ETHYLENE GLYCOL POISONING

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Alcohol poisonings, accidental or intentional, constitute a serious toxicological problem in many countries. Methanol, ethylene glycol (EG) and diethylene glycol poisonings remain a rare but important presentation to emergency toxicology departments. Some glycol ethers are also metabolized to toxic intermediates, but their poisonings are less severe with few common features (1).

Ethylene glycol metabolism and pathophysiological effects of its metabolites

The EG itself only causes an initial alteration in mental status similar to ethanol ingestion; the real toxicity is due to metabolite production via alcohol dehydrogenase (ADH) pathway. The rate-limiting step in this metabolic process is the conversion of EG to glycol aldehyde by aldehyde dehydrogenase. Both oxidative steps, ADH and aldehyde dehydrogenase, lead to the reduction of NAD^+ to HADH, thereby depleting the cells from NAD^+ , changing the redox potential, and promoting lactate production. Once glycol aldehyde is metabolized, both lactate and glycolic acid cause a severe metabolic acidosis with significant effects on cardiorespiratory function; most commonly, tachycardia, tachypnoea, arterial hypertension and congestive cardiac failure. In addition, the inhibition of Krebs cycle and the accumulation of oxalic acid have a contribution to the metabolic acidosis. Death most often occurs in this stage 12-36 hours post ingestion. After 24-36 hours post ingestion, renal failure may develop due to combination of oxalate crystal deposition and cardiovascular instability (2).

The EG toxicity is complex and not fully understood, but is mainly due to the severe glycolate-induced metabolic acidosis and to the calcium oxalate precipitation (3). Several factors may affect susceptibility to EG-induced toxicity, including genetic factors that determine individual variations in liver ADH activity and the presence of the respective isoenzyme, and nutritional deficiencies, specifically lack of the vitamins thiamine or pyridoxine (the two vitamins-derived cofactors mediate metabolic EG detoxification).

The diagnosis of EG intoxication can be challenging

The EG poisoning may pose diagnostic difficulties if the history of ingestion is not volunteered, or if the presentation is delayed. Definitive testing for EG is not readily available and clinical decisions are often based on clinical suspicion and the results of more readily available tests (4). Emergency toxicology departments often face cases of unconsciousness in patients presenting with profound metabolic acidosis. Considering poisoning in cases with neurological depression, and, especially, EG poisoning is essential for timely diagnosis and beneficial treatment outcome. In some cases, even the combination of presence of high anion gap metabolic acidosis with significantly elevated lactate along with an elevated osmolal gap and calcium oxalate crystals in the urine can be seen collectively in a patient yet their cause is different from EG poisoning (5).

The most reliable method of diagnosing EG intoxication is by measuring blood EG concentration. There are guidelines recommending that an 'urgent' test producing results within four hours for EG blood concentrations should be available, however, these are difficult to deliver in practice. In fact, most hospital laboratories are unable to perform this analysis. In many cases, the sample has to be sent to a centralized laboratory in another city and the results would only be available as an average on day 3 upon admission.

A lot of research effort is put against identifying and establishing a reliable assay for fast EG identification and quantification. Current literature survey discloses several publications in this line. A validation of an automated assay for EG measurement on an Abbott Architect using both a commercially available kit (Catachem) and gas chromatography-mass spectrometry method is reported by Robson *et al.* (2017). The assay is suitable for diagnosis of EG poisoning and is now in routine use, enabling the laboratory to provide a rapid 24-hour service with support by gas chromatography-mass spectrometry as necessary (6).

Assessment of a semi-quantitative enzymatic spectrophotometric assay for EG compatible with automated platforms shows a good correlation with results produced from a quantitative method on an automated

analyzer but with an apparent under-recovery. The assay is able to discriminate well between EG-containing samples and those with other causes of acidosis (4).

One of the findings in EG poisoning is hypocalcemia, presumable through complexation with the EG metabolite oxalate. A retrospective review of all patients admitted to a tertiary care hospital between 2005 and 2013 with laboratory-confirmed EG intoxication, whose serum calcium on presentation was compared to blood gas pH as well as serum bicarbonate, established that hypocalcemia was not commonly observed following EG poisoning, even in acidotic patients. No relationship between calcium and serum pH and an inverse relationship between serum calcium and bicarbonate were established (7).

Methemoglobinemia should also be considered as a potential condition and risk after a massive ingestion of antifreeze (8). Only substances that comprise more than 1% of a given product are required by the occupational safety and health administration hazard communication standards to be reported on the safety data sheets, many of them below the threshold of 1% remain unknown to the consumer and the medical services. For instance, in a case of antifreeze ingestion resulting in clinically significant methemoglobinemia caused by an identified agent, the manufacturer's representative disclosed upon request by the clinicians the presence of nitrite (0.27%) and nitrate (0.08%) in the antifreeze product. As these compounds are not universally included in all formulations, methemoglobinemia has not been consistently observed after antifreeze ingestions (8).

In conclusion, epidemiological profile data from retrospective investigations of poisoning deaths over certain period of time (9) and shared clinical practices for the diagnosis and treatment of these as the publication of Marinov *et al.* (2017) (10) in this issue may be very useful for clinicians to develop preventive programmes and to effectively apply timely and relevant therapeutic approaches in the emergency environments.

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