editorial

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Treatment of severe alcohol poisoning

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Poisoning induced by alcohols (methanol, ethanol, or ethylene glycol) may cause severe metabolic acidosis with high anion and/or osmolal gaps, neurological changes ranging from confusion to deep coma, amaurosis, and death. Some patients may also develop acute renal failure.[1-3] Despite intensive treatment, morbidity and mortality of these poisonings continue to be very high, mainly because of the delay in diagnosis and start of treatment.[4,5] If there is no history of methanol, ethanol, or ethylene glycol intake, initial diagnosis is difficult. Measurement of serum levels of toxic alcohol is helpful, but is not always readily available on hospital admission. Diagnosis is often based on an obvious epidemiological context, and above all on the finding of metabolic acidosis with an elevated anion gap and/or osmolal gap.[1-3] In some cases, osmolal gap may overestimate the amount of alcohols present in serum,[6,7] but a good linear correlation usually exists between them, and in the absence of toxic alcohol levels, osmolal gap allows for a quite approximate indirect estimation.[8,9] Depending on the time elapsed since toxic exposure, both biochemical changes may be present to a greater or lesser extent. In the earliest phase of poisoning, the osmolal gap is greater and the anion gap is lower, while as the alcohol is metabolised the osmolal and anion gaps approximate to each other (both being elevated), and in the latest phase the osmolal gap tends to normalise and the anion gap continues to increase.[3,8,9] While less commonly, poisoning by other alcohols such as diethylene glycol and propylene glycol may also cause metabolic acidosis with elevation of the anion and/or osmolal gap, whereas isopropanol only causes elevation of osmolality.[3]

Methanol poisoning may result from a suicidal attempt, accidental intake, or consumption instead of ethanol in chronic drinkers. Methanol is a small molecule (32 Da) that is not bound to protein. Its distribution volume is therefore relatively small (0.6-0.7 L/kg), which allows for a particularly effective removal by haemodialysis (HD). Development of toxicity is related to plasma levels of methanol and its metabolites.[10] Its lethal dose is 50 to 100 mL, but smaller amounts may induce permanent amaurosis[1] and in some patients necrosis of basal ganglia, more specifically the putamen, or bleeding.[11-13] However, there are reports of patients surviving with no organic damage to much higher methanol intakes.[11] Among subjects who experienced seizures, coma, or an initial pH < 7, mortality was higher than 80%.[14] By contrast, in the absence of these findings, the mortality rate was less than 6%. In another series, morbidity was also high, and mortality occurred in up to 44% and 48% of cases.[4,5] The mortality rates in three large series recently reported were 18%, 19%, and 44% respectively. Methanol is metabolised by the enzyme alcohol dehydrogenase (ADH) to yield formic acid, responsible for metabolic acidosis.[18,19] Management of severe methanol poisoning includes administration of ethanol or fomepizole and early start of HD.[11,20-22] Indications for ethanol administration include methanol levels > 20 mg/dL or an osmolal gap > 10 mosm/L in the event of recent intake or when poisoning is strongly suspected. General indications of HD include high serum methanol levels (> 50 mg/dL), metabolic acidosis, and visual and mental changes.[3] In addition, in methanol poisoning folic acid is effective for accelerating formate metabolism into carbon dioxide and water.[11,22]

Ethylene glycol is a component of antifreezes and solvents. Poisoning is usually due to accidental intake. Ethylene glycol is a small molecule (62 Da) that is not bound to protein and has a distribution volume of 0.5-0.8 L/kg. Its lethal dose is approximately 100 mL. Earliest findings include neurological changes ranging from confusion to deep coma. If untreated, these findings may be followed by cardiopulmonary symptoms (tachypnoea and pulmonary oedema) and acute renal failure, that may be associated to marked crystalluria in urinary sediment (oxalate crystals).[23] Acid-base changes and clinical symptoms are due to accumulation of toxic metabolites, rather than to the original toxic compound.[1-3] Ethylene glycol is metabolised by ADH to a variety of toxic compounds including glycolic acid (that may be toxic for renal tubules) and oxalic acid (that may precipitate in the tubules).[23,24] The mortality rate of ethylene glycol poisoning is variable, ranging from 1%-22%.[25] The highest mortality is found in patients with most severe metabolic acidosis and longer delay in treatment start. Management of severe ethylene glycol poisoning includes administration of ethanol or fomepizole and early start of HD.[3,24,26,27] General indications for HD include high

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ethylene glycol plasma levels (over 20 mg/dL), severe metabolic acidosis and/or an osmolal gap also elevated. In ethylene glycol poisoning, vitamins thiamine and pyridoxine may be effective for promoting conversion of glycolic acid into β-hydroxy-β-ketoadipate and glyoxylate into metabolites less toxic than oxalate, such as glycine.[27,28] Moreover, during ethylene glycol poisoning, forced diuresis may preserve kidney function by minimising tubular blockade by oxalate crystals.

Ethanol has a molecular weight of 46 Da and a distribution volume of 0.5 L/kg.[1-3] Ethanol exerts its actions through several mechanisms. Thus, it is directly bound to the gamma-aminobutyric acid (GABA) receptor in the CNS and causes sedative effects similar to benzodiazepines, which bind to the same GABA receptor. Ethanol levels peak 30-60 min after intake. Ethanol absorption starts at the oral mucosa and continues in the stomach and bowel. Ethanol is mainly metabolised in the liver. Approximately 90% of an ethanol overload is metabolized in the liver, and the remaining 10% is eliminated by the kidneys and lungs. In the liver, ethanol is converted by the action of ADH into acetaldehyde, which is then metabolised to acetic acid by acetaldehyde dehydrogenase. Acetic acid enters the Krebs cycle and is finally converted into carbon dioxide and water. Clinical findings with different ethanol concentrations may be classified as follows: poisoning 100-150 mg/dL, loss of muscle coordination 150-200 mg/dL, decreased level of consciousness 200-300 mg/dL, and death 300-500 mg/dL. Alcoholic ketoacidosis syndrome is uncommon and usually occurs in patients with chronic ethanol ingestion and hepatic disease.[29-32] The syndrome occurs during periods of high ethanol intake and low food intake. It is therefore common to find metabolic acidosis with a high anion gap and sometimes with an also elevated osmolal gap. HD is able to efficiently clear ethanol from blood, but should not be routinely used because it is an invasive procedure. In addition, HD has only been used in some isolated cases of acute ethanol intoxication in pregnant women.

Alcohol absorption from the gastrointestinal tract is rapid. Thus, gastric lavage, vomiting induction, or use of activated charcoal should be started in 30-60 minutes to be beneficial. Treatment of metabolic acidosis with bicarbonate is a priority that also allows for increasing renal excretion of formic cid and glycolate.[15,33-35] Bicarbonate may be administered by the intravenous route or HD. Administration of ethanol or fomepizole to delay metabolism of alcohols, methanol and ethylene glycol, is an integral part of therapy. Though it has never been approved by the FDA, ethanol has been used for the treatment of poisoning by methanol and ethylene glycol for many years.[11,20,28,36] Ethanol has a 10 to 20-fold greater affinity for ADH as compared to other alcohols, and completely inhibits ADH at a serum concentration of 100 mg/dL.[3] Fomepizole (4-methylpyrazole, Antizol; Jazz Pharmaceuticals, Palo Alto, CA) has approximately a 500 to 1,000-fold greater affinity for ADH as compared to ethanol and may completely inhibit the enzyme at a much lower serum concentration.[11,37] Fomepizole has a distribution volume of 0.6 to 1 L/kg and a low protein biding, and is eliminated by metabolism in the liver and renal excretion. Studies in humans have confirmed its effectiveness for preventing metabolism of methanol and ethylene glycol to its toxic products. Fomepizole is therefore approved by the US FDA for the treatment of both poisonings. Fomepizole is removed by HD, and its dose should therefore be increased during the dialysis procedure. The problems for use of fomepizole are its unavailability in many countries and its high price (approximately 7800 € per treatment).[15] In addition, a recent study conducted on 20 patients treated with fomepizole and/or ethanol could not elucidate in practice the superiority of one over the other, and controversy therefore continues.[37]

Ethanol is dialysable, and when HD is required the dose of ethanol to be administered should be adjusted. Reduction in ethanol levels during HD may be prevented by increasing infusion rate or by adding ethanol directly to the dialysis bath.[10,38,39] Efficacy of ethanol administration for inhibiting ADH is higher when plasma ethanol levels are from 100 to 200 mg/dL. These levels may be reached by administering ethanol IV at the following dosage regimen: a loading dose of 0.6 g/kg body weight, plus an hourly maintenance dose of 66 mg/kg in non-drinkers, 154 mg/kg in drinkers, and 240 mg/kg when HD is started.[3] Regardless of how ethanol is administered, ethanol plasma levels should be monitored whenever possible, because many patients will require dose adjustments. Ethanol infusion and HD should be continued until the serum levels of the toxic are sufficiently low or have completely disappeared. When poisoning by these toxic alcohols is clinically suspected, even before pharmacological confirmation is obtained, treatment with ethanol and HD should be started as soon as possible. Conventional HD may rapidly decrease plasma levels of these alcohols, and also of their toxic metabolites, simultaneously correcting electrolyte and acid-base disorders. Continuous procedures have been used in some isolated cases,[40] but results superior to those reported with HD have not been shown to date.

Randomised, controlled studies would be useful to provide evidence-based guidelines for the treatment of the different phases of alcohol-induced poisoning. While no such controlled studies allowing for assessing the value of the different therapies are available, the study published in this issue of NEFROLOGIA[41] demonstrates that early start of HD techniques using a bicarbonate bath enriched with phosphorus and potassium[39,41,42] and high efficiency dialysers achieves an excellent removal of methanol, ethanol, and ethylene glycol, as well as their toxic metabolites, producing at the same time a rapid correction of water, elec-

trolyte, and acid-base disturbances. Measures implemented in this study represent a combination of relatively simple and safe procedures that decrease morbidity and mortality, allowing for a shorter hospital stay. However, our study was limited by its relatively small number of patients, though this was the largest series (of cases from a single centre) reported to date in Spain. Taking into account that there has been in recent years in the Madrid Autonomous Community an increase in the number of cases of methanol poisoning among immigrants who massively drank methanol during social events and who were referred to different hospitals, it would be appropriate for centres to coordinate their action protocols, and to share databases in order to be able to conduct cooperative studies.

REFERENCES

1. Sivilotti ML, Winchester JF. Methanol and ethylene glycol intoxication. Version 15.3. UpToDate Inc. Wellesley, USA, 2008.
2. Seyffart G. Methyl alcohol; in Seyffart G (ed): Poison index: the treatment of acute intoxication. Lengerich, Pabst Science Publishers, 1997; pp. 457-464.
3. Kraut JA, Kurtz I. Toxic alcohol ingestions: Clinical features, diagnosis, and management. *Clin J Am Soc Nephrol* 2008; 3: 208-225.
4. Nolla-Salas J, Nogué Xarau S, Marruecos Sant L, Palomar Martínez M, Martínez Pérez J. Methanol and ethylene glycol poisoning. Study of 18 cases. *Med Clin (Barc)* 1995; 104: 121-125.
5. Hassanian-Moghaddam H, Pajoumand A, Dadgar SM, Shadnia Sh. Prognostic factors in methanol poisoning. *Hum Exp Toxicol* 2007; 26: 583-586.
6. Meatherall R, Krahn J. Excess serum osmolality gap after ingestion of methanol. *Clin Chem* 1990; 36: 2004-2007.
7. Haviv YS, Rubinger D, Zamir E, Safadi R. Pseudo-normal osmolal and anion gaps following simultaneous ethanol and methanol ingestion. *Am J Nephrol* 1998; 18: 436-438.
8. Hovda KE, Hunderi OH, Rudberg N, Froyshov S, Jacobsen D. Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. *Intensive Care Med* 2004; 30: 1842-1846.
9. Hunderi OH, Hovda KE, Jacobsen D. Use of the osmolal gap to guide the start and duration of dialysis in methanol poisoning. *Scand J Urol Nephrol* 2006; 40: 70-74.
10. Wadgymar A, Wu GG. Treatment of acute methanol intoxication with hemodialysis. *Am J Kidney Dis* 1998; 31: 897.
11. Barceloux B, Bond GR, Krenzelok EP, Cooper H, Vale JA. American Academy of Clinical Toxicology Practice Guidelines for the Treatment of Methanol Poisoning. *J Toxicol Clin Toxicol* 2002; 40: 415-446.
12. Anderson CA, Rubinstein D, Filley CM, Stears JC. MR enhancing brain lesions in methanol intoxication. *J Comput Assist Tomogr* 1997; 21: 834-836.
13. Hernández MA, Holanda MS, Tejerina EE, González C, López M. Methanol poisoning and heparin: a dangerous couple? *Am J Emerg Med* 2004; 22: 620-621.
14. Liu JJ, Daya MR, Carrasquillo O, Kales SN. Prognostic factors in patients with methanol poisoning. *J Toxicol Clin Toxicol* 1998; 36: 175-181.
15. Hovda KE, Hunderi OH, Tafjord AB, Dunlop O, Rudberg N, Jacobsen D. Methanol outbreak in Norway 2002-2004: epidemiology, clinical features and prognostic signs. *J Intern Med* 2005; 258: 181-190.
16. Brahmi N, Blel Y, Abidi N, Kouraichi N, Thabet H, Hedhili A, Amamou M. Methanol poisoning in Tunisia: report of 16 cases. *Clin Toxicol (Phila)* 2007; 45: 717-720.
17. Paasma R, Hovda KE, Tikkerberi A, Jacobsen D. Methanol mass poisoning in Estonia: Outbreak in 154 patients. *Clin Toxicol* 2007; 45: 152-157.
18. Hantson P, Haufroid V, Wallemacq P. Formate kinetics in methanol poisoning. *Hum Exp Toxicol* 2005; 24: 55-59.
19. Elwell RJ, Darouian P, Bailie GR. Delayed absorption and postdialysis rebound in a case of acute methanol poisoning. *Am J Emerg Med* 2004; 22: 126-127.
20. Jacobsen D, McMartin KE. Antidotes for methanol and ethylene glycol poisoning. *J Toxicol Clin Toxicol* 1997; 35: 127-143.
21. Brent J, McMartin K, Phillips S, Aaron C, Kulig K. Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 2001; 344: 424-429.
22. Kerns W, Tomaszewski C, McMartin K, Ford M, Brent J. Formate kinetics in methanol poisoning. *J Toxicol Clin Toxicol* 2002; 40: 137-143.
23. Eder AF, McGrath CM, Dowdy YG, Tomaszewski JE, Rosenberg FM, Wilson RB, Wolf BA, Shaw LM. Ethylene glycol poisoning: toxicokinetic and analytical factors affecting laboratory diagnosis. *Clin Chem* 1998; 44: 168-177.
24. Ammar KA, Heckerling PS. Ethylene glycol poisoning with a normal anion gap caused by concurrent ethanol ingestion: importance of the osmolal gap. *Am J Kidney Dis* 1996; 27: 130-133.
25. Porter WH, Rutter PW, Bush BA, Pappas AA, Dunnington JE. Ethylene glycol toxicity: the role of serum glycolic acid in hemodialysis. *J Toxicol Clin Toxicol* 2001; 39: 607-615.
26. Peterson CD, Collins AJ, Himes JM, Bullock ML, Keane WF. Ethylene glycol poisoning: pharmacokinetics during therapy with ethanol and hemodialysis. *N Engl J Med* 1981; 304: 21-23.
27. Brent J. Current management of ethylene glycol poisoning. *Drugs* 2001; 61: 979-988.
28. Barceloux DG, Krenzelok EP, Olson K, Watson W. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee. *J Toxicol Clin Toxicol* 1999; 37: 537-560.
29. Wrenn KD, Slovis CM, Minion GE, Rutkowski R. The syndrome of alcoholic ketoacidosis. *Am J Med* 1991; 91: 119-128.
30. Fulop M. Alcoholic ketoacidosis. *Endocrinol Metab Clin N Am* 1993; 22: 209-219.
31. Umpiérrez GE, DiGirolamo M, Tuvlin JA, Issacs SD, Bhoola SM, Kokko JP. Differences in metabolic and hormonal milieu in diabetic and alcohol-induced ketoacidosis. *J Crit Care* 2000; 15: 52-59.
32. Elisaf M, Merkouropoulos M, Tsianos EV, Siamopoulos KC. Acid-base and electrolyte abnormalities in alcoholic patients. *Miner Electrolyte Metab* 1994; 20: 274-281.
33. Megarbane B, Borron SW, Baud FJ. Current recommendations for treatment of severe toxic alcohol poisonings. *Intensive Care Med* 2005; 31: 189-195.
34. Moreau CL, Kerns W, Tomaszewski CA, McMartin KE, Rose SR, Ford MD, Brent J. Glycolate kinetics and hemodialysis clearance in ethylene glycol poisoning. *J Toxicol Clin Toxicol* 1998; 36: 659-666.
35. Garella S. Extracorporeal techniques in the treatment of exogenous intoxications. *Kidney Int* 1988; 33: 735-754.
36. Peces R, Álvarez R. Effectiveness of hemodialysis with high-flux polysulfone membrane in the treatment of life-threatening methanol intoxication. *Nephron* 2002; 90: 216-218.
37. Green R. The management of severe toxic alcohol ingestions at a tertiary care center after the introduction of fomepizole. *Am J Emerg Med* 2007; 25: 799-803.
38. Chow MT, Silvestro VA, Yung CY, Nawab ZM, Leehey DJ, Ing TS. Treatment of acute methanol intoxication with hemodialysis using an ethanol-enriched, bicarbonate-based dialysate. *Am J Kidney Dis* 1997; 30: 568-570.
39. Dorval M, Pichette V, Cardinal J, Geadah D, Ouimet D, Leblanc M. The use of an ethanol- and phosphate-enriched dialysate to maintain stable serum ethanol levels during haemodialysis for methanol intoxication. *Nephrol Dial Transpl* 1999; 14: 1774-1777.

40. Kan G, Jenkins I, Rangan G, Woodroffe A, Rhodes H, Joyce D. Continuous haemodiafiltration compared with intermittent haemodialysis in the treatment of methanol poisoning. *Nephrol Dial Transplant* 2003; 18: 2665-2667.
41. Peces R, Fernández R, Peces C, González E, Olivas E, Renjel F, Jiménez M, Costero O, Montero A, Selgas R. Eficacia de la hemodiálisis precoz con membranas de alto flujo en el tratamiento de las intoxicaciones graves por alcoholes. *Nefrología* 2008; 28 (4): 413-418.
42. Chebrolu SB, Hariman A, Eggert CH, Patel S, Kjellstrand CM, Ing TS. Phosphorus-enriched hemodialysis for the treatment of patients with severe methanol intoxication. *Int J Artif Organs* 2005; 28: 270-274.