Incorporation of Therapeutic Interventions in Physiologically Based Pharmacokinetic Modeling of Human Clinical Case Reports of Accidental or Intentional Overdosing with Ethylene Glycol

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INTRODUCTION

Ethylene glycol (EG) is a high production volume (HPV) chemical capable of producing renal and developmental toxicity in animals (Carney, 1994; Cruzan et al., 2004; Depass et al., 1986; Gaunt et al., 1974; NTP, 1993). Kidney toxicity has also been a consistent finding in several human case reports of intentional or accidental overdoses with EG. After consuming significant quantities of EG (typically >100 ml in adults), toxicity in humans generally progresses from an initial stage of central nervous system depression or coma (~0.5–12 h), followed by a cardiopulmonary stage associated with metabolic acidosis (~12–24 h) and ultimately renal toxicity (~1–3 days), depending on the total amounts consumed and how quickly an effective treatment regimen is instituted (see Table 1). Each of these stages of acute toxicity has been associated with the progression of EG metabolism (Fig. 1) and elimination. Central nervous system depression has been attributed to the initially high circulating levels of EG, whereas metabolic acidosis has been associated with the acid metabolites of EG, most notably glycolic acid. Renal damage largely results from a build-up of the terminal metabolite, oxalic acid, which can precipitate with calcium to form crystals.

In addition to an extensive animal toxicity database, much of the information supporting a common mode of action for renal toxicity in animals and humans (calcium oxalate crystal deposition) comes from research into the mechanisms of human kidney stone formation, which is predominately calcium oxalate, and human case reports of intentional or accidental overdosing with EG (see Table 1). Differences between sexes, strains, and species appears to be mostly quantitative in nature, although little is reported on potential differences in sensitivity of renal epithelial cells to oxalic acid or calcium oxalate crystals once they are formed.

For developmental toxicity, human relevance is less clear. Although all laboratory mammals and humans appear to metabolize EG similarly, and all have the potential to form the proximate toxicant, glycolic acid, developmental toxicity has been observed only in rodent species (rats and mice). Ethylene glycol does not cause developmental toxicity in nonrodent species (i.e., rabbit), and there have not been any reported cases of human developmental effects induced by EG. In one recent review, the likelihood of developmental toxicity...
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<th>Reference</th>
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<tbody>
<tr>
<td>Male, Caucasian, age 19 (case 1 of 3)</td>
<td>~300 ml antifreeze containing 49% EG</td>
<td>CNS, acidosi, seizures associated with epilepsy</td>
<td>Bicarbonate, fomepizole, phenobarbital, clonazepam</td>
<td>EG (t1/2: 15 h)</td>
<td>Colorimetric</td>
<td>Baud et al., 1987</td>
</tr>
<tr>
<td>Female, Algerian, age 26 (case 2 of 3)</td>
<td>100–200 ml antifreeze</td>
<td>CNS</td>
<td>Spontaneous vomiting, bicarbonate, ethanol, gastric lavage, fomepizole</td>
<td>EG (t1/2: 14 h); OX (t1/2: 15.1 h)</td>
<td>Colorimetric</td>
<td>Baud et al., 1987</td>
</tr>
<tr>
<td>Male, Chinese, age 28 (case 3 of 3)</td>
<td>100 ml antifreeze</td>
<td>None</td>
<td>Gastric lavage, fomepizole</td>
<td>EG (t1/2: 11 h); OX (t1/2: 15.8 h)</td>
<td>Colorimetric</td>
<td>Baud et al., 1987</td>
</tr>
<tr>
<td>Male, age 42</td>
<td>1500 ml antifreeze containing 92% EG</td>
<td>CNS, acidosi</td>
<td>Gastric lavage, charcoal, bicarbonate, ethanol, dextrose, fomepizole</td>
<td>EG (t1/2: 11.5 h; CLEG: 31.5 ml/min); OX in urine</td>
<td>GC/MS</td>
<td>Baud et al., 1988</td>
</tr>
<tr>
<td>Male, age 43 (case 1 of 2)</td>
<td>Unknown amount of antifreeze</td>
<td>CNS, Acidosis, Death</td>
<td></td>
<td>EG</td>
<td>GC/FID</td>
<td>Bowen et al., 1978</td>
</tr>
<tr>
<td>Male, age 42 (case 2 of 2)</td>
<td>500 ml EG, tranquilizers; Unknown amount of antifreeze; some ingested ethanol, drugs, or gasoline as well</td>
<td>CNS, acidosi, death; CNS, acidosi, renal injury of 10/19</td>
<td>Bicarbonate, ethanol, Fomepizole, hemodialysis if patients with metabolic acidosis or renal toxicity, bicarbonate</td>
<td>EG; GA</td>
<td>GC/FID</td>
<td>Bowen et al., 1978</td>
</tr>
<tr>
<td>Male, age 73 (one of 19)</td>
<td>Unknown amount of antifreeze</td>
<td></td>
<td>Fomepizole, hemodialysis</td>
<td>EG; GA</td>
<td>GC/FID</td>
<td>Brent et al., 1999</td>
</tr>
<tr>
<td>Female, age 35 (one of 19)</td>
<td>Unknown amount of antifreeze</td>
<td>CNS, acidosi, renal</td>
<td>Fomepizole, hemodialysis</td>
<td>EG</td>
<td>GC/FID</td>
<td>Brent et al., 1999</td>
</tr>
<tr>
<td>Male, age 25</td>
<td>~280 ml antifreeze containing 95% EG</td>
<td>CNS, acidosi</td>
<td>Bicarbonate, ethanol-induced vomiting, hemodialysis</td>
<td>EG; GA (t1/2: 5.5 h)</td>
<td>GC/FID</td>
<td>Cheng et al., 1987</td>
</tr>
<tr>
<td>Male, Black, age 64</td>
<td>Several cups of antifreeze plus unidentified pills</td>
<td>None</td>
<td>Gastric lavage, ethanol, charcoal, hemodialysis, thiamine, Mg citrate</td>
<td>EG</td>
<td>OG</td>
<td>Curtain et al., 1992</td>
</tr>
<tr>
<td>Male, Polish, age 73</td>
<td>~591 ml antifreeze (50% EG)</td>
<td>Acidosis</td>
<td>Charcoal, ethanol, hemodialysis</td>
<td>EG</td>
<td>Colorimetric</td>
<td>Eder et al., 1998</td>
</tr>
<tr>
<td>Male, Polish, age 73</td>
<td>500 ml antifreeze (99% EG)</td>
<td>CNS, acidosi, renal, death</td>
<td>Spontaneous vomiting, gastric lavage, bicarbonate, ethanol, althesin (sedative), methylprednisolone (reduce adult respiratory distress syndrome), mannitol (increase urine output), peritoneal dialysis, ventilation</td>
<td>EG; OX</td>
<td>Method not stated</td>
<td>Gordon and Hunter, 1982</td>
</tr>
<tr>
<td>Male, age 30</td>
<td>100 g (111 ml)</td>
<td>None</td>
<td>Gastric lavage, charcoal, fomepizole</td>
<td>EG (t1/2: 16 h; CLAG: 24 ml/min)</td>
<td>GC/FID</td>
<td>Harry et al., 1994</td>
</tr>
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TABLE 1—Continued

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Estimated dose</th>
<th>Stages of toxicity</th>
<th>Treatment(^a)</th>
<th>Metabolites in blood(^b)</th>
<th>Analytical method(^c)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, age 2 (case 1 of 2)</td>
<td>Unknown amount of antifreeze</td>
<td>CNS, acidosis</td>
<td>Gastric lavage, charcoal, bicarbonate, ethanol</td>
<td>EG</td>
<td>EG: GC/FID, OG</td>
<td>Hewlett and McMartin, 1986</td>
</tr>
<tr>
<td>Male, age 46 (case 2 of 2)</td>
<td>Glassful of antifreeze</td>
<td>CNS, acidosis, renal</td>
<td>Gastric lavage, charcoal, bicarbonate, ethanol, ventilation, hemodialysis</td>
<td>EG</td>
<td>EG: GC/FID, OG</td>
<td>Hewlett and McMartin, 1986</td>
</tr>
<tr>
<td>Female, Black, age 36 (case 1 of 2)</td>
<td>''Jar'' of antifreeze</td>
<td>CNS, acidosis, renal</td>
<td>Charcoal lavage, bicarbonate, ethanol, hemodialysis</td>
<td>EG ((t_{1/2}: 8.4) h before therapy; 3–102 h during therapy) GA ((t_{1/2}: 2.4–7) h)</td>
<td>GC/FID; HPLC/UV</td>
<td>Jacobsen et al., 1988</td>
</tr>
<tr>
<td>Female, Black, age 38 (case 2 of 2)</td>
<td>~240 ml antifreeze</td>
<td>CNS, acidosis, renal</td>
<td>Bicarbonate, ethanol, hemodialysis</td>
<td>EG</td>
<td>EG: GC/FID, OG; GA: HPLC/UV</td>
<td>Jacobsen et al., 1988</td>
</tr>
<tr>
<td>Male, age 37 (case 1 of 2)</td>
<td>Unknown amount of antifreeze, alcohol; closed garage with car running</td>
<td>CNS, acidosis, death</td>
<td>Ventilation, ethanol, hemodialysis</td>
<td>EG ((t_{1/2}: 4.5) h during dialysis, 12.5 h without)</td>
<td>EG by GC/FID</td>
<td>Malmlund et al., 1991</td>
</tr>
<tr>
<td>Male, age 22 (case 2 of 2)</td>
<td>Unknown</td>
<td>CNS, acidosis, renal</td>
<td>Bicarbonate, tris buffer, ethanol, hemodialysis</td>
<td>EG</td>
<td>EG by GC/FID, GA by GC/MS</td>
<td>Malmlund et al., 1991</td>
</tr>
<tr>
<td>Male, age 39 (case 2 of 3)</td>
<td>500–2000 ml antifreeze</td>
<td>CNS, acidosis, renal, convulsions, death</td>
<td>Gastric lavage, charcoal, ethanol, bicarbonate, hemodialfiltration, diazepam &amp; phenytoin for seizures</td>
<td>EG</td>
<td>EG: method not stated</td>
<td>Walder and Tyler, 1994</td>
</tr>
</tbody>
</table>

\(^a\)Toxicity progresses from an initial stage of central nervous system (CNS) depression or coma (~1–12 h), followed by a cardiopulmonary stage associated with metabolic acidosis (~12–24 h) and ultimately renal toxicity (~1–3 days). A fourth stage of toxicity has been suggested consisting of cranial nerve deficits occurring 6–18 days after EG ingestion.

\(^b\)Treatment generally consists of standard supportive care (i.e., fluids, bicarbonate, ventilation, electrolytes), gastric lavage (with or without activated charcoal), hemodialysis, metabolic competitors or inhibitors (i.e., ethanol or fomepizole [4-methylpyrazole, 4-MP] for the conversion of EG to GA) or cofactors that favor detoxification pathways (i.e., thiamine for conversion of GA to \(\alpha\)-OH-\(\beta\)-ketoadipate and pyridoxine for conversion of GA to glycine). Other treatment regimens employed dependent upon initial diagnosis or other complicating factors (e.g., background disease or co-exposure to other drugs or chemicals).

\(^c\)Chemical analyses for EG, GA, or OX conducted to confirm diagnosis or follow the progress of treatments. Pharmacokinetic constants (half-life or clearance) either reported by authors or calculated from data during therapeutic intervention unless otherwise noted using either PK Solutions (v. 2.0) or Excel.

\(^d\)Analytical methods included highly selective, chemical-specific methods such as gas chromatography/mass spectrometry (GC/MS); moderately selective methods such as gas chromatography/flame ionization detection (GC/FID), high-pressure liquid chromatography/ultraviolet detection (HPLC/UV), isochrophoresis-conductivity detection (ISO/CON), or nuclear magnetic resonance (NMR); or semi-specific methods such as colorimetric assays. Indirect, nonspecific methods such as the osmolal gap (OG) in serum (measured osmolality – calculated osmolality; normal osmolality is 281–289 mM with a normal gap <10 mM), which has been correlated with ethylene glycol levels or the anion gap (AG) in blood (the difference between measured cations (i.e., \(\text{Na}^+ + \text{K}^+\)), and anions (i.e., \(\text{Cl}^- + \text{HCO}_3^-\)) has been correlated with glycolic acid level.
incurred in humans through occupational or consumer exposures was considered negligible, primarily because of the high dose rates needed to produce this effect in rodents (CERHR, 2004). The same review recommended the development of a PBPK model for rodents and humans to facilitate inter-species extrapolations and the dose-rate effects on pharmacokinetics that are critical to developmental toxicity.

In a companion study to this report (Corley et al., 2005), a physiologically based pharmacokinetic (PBPK) model for EG and its major metabolite responsible for developmental toxicity, glycolic acid, was developed for adult rats and humans. However, only limited controlled exposure studies, below levels leading to the saturation of metabolic and clearance processes, were available to confirm the ability of the model to simulate human exposures (i.e., validate the human PBPK model). Therefore, the purpose of the present study was to extend the human PBPK model developed in the companion study to include the major treatment regimens used in accidental or intentional overdosing case reports. Although human case reports are often confounded by inadequate descriptions of the total amounts of EG consumed, the presence of other chemicals or drugs, or the effect of therapeutic regimens or toxicity, many of the case reports summarized in Table 1 included relatively extensive analyses of the kinetics of EG and/or glycolic acid to confirm the diagnosis and monitor the effectiveness of the various treatments. Such data are potentially useful for model validations once the effects of various treatment regimens have been adequately accounted for.

Thus, the initial human PBPK model developed in the companion study (Corley et al., 2005) was modified to include the basic treatment regimens that have been shown to alter the kinetics of EG and glycolic acid: metabolic inhibition by ethanol or fomepizole (4-methyl pyrazole, 4-MP), and hemodialysis. The other major treatment for EG intoxication that affects kinetics, gastric lavage, was handled simplistically by reducing the total dose of EG available for absorption. Once the model was modified to include therapeutic interventions, the additional data sets summarized in Table 1 provided a unique opportunity for additional validation of the human PBPK model for high oral doses, where metabolism or clearance processes can be saturated. The resulting model can also serve as a useful tool in the evaluation of the effectiveness of various treatment regimens on the kinetics of EG and glycolic acid.

**MATERIALS AND METHODS**

**Model structure.** The human PBPK model of Corley et al. (2005) was modified to include common treatment regimens that alter the disposition of EG and its metabolites. These treatments include gastric lavage to remove unabsorbed EG, hemodialysis to facilitate clearance of EG and its metabolites responsible for toxicity (glycolic acid and oxalic acid), and the use of inhibitors of EG metabolism (e.g., ethanol and fomepizole) to prevent or reduce metabolic acidosis and renal toxicity. Bicarbonate is often used to control metabolic acidosis, although it does not affect the disposition of EG and glycolic acid. Thiamine or pyridoxine is sometime given to facilitate the metabolism of glyoxylic acid to α-OH-β-ketoadipate or glycine to compete against oxalate formation (Fig. 1, Table 1). However, the effectiveness of the latter treatments is unknown.

All of the human case reports listed in Table 1 were the result of intentional or accidental oral ingestion of large amounts of EG. The absorption of EG into gastrointestinal tissues of humans was described as a first-order process as was used in the rat PBPK model of Corley et al. (2005):

\[
AOEG = \text{Dose} - \text{Dose} \times e^{-(KAS \times T)}
\]

where \(AOEG\) is the amount of EG absorbed (mg), \(KAS\) is the first-order rate constant (h\(^{-1}\)) and \(\text{Dose}\) is the total amount of EG consumed (mg). The mass-balance equation for the gastrointestinal tissues is thus:

\[
RAGI_{GI} = QGI(\text{CA}_{EG} - \text{CVGI}_{EG}) + KAS \times AOEG
\]

where \(RAGI_{GI}\) is the rate of absorption of EG in gastrointestinal tissues (mg/h), \(QGI\) is the relative blood flow to the gastrointestinal tissues (l/h), \(\text{CA}_{EG}\) is the arterial blood concentration of EG (mg/l), and \(\text{CVGI}_{EG}\) is the concentration of EG in venous blood draining the gastrointestinal tissues (mg/l).

As observed in the rat pharmacokinetic studies (especially fasted vs. non-fasted animals) described in the companion study (Corley et al., 2005), the oral absorption rate constant, \(KAS\), can be affected by a number of factors including the amount of food in the stomach or other drugs or liquids consumed. Generally, a default value of \(KAS\) of 1 h\(^{-1}\) was used in all human simulations, with occasional increases necessary to fit the peak blood concentration of EG (if the dose and time of dosing were well-documented) as noted in the Results. The values for \(KAS\) were all within the range of values (1–5 h\(^{-1}\)) used for fasted versus non-fasted rats (Corley et al., 2005). For those case reports with poor documentation of the total amounts of EG consumed, the total dose was estimated by fitting the model to the initial peak blood concentration of EG. When vomiting occurred or gastric lavage was included in the treatment regimen, the total dose (if estimated) was also reduced to fit the initial blood concentration of EG.

Inhibition of the metabolism of EG by ethanol or fomepizole was described with the competitive metabolism equation, as described by Tardif et al. (1993).
Using ethanol inhibition as an example, the rate of metabolism of EG (RateEG, mg/h) was described by:

\[
\text{RateEG} = \frac{V_{\text{maxEG}} \times CV_{\text{EG}}}{K_mEG \times (1 + \frac{CV_{\text{EtOH}}}{K_{IEtOH}}) + CV_{\text{EtOH}}} \quad (3)
\]

where \(V_{\text{maxEG}}\) is the maximum velocity for EG metabolism (mg/h), \(CV_{\text{EG}}\) is the concentration of EG in the venous blood draining the liver (mg/l), \(K_mEG\) is the Michaelis constant for EG metabolism (mg/l), \(K_{IEtOH}\) is the inhibitory constant for ethanol metabolism (mg/l), and \(CV_{\text{EtOH}}\) is the concentration of ethanol in venous blood draining the liver. The mass-balance equation for the liver was thus:

\[
R_{\text{ALEG}} = (Q \times CVEG) + QG\times CVGIEG - Q^\ast CVEG - \text{RateEG}, \quad (4)
\]

where \(R_{\text{ALEG}}\) is the rate of change in the amount of EG in the liver (mg/h) and \(Q\) is the relative blood flow to the liver (l/h).

The inhibitory constant, \(K_{IEtOH}\), is the same as the \(K_m\) for ethanol metabolism. Although Pastino et al. (2000) reported a range of 0.08–3.4 mM for different isoforms, the same average value of 2.7 mM (124.2 mg/l) used in the ethanol PBPK model of Pastino et al. (1997) was used as the inhibition constant for ethanol metabolism because the phenotypes of the individuals described in the case reports were unknown.

The study-specific time course for the inhibition of EG metabolism by ethanol was modeled using Discrete Schedules in SimuSolv (Registered trademark of The Dow Chemical Company, Midland, MI) where the inhibition constant, \(K_{IEtOH}\), was switched from a very high value (e.g., \(10^3\)) that effectively results in no inhibition, to 124.2 mg/l for ethanol for the duration of each therapy. The average concentration of ethanol \(CV_{\text{EtOH}}\) reported in each case report was used to complete the inhibition calculation.

The same equations were used to describe the inhibition of EG metabolism by fomepizole (4-MP), which is nearly complete at therapeutic concentrations (e.g., ~150–200 μM or ~12.3–16.4 mg/l; Brent et al., 1999) because of its very low Ki. KIs for fomepizole inhibition of alcohol dehydrogenases have been reported to be on the order of 0.08–2.75 mM in rats, cats, dogs, and humans (Connally, et al., 2000; Li and Theorell, 1969; Reynier, 1969); a value of 0.2 μM, determined by Li and Theorell (1969) for purified human liver alcohol dehydrogenase, was used in all human simulations, although any Ki in the reported range for fomepizole would have worked equally well because of the very high \(K_m\) for EG metabolism (23.8 mM).

Hemodialysis was also scheduled according to the treatment regimens used in each case report using the Discrete function of SimuSolv. Hemodialysis was modeled simply as a partitioning of venous blood into dialysate according to:

\[
\text{HEMOEG}_{\text{TS}} = \frac{\\text{HDR}^\ast CV_{\text{TS}}}{\\text{PBS}_{\text{TS}}} \quad (5)
\]

where \(\text{HEMOEG}_{\text{TS}}\) is the rate of clearance of EG by hemodialysis (mg/h), \(\text{HDR}\) is the blood flow rate used in hemodialysis as reported in the clinical case reports (average levels were typically 12–18 l/h), \(CV_{\text{TS}}\) is the concentration of EG in pooled venous blood (mg/l), and \(\text{PBS}_{\text{TS}}\) is the blood/saline partition coefficient (surrogate for dialysate) for EG determined in the companion study (e.g., 1.14). Identical equations were used for hemodialysis of glycolic acid with a measured \(\text{PBS}_{\text{TS}}\) of 3.36. The mass-balance equation for EG in the venous blood compartment was thus:

\[
\text{RV}_{\text{EG}} = (\sum Q_i^\ast CV_{\text{EG}}) - QC^\ast CV_{\text{EG}} - RAU_{\text{EG}} - \text{HEMOEG}_{\text{TS}} \quad (6)
\]

where \(\text{RV}_{\text{EG}}\) is the rate of change in the amount of EG in the mixed venous blood compartment (mg/h); \(Q_i\) and \(CV_{\text{EG}}\) are the relative blood flows (l/h) and concentrations of EG (mg/l) in venous blood draining each “i” tissue, respectively; \(QC\) is the cardiac output (l/h); and \(RAU_{\text{EG}}\) is the rate of elimination of EG in urine (mg/h). Similar mass-balance equations for the venous blood compartment were used for glycolic acid, except that the urinary clearance of glycolic acid was included in the kidney compartment as described by Corley et al. (2005). All other physiological and biochemical parameters used in the human PBPK model are from the companion study (Corley et al., 2005).

**Simulations of human case reports.** As summarized in Table 1, there are several accidental or intentional human poisoning case reports in the literature where either EG or its metabolites (glycolic acid or oxalic acid) were analyzed in human blood or urine to confirm diagnosis and follow the progression of treatments. To validate the human PBPK model, the actual reported conditions from each case report were used to initiate simulations. If not reported, body weights were assumed to be 70 kg for an adult male and 58 kg for an adult female (ICRP, 1975). If vomiting occurred or gastric lavage was used in treatment regimens, the total amount of EG consumed (if estimated in the case report) was arbitrarily reduced to fit the initial (usually peak) blood concentration of EG with no further adjustment. As discussed above, the default, first-order absorption rate constant of 1 h⁻¹ was used in all but two simulations, where it was raised to 2.5 h⁻¹ (Harry et al., 1994) or 5 h⁻¹ (Hewlett and McMartin, 1986) to decrease the time needed to simulate the peak concentration of EG in blood. Actual average blood levels of ethanol and fomepizole were used in the model, if reported, assuming the average levels were reached instantaneously and maintained as a constant for the duration of each therapy. If actual blood concentrations were not determined, typical therapeutic blood concentrations (e.g., 1350 mg/l for ethanol and 15 mg/l for fomepizole) were used in the simulations. A similar approach was used to simulate hemodialysis. If the blood flow rate used in hemodialysis was not reported, a typical value of 15 l/h was used for the duration of each therapy. No other adjustments were made to physiological or biochemical parameters to improve the fit to the data. Subject demographics (e.g., age, weight, sex, race or ethnicity) and treatment regimens, when reported, were included in each case description.

**RESULTS**

Because of the large number of studies available for simulation (see Table 1), only representative results are presented. The remaining simulations of the data of Baud et al. (1987, 1988), Bowen et al. (1978), Brent et al. (1999), Cheng et al. (1987), Curtain et al. (1992), Gordon and Hunter (1982), Hewlett and McMartin (1986), Malmlund et al. (1991), and Walder and Tyler (1994) are presented as Supplementary Materials online.

Eder et al. (1998) described the pharmacokinetics of EG in a 58-year-old man who consumed ~20 oz of antifreeze. Treatments consisted of activated charcoal, ethanol, and hemodialysis. Serum ethanol concentrations were maintained between 77 and 194 mg/dl. Simulations were conducted assuming a 70 kg body weight, average ethanol concentrations (135.5 mg/dl), and an assumed hemodialysis rate of 15 l/h. Initial simulations using dose levels estimated by the authors to be 20 oz (which is ~591 ml, not 56 ml as reported) of 50% EG did not match the blood levels as shown in Figure 2. Because one empty and one half-full container of reportedly half-strength antifreeze was found with the patient, the actual amount consumed was unknown. Therefore, the dose was increased from 4700 to 7000 mg/kg to fit the initial peak blood concentration. This change in the total dose resulted in an overall improvement in simulating the complex kinetics of EG in this patient after both metabolic inhibition and hemodialysis.
Jacobsen et al. (1988) described the pharmacokinetics of EG and glycolic acid in two women who consumed antifreeze. In the first case, a 36-year-old black woman (95 kg) consumed a jar of antifreeze. Treatments consisted of naloxone, activated charcoal, gastric lavage, bicarbonate, ethanol, and hemodialysis. Simulations, shown in Figure 3, were conducted assuming a jar is equivalent to ~500 ml of antifreeze (~5270 mg/kg), an average reported level of ethanol in blood (60 mg/dl), and the reported hemodialysis flow rate (21 l/h). On balance, the resulting simulations provided a reasonable fit to kinetics of EG in plasma, although the model overpredicts the concentration of EG in plasma during the first few hours after hospitalization (2540 mg/l observed vs. 4095 predicted 2 h after hospitalization) and slightly underpredicted the peak glycolic acid concentration (2015 mg/l observed vs. 1700 mg/l predicted 9 h after hospitalization). In this case, neither reducing the estimated dose to fit the initial concentration of EG in blood after gastric lavage nor adjusting the first-order oral absorption rate improved the simulation.

In the second case, a 38-year-old black woman (66 kg) consumed ~240 ml of antifreeze the night before she was admitted to the hospital in a comatose state. Treatments consisted of bicarbonate, ethanol, and hemodialysis. Simulations were conducted using the average reported level of ethanol in blood (~40 mg/dl) and reported blood flows in dialysis (13.5 l/h) as shown in Figure 4. Using the estimated dose of EG (240 ml or 3644 mg/kg) resulted in a significant underprediction of the levels of both EG and glycolic acid in blood. Increasing the dose to 395 ml (6000 mg/kg) to fit the initial peak blood concentration of EG improved the simulations of the complex kinetics of both EG and glycolic acid, although the simulated rise in EG concentrations in blood immediately after hemodialysis was not as extensive as observed.

Hewlett and McMartin (1986) described the pharmacokinetics of EG and glycolic acid in two human case reports. In the first case, a 2-year-old female was admitted to the hospital approximately 1.5 h after ingestion of an unknown amount of EG. Treatments consisted of gastric lavage, activated charcoal, bicarbonate, and ethanol. Simulations were conducted assuming a 12 kg body weight (from ICRP, 1995 growth tables), an estimated dose of 2000 mg/kg, and an average reported blood level of ethanol (175 mg/dl), as shown in Figure 5. Although the data on glycolic acid blood levels were limited, the clearance of glycolic acid may have been faster than predicted simply by scaling biochemical parameters determined in adults to the body weight of a child. The second case, of a 46-year-old man who consumed a glassful of antifreeze, is presented in the Supplementary Material online.

Harry et al. (1994) described the pharmacokinetics of EG in a 30-year-old man (74 kg) who reportedly ingested ~100 g of EG. Treatments included gastric lavage, activated charcoal, fomepizole. Simulations were conducted using reported average blood concentrations of fomepizole (~25 mg/l). Initial simulations were conducted using the estimated 100 g of EG ingested; however, this resulted in an approximately twofold

FIG. 2. Data (symbols) and simulations (lines) of the concentration of EG in the serum of a 58-year-old man who ingested ~591 ml of 50% antifreeze (4700 mg/kg, dashed line; data from Eder et al., 1998). The actual quantity and concentration of EG was in question; therefore the dose was increased to 7000 mg/kg (solid line) in simulations to fit the peak blood concentration. Metabolism of EG was inhibited by ethanol treatment, and hemodialysis (HD) was performed twice as indicated.

FIG. 3. Data (symbols) and simulations (lines) of the concentrations of (a) ethylene glycol (EG) and (b) glycolic acid in plasma of a 36-year-old black woman who consumed a jar of antifreeze (data from Jacobsen et al., 1988). Metabolism of EG was inhibited by ethanol treatment, and hemodialysis (HD) was performed as indicated.
underprediction of the concentrations of EG in plasma as well as in the cumulative amounts of EG eliminated in the urine (Fig. 6). Increasing the dose nearly twofold (~2600 mg/kg) resulted in improved fits to both sets of data, lending confidence to the assumption that the reported dose may have been an underestimate.

Brent et al. (1999) described the pharmacokinetics of glycolic acid in 19 human cases (2 females/17 males) of confirmed EG poisoning enrolled in a clinical study to evaluate the effectiveness of fomepizole treatment. Treatments also included hemodialysis in 14 patients after the initial loading dose of fomepizole. The results from these composite simulations are presented in the Supplementary Material online.

In the first of the individual cases described in detail by Brent et al., a 73-year-old man (68 kg) ingested an unknown amount of antifreeze. In the second case, a 35-year-old woman also consumed an unknown amount of antifreeze and ethanol. Simulations were conducted using individual hemodialysis schedules and average fomepizole blood concentrations (~15 mg/l) for each patient and are shown in Figure 7. Dose levels in each case (3250 and 5000 mg/kg for case 1 and 2, respectively) were adjusted to fit the initial blood concentration of EG. Using the individual treatment scheduled resulted in an excellent fit of the model to the complex kinetics of EG in both cases. However, the model overpredicted the concentration of glycolic acid in the blood of the 73-year-old man ($C_{\text{max}}$ observed was 772 mg/l versus 1476 mg/l predicted) although the predicted rate of clearance of glycolic acid was consistent with the data.

**DISCUSSION**

The PBPK model developed to describe the pharmacokinetics of EG and glycolic acid in rats and humans in a companion paper (Corley et al., 2005) was modified to include various treatment regimens associated with human case reports of accidental or intentional overdosing with EG. The modifications included the addition of competitive inhibition of metabolism by ethanol or fomepizole according to Tardif et al. (1993) and hemodialysis, based upon reported therapeutic blood concentrations and dialysis rates used in the clinical case studies. The ability to incorporate these treatment regimens enabled the successful simulation of a variety of human case reports of males and females of different races and ages that consumed a broad range of doses of EG (see Table 1 and the Supplementary Material online). Case reports, by nature, contain sketchy information regarding the actual dose levels, timing of blood samples from consumption, impact of other chemicals consumed (drugs, alcohol), impact of underlying toxicity, and treatment regimens. Variability in this information may contribute to potential alterations in the pharmacokinetics of EG and glycolic acid, yet the overall successful simulation of data from such reports served as an additional validation of the human PBPK model described by Corley et al. (2005), as modified herein.

In each of these cases, best estimates were made on the amounts of EG consumed (or the amounts reported), with the dosage adjusted downward if the case reports described...
vomiting or gastric lavage to fit the initial blood concentrations of EG without further modifications to the model. This downward adjustment to the dose due to vomiting or gastric lavage can be verified in those instances where either the concentrations of glycolic acid in blood or the amounts of EG eliminated in urine were also determined. In these cases, adjusting the total dose available to be absorbed and scheduling the appropriate treatment regimen results in a simulation that fits the pattern of EG clearance from blood, the overall pattern of the formation and clearance of glycolic acid, and the elimination of EG and glycolic acid in urine. Although the model may not perfectly simulate each human case report, given all the uncertainties associated with poisoning cases that are difficult to control, the overall ability to simulate these often drastic situations was remarkably good. Thus, the simulations served to confirm that the general PBPK model structures and parameters derived from in vitro and controlled in vivo studies, as described in the companion paper by Corley et al. (2005), are capable of providing reasonable simulations of human exposures to EG over a broad range of doses that are critical for assessing human health risks.

The current PBPK model can also be used to compare various treatment regimens commonly used in treating EG poisoning to evaluate their effects on pharmacokinetics of EG and glycolic acid. For example, as shown in Figure 8, fomepizole is a more effective inhibitor of the metabolism of EG to glycolic acid than ethanol because of its significantly lower KI when each simulation is conducted at normal therapeutic levels for each treatment. The simulation indicates that fomepizole treatment should result in a more rapid lowering of blood glycolic acid concentrations, along with a lower urinary glycolate excretion. These results would imply a more complete inhibition of metabolism by fomepizole compared to ethanol, as indicated by the slower elimination of EG from the blood (Fig. 8a) and higher excretion in the urine (Fig. 8c).

There are no controlled studies in humans that have compared the efficacy of ethanol and fomepizole on EG pharmacokinetics. However, such a comparative study has been conducted in dogs overdosed with EG (173 mmol/kg) and given therapeutic concentrations of either fomepizole or ethanol (Grauer et al., 1987). In this study, fomepizole increased urinary EG excretion to a greater extent than ethanol, demonstrating a greater inhibition of metabolism as suggested by this PBPK model. Fomepizole also leads to a more substantial reversal of the EG-induced decrease in serum bicarbonate concentrations. Because decreased bicarbonate is a surrogate measure of serum glycolic acid concentrations, these data would suggest that fomepizole had a greater ability...
to lower glycolate levels than does ethanol, as suggested by this model. Recent studies in the same laboratory (Connally and Thrall, manuscript in preparation) have demonstrated that fomepizole indeed lowers plasma glycolate concentrations to a greater extent than does ethanol.

Hemodialysis is also an effective treatment for decreasing the body burdens of EG and glycolic acid as shown in Figure 9. The simulations indicate a rapid lowering of serum EG and glycolate concentrations, which corresponds to scenarios reported in human clinical cases in which dialysis has been used (Barceloux et al., 1999; Brent et al., 1999). The lower serum glycolate level is important in reversing the metabolic acidosis and hence toxicity (Jacobsen et al., 1984), while the decreased body burden of EG lowers the potential for toxicity in these patients and allows for a shorter hospital stay. As such, hemodialysis has been an often-used component of EG therapy, even though it is an invasive procedure with possible adverse effects.

It is interesting to compare the effect of dialysis alone (Fig. 9) with that of fomepizole alone (Fig. 8b) on serum glycolic acid concentrations. The model predicts that fomepizole alone would lower serum glycolate levels more rapidly than would hemodialysis. As such, it is likely that treatment of EG-poisoned patients with fomepizole should be more effective at reversing the acidosis than the use of dialysis. Several authors have, in fact, recommended that therapy with fomepizole and bicarbonate alone should be sufficient in most cases of EG poisoning.
poisoning, with dialysis reserved for only those cases with serious morbidity such as renal failure (Borron et al., 1999; Harry et al., 1998). Because of the kidney failure in these cases, a major pathway for eliminating both EG and glycolic acid would be inactive, and dialysis would be needed to remove them. These results have important implications for the treatment of EG poisoning in humans. Fomepizole has become the metabolic inhibitory treatment of choice over ethanol for a number of reasons (Barceloux et al., 1999), including validated efficacy (Brent et al., 1999), predictable pharmacokinetics, ease of administration, and lack of adverse effects. This model and the cited animal studies would suggest another advantage of fomepizole over ethanol—a greater inhibitory effect on metabolism, leading to a more rapid lowering of toxic glycolate levels.

Lastly, the modifications to the human PBPK described in this article to include various treatment regimens used clinically to treat accidental or intentional ingestions of EG enabled Corley et al. (2005) to compare internal dose surrogates of the intermediate metabolite, glycolic acid, over a broad dose range in rats and humans with a greater degree of confidence. Work is in progress to develop a more explicit gestational model to describe the disposition of glycolic acid in rat embryos, and additional data are being collected in an effort to improve the description of oxalic acid and calcium oxalate dosimetry in the kidneys of rats and humans that could be used to further refine internal dose surrogates for human health risk assessments.

SUPPLEMENTARY MATERIAL

Supplementary information is available online at www.toxsci.oupjournals.org.

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