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Invited critical review

Ethylene glycol poisoning: Quintessential clinical toxicology; analytical conundrum

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ABSTRACT

Ethylene glycol poisoning is a medical emergency that presents challenges both for clinicians and clinical laboratories. Untreated, it may cause morbidly or death, but effective therapy is available, if administered timely. However, the diagnosis of ethylene glycol poisoning is not always straightforward. Thus, measurement of serum ethylene glycol, and ideally glycolic acid, its major toxic metabolite in serum, is definitive. Yet measurement of these structurally rather simple compounds is but simple. This review encompasses an assessment of analytical methods for the analytes relevant for the diagnosis and prognosis of ethylene glycol poisoning and of the role of the ethylene glycol metabolites, glycolic and oxalic acids, in its toxicity.

Contents

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1. Introduction

Ethylene glycol poisoning is a quintessential study in clinical toxicology; it may cause significant morbidly and mortality, toxicity is due to its acid metabolites, expensive or invasive therapy is effective if administered timely, and it has notoriety as a homicide weapon and for intentional infantile poisoning. Glycolic acid is the principle toxic metabolite in serum and its concentration correlates with severity. Absent complete metabolic transformation, serum ethylene glycol measurement can establish the correct diagnosis and current therapeutic guidelines are based in part on these values despite their lack of clinical correlation. Ethylene glycol measurement is an analytical challenge and its misidentification in one case caused false imprisonment for murder. Rapid, robust and accurate methods for ethylene glycol and ideally also glycolic acid are necessary to avoid such tragedies and to quickly make or exclude the diagnosis but such methods are difficult to implement in most clinical laboratories. Absent such capability, surrogate tests such as osmolal gap for ethylene glycol and anion gap for glycolic acid are commonly utilized despite their limitations.

2. Clinical toxicology

2.1. Overview

Ethylene glycol, a sweet-tasting ingredient in antifreeze and some other industrial products when accidently, intentionally or criminally ingested in sufficient amount produces neurological impairment, cardiopulmonary dysfunction, metabolic acidosis, renal failure and death. Ethylene glycol itself is relatively non-toxic, causing inebriation similar to ethanol. The variably delayed serious symptoms are caused by the metabolites glycolic acid and oxalic acid. Gycolate accumulates in serum and its concentration, unlike that for ethylene glycol, correlates with clinical severity. Calcium oxalate crystals may be deposited in renal tubules which may cause acute renal failure and may also cause or contribute to cerebral and other organ toxicity. Hypocalcemia is common in serious intoxications. Metabolic acidosis is a hallmark of ethylene glycol toxicity.

2.2. Clinical presentation

The clinical presentation is often described in sequential phases: neurological (0.5–12 h), cardiopulmonary (12–24 h), and renal failure (24–72 h) [1–3]. However, there may be considerable overlap in these stages, one or more may predominate and the chronology is dose dependent [2]. The neurological manifestations include initial inebriation but as metabolic acidosis develops, CNS depression occurs. Additional neurological symptoms include ataxia, myoclonus, nystagmus, ophthalmoplegias and seizures. In rare cases, delayed cranial nerve neuropathy especially involving facial nerves has occurred 5–20 days post ingestion [4]. Cardiopulmonary symptoms include tachycardia, tachypnea, hypertension, congestive heart failure, pulmonary edema, and shock. Renal complications are flank pain, oliguria and renal failure.

2.3. Metabolism

The initial step in ethylene glycol metabolism is its conversion to glycoaldehyde by hepatic alcohol dehydrogenase (Fig. 1). Aldehyde dehydrogenase converts glycoaldehyde to glycolic acid, which is subsequently oxidized to glyoxylic acid [1,2].

Insight into the fate of glyoxylic acid, a probable normal product of hydroxyproline metabolism [5], has been gained from investigation of the inherited metabolic disorders, primary hyperoxaluria type 1 and type 2[6]. Normally 99% of glyoxylic acid is converted to glycine by peroxisomal alanine:glyoxylate aminotransferase (AGT) [7], with only small amounts of glycolate and oxalate formed and excreted in urine [8]. Alanine:glyoxylate aminotransferase is deficient in type 1 primary hyperoxaluria, which results in shunting of glyoxylate to oxalate and glycolate (Fig. 1). Thus hallmarks of this condition are increased urinary excretion of oxalate and glycolate and deposition of calcium oxalate crystals in renal tissue which may cause renal failure. Type 2 is caused by a deficiency in glyoxylate reductase (GR) in which case glyoxylate is shunted to oxalate absent a concomitant increase in glycolate formation. Apparently AGT becomes saturated resulting in increased oxalate formation.

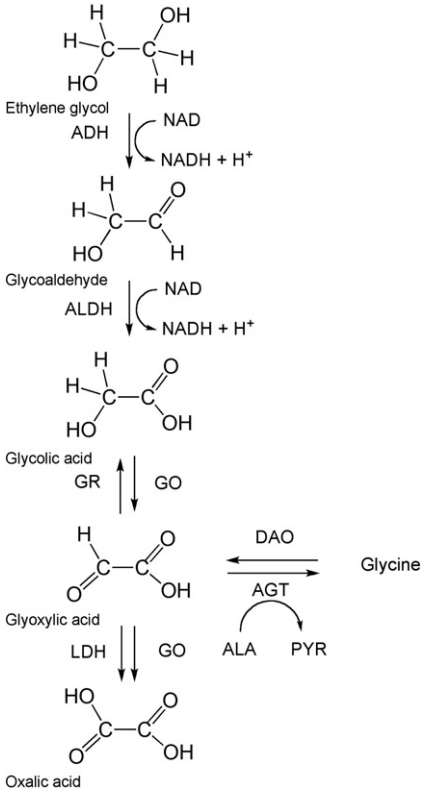

Fig. 1. Ethylene glycol metabolism. ADH, alcohol dehydrogenase; ALD, aldehyde dehydrogenase; GO, glycolate oxidase; GR, glyoxylate reductase; LDH, lactate dehydrogenase; AGT, alanine:gloxylate aminotransferase; DAO, D-amino acid oxidase; ALA, alanine; PYR, pyruvate; NAD/NADH, nicotinamide adenine dinucleotide. (Adapted from Baker et al, Am. J. Physiol. Cell Physiol, 287 (2004) c 1359–c1365).