly strongly elevated (Figure 1) (Hovda *et al*., 2004).

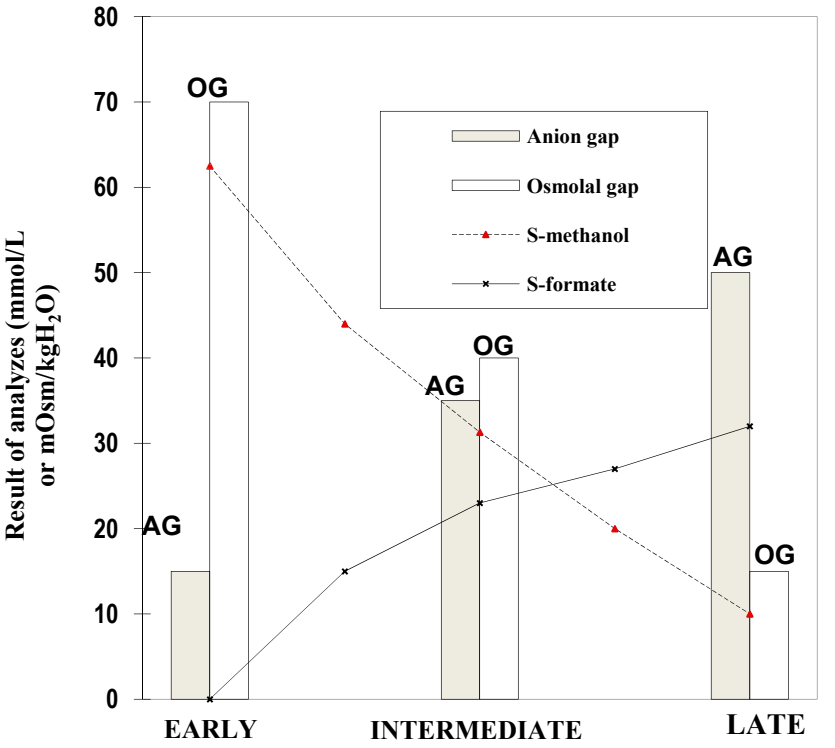


Figure 1. Three stages of methanol poisoning. AG – anion gap, OG – osmolal gap. Adapted from Hovda KE (Hovda *et al*., 2004).

The above mentioned difficulties often result in a delayed diagnosis of methanol poisoning, with a subsequent delay in treatment that is associated with fatal outcomes.

2.5. Treatment of methanol poisoning

Unlike many other poisonings, methanol poisoning needs both specific therapeutic modalities and general supportive treatment. The treatment of methanol poisoning consists of a buffer to correct metabolic acidosis, an antidote (ethanol or fomepizole) to block ADH from producing toxic formic acid, and haemodialysis (HD) to remove methanol and its toxic metabolites and to correct the metabolic acidosis. Finally, the ingestion of folinic acid is recommended to increase the endogenous formate metabolism.

Bicarbonate treatment also decreases the amount of non-dissociated formic acid, which easily accesses the central nervous system (CNS) and thereby causes toxicity. The aggressive treatment of acidosis may therefore reduce the

sequelae of methanol poisoning, particularly the VDs (Liu *et al*., 1998). Furthermore, considering the renal elimination of anions, buffering acidosis may increase the elimination of formate in the urine (Hovda *et al*., 2005c). In parallel with alkaline treatment, administering antidotes, such as ethanol or fomepizole, is important to avoid so-called "bicarbonate-resistant acidosis". This condition may develop because formic acid is continuously produced from methanol. The recommended therapeutic blood S-ethanol level is approximately 22 mmol/L (100 mg/dL). The recommended dose of fomepizole (4-methyl-pyrazole) is 15 mg/kg as a loading dose, followed by 10 mg/kg every 12 hours (Hovda *et al*., 2005c). The antidote treatment can be discontinued when the methanol level decreases to below 6 mmol/L (20 mg/dL) if there is no acidosis or VDs. During HD, the antidote dose must be increased because of the dialysability of the antidotes.

Methanol is easily removed by dialysis because of its low MW (32 g/mol), lack of protein binding, and low volume of distribution (0.6–0.7 L/kg) (Jacobsen *et al*., 1982; Hovda *et al*., 2008; Gonda *et al*., 1978). Similarly, formate has a low MW 46 g/mol, lack of protein binding, and low volume of distribution (approximately 0.5 L/kg) (Hovda *et al*., 2005b). The reported dialysis clearance rates for methanol and formate are 150–200 mL/min and 140–150 mL/min, respectively, depending on the blood flow and the surface area in the dialyser. According to the current guidelines, the absolute indication for HD are VDs in patients with detectable serum methanol concentrations or severe metabolic acidosis. Other proposed indications are severe bicarbonate-resistant metabolic acidosis and a serum methanol concentration above 16 mmol/L (50 mg/dL). The suggested duration of intermittent HD is eight hours (Jacobsen *et al*., 1997) when serum methanol concentrations (or the OG, as a substitute) are not available (Jacobsen *et al*., 1986). The endpoint for dialysis is an undetectable serum methanol concentration or a concentration below 25 mg/dL (250 mg/L), without acid-base imbalance. When methanol concentrations are high, longer dialysis of up to 18–21 hours may be required to reach these endpoints (Hoy *et al*., 1983; Burgess 1992). To increase the endogenous metabolism of formate, a folic acid intravenous (IV) infusion of 1 mg/kg, reaching up to 50 mg every six hours, is recommended (Barceloux *et al*., 2002).

2.6. Outbreaks of methanol poisoning and prognostic markers

Methanol poisonings typically present as one or a few patients with suicidal attempts, or as smaller or larger outbreaks (Bennett *et al*., 1953; Swartz *et al*., 1981; Sejersted *et al*., 1981; Krishnamurthi *et al*., 1968; Naraqi *et al*., 1979; Hovda *et al*., 2005a; Ahmad 2000). Because the diagnosis remains difficult and because outbreaks often occur in the developing world, a large proportion of the

patients is likely to die without ever receiving the correct diagnosis. Raising the awareness and knowledge of these poisonings is therefore highly dependent on reports from various outbreaks, with the value of these reports increasing with the amount of data collected onsite. The outbreaks often overwhelm health-care facilities in general and ICU beds, ventilators, and dialysis equipment in particular. Epidemiological reports highlight both the relevance of different treatment modalities and their limitations during actual usage. Prognostic features are invaluable tools for triage and resource prioritisation. Thus, the education of medical personnel is dependent on knowledge of the different presentations of methanol poisoning, which are best described from large outbreaks in a clinical setting, rather than from animal models or single case reports.

In 1942, Roe described 16 cases of methanol poisoning (Roe 1943). The patients were followed for three to six months after the poisoning episode, which was the longest follow-up period after methanol poisoning before the present thesis. The author postulated that acidosis resulted from the inhibition of the processes of oxidation and was thus mainly due to lactic acid. In these patients, severe acidosis was associated with amblyopia, and the parallel use of ethanol was associated with an improved outcome. A secondary diminution of vision was observed in all the cases, in which the normal acuity of vision was not restored. Such a gradual decline in the retina's functional capacity is most likely due to the atrophy of its blood vessels.

In later publications, various prognostic factors were identified. Bennet et al. described a large outbreak in Atlanta in which 323 patients were poisoned over the course of five days. Of these patients, 44 died, but only 31 were hospitalised (Bennett *et al*., 1953). A large number of victims were treated in emergency rooms for 24 hours or longer. The researchers suggested that the degree of acidosis was an important predictor of the outcome; in their study, the mortality rate in patients with severe acidosis was 50%, compared with 19% in patients with none to mild acidosis. In addition, Naraqi et al. found coma, seizures, and prolonged acidosis to be indicators of poor outcome (Naraqi *et al*., 1979). Similar prognostic factors were described by Liu and co-authors, who showed that patients presenting with coma or seizures had a mortality rate of 84% (16/19), compared with 6% (2/31) for the patients without those symptoms (Liu *et al*., 1998). Respiratory arrest (6/9 died) and coma (8/12 died) were also reported to be predictors of poor outcome (Hovda *et al*., 2005a). Similar findings were published by Hassanian-Moghaddam et al. (Hassanian-Moghaddam *et al.,* 2007), who confirmed a high mortality rate in comatose patients (90%, 9/10), compared with 20% (3/15) in awake patients.

In methanol poisoning, the use of the initial (low) pH as a prognostic factor was shown by Liu et al., who reported that pH<7 was associated with a high mortality rate of 89% (Liu *et al*., 1998). These observations were later confirmed by Hovda et al., who found that pH<6.9 upon admission was a predictor of a poor outcome. Additionally, Hassanian-Moghaddam et al. showed

that poisoning survivors had a higher pH upon admission (7.15±0.06) than the patients who died (6.82±0.03). Among patients with VDs upon admission, Liu et al. further described that those individuals who had prolonged acidosis also developed persistent VDs (Liu *et al*., 1998). Moreover, Hassanian-Moghaddam et al. showed that the parallel use of opium was associated with a worsening of outcome (Hassanian-Moghaddam *et al.,* 2007), which may be due to a lack of hyperventilation because of the respiratory depression caused by opioids.

As discussed before, methanol itself is not toxic; the toxicity of this alcohol is mainly caused by the metabolite formic acid. Despite this fact, Liu et al. and Brahmi et al.(Liu *et al*., 1998, Brahmi *et al.*, 2007) found that serum methanol concentrations in patients who died from poisoning were higher than in survivors. In contrast, Hovda et al., Hassanian-Moghaddam et al. and Lushine et al. did not find any correlation between methanol concentrations and outcome (Hovda *et al*., 2005a; Hassanian-Moghaddam *et al.,* 2007; Lushine *et al*., 2003).

Fomepizole was used as the antidote of choice for the first time during an outbreak of methanol poisoning in Norway, in 2002–2005 (Hovda *et al*., 2005a). The new antidote seemed to reduce the need for mechanical ventilation, the administration of the antidote was easy to manage, and in certain cases, HD could be safely delayed or even avoided (Hovda *et al*., 2005c). These features are important due to limitations in resources and logistics. The report also described the patients' ability to hyperventilate and thereby compensate for metabolic acidosis, which is a good prognostic marker.

The literature on methanol poisoning outbreaks are limited and the prognostic factors of methanol poisoning are not fully understood. Studies of large-scale clinical cohorts are therefore still needed to identify the prognostic factors more precisely. There is also a lack of long-term studies following methanol poisoning in which neurological and visual sequelae are monitored over a longer period of time.

3. AIMS OF THE THESIS

The goals of the present thesis were to describe the clinical management of a large outbreak of methanol poisoning, to study the use of two different antidotes, to investigate the long term outcome from, and to identify prognostic factors of methanol poisoning. More specifically, this thesis aimed to answer the following questions:

1. How may limitations in health care resources influence the management and outcome of mass methanol poisoning?
2. Is there a difference between the two antidotes, ethanol and fomepizole, in their effectiveness in treating methanol poisoning?
3. Which prognostic markers are the strongest predictors of the outcomes of methanol poisoning?
4. What are the long-term consequences of methanol poisoning?

4. PATIENTS AND METHODS

4.1. Patients

A total of 363 patients from four countries were screened, and of these patients, 265 were included in the research presented here. The origins of the patients enrolled in the different studies are shown in Table 1.

Table 1. The origin of the patients from the various studies in the thesis

Study/Country	Estonia	Norway (Sejersted et al., 1981; Hovda et al., 2005a)	Tunisia (Brahmi et al., 2007)	Iran (Hassanian-Moghaddam et al., 2007)	Iran (Mashhad, 2008–2010)
Study I (n=154)	154				
Study II (n=203)	92	61	16	24	10
Study III (n=53)	53				

Study I is solely based on data from the Estonian outbreak (Figure 3) that occurred between the 9th and the 17th of September, 2001. Illegal spirits containing 50–100% methanol were sold and consumed in the Pärnu region of Estonia. The methanol was mostly diluted with water, but ethanol was also used in a few cases (the number of individuals who consumed the latter is not known). Most patients had a history of "normal" alcohol consumption, and a few individuals were regular drinkers. A total of 141 patients were admitted to the local hospital in Pärnu, and six were admitted to other hospitals. Of these 147 patients, 36 did not have detectable S-methanol levels upon admission, leaving a total of 111 hospitalised patients with verified methanol exposure. During this outbreak, there were 68 fatalities: 25 in the hospital and 43 found dead from methanol poisoning outside of the hospital. Thus, a total of 154 patients exhibited verified methanol poisoning.

Study II compares data from individuals and outbreaks in four different countries (Figure 2). In total, 320 patients were included. The following observational case series were retrospectively collected from two different clusters of methanol poisonings in Norway (1979 and 2002–2005), one cluster in Estonia (2001), and one cluster in Tunisia (2003/2004). Additional data were obtained from two centres in Iran (Logham-Hakim Hospital, 2004–2009; Mashhad University Hospital, 2009–2010). The study was designed as a retrospective observational case series study, with the following inclusion and exclusion criteria:

1) Patients admitted to the hospital were alive with a diagnosis of methanol poisoning that was made upon admission or later verified by a positive S-methanol analysis.
2) A blood-gas analysis was performed at the time of admission.
3) All patients who were administered any treatment before admission that could potentially interfere with the analysis (including mechanical ventilation or buffer or antidote use) were excluded from the study. A few patients who were intubated to secure their airways before admission but were not mechanically ventilated were included.

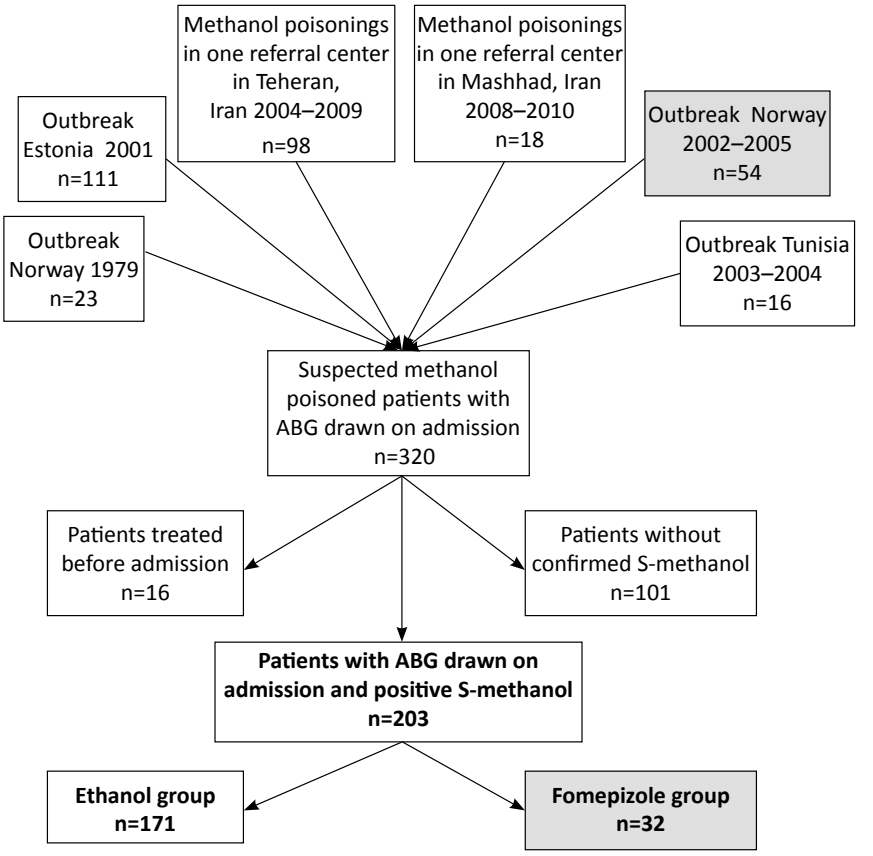


Figure 2. The patients in Study II

Study III describes the long-term findings in 53 of the 86 patients who survived the outbreak in 2001 (Figure 3). The surviving victims from the methanol poisoning outbreak in 2001 in Pärnu, Estonia, were traced through hospital records and invited by letter and telephone to an interview and a clinical evaluation. Patients who failed to respond were traced through the Estonian Register of Population and the patients' general practitioners.

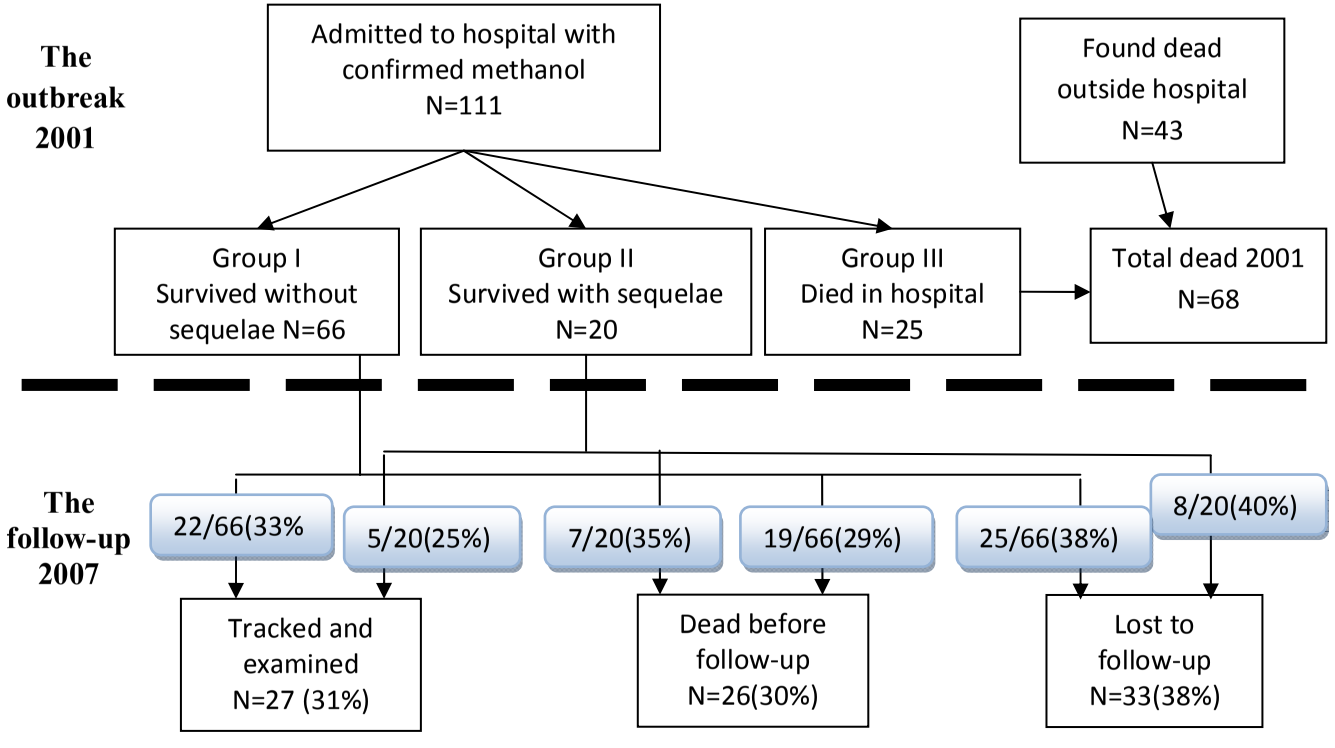


Figure 3. Patients in the Estonian outbreak of 2001 (Study I) and in the follow-up study in 2007 (Study III)

The follow-up patients were classified into two groups: those individuals who survived the outbreak without sequelae (Group (Gr) 1) and those patients who survived with sequelae (Gr 2). There were 66 patients in Gr 1 and 20 patients in Gr 2, for whom VDs and NI were the most common sequelae.

4.2. Study design

Study I was a retrospective study based on the large methanol poisoning outbreak that occurred in Pärnu County in September 2001. To evaluate both morbidity (defined as patients discharged with sequelae; see below) and mortality, the patients were divided into three groups: Gr 1: survivors without sequelae; Gr 2: survivors with sequelae (VDs or brain damage on discharge); and Gr 3: patients who died.

Study II was an observational case series study in which data were collected from four different countries and six different centres/outbreaks. Upon admission, before any treatment was given, the following data were recorded: state of consciousness (with a coma defined as a Glasgow Coma Scale (GCS) score <8, recorded in the chart as either "coma" or a numeric GCS score), S-methanol concentration (not necessarily drawn upon admission but verified as positive for all included patients), pH, pCO_2 levels, base deficit (BD), HCO_3^- levels, S-potassium (S-K) levels, and S-creatinine levels.

All patients from Estonia were evaluated for consciousness after one hour in addition to the original evaluation (the other parameters were only measured once), as follows: "awake", the patients who stayed awake after the initiation of ethanol treatment; "awake-coma", the patients who were admitted awake but lost their consciousness after the initiation of ethanol treatment; and "coma", the patients who were unconscious upon admission. The outcome was defined as the status at discharge from the hospital, and the outcome groups were defined as in Study I.

Study III was a prospective study in which the patients who survived the methanol poisoning outbreak in 2001 were invited to participate. The patients answered a questionnaire regarding their history of diseases before and after the incident in 2001 and present diseases (including diabetes). The participants were questioned about their drinking habits before and after the outbreak in 2001. Furthermore, all prescription medications used in 2001 and at present were recorded. Medical and neurological examinations were performed by a physician, and an ophthalmological examination was conducted by an ophthalmologist. All the findings were compared with the clinical status at discharge six years earlier. The data were categorised in a descriptive manner, so no statistical analyses were performed.

4.3. Laboratory methods

In Study I, the methanol and ethanol concentrations in the serum were measured by gas chromatography using a headspace injector (Hewlett Packard chromatograph HP 4890D and Headspace Sampler HP 7694E) and flame ionisation detector (GC-FID). Because this chromatograph was replaced by a newer device a few days after the outbreak, exact data on the sensitivity and coefficient of variation were not obtained. However, experience from use over years indicated a sensitivity of at least 2 mmol/L for each alcohol (6 mg/dL for methanol and 9 mg/dL for ethanol) and a day-to-day coefficient of variation in the range of 5–10%.

In Study II, the methanol concentrations were measured with different instruments. A Pye Unicam Model 104 gas chromatograph equipped with a single-flame ionisation detector was used in Norway in 1979, and a gas chromatography system with a flame ionisation detector and a headspace injector (Fisons GC 8000; Rodano, Italy) (sensitivity of 1.3 mmol/L and day-to-day coefficient of variation of 5%) was used in 2002–2005. In contrast, a UV-Vis spectrophotometer (Spectronic-20D; *Milton Roy, Belgium*) operating at a wavelength of 570 nm was used in Iran. A gas chromatography system with a headspace injector (Hewlett Packard 4890D chromatograph and HP 7694E headspace sampler) and a flame ionisation detector (GC-FID) was used in Estonia. In Tunisia, the methanol concentrations were measured using two different methods: the CORDEBARD enzymatic method (oxidoreduction), using an Integra 400 system (coefficient of variation of 4.2%), and a novel gas chromatography technique, using a Shimadzu instrument with a manual injector.

4.4. Statistical methods

Statistical analyses were performed using SPSS version 19.0.

In Study I, the admission data for the different groups were compared among groups using a Mann-Whitney U-test (non-normaly distributed data). A Pearson's chi-square test was used to compare the patients who survived with those patients who had died following the additional intake of ethanol. Additionally, the correlation between pH and pCO_2 levels was determined by regression analysis.

In Study II, a multivariate logistic regression analysis was used to identify which variables were potentially associated with a poor outcome (in statistical terms, a decision tree). In this analysis, death was the dependent variable, whereas a selection of other variables, such as coma, pH, pCO_2 levels, HCO_3^- levels, BD, S-K levels, and S-creatinine levels, was used as independent variables. A backward variable selection was then performed until all the remaining variables were significant ($p<0.05$).

Table 2. The factors associated with a poor outcome based on multivariate analysis.

Independent variable	Odds ratio (OR)	95% confidence interval (CI)	p-value
Coma (yes vs. no)	10.2	3.3–32.0	p<0.001
pH (0.1-unit increase)	0.58	0.46–0.75	p<0.001

Clinical interpretation: if the pH is increased by 0.1 units, the odds of a poor outcome are reduced by 42%.

The associations between the different blood gas parameters, S-K levels, and S-creatinine levels with outcome were analysed. The data were considered sufficiently close to the normal distribution to be compared by one-way analysis of variance (ANOVA) with Bonferroni's correction for pairwise group comparisons.

To further confirm the associations between the different parameters and death, we performed a receiver operating characteristic (ROC) curve test, in which the area under the ROC curve was used as a measure of the strength of the association between the continuous parameters and mortality.

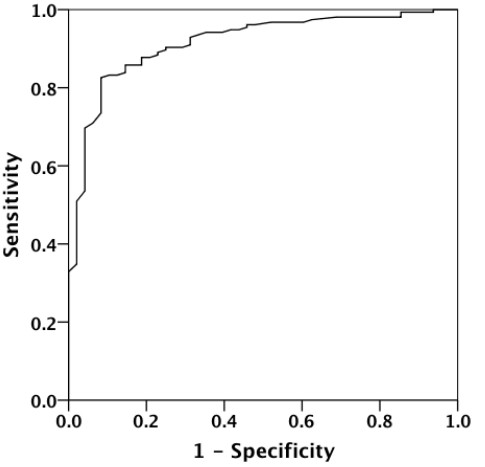


Figure 4. The area under the ROC curve was 0.918, demonstrating a strong connection between pH and death.

The threshold values, OR, and 95% CIs are presented in Table 3

Table 3. Prognostic factors arranged by OR* (unadjusted results; performed by univariate analysis). S-methanol was not included because this parameter was not measured upon admission in all cases.

Prognostic marker	Threshold	OR (95% CI)	ROC area
Coma	yes/no	48.2 (18.1–128.7)	–
pH	7.00	35.4 (14.1–88.8)	0.918
Creatinine (μmol/L)	106	15.0 (3.9–58.2)	0.800
BD (mmol/L)	25	13.1 (5.1–33.8)	0.864
HCO_3^- (mmol/L)	5	6.6 (3.1–14.1)	0.761
pCO_2 (kPa)**	3.1	5.0 (1.2–4.7)	0.672
Serum-K (mmol/L)	5.1	3.0 (0.97–9.3)	0.786

* Independent prognosticators.
** Only calculated for the patients in a coma with a pH of 6.74–6.99.

Independent t-tests were used to compare the means of different outcome groups when the groups were sufficiently large.

A risk assessment chart was created by initially separating the patients according to their state of consciousness (yes/no coma (GCS<8)). With the use of an ROC curve, the two groups were then separated based on pH, with the highest combined sensitivity and specificity to separate the survivors from the patients who died. The high-risk group (pH<7.00) was split into two subgroups based on the median, so the ensuing assessment was based on three different pH groups. Finally, the patients in a coma with a pH between 6.74 and 6.99 were evaluated for the ability to hyperventilate, defined by a low pCO_2. This threshold pCO_2 value was estimated using the ROC curve to obtain the highest possible combined sensitivity and specificity. Fisher's exact test was used when analysing contingency tables with small sample sizes.

5. RESULTS

5.1 Management and outcome of a large outbreak of methanol poisoning with limited resources (Study I)

Table 4 presents the patients admitted per day and the number of admitted patients who had positive methanol levels in their blood upon admission. Due to the large number of patients and limited resources, only 31 patients were treated in Pärnu Hospital. For the remaining 80 patients, triage and initial treatment were started in Pärnu before the patients were transferred to other hospitals. Only the acid-base status was available in addition to the patient history and clinical features. Methanol samples were sent to Tartu and Tallinn, and 24–72 hours elapsed before the analyses were performed.

Table 4. Number of patients admitted per day.

Day	Hospitalised patients	Patients positive for S-methanol
1	17	16
2	39	31
3	46	36
4	18	12
5	12	10
6	4	2
7	3	1
8	5	2
9	3	1
Total	**157**	**111**

The most common clinical symptoms and signs upon admission were gastrointestinal (GI) problems (49%), VDs (37%), and dyspnoea (20%). A total of 96 patients (87%) received ethanol as an antidote, 94 (85%) received $NaHCO_3$ as a buffer to correct their metabolic acidosis, 79 (71%) were dialysed, and 68 (61%) were given mechanical ventilation. Because heparin is used as an anticoagulant in the present dialysers (rather than citrate), intracerebral bleeding was a contraindication for HD. CT scans were performed prior to HD when the patients were unconscious.

Because of delayed results of the S-methanol levels, 14 patients (13%) with normal ABG results, no clinical symptoms, and a median S-methanol concentration of 11 mmol/L (range of 1–80 mmol/L) were sent home without any treatment before their methanol levels were determined. None of these patients died. Six years later, follow-up was conducted for four of these 14

patients, of whom three did not have any clinical symptoms, and one had developed neurological and visual impairment. In addition, four of the 14 patients had died during the previous years.

Of the 72 patients who were conscious upon admission and given ethanol, 29 (40%) became comatose due to the bolus infusion of ethanol. These patients were then intubated and mechanically ventilated.

The hospitalised patients (n=111) were divided by outcome into three groups (Figure 3): patients who survived without sequelae (Gr 1; n=66, 60%), patients who survived with sequelae (with VDs and/or NI) (Gr 2, n=20, 18%), and patients who died (Gr 3; n=25, 22%).

5.2. Comparison of ethanol and fomepizole as antidotes (Study II)

For the first time in the literature, we compared the efficacy of the two antidotes that are commonly used to treat methanol-poisoned patients. Fomepizole was the antidote of choice in 32 of the patients (Norway, 2002–2005) (Hovda *et al*., 2005a), whereas ethanol was used in the remaining 171. There appeared to be a trend towards a "positive" leftward shift in morbidity and mortality; patients with a lower blood pH (i.e., more acidotic) seemed to survive with sequelae in the fomepizole group but die in the ethanol group. Moreover, patients with comparable pH values survived with sequelae in the ethanol group but survived *without* sequelae in the fomepizole group; however, this difference was not significant (Figure 5A).

Due to the limited number of subjects in the fomepizole group, the analysis of these patients was more susceptible to the effects of outliers. For instance, one patient in the group of fomepizole-treated patients who died was admitted with a pH of 7.13. However, the diagnosis of this patient was delayed, and treatment was not commenced until 6 hours post-admission, at which time the patient was already severely acidotic (pH 6.8) and in a coma. If this outlier with such a delayed diagnosis is excluded from the analysis, the difference between the ethanol and fomepizole groups becomes significant (p=0.038) (Figure 5B)

The ability to hyperventilate seemed to be an important prognostic marker among the patients in the fomepizole group who died, whereas the patients who were given ethanol as an antidote tended to die despite a better initial ability to hyperventilate (before ethanol treatment was initiated). More specifically, the patients in the ethanol group seemed to die significantly more often despite hyperventilation than the patients in the fomepizole group (p=0.034) (Figures 6A and 6B).

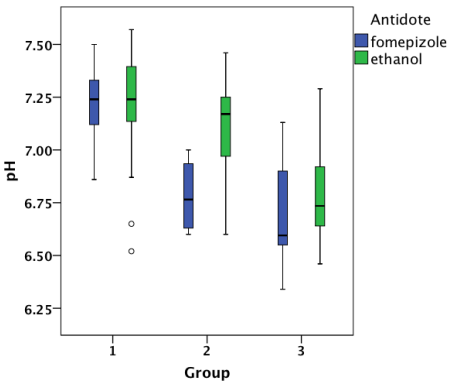


Figure 5A. pH vs. outcome groups.

Gr 1: Survived without sequelae (n.s.)
Gr 2: Survived with sequelae (N/A)
Gr 3: Died (n.s.)
º – outliers

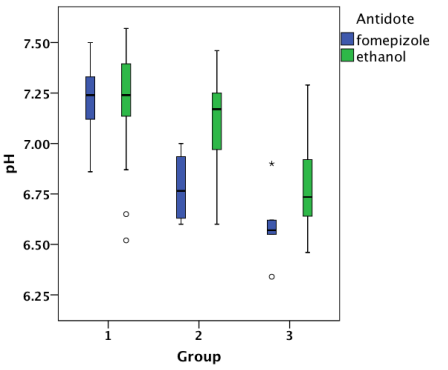


Figure 5B. pH vs. outcome groups, excluding one outlier treated with fomepizole

Gr 1: Survived without sequelae (n.s.)
Gr 2: Survived with sequelae (N/A)
Gr 3: Died (p=0.038)
*– significant difference
º – outliers

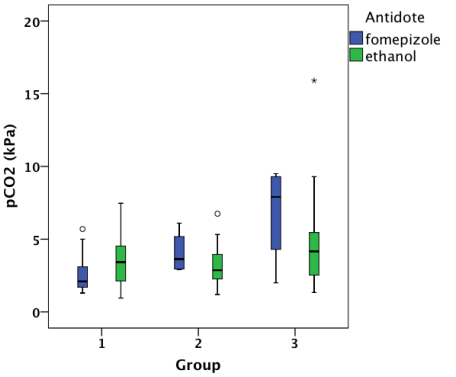


Figure 6A. pCO_2 vs. outcome groups.

Gr 1: Survived without sequelae (n.s.)
Gr 2: Survived with sequelae (N/A)
Gr 3: Died (p=0.034)
*– significant difference
º – outliers

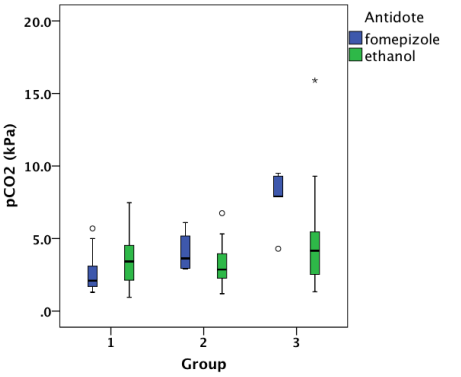
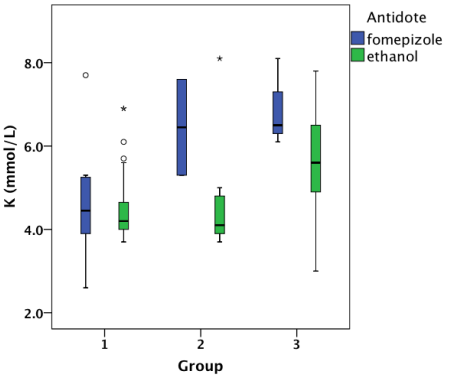


Figure 6B. pCO_2 vs. outcome groups, excluding one outlier treated with fomepizole.

Gr 1: Survived without sequelae (n.s)
Gr 2: Survived with sequelae (N/A)
Gr 3: Died (p=0.006)
*– significant difference
º – outliers

The fact that there seemed to be a poorer outcome for the ethanol group despite normal S-K levels also indirectly points to a possibly worse outcome despite a similar acid-base status between the two groups (Figures 7A and 7B). However, there were too few patients in the fomepizole Gr 2 and Gr 3 to make statistical comparisons.



7A. S-K vs. outcome groups.

Gr 1: Survived without sequelae (n.s)
Gr 2: Survived with sequelae (N/A)
Gr 3: Died (N/A)
*– significant difference
º – outliers

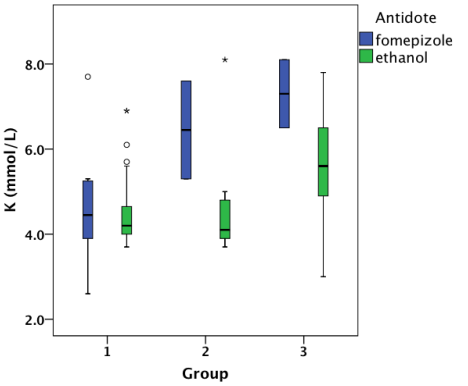


Figure 7B. S-K vs. outcome groups, excluding one outlier treated with fomepizole.

Gr 1: Survived without sequelae (n.s)
Gr 2: Survived with sequelae (N/A)
Gr 3: Died (N/A)
* – significant difference
º – outliers

In the Estonian outbreak, 29 of 72 (40%) of the patients who were awake upon admission fell into a coma after the initiation of ethanol therapy as an antidote. To analyse this phenomenon further, the patients were divided into three groups: "awake", patients who were awake and stayed awake; "awake-coma", patients who were awake upon admission but fell into coma during the first hour after admission; and "coma", patients who were in a coma upon admission. None of the patients in the first group ("awake") died, whereas six (22%) in the second group ("awake-coma") died (p=0.007, Fisher's exact test). The "awake-coma" group seemed to be more acidotic than the "awake" group (p=0.005 in Gr 1), and the "coma" group appeared to be more acidotic than the "awake-coma" group (p=0.001 in Gr 3), as illustrated in Figure 8. Too few patients were included in Gr 2 to allow a statistical comparison.

The patients in the "awake-coma" group died despite lower pCO_2 values (p=0.019 in Gr 3), suggesting that their respiratory drive upon admission was sufficient, whereas the administration of ethanol removed this protective factor (Figure 9).

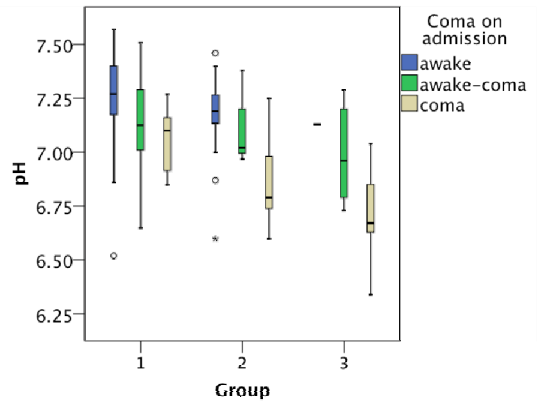


Figure 8. pH vs. outcome groups based on the Estonian patients' consciousness after ethanol therapy. A significant difference was found in Gr 1 between the "awake" and the "awake-coma" groups (p=0.024) and between the "awake" and the "coma" groups (p=0.023). Similarly, in Gr 3, a difference was observed between the "awake-coma" and "coma" groups (p=0.019). Gr 2 was too small to allow a statistical comparison.

Gr 1: Survived without sequelae
Gr 2: Survived with sequelae
Gr 3: Died
*– significant difference
º – outliers

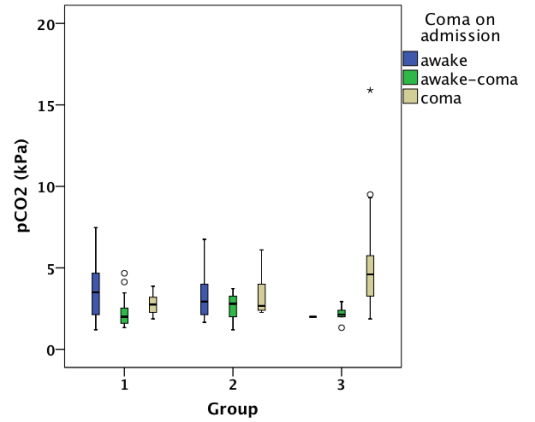


Figure 9. pCO_2 vs. outcome groups based on the Estonian patients' consciousness after ethanol therapy. A significant difference was found in Gr 3 between the "awake-coma" and the "coma" groups (p=0.006).

Gr 1: Survived without sequelae
Gr 2: Survived with sequelae
Gr 3: Died
*– significant difference
º – outliers

5.3. Prognostic factors that determine the outcome of methanol poisoning (Study II)

pH and coma were the strongest prognostic factors in methanol poisoning, along with the patients' ability to lower their pCO_2 values when acidotic. HCO_3^- levels, BD, and S-creatinine levels were significant predictors of poor outcome, but these parameters were dependent on pH. Thus, the significance disappeared following correction for pH by multiple regression analysis. High S-K levels were significantly correlated with a poorer outcome, particularly in the fomepizole group (Figures 7A and 7B), but this association was also dependent on pH. The prognostic markers, along with their thresholds, ORs, and 95% CIs, are presented in Table 3.

The ability to hyperventilate to compensate for severe metabolic acidosis as a good prognostic marker, reported by Hovda et al. (Hovda *et al*., 2005a), was confirmed in our retrospective multicentre study. Among the survivors of the methanol poisoning outbreak, there was a trend towards decreased pCO_2 levels at lower pH values. An opposite trend was found among the patients who died. The difference between the groups was highly significant ($p<0.001$) (Figure 10).

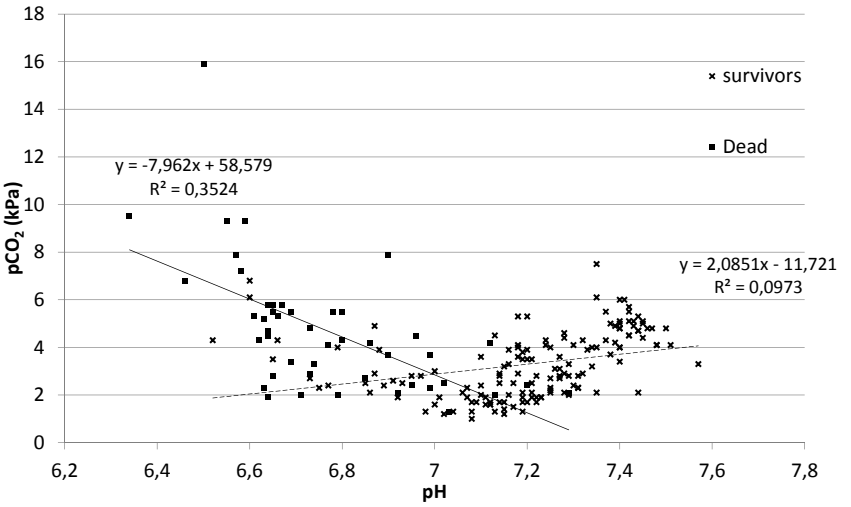
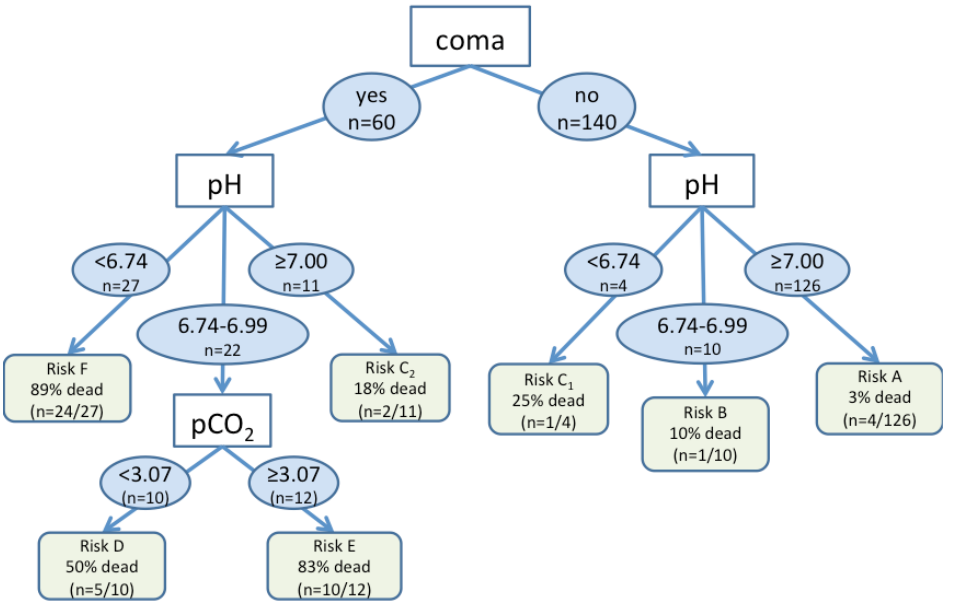


Figure 10. The association between pH and serum pCO_2 levels as a prognostic factor.

Based on the collected data, we also established a simple risk assessment scheme to help clinicians in the prognostication and triaging of methanol-poisoned patients (Figure 11).



Risk group	Name on figure	Number in total	Dead in group	Total mortality risk	Odds ratio (95% CI) *
1	A and B	136/200	5/136	4%	1
2	C_1 and C_2	15/200	3/15	20%	7 (1–30)
3	D	10/200	5/10	50%	26 (6–120)
4	E	12/200	10/12	83%	131 (23–762)
5	F	27/200	24/27	89%	210 (47–936)

Figure 11. A risk assessment chart for the evaluation of outcome based on admission parameters, corresponding with a risk score outlined in this chart. The pCO_2 values are given in kPa, and the conversion factor for mmHg to kPa is 7.5:1.

* OR and 95% CIs for death in all groups compared to risk group 1.

5.4 Long-term outcomes after methanol poisoning (Study III)

After the methanol poisoning outbreak in 2001, there were 86 survivors (66 without and 20 with sequelae). Six years later, 26 of these individuals were dead, 33 were lost before follow-up, and 27 (31%) were ultimately found and examined (Figure 3).

In Gr 1, 22 of 66 patients who survived without sequelae in 2001 were search and found; two of these patients were identified as having NI, two patients experienced VDs and six patients experienced both. The visual complications were all confirmed by an ophthalmologist. None of the patients had diabetes. In Gr 2, five of 20 patients who survived with sequelae in 2001 were tracked. 20 patients survived with sequelas of whom 17 patients had visual sequelae, two patients had neurological sequelae and one had both. Six years later, four patients with VDs in 2001 were tracked and examined, and VDs were still present in all of these individuals. The most common VDs that were present at the time of the follow-up (in both the patients with symptoms that were present at discharge and the patients who acquired symptoms after discharge) were optical nerve atrophy, temporal pallor of the optic nerve head, visual field defects, and a loss of visual acuity (severe to deep blindness). Among the patients with NI upon discharge from the hospital six years earlier, NI was still present in all of the individuals, and one additional patient had developed NI six years after the initial discharge (Table 5).

The clinical signs and symptoms in the patients with NI were the same whether present at discharge or acquired after discharge: polyneuropathy and encephalopathy (from light to severe), ataxic gait (unstable walking), positive Romberg test (patients cannot remain upright with their eyes closed), and sensory loss in the distal part of the legs.

Among the 26 patients who died after discharge in 2001, 19 were from Gr 1 (survivors without sequelae) and seven were from Gr 2 (survivors with sequelae) (Figure 3). Alcohol intoxication (unknown type of alcohol and origin) was the most frequent cause of death (7/26). Other causes of death were cardiac problems (n=6, including cardiomyopathy (n=2) and myocardial infarction (n=2)), trauma (n=3), CO poisoning (n=3), and pneumonia (n=2). Unfortunately, only a few of the patients changed their drinking habits after the outbreak. Regarding the survivors' quality of life and disability, we found that six of the 27 individuals tracked six years later were now in need of help with their daily living activities.

Table 5. Patients with VDs or NI in 2007.

					VDs in 2007				NI in 2007				
Patient	Gender and age in 2007	Group in 2001	VD in 2001?	NI in 2001?	Optical nerve atrophy	Temporal pallor of the optic nerve head	Visual field defects	Loss of visual acuity	Poly-neuro-pathy	Encephalo-pathy	Ataxic gait (unstable walking)	Positive Rom-berg test	Sensory loss of distal parts of legs
1	F68	1					+						
2	F62	1								+			
3	M41	1				+	+			+	+	+	+
4	M47	1					+			+	+		
5	M51	1				+							
6	M65	1			+	+	+	+	+	+		+	
7	M68	1							+	+	+		+
8	M53	1					+		+	+	+	+	
9	M52	1			+				+		+	+	+
10	M48	1				+	+			+	+		
11	M65	2	+	+		+	+	+	+	+	+		+
12	F55	2	+	+	+			+	+	+	+	+	+
13	M55	2	+		+			+					
14	M47	2		+					+	+	+		+
15	M59	2	+		+		+	+	+	+	+		+

6. DISCUSSION

6.1. The challenges of outbreaks

The published methanol poisoning outbreaks range from large clusters to smaller case series. In certain reports, multiple patients were admitted during a very short time span (Bennett *et al*., 1953; Krishnamurthi *et al*., 1968; Naraqi *et al*., 1979; Ahmad 2000), whereas in other reports, patients were admitted over the course of weeks (Sejersted *et al*., 1981; Scrimgeour *et al*., 1980; Smyth *et al*., 1997; Teo *et al*., 1996), months (Swartz *et al*., 1981; Hassanian-Moghaddam *et al*., 2007; Brahmi *et al*., 2007; Chen *et al*., 1978; Ravichandran *et al*., 1984), or even years (Hovda *et al*., 2005a; Liu *et al*., 1998; Meyer *et al*., 2000). The present study includes the second largest cohort of methanol outbreak ever reported in scientific medical literature.

To manage mass methanol poisonings, it is necessary to have enough beds, both in the ICU and in the general wards. The number of available ventilators and dialysers may also be a limitation. To diagnose and evaluate the stage of methanol poisoning and the effect of treatment on poisoned individuals, various types of laboratory equipment are needed. Measurements of ABGs; osmolality to calculate the OG; electrolytes (including chlorine to calculate the AG); and ethanol, methanol, and formate levels require different analysers, but the availability of the appropriate facilities is highly variable, particularly in the areas in which methanol poisonings most often occur (Ravichandran *et al*., 1984). Among the treatment options, antidotes (ethanol or fomepizole, to block methanol metabolism), $NaHCO_3$ (to correct acidosis), and dialysis (to remove methanol and formate from the blood) are crucial for a beneficial outcome. Known methanol outbreaks mostly occur in developing countries in which the resources that are necessary to manage such outbreaks are very limited (Krishnamurthi *et al*., 1968; Ahmad 2000; Hassanian-Moghaddam *et al*., 2007; Brahmi *et al*., 2007). Due to low awareness of rare medical conditions, such as methanol poisoning, delayed diagnosis and initiation of treatment is the rule rather than the exception, particularly for the first patients in an outbreak. The potential for a high number of patients during a short time frame may also overwhelm local resources, including ICU beds and dialysers. Thus, an increased understanding of methanol poisoning and plans for local and regional cooperation between health care providers may prove beneficial.

If many patients are admitted during a short time span, this event will not only affect the local hospital but also the national/regional health care system. The 2001 outbreak was a large task for a hospital as small as Pärnu Hospital, with 155 beds, two beds in the Emergency Department, and five ICU beds. The hospital also lacked the resources for handling such an outbreak, with a total of four ventilators and one dialyser (continuous veno-venous HD (CVVHD)). This lack of equipment was the main reason for transferring 35 patients to Tartu and 45 to Tallinn for further treatment. The close cooperation between the different

hospitals and ambulance services across Estonia was also important in lowering the number of fatalities.

6.2. Diagnostic challenges

Early diagnosis is important but difficult in methanol-poisoned patients. The main reason for this difficulty is that methanol poisoning has few specific clinical features and therefore often resembles a variety of other medical conditions. Diagnosis solely based on clinical features is frequently delayed. Meanwhile, formic acid/formate accumulates, and the patient's acidosis becomes more and more severe. In the Estonian outbreak, the most common clinical features upon admission were GI symptoms and VDs, followed by neurological findings. The reported clinical features varied according to the treating physicians' ability to recall and describe the symptoms. For example, hyperventilation due to metabolic acidosis may be perceived as dyspnoea. Hence, differences in the registration of hyperventilation may also have occurred.

The clinical features of methanol poisoning are not very different between outbreaks (Table 6), but it is important to remember that these features depend upon the time interval between methanol ingestion and admission and whether ethanol was co-ingested.

Table 6. Incidence of symptoms upon admission in different outbreaks.

Outbreak Symptoms	Estonia 2001	Baltimore, USA, 1951 (Bennett et al., 1953)	Michigan, USA, 1979 (Swartz et al., 1981)	Norway, 1979 (Sejersted et al., 1981)	Norway, 2002–2004 (Hovda et al., 2005a)
GI	49%	52%	67%	18%	41%
VDs	37%	not reported	50%	55%	33%
Dyspnoea	20%	25%	not reported	15%	41%
Other clinical symptoms	35%	not reported	not reported	not reported	not reported

Regarding specific diagnostic tools, ABG analysers are most readily available. In the Estonian outbreak, ABG was determined upon admission for every patient. Because of the delay in S-methanol measurements, the initial treatment with bicarbonate and the antidote (ethanol) was started based on the severity of the patient's metabolic acidosis. Alternative tools, such as the well-described indirect method of using OG and AG, are good diagnostic options. An earlier publication (Hovda *et al*., 2004) showed that use of the OG and AG may be helpful in diagnosing these poisonings and even in predicting the different

stages of methanol poisoning. Unfortunately, these gaps are not commonly measured in Estonia, despite the fact that methanol poisonings are not rare in this country. This lack of testing is also the case in many other areas in which methanol poisonings are frequently observed.

The specific tools used to diagnose methanol poisoning are measurements of S-methanol and/or formate concentrations. Methanol analyses are expensive and even less available than measurements of osmolality. Typically, the best-case scenario would be that testing results are available after a delay of 24–48 hours. In the Estonian outbreak, it took 24–72 hours to obtain results, and certain asymptomatic, non-acidotic methanol-poisoned patients were therefore discharged without any treatment. In contrast, an enzymatic formate test is a simple and cheap method with a high sensitivity and specificity (Buttery *et al*., 1988; Hovda et al., 2005b) that can be used on common spectrophotometric analysers.

6.3. Treatment options

Two antidotes are available for the treatment of methanol poisoning. Ethanol is widely available and relatively inexpensive and has been used for decades, whereas fomepizole is more expensive and has a more limited availability. Ethanol is, however, difficult to maintain at a stable therapeutic S-level of 100 mg/dL (Hovda *et al*., 2004; Glaser *et al*., 1996; O`Neill *et al*., 1983), leading to frequent underdosing, particularly during HD (Hantson *et al.,* 2002). Therefore, frequent monitoring of S-ethanol is necessary. Ethanol also has an unwanted CNS-depressive effect, which may interfere with the patient's ability to compensate for their metabolic acidosis by hyperventilation (McCoy *et al*., 1979; Hantson *et al*., 2002). Additionally, the ethanol-treated patients become drunk and are often difficult to handle from a nursing perspective.

Fomepizole has a stronger affinity for ADH than ethanol and is easy to administer, including during HD. The monitoring of S-levels is not necessary, and fomepizole has no reported CNS-depressive effects. Because this antidote is well tolerated, it may be administered for days (the half-life of S-methanol is reported to be 50–80 hours during antidote administration). Moreover, fomepizole may postpone or even obviate the need for HD and reduce the need for treatment in the ICU (Brent *et al*., 2001; Megarbane *et al*., 2005; Hovda *et al*., 2005d; Jacobsen *et al*., 1990; Mycyk *et al*., 2003; Hovda *et al.,* 2008).

The morbidity and mortality associated with methanol poisoning depend on the time elapsed between methanol intake and the initiation of treatment, the amount of formic acid produced, and the degree of metabolic acidosis. It is therefore not possible to directly compare the outcomes from the two antidotes in retrospective studies. We compared these outcomes indirectly using the admission parameters (where the pre-admission factors would already have been acknowledged), and similar treatments were assumed to have been given

to the two groups. We found a trend towards a "positive" leftward shift in morbidity and mortality, which may support fomepizole being superior to ethanol as an antidote for methanol poisoning. The design of Study II, however, does not allow for a firm conclusion.

Providing optimal treatment seems to be one of the major problems associated with the use of ethanol to treat methanol poisoning. Our data indicate that the CNS-depressive effect of ethanol may interfere with treatment and the need for mechanical ventilation and may negatively influence the outcome.

Table 7. Consciousness upon admission and one hour after admission.

Consciousness	Estonia	Norway (Hovda et al., 2005a)
Awake upon admission	65%	76%
Unconscious upon admission	35%	24%
Unconscious 1 hour after admission	61%	not reported

Table 7 shows the mental status of the patients upon admission and during the first hour after admission. Compared with the data from the Norwegian outbreak in 2002–2004, we observed both similarities and certain differences. There were more unconscious patients upon admission in Estonia than in Norway (35% vs. 24%, respectively). The reason for this disparity is unclear because the patients were comparable in terms of the degree of their metabolic acidosis. One potential reason is the higher methanol concentration in the Estonians, but on the other hand, the CNS-depressive effect of methanol is very weak. The most interesting element of Table 7 is the increase in unconsciousness one hour after admission in Estonia, which most likely was a result of the IV administration of ethanol as an antidote. This development further complicated the treatment and logistics.

The patients who became unconscious (the "awake-coma" group) during the first hour after admission due to ethanol infusion seemed to be more acidotic than the "awake" group, but less acidotic than the "coma" group, suggesting that the susceptibility of methanol-poisoned patients to fall into a coma following ethanol treatment increases with poisoning severity (Figure 8). Furthermore, the ethanol-treated patients died despite a higher degree of hyperventilation upon admission (Figure 9), reflecting the fact that the removal of their physiological ventilation "drive" after the addition of a CNS depressant may be associated with a poorer outcome. Similar findings suggesting that CNS depression affects outcome were also reported by Hassanian-Moghaddan et al., who found that methanol co-ingestion with opium are associated with a poorer outcome (Hassanian-Moghaddam *et al*., 2007).

It is important to avoid normoventilation in those methanol-poisoned patients who need mechanical ventilation. Physiologically, when the patients are awake, they compensate for severe metabolic acidosis by hyperventilation,

and it is critical to continue this process via mechanical ventilation to avoid fatal worsening of the acidosis.

In 2006, approximately 80% of the world's dialysis patients were treated in Europe, North America, and Japan (Aviles-Gomez *et al*., 2006), indicating that the availability of dialysis is very limited in many places. Even if HD is available during methanol poisoning outbreaks, it is difficult to comply with the recommended time for HD due to limited resources. Eight hours of HD is often recommended if methanol analyses are unavailable (Jacobsen et al., 1986). However, the mean length of conventional HD in the Estonian outbreak was slightly shorter (6.3 hours, with a range of 3–20 hours), mainly because of the high number of patients and limited dialysis capacity.

The superiority of conventional HD over CVVHD (CVVHD mean duration in the Estonian outbreak was 15.8 hours, with a range of 13–22 hours) regarding the removal of methanol has been demonstrated (Kan *et al*., 2003). CVVHD was used in the Estonian outbreak, mainly because of limited access to conventional intermittent HD (IHD) but also because certain patients had unstable circulatory system and thus may not have tolerated IHD. The limited dialysis capacity also explains why certain patients had to wait for up to 68 hours before this procedure could be initiated. The main reasons why 32 of the 111 (29%) patients were not dialysed were as follows:

1) The patients died before HD was available.
2) CT revealed intracerebral bleeding, a typical contraindication for HD. In the literature, many authors have described haemorrhagic cerebral infarction in methanol poisoning (Patankar *et al*., 1999; Ganguly *et al*., 1996; Phang *et al*., 1988; Mittal *et al*., 1990). One group attributed such changes to systemic anticoagulation during HD (Phang *et al*., 1988), whereas another group described such a finding before HD (Patankar *et al*., 1999). This disagreement means that systemic anticoagulation is not the sole reason for cerebral bleeding. In the Estonian outbreak, HD was not initiated in cases in which haemorrhages were found before the start of dialysis.
3) Certain patients were discharged due to delayed methanol analysis and were therefore not dialysed.

6.4. Outcome

Comparing the outcomes of different outbreaks is difficult. The main confounding variables are different time intervals between methanol intake and the development of clinical features/hospitalisation and varying degrees of the parallel use of ethanol. Physicians may not recognise methanol poisoning in the early stages, so correct treatment is often delayed. In the Estonian outbreak, the problem of not recognising the poisoning only occurred in the first patient, who was sent to a psychiatric ward due to assumed psychosis. Hours later, the patient developed severe acidosis and cardiac arrest, at which point he was

transferred to the ICU, where he died hours later. For the ensuing patients, a standard protocol to manage methanol intoxication was composed and strictly followed. This protocol, combined with the fact that most patients were admitted to the same hospital ("learning by doing"), may have outweighed the negative impact of the limited resources available in Pärnu.

In Table 8, the outcomes of different outbreaks are shown. The high overall mortality in the Estonian outbreak (44%) was mainly due to the high number of patients who died before reaching the hospital.

Table 8. Outcome in various methanol outbreaks.

	Estonia, 2001	**Toronto, Canada, 1982–1992 (Liu *et al*., 1998)**	**Norway, 2002–2004 (Hovda *et al*., 2005a)**	**Iran, 1999–2000 (Hassanian-Moghaddam *et al*., 2007)**	**Tunisia, 2003–2004 (Brahmi *et al*., 2007)**
Survived without sequelae	66/86 (77%)	25/32 (78%)	37/42 (88%)	10/13 (77%)	6/11 (53%)
Survived with sequelae	20/86 (23%)	7/32 (22%)	5/42 (12%)	3/13 (23%)	5/11 (47%)
Mortality in hospital	25/111 (22%)	18/50 (36%)	9/51 (18%)	12/25 (48%)	3/16 (19%)
Overall mortality	68/154 (44%)	not reported	18/60 (30%)	not reported	not reported

During outbreaks, it is very important to establish an aggressive warning system through the media and word of mouth to avoid the further spread of poisonings. During the Estonian outbreak, more patients were unconscious upon admission than in the Norwegian outbreak in 2002–2004. One explanation for such findings is that massive publicity about and the slow onset of the Norwegian outbreak made people more aware of the symptoms of poisoning, so the poisoned individuals sought help in an earlier phase of poisoning than in Estonia. The publicity also helped the physicians be more aware of poisoning as a cause of metabolic acidosis of unknown origin. However, the first cases also took too long to diagnose in Norway. The first hospitalised patient in the 1979 outbreak died a few hours after admission with a diagnosis of metabolic acidosis of unknown origin, which was solely treated with bicarbonate infusions ("bicarbonate-resistant metabolic acidosis") (Ostborg *et al*., 1981).

In certain cases, a so-called "self-treatment" of methanol poisoning with ethanol may occur. During the Estonian outbreak, 14 patients were sent home without any treatment. The reason for this early discharge was the delay in obtaining S-methanol, a normal ABG measurement, and no clinical features

related to methanol intake. Because none of these patients died, these individuals most likely treated themselves with continuous ethanol ingestion at home. Unfortunately, we were unable to measure the patients S-ethanol concentrations when they were discharged.

6.5. Prognostic parameters, the key to handling large outbreaks

Prognostic parameters are necessary to predict the outcome of a poisoning outbreak, particularly when the number of patients is very high or there is a lack of treatment resources. Coma upon admission and severe metabolic acidosis are two markers of poor prognosis in methanol poisoning. One previous study (Hovda *et al*., 2005a) has also shown that the ability to hyperventilate in response to severe metabolic acidosis is a good prognostic sign. These three parameters were also identified in our studies.

To simplify the triage of methanol-poisoned patients during large methanol poisoning outbreaks with many victims during a short time span, we created an easy-to-use risk-assessment flow-chart and a corresponding risk-scoring system (Figure 11). This flow-chart can also be used as a simple assessment to predict the patient's outcome upon admission. The flow-chart is based on the three strongest prognostic parameters: coma upon admission, pH, and pCO_2 vs. pH. When ranking the prognostic parameters from Study II according to the parameters' abilities to predict outcome, pH ranked as the most important parameter, followed by coma upon admission and pCO_2 vs. pH (i.e., the ability to compensate for metabolic acidosis by hyperventilation). A high pH (>7.00) seemed to have a protective effect, even when the patients became comatose (see risk group C_2, Figure 11). There was also an obvious benefit for patients who were hyperventilating (see risk group D vs. E, Figure 11) and a protective effect of staying awake (see risk group C_1 vs. F, Figure 11), indicating the need for a more focused and aggressive initiation of treatment in these patients.

A high BD, reflecting metabolic acidosis, was also clearly associated with a poor outcome, but the impact of the BD was dependent on pH. This finding is not surprising because the BD solely reflects the metabolic components of acidosis. Regarding S-K levels, there were significant differences between Gr 1 and 2 and between Gr 2 and 3, but these differences were also dependent on pH. Despite this pH dependence, S-K levels could still be used to support the prognostic evaluation of the patients.

By comparing the outcome groups, we found significant differences between the groups with respect to HCO_3^- (all groups) and pCO_2 (Gr 1 vs. Gr 3 and Gr 2 vs. Gr 3), although neither difference was independent of pH. These values are normally not reported, and there are two likely reasons for this discrepancy. Our study included a large number of patients, giving more power to the analysis. Except for three poisoning clusters (Naraqi *et al*., 1979; Hovda *et a*l., 2005a;

Hassanian-Moghaddam *et al*., 2007), in previous studies, patients were not typically separated into three different groups based on outcome to evaluate both morbidity and the mortality. Combining all survivors, rather than separating these individuals into two groups, is likely to bias the results.

6.6. Lessons to learn from long-term outcome

The follow-up study (Study III) was performed to evaluate the patients in the aftermath of a methanol-poisoning outbreak. We found that VDs present at discharge were still present in all of the patients six years later and were of the same magnitude, supporting previous findings (Roe 1943). These complications were also found six years later in eight of 22 patients who were discharged without VDs in 2001. The patients were all evaluated by an ophthalmologist, who considered the methanol poisoning to be the most likely cause of the patients' visual impairment. There may be two explanations for the emergence of VDs after discharge. First, many of those patients were discharged without a clinical evaluation by an ophthalmologist, and minor visual impairment may gradually develop over time. Second, the visual complications could have been a purely late-onset complication or the result of additional methanol intake. Regardless, the incidence of VDs after discharge raises the question of whether this phenomenon is an underreported feature in other poisoning outbreaks.

NI was generally increased during the six years since discharge, most likely due to the continuous ingestion of excessive alcohol. Polyneuropathy, encephalopathy, ataxic gait, a positive Romberg test, and sensory loss in the distal part of the legs were the main neurological findings in eight of 22 patients who were discharged without NI six years earlier. We also found that fewer patients changed their drinking habits among those individuals who developed NI than among the patients who did not develop such complications.

During the six years after the methanol poisoning outbreak, there was a high death toll (30%) among the patients who were discharged alive in 2001. The mortality in the same age groups in the reference population was 2.5%, indicating a 12-fold higher mortality for the patients who survived the outbreak in 2001. The main causes of death were alcohol intoxication (27%), cardiac diseases (23%), and trauma (19%), indicating that this group was exposed and vulnerable.

Unfortunately, the drinking habits of many of the patients did not improve over time. Many of the patients were still ingesting excessive amounts of alcohol despite the serious methanol-poisoning incident. The fact that only 12 patients were tracked and found alive and without sequelae six years later further supports this assumption. This finding indicates that individuals who have been affected by a methanol-poisoning outbreak may benefit from counselling and other efforts aimed at reducing alcohol abuse.

6.7. Limitations of the studies

The most important limitation of the studies presented in this thesis is the retrospective design in two of the three papers, as is the case for most of the literature on the topic. To assess the prognosis of methanol-poisoned patients, the main relevant factors are the time elapsed between intake and the development of clinical signs and symptoms and the possible additional intake of ethanol. This time interval is typically not known, and the use of ethanol also remains unknown because hospitalised patients often present in the late stages of poisoning (in a coma).

6.8. Summary and future research

Methanol poisonings are infrequent in the developed part of the world, yet outbreaks are regularly observed on a global basis. Morbidity and mortality remain high despite effective treatment, mainly because of delayed diagnosis and a lack of resources. The poisonings often occur in developing countries and during a short time span, and a limited availability of diagnostic tools, ventilators, antidotes, and HD equipment is very common. The management of such outbreaks requires specific knowledge, good hospital-staff coordination, and cooperation between different hospitals to properly manage patients.

Regional/national health care resources may also be needed to manage large outbreaks and to coordinate the handling of the media. Prophylaxis is highly important, and one of the most effective ways of limiting the consequences of poisoning outbreaks is communicating early information through the local and regional media or simply by word of mouth. The present thesis provides important insights into the epidemiology of methanol poisonings.

There is limited knowledge about how formate passes through the blood-brain barrier and about the local effects of formate on the brain. Future studies should therefore focus on formate accumulation in the CNS. The use of formate analysis in the diagnosis of methanol poisoning should also be encouraged and studied in the context of larger outbreaks, particularly in developing countries in which diagnostic resources are limited. The diagnosis of methanol poisoning is crucial, yet often difficult, and the availability of treatment options is of limited value if one does not know whom to treat.

7. CONCLUSIONS

1. During the methanol poisoning outbreak in 2001 in Estonia, there was a lack of diagnostic tools and therapeutic equipment. Although this limitation represented an obstacle for the local hospital that was primarily involved and the entire health care system of Estonia, cooperation, the rapid establishment of a treatment protocol, and good patient logistics partly compensated for the lack of basic resources. As such, most patients were treated adequately, with a mortality rate of 22%, which is comparable with earlier published data.
2. Both ethanol and fomepizole are effective, with the former antidote being more difficult to administer properly, particularly during dialysis. The other main differences are related to cost and availability. Based on our data, there seems to be a trend towards a "positive" leftward shift in morbidity and mortality when using fomepizole as an antidote, but a definite conclusion would require a prospective approach or a larger fomepizole group. Furthermore, the use of ethanol as an antidote causes CNS depression, and this side effect may increase the risk of death unless the CNS-depressive effects are counteracted by free airways, or if necessary, artificial hyperventilation.
3. Coma and low pH are the strongest predictors of negative outcome. Ability to hyperventilate is a protective factor. Based on the three strongest prognostic parameters (coma upon admission, severity of acidosis, and the ability to compensate for metabolic acidosis by hyperventilation), a simple flow-chart can aid the early identification of those patients who are at risk of a poor outcome. In patients requirering endotracheal intubation it is important to continue hyperventilation and to avoid normoventilation. Otherwise, the start of mechanical ventilation may cause a fatal worsening of the patient's metabolic acidosis.
4. VDs and NI are well-known sequelae after methanol poisoning. We confirm that the visual and neurological deficits are permanent. Possibly due to the continuous use of alcohol, certain patients who survived without sequelae developed visual and neurological complications six years later. Unfortunately, many of the patients who suffered from methanol poisoning were still drinking alcohol, even in the same amount as before.

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SUMMARY IN ESTONIAN

Metanoolimürgistuste kliiniline uuring: massiliste mürgistuste käsitlemine, ravi antidootidega ja pikaaegne prognoos

Mürgistused on tänapäeva ühiskonnas aktuaalne probleem. Eestis on igal aastal ägedate mürgistustega seoses ligikaudu 3000 kiirabi kutset, hospitaliseeritakse rohkem kui 1000 inimest ning sureb 350–420 inimest (EstTox2009-ägedate mürgistuste epidemioloogiline uuring Eestis – käsikiri valmimisel)). Oluline roll nende hulgas on metanoolimürgistustel.

Mitteprimaatidest katseloomadele metanool toksiline ei ole. Loomeksperimendid on seetõttu ebainformatiivsed ning meie teadmised metanooli toimest inimorganismile põhinevad vaid mürgistusjuhtumite kirjeldustel. Teaduskirjanduses on metanoolimürgistusi kirjeldatud enamasti teatud ajaperioodi jooksul esinenud üksikjuhtude kokkuvõttena (Hassanian-Moghaddam *et al*., 2007; Brahmi *et al*., 2007), harvemini ka massiliste mürgistuste ülevaatena (Bennett *et al*., 1953; Swartz *et al*., 1981; Sejersted *et al*., 1981; Krishnamurthi *et al*., 1968; Naraqi *et al*., 1979; Hovda *et al*., 2005a; Ahmad 2000).

Metanool ise on inimestele madala toksilisusega. Mürgistuse põhjuseks on tema metaboliidid. Metanool metaboliseerub organismis alkohol dehüdrogenaasi toimel formaldehüüdiks ning edasi kiiresti aldehüüd dehüdrogenaasi toimel juba sipelghappeks (HCOOH). Just viimasel metaboliidil on peamine roll metanooli toksilisusel (Barceloux *et al*., 2002; McMartin et *al*., 1980). Foolhappe toimel muutub sipelghape mittetoksiliseks süsihappegaasiks. Mitteprimaatidel on suur foolhappe varu ja sipelghape metaboliseerub edasi ning ei akumuleeru. Primaatidel on foolhappe varu aga tagasihoidlik; sipelghape kuhjub ning see tingib metanooli toksilise toime. Formiaadi (sipelghappe aniooni $HCOO^-$) toksiline efekt on kaheastmeline: esialgu kujuneb metaboolne atsidoos, mis on põhjustatud metanooli metabolismist sipelghappeks (sipelghape $\leftrightarrow$ H^+ + formiaat). Akumuleeruv sipelghappe anioon pärsib mitokondriaalset tsütokroom oksüdaasi, mis omakorda katkestab aeroobse energiasünteesi rakus.

Metanooli aeglane metabolism on põhjuseks, miks mürgistuse kliiniline pilt kujuneb alles 12–24 tundi pärast metanooli tarvitamist. Samaaegne etanooli tarvitamine lükkab metanooli metabolismi edasi, kuna etanoolil on kõrgem afiinsus alkoholi dehüdrogenaasile ja seetõttu võivad metanoolimürgistuse sümptomid avalduda veelgi hiljem.

Metanoolimürgistuse diagnostika teeb keeruliseks spetsiifiliste sümptomite puudumine. Esmaste sümptomite hulka võivad kuuluda nägemishäired, kõhuvalu ja düspnoe/hüperventilatsioon. Mürgistuse hilises faasis süvenevad nägemishäired ("topeltnägemisest" kuni täieliku pimeduseni), süveneb hüperventilatsioon ja kujuneb välja neuroloogiline defitsiit. Süvenev atsidoos suurendab sipelghappe difusiooni rakku, kahjustades ennekõike nägemisnärvi diski ja *nervus opticuse* retrolaminaarset osa, mis võib põhjustada nägemisnärvi

diski ödeemi ja *nervus opticuse* lesioone (Martin-Amat *et al*., 1978; Benton *et al*., 1952). Enim esinevad neuroloogilised sümptomid kerge ja keskmise metanoolimürgistuse korral on peavalu, tasakaaluhäired, letargia ja lihastõmblused. Krampide ja kooma esinemine on raske mürgistuse tunnusteks. Patoloogilisteks leidudeks, mis on seotud neuroloogiliste kaebustega on peaaju basaalganglionite piirkonna turse ja nekrootiline kahjustus, samuti hemorraagiad subkortikaalses valgeaines, mida on leitud nii magnetresonantsuuringul (MRI) (Server *et al*., 2003), kompuutertomograafilistes(CT) uuringutes (Feany *et al*., 2001; Taheri *et al*., 2010), kui ka lahangul.

Metanoolimürgistuse diagnoosimine on keeruline, ka vajalikud diagnostikameetodid ei ole kõikjal kättesaadavad. Metanoolimürgistusele omased muutused laboratoorsetes analüüsides on metaboolne atsidoos, tõusnud anioonide ja osmolaarsuse vahed, tõusnud S-metanooli ja S-sipelghappe plasmakontsentratsioon. Metanoolimürgistuse diagnostikas on enimkasutatud arteriaalse vere gaaside ja happe-alus tasakaalu analüüs. Metanooli plasmakontsentratsioon kinnitab küll diagnoosi, kuid ta pole mürgistuse prognostiline faktor. Metanoolimürgistuse diagnoosimiseks vajalikud spetsiifilised laboratoorsed analüüsid on tihtipeale kättesaamatud just piirkondades, kus mürgistused sagedamini aset leiavad.

Metanoolimürgistuse ravi koosneb nii spetsiifilisest ravist kui ka toetavast ravist. Metanooli antitootidena on kasutusel etanool ja fomepisool, mis mõlemad takistavad alkoholdehüdrogenaasi blokeerimise kaudu toksilise sipelghappe produktsiooni. Hemodialüüsi kasutatakse metanooli ja tema metaboliitide eemaldamiseks ning atsidoosi korrigeerimiseks. Viimasel eesmärgil on näidustatud ka sooda manustamine. Foolhapet soovitatakse sipelghappe endogeense metabolismi kiirendamiseks.

Metanoolimürgistuse prognoosi ja ravi kaugtulemusi on andmete vähesuse tõttu ebapiisvalt uuritud. Nii näiteks ei ole teada, kumb antidootidest – etanool või fomepisool – on mürgistuse ravimisel efektiivsem. Samuti ei ole uuritud metanoolimürgistuse kaugtulemusi ega prognoosifaktoreid. Käesolev uurimus baseerub suures osas 2001. aastal Eestis toimunud massmürgistuse kliinilisel materjalil, mis kannatanute suure arvu tõttu võimaldab antud küsimusi täpsemalt analüüsida.

Uurimistöö eesmärk:

Antud uurimistöö eesmärgiks oli kirjeldada massilise metanoolimürgistuse kliinilist käsitlust, võrrelda kahte antidooti ning teha kindlaks mürgistuse kaugtulemusi määravad prognostilised faktorid. Püstitatud uurimisküsimused olid alljärgnevad:

1. Kuidas mõjutavad piiratud ressursid massilise metanoolimürgistuse käsitlust ja tulemusi?
2. Kas kahel metanooli antidoodil – etanoolil ja fomepisoolil – on erinevusi ravi efektiivsuses?

3. Millistel prognostilistel faktoritel on tugevaim mõju metanoolimürgistuse ravitulemusele?
4. Millised pikaaegsed tüsistused esinevad metanoolimürgistuse tagajärjel?

Materjal ja meetodid

Teesides on käsitletud ja analüüsitud 265 metanoolimürgistusega patsiendi andmeid.

Esimene uuring baseerub 2001. aasta septembris Eestis, Pärnu maakonnas toimunud laialdasel metanoolimürgistuse lainel. Üheksa päeva jooksul hospitaliseeriti metanoolimürgistuse kahtlusel 141 patsienti kohalikku ja 6 teistesse haiglatesse. 36–l hospitaliseeritud patsiendil ei leitud vereplasmas metanooli, seega leidis metanoolimürgistus kinnituse 111 juhul. 68 patsienti suri, neist 43 haiglaeelselt ja 25 haiglas. Retrospektiivses uuringus jagasime patsiendid tüsistuste ja suremuse hindamiseks kolme gruppi: Grupp 1: patsiendid, kes tervenesid; Grupp 2: patsiendid, kes jäid elama tüsistustega; Grupp 3: patsiendid, kes surid.

Teises uuringus võrdlesime neljast erinevast riigist pärit 320 patsiendi andmeid. Retrospektiivsesse ülevaatlikku analüüsi kogusime andmed kahest metanoolimürgistuse lainest Norras (1979 ja 2002–2004), Eesti 2001. aasta metanoolimürgistusest, ühest keskusest Tuneesias (2003/2004) ning kahe keskuse andmetest Iraanis. Uuringusse lülitamise kriteeriumiteks olid:

1) patsiendid hospitaliseeriti haiglasse elusana, metanoolimürgistus leidis kinnitust hilisema positiivse seerumi metanoolikontsentratsiooni näol.
2) arteriaalse vere gaaside ja happe-alustasakaalu analüüsi olemasolu vastuvõtul. Kõik patsiendid, kes said mingitki ravi enne veregaaside analüüsimist, mis võiks mõjutada analüüsi (kaasa arvatud mehhaaniline ventilatsioon, sooda või antidoodi manustamine), lülitati uuringust välja.

Hospitaliseerimisel (enne igasuguse raviga alustamist) koguti alljärgnevad andmed: teadvusseisund, vereseerumi metanooli kontsentratsioon, pH, pCO_2, alusliig, HCO_3^-, vereseerumi kaaliumi ja kreatiniini kontsentratsioon. Lisaks dokumenteeriti Eesti patsientidel teadvusseisund ka 1h pärast antidootravi alustamist etanooliga ning patsiendid jaotati järgnevalt: „ärkvel" – patsiendid, kes jäid ärkvele ka pärast etanoolinfusiooniga alustamist; „ärkvel-koomas" – patsiendid, kes hospitaliseerimisel olid teadvusel, kuid kaotasid teadvuse pärast etanooli infusiooniga alustamist; „kooma" – patsiendid, kes olid teadvuseta juba saabumisel haiglasse.

Kolmanda uuringu puhul oli tegemist prospektiivse uuringuga, mis kirjeldas metanoolimürgistuse pikaaegseid tüsistusi 53 patsiendil 86-st, kes kirjutati haiglast välja 2001. aastal. Kõiki patsiente, kes 2001. aastal paranesid metanoolimürgistusest ja lahkusid haiglast, kutsuti kirja teel, telefonitsi või perearsti kaudu osalema järeluuringus. Uuringus osalejate tervislik seisund ja neuroloogiline staatus hinnati anestesioloogi poolt ja oftalmoloogiline staatus silmaarsti poolt. Kogutud andmeid võrreldi patsientide 2001-se aasta andmetega.

Tulemused ja diskussioon

2001-se aasta septembris suunati suure patsientide hulga ning Pärnu Haigla piiratud ressursside tõttu 80 patsienti pärast esmast diagnostikat ja ravi alustamist teistesse Eesti haiglatesse. Metanoolimürgistuse diagnoos baseerus anamneesil, kliinilisel pildil ning arteriaalse vere gaaside ja happe-alustasakaalu analüüsil. Kõigilt patsientidelt võeti veri ka metanooli plasmakontsentratsiooni määramiseks, kuid kuna analüüse teostati Tartus ja Tallinnas, siis vastused saabusid 24–72 tunnise hilinemisega. Seega põhines esialgne diagnoos kõigil juhtudel kaudsetel mürgistuse tunnustel. Hospitaliseerimisel enamesinenud kliinilised sümptomid olid gastrointestinaalsed vaevused (49%), nägemishäired (37%) ja düspnoe (20%). Võrreldes varasemate sarnaste publikatsioonidega oli kliiniliste sümptomite esinemissagedus sarnane (Tabel 6), kuid unustada ei tohi, et sümptomite esinemisspektrit mõjutavad aeg metanooli tarvitamisest hospitaliseerimiseni ning etanooli paralleelne kasutamine. Mürgistuse raviks kasutati 96 patsiendil (87%) etanooli antidoodina, 94 (85%) patsiendile manustati $NaHCO_3$ atsidoosi korrigeerimiseks, 79 (71%) patsienti dialüüsiti ning 68 patsiendil (61%) oli vaja rakendada kopsude kunstlikku ventilatsiooni. Hemodialüüsi seansi soovitav kestvus metanoolimürgistuse korral on kaheksa tundi (Jacobsen *et al*., 1986). 2001-el aastal olime sunnitud Eestis kasutama veidi lühemat aega (keskmiselt 6,3 tundi; 3-st kuni 20-ne tunnini), kuna väga suure patsientide hulga tõttu oli hemodialüsaatorite ressurss piiratud. Kuigi vahelduva hemodialüüsi eelised pideva venovenoosse dialüüsi ees on selgelt näidatud (Kan *et al*., 2003), kasutasime mõningatel juhtudel ka viimast ja seda just vahelduva dialüüsi võimaluste nappuse tõttu, osalt ka ebastabiilse hemodünaamikaga patsientide ravi läbiviimiseks.

Kuigi etanool on odav ja enimlevinud metanooli antidoot, on tema vajaliku terapeutilise kontsentratsiooni 100 mg/dL säilitamine keeruline (Hovda *et al*., 2004; Glaser *et al*., 1996; O`Neill *et al*., 1983), eriti hemodialüüsi ajal ja vajalik on pidev etanooli plasmakontsentratsiooni hindamine. Võrreldes kahte antidooti – etanooli ja fomepisooli – omavahel, ilmnes, et fomepisooli saanud madala pH-ga patsiendid jäävad ellu, kuna sarnased patsiendid etanooli grupis surevad. Etanooliga ravitud ellujäänute hulgas oli metanoolimürgistuse tüsistusi rohkem, kui fomepisooli grupis. Etanooli antidoodina kasutamisel on probleemiks tema kesknärvisüsteemi pärssiv efekt, mis avaldub intubatsiooni ja juhitava ventilatsiooni vajadusena ning võib mõjutada ka ravitulemusi. Oluline on märkida, et üks tund pärast etanoolravi alustamist oli 29 haiget 72-st(40%), haiglasse saabudes teadvusel olnud haigest, muutunud komatoosseks („ärkvel-koomas" grupp). Selle tõenäoliseks põhjuseks võib pidada just etanooli infusiooni. Nendest haigetest suri kuus (22%, p=0,007), võrreldes patsientidega, kes jäid haiglas olles teadvusele („ärkvel grupp"). Patsiendid „ärkvel-koomas" grupis olid rohkem atsidootilised, kui „ärkvel" grupis (p=0,005). Samuti leidsime, et patsiendid „ärkvel-kooma" grupis surid hoolimata madalast esialgsest pCO_2-st (p=0,019), mis näitab, et saabudes oli nende füsioloogiline

suutlikus hüperventileerida piisav, kuid etanoolravi käigus see kaitsev mehhanism kadus.

Kasutades mitmest regressioonanalüüsi ja ROC-kõverat leidsime, et metanoolimürgistuse elulemust mõjutavad tugevaimad prognostilised faktorid on pH ja koomaseisund saabumisel, koos võimega kompenseerida atsidoosi hüperventilatsiooniga. Ellu jäänud patsientide seas esines trend, kus madalatele pH väärtustele vastasid langenud pCO_2 väärtused. Patsientidel, kes surid, esines vastupidine seos – metaboolse atsidoosi respiratoorset kompensatsiooni ei esinenud ($p<0,001$). Baseerudes tehtud andmeanalüüsile koostasime lihtsa riskihindamise skaala, et klinitsistidel oleks kergem triažeerida patsiente ja hinnata nende prognoosi eriti just massiliste metanoolimürgistuste korral (Joonis 11).

Kuus aastat pärast metanoolimürgistust Pärnumaal, milles jäid elama 86 patsienti (66 ilma tüsistusteta ja 20 tüsistustega) kutsusime kõiki patsiente järelkontrollile, et hinnata nende tervislikku seisundit ja tüsistuste esinemist. 26 patsienti olid vahepeal surnud, 33-ga ei õnnestunud ühendust saada. Terviseseisundi hindamiseks pöördusid järelkontrolli seega 27(31%) patsienti. 22-st patsiendist, kes lahkusid haiglast 2001. aastal tüsistusteta, esines nüüd kahel nägemishäire, kahel neuroloogiline defitsiit ja kuuel nii nägemishäire kui ka neuroloogiline defitsiit. Viiel patsiendil, kellel juba 2001. aastal esinesid tüsistused, püsisid need ka 6 aastat hiljem. Enim esinevad nägemishäired olid: silmanärvi atroofia, nägemisvälja kahjustus, nägemisnärvi diski temporaalne kahvatus, nägemisteravuse kadu ning neuroloogilised kahjustused: polüneuropaatia, entsefalopaatia, ataktiline kõnnak, positiivne Rombergi test, alajäsemete sensoorsed tundehäired. Kahjuks polnud paljud patsiendid muutnud oma alkoholitarbimise harjumusi ning 6/27 vajasid igapäevast kõrvalist abi enesega toimetulekuks.

Järeldused:

1. Metanoolimürgistuse laine ajal 2001. aastal oli Pärnus puudu nii diagnostilistest võimalustest kui ka ravivahenditest. Hoolimata sellest rakendati kiiresti raviprotokoll, kaasati olukorra lahendamisse teised tervishoiuteenuse osutajad, ning tänu korraldatud patsientide logistikale õnnestus suremus hoida 22% juures, mis on võrreldav varasemate avaldatud uuringutega.
2. Mõlemad metanooli antidoodid – nii etanool kui ka fomepisool on efektiivsed, kuid etanooli manustamine on tunduvalt keerulisem, eriti just hemodialüüsi ajal. Kahe antidoodi põhiline erinevus on nende hinnas ja kättesaadavuses. Fomepisool tundub olevat efektiivsem raske mürgistuse s.o. madala pH-ga patsientide ravis. Selle väite lõplikuks kinnitamiseks oleksid vajalikud prospektiivsed lisauuringud.
3. pH on lisaks koomale tugevaim prognostiline marker metanoolimürgistuse suremuse ennustamisel. Võime hüperventileerida on hea prognoosi näitaja ning seotud parema elulemusega. Baseerudes kolmel eelpool loetletud prognostilisel markeril moodustasime lihtsa riski hindamise skaala.

Patsientide puhul, kes vajavad trahhea intubatsiooni tuleks hoiduda normoventilatsioonist ning rakendada hüperventilatsiooni kompenseerimaks metaboolset atsidoosi.

4. Nägemishäired ja neuroloogilised ärajäämanähud on tüsistused, mis püsivad ka aastaid pärast metanoolimürgistust. Jätkuv alkoholi tarvitamine võib olla põhjuseks, miks osadel patsientidel, kes lahkusid 2001 aastal haiglast ilma tüsistusteta, on kujunenud tüsistused 6 aastat hiljem.

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PUBLICATIONS

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Teadustegevus:
Peamiseks uurimisvaldkonnaks on toksikoloogia ja täpsemalt metanoolimürgistused, metanooli toime inimorganismis ja tema ravivõimalused. Mitmed ettekanded rahvusvahelistel konverentsidel ja kongressidel.

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