ORIGINAL ARTICLE

Analysis of Fomepizole Elimination in Methanol- and Ethylene Glycol-Poisoned Patients

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Abstract

Introduction Fomepizole is an anti-metabolite therapy that is used to diminish the toxicity from methanol or ethylene glycol. Although its elimination kinetics have been well described in healthy human subjects, the elimination in poisoned patients have only been described in a few isolated cases. This study was designed to relate the elimination of fomepizole in a series of poisoned patients to that in healthy humans.

Methods Plasma samples from 26 patients in the clinical trials of the use of fomepizole for methanol and ethylene glycol poisoning were analyzed for fomepizole concentrations. The elimination of fomepizole was assessed after individual doses, both during and without intermittent hemodialysis.

Results In methanol- and ethylene glycol-poisoned patients, fomepizole had a volume of distribution of 0.66–0.68 L/kg. After repeated doses of fomepizole, the minimum trough concentration averaged 86–109 µmol/L, which is 10 times higher than the minimum therapeutic concentration. In healthy human subjects, fomepizole elimination follows Michaelis–Menten kinetics and has been calculated as zero-order elimination rates. Zero-order elimination rates averaged 13 and 17 µmol/L/h in methanol and ethylene glycol patients, respectively, compared to 6–19 µmol/L/h in healthy subjects. Elimination during intermittent hemodialysis followed first-order kinetics, with a half-life of 3 h.

Conclusions Plasma concentrations during the repeated dosing confirmed that the recommended dosing schedule, with and without intermittent hemodialysis, maintained therapeutic concentrations throughout the treatments. Fomepizole elimination in poisoned patients at therapeutic plasma concentrations appears be similar to that reported previously in healthy human subjects.

Keywords 4-Methylpyrazole · Zero-order elimination · Methanol poisoning · Ethylene glycol poisoning · Pharmacokinetics

Introduction

Fomepizole, chemically known as 4-methylpyrazole (4-MP), is widely available in much of the developed world for the treatment of methanol and ethylene glycol (EG) poisoning. Fomepizole acts as a potent competitive inhibitor of alcohol dehydrogenase (ADH) [1], thereby reducing the conversion of methanol and EG to their toxic metabolites. In animals in vivo, it reduces metabolite formation if given early and without using dialysis, allowing the body to endogenously clear accumulated metabolites and to reverse the severe metabolic acidosis [2, 3]. Case reports of its use in the treatment of EG poisoning first appeared in the late 1980s [4, 5] and in methanol poisoning in 1997 [6]. A multicenter prospective clinical trial (phase II/III) in the USA confirmed its efficacy for the treatment of EG [7] and of methanol [8] poisonings. Because it has a higher safety profile and is more easily used in human patients, fomepizole has generally replaced ethanol for ADH-inhibitory therapy in methanol and EG poisoning in North America [9]. Ethanol, however, is still widely used in much of the world or when fomepizole is not readily available.

The pharmacokinetic profile of fomepizole is well characterized in animals and healthy human subjects. In healthy

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human subjects, fomepizole is rapidly distributed following intravenous (IV) infusion to total body water (volume of distribution of 0.6 L/kg) and is mostly (> 90%) eliminated by metabolism [10]. At doses in the therapeutic range (i.e., 5–15 mg/kg), fomepizole is eliminated by saturable or Michaelis–Menten kinetics. Elimination of fomepizole in five healthy subjects after a single IV dose (7 mg/kg) showed saturable kinetics [10], with a zero-order elimination rate of 5.9 μmol/L/h, an apparent Km of about 2.5 μmol/L, and $Vmax$ of 6.5 μmol/L/h. Similarly, 10 healthy subjects given 15 mg/kg (the recommended loading dose) showed Michaelis–Menten elimination kinetics with the Km and $Vmax$ calculated as 0.9 μmol/L and 18.6 μmol/L/h, respectively [11]. The Km determined for fomepizole in these two studies (0.9–2.5 μmol/L) readily explains why, even at the assumed minimal therapeutically effective plasma concentration of 10 μmol/L [12], fomepizole elimination is likely to be saturated (zero order) in nearly all human subjects.

Few data exist on fomepizole kinetics in patients being treated for methanol or EG poisoning. Nonlinear elimination kinetics have been observed in a methanol-poisoned patient treated with fomepizole (IV, 15 mg/kg) [13] and in an EG-poisoned patient (IV, two doses, 8 and 16 mg/kg) [14], with zero-order elimination rates of 16.9 μmol/L/h and 7.0 μmol/L/h. In contrast, a publication from studies in four poisoned patients [15] has suggested that, after multiple doses of fomepizole, the elimination appears to follow first-order kinetics with a half-life of about 14 h. However, this analysis was conducted at later time intervals, after the patients had received multiple doses of fomepizole. In the study in healthy subjects given multiple doses [10], the elimination after the first few doses followed zero-order kinetics, but after about 4 days, the elimination converted to a first-order elimination.

Some alcohols appear to decrease the elimination of fomepizole, suggesting a possible mutual inhibition of metabolism. In human volunteers, blood ethanol concentrations from 50 to 150 mg/dL (11–33 mmol/L) decrease fomepizole elimination by about 50% [16]. Ethanol decreases the urinary excretion of the primary fomepizole metabolite 4-carboxypyrazole (4-CP) [16], suggesting that it inhibits a step in the conversion of fomepizole to 4-CP. In monkeys, high doses of methanol (2–3 g/kg) decrease the rate of fomepizole elimination by 25% [12]. In poisoned humans, one could expect that the presence of ethanol or methanol will slow the rate of fomepizole elimination because of this interaction. Although not formally studied, it is possible that EG will act in a similar fashion.

The Methylpyrazole for Toxic Alcohols (META) trials assayed plasma concentrations of fomepizole in methanol- and EG-poisoned patients [7, 8], but did not report an analysis of its pharmacokinetic parameters. Fomepizole elimination in poisoned patients may differ from that which has been well characterized in healthy subjects, particularly because of possible effects of co-exposure to methanol and EG. Because elimination kinetics in poisoned patients have been rarely reported and because such information has not been published from the large number of methanol- or EG-poisoned patients in the META trials, the present study was conducted to analyze the elimination of fomepizole in these methanol- and EG-poisoned patients. Such information will be useful to the clinical toxicology community, today and in the future, because of the potential use of fomepizole in the treatment of certain cases of acetaminophen poisoning [17]. A better understanding of fomepizole's elimination kinetics may therefore be useful in the development of future treatment regimens for indications other than for EG or methanol.

Materials and Methods

Patients

The patients for this study were those that were enrolled in the META prospective clinical trial of the use of fomepizole for treatment of methanol and EG poisonings. The detailed methods and results of this trial have been previously published [7, 8]. These included 19 and 15 patients with confirmed or possible EG or methanol poisoning, respectively. The criteria for enrollment were an age ≥ 12 years and one of the following three sets of characteristics: a plasma EG or methanol concentration ≥ 20 mg/dL (3.2 or 6.2 mmol/L, respectively); suspected ingestion of EG or methanol and two of three specific laboratory findings (arterial pH < 7.3, serum bicarbonate concentration < 20 mmol/L, serum osmol gap > 10 mOsm/L); or suspected ingestion of EG or methanol within the preceding hour and serum osmol gap > 10 mOsm/L. The exclusion criteria were the administration of ethanol at the participating hospital, known reactions to pyrazoles, and pregnancy; no patients were excluded on the basis of these criteria. The study was approved by the appropriate institutional review boards at all the participating centers. The study was done under an Investigational New Drug application (IND) approved by the US Food and Drug Administration (FDA). Informed consent was obtained as previously described [7, 8]. Among the 19 and 15 patients initially enrolled in the EG and methanol studies, respectively, some who met the criteria for enrollment were subsequently found to not have plasma EG or methanol concentrations > 20 mg/dL or to not meet other criteria for entry; these patients were excluded from the kinetic analysis such that 15 EG patients and 11 methanol patients were included. Baseline demographic and laboratory characteristics of the patients from the clinical trial publications [7, 8] have been expanded upon and are presented in Supplemental Table 1.

Fomepizole (Antizol, provided by Orphan Medical, Minnetonka, MN) was administered intravenously as a loading dose of 15 mg/kg, followed by bolus doses of 10 mg/kg every 12 h. After 48 h, the bolus doses were increased to 15 mg/kg every 12 h. Dosing was altered during and after periods of hemodialysis (HD) by prescribed criteria as outlined previously [7, 8].

Blood samples for analysis were collected at base line and at predetermined intervals, ranging from 1 to 12 h, until 24 h after the plasma EG or methanol concentration was < 20 mg/dL. Collected blood was spun and the plasma separated and frozen (− 20 °C) until analyses were performed. Plasma fomepizole concentrations were measured by a modification of the method of high-performance liquid chromatography, in which 3-methylpyrazole is used as an internal standard as previously described [18, 19]. The detection limit under these conditions was 5 µmol/L with a coefficient of variation of 4.5% at 25 µmol/L. These analytical studies were approved by the Institutional Review Board for Human Research of LSUHSC in Shreveport and were conducted under the FDA-approved IND.

The number of blood sampling points after each dose of fomepizole was limited in this study because of the study protocol that was designed to examine the safety and efficacy of fomepizole. The protocol designated sample draws to obtain safety and efficacy data, while minimizing the inconvenience that more frequent blood draws would have presented to the patient and the staff. As noted in Figs. 1 and 2 (and Supplemental Figs. 1-5), where plasma concentrations are plotted using linear and also semilog coordinates, it is difficult to establish whether the elimination after each various dose during the non-dialysis periods was better characterized by first-order or zero-order kinetics. Definitely, the number of data points after each dose was insufficient to calculate the Michaelis–Menten parameters (*Km* and *Vmax*). Previous pharmacokinetic studies in healthy human subjects [10, 11], in dogs [20], and in rats [21] have established that fomepizole is eliminated by nonlinear Michaelis–Menten kinetics in the dose range used in this study and that in order to compare elimination characteristics between treatment groups, calculation of the zero-order elimination rate is sufficient [10]. Thus, in order to be able to compare the elimination in these poisoned patients with the zero-order elimination parameters that have been reported in healthy human subjects [10, 11], the rate of the zero-order phase of elimination was computed in these patients during time periods when there was no dialysis; as such in some patients, there were multiple time periods in which the rates were determined. To determine such a rate, a minimum of three plasma samples had to be present during that time period. The program GraphPad Prism 5.0 was used to calculate the zero-order rate of elimination by determining the slope of the zero-order phase by linear regression analysis. The effect of EG or methanol on fomepizole elimination rates during non-dialysis periods was examined by relating the EG concentration or the methanol concentration at the beginning of each respective time period, during which fomepizole elimination rates were calculated, to the elimination rate during that period.

Elimination rates were also determined during the intermittent hemodialysis periods, if there were a minimum of three samples during this time period. Because dialysis clearance dominates the total plasma clearance of fomepizole during dialysis periods and dialysis clearance is a first-order process, the elimination rate constant (K_e) during dialysis was calculated by linear regression analysis of the log-linear plasma fomepizole concentrations. Half-life ($T_{1/2}$) and plasma clearance (CL_p) were determined by the equations: $T_{1/2} = 0.693/K_e$ and $CL_p = K_e * V_d$. Data for various linear regression analyses were first confirmed as parametric using the D'Agostino-Pearson normality test.

Other pharmacokinetic parameters indicating maximal peak and minimal trough plasma concentrations were determined from analysis of the plasma concentration/time graphs. Although there would be peak and trough plasma concentrations after each fomepizole infusion, the highest plasma concentration after any of the doses was designated the maximal peak concentration. Similarly, the lowest value after any dose was designated the minimal trough concentration. The volume of distribution (V_d) was determined by the formula: $Dose/C_o$, where C_o was the plasma concentration at time 0. C_o was obtained from the measured initial plasma concentration after the first dose or, in cases where there was no measured initial plasma concentration, from the C_o estimated by back extrapolation of the subsequent plasma concentrations after the first dose (by linear regression analysis to time 0). The method that was used in each case is listed in the tables in the "Results" section.

The various parameters were determined for each patient and then group statistics (mean, standard deviation (SD), median, interquartile range (IQR)) were calculated. Statistical comparisons of parametric group mean data (validated using the D'Agostino-Pearson normality test) were performed with the unpaired Student's *t*-test, with $p < 0.05$ as the level of statistical significance. Values reported in the text represent the group mean ± SD or group median ± IQR, as noted. Statistical values and comparisons were conducted using GraphPad Prism 5 (La Jolla, CA).

Results

Patients in the META trial were dosed initially with fomepizole as a 30-min infusion of 15 mg/kg (182.7 µmol/kg). Because of a mistake in body weight, one patient (#18) actually received a loading dose of 21.9 mg/kg. Subsequent

Fig. 1 Plasma concentrations of fomepizole in four ethylene glycol (EG)-poisoned patients. Plasma samples were analyzed for fomepizole concentrations by HPLC method as described in the "Materials and Methods" section and are plotted at each time for four representative patients either on linear coordinates (left side) or semilog coordinates (right side). The shading indicates the time periods during which intermittent hemodialysis (IHD) was conducted. The arrows show the times of fomepizole administration, with the first dose being the loading dose of 15 mg/kg and subsequent doses being 10 mg/kg
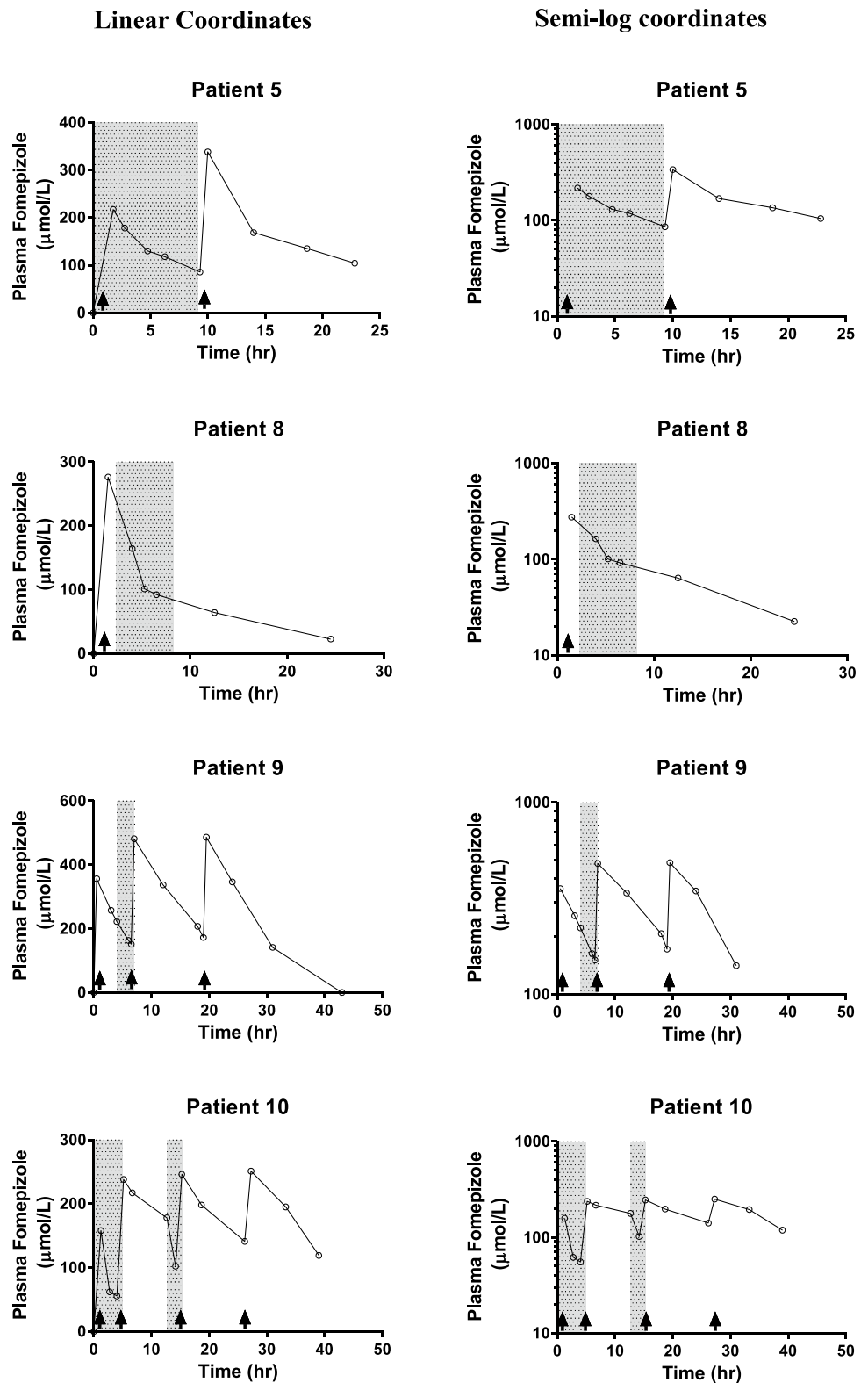
dosing with fomepizole occurred via a defined protocol, but was somewhat variant among the patients because of variations in the timing and duration of hemodialysis periods, which, according to protocol, altered fomepizole dosing.

Hence, it was not possible to summarize plasma concentrations of fomepizole at designated time intervals. The patterns of plasma fomepizole concentrations from four EG and from four methanol patients are displayed in Figs. 1

Fig. 2 Plasma concentrations of fomepizole in four methanol-poisoned patients. Plasma samples were analyzed for fomepizole concentrations by HPLC method as described in the "Materials and Methods" section and are plotted at each time for four representative patients either on linear coordinates (left side) or semilog coordinates (right side). The shading indicates the time periods during which intermittent hemodialysis (IHD) was conducted. The arrows show the times of fomepizole administration, with the first dose being the loading dose of 15 mg/kg and subsequent doses being 10 mg/kg
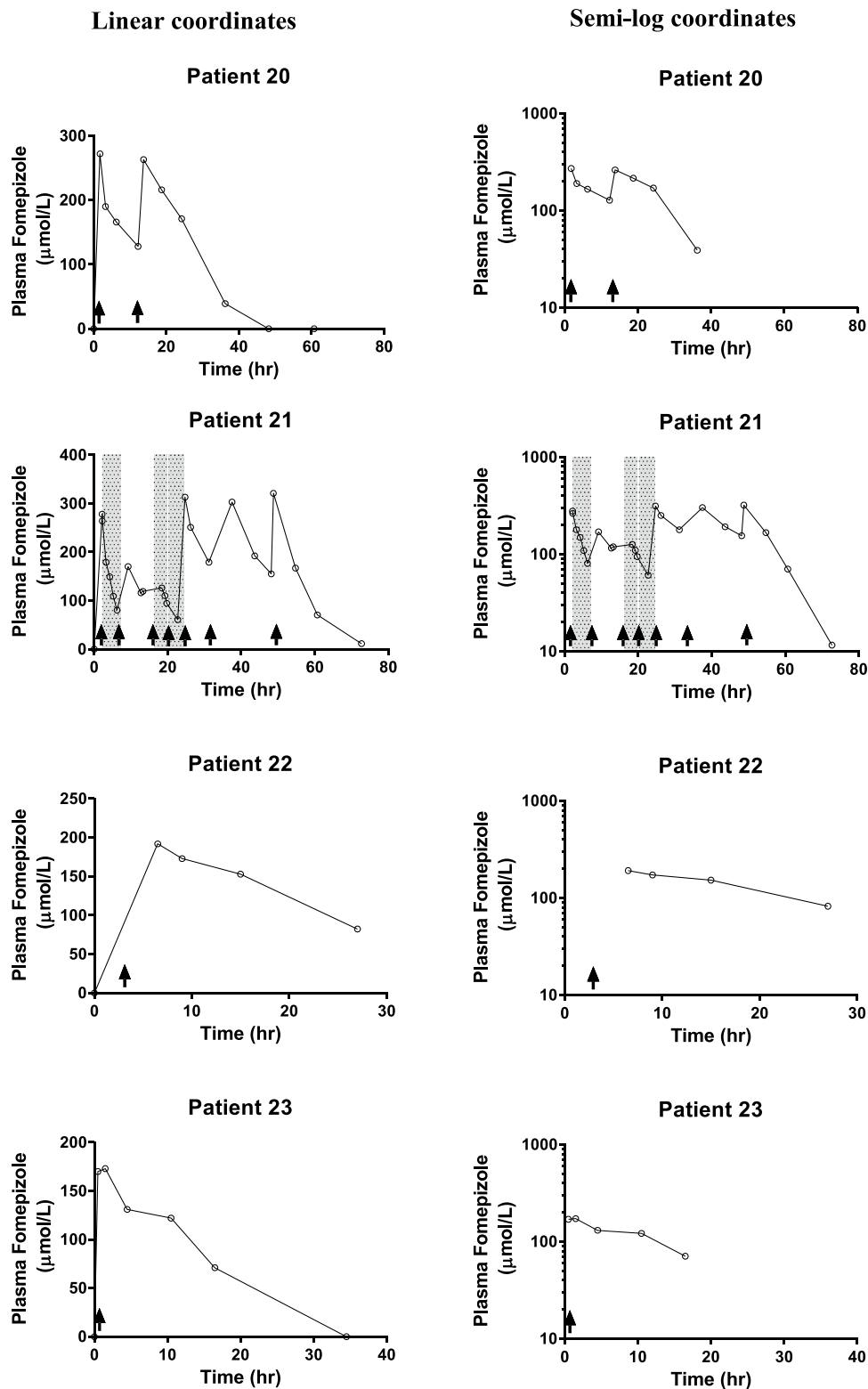
and 2, respectively, where the shading indicates the periods of intermittent hemodialysis and the arrows represent the times of the fomepizole doses. Figures from the other patients are included as supplemental data. Because of the repeated dosing with fomepizole, there were defined peaks and troughs in the plasma concentration profile of most patients. The maximum peak fomepizole and minimum trough concentrations (level and time), which could

occur after any of the doses, for EG and methanol patients are shown in Tables 1 and 2, respectively. For EG patients, the maximum peak level ranged from 230 to 740 μmol/L, with mean and median values of 367 ± 133 and 328 ± 169, respectively; for methanol patients, the maximum peak level ranged from 173 to 560 μmol/L, with mean and median values of 310 ± 132 and 272 ± 250, respectively. The time of the maximum peak level (median value) was 5.3 ± 11.3 h for EG patients and 3.8 ± 13 h for methanol patients. The minimum concentrations of fomepizole in the various troughs were determined with mean and median values of 106 ± 50 and 92 ± 79 μmol/L, respectively, for EG patients and 86 ± 72 and 61 ± 134 μmol/L, respectively, for methanol patients. The times of the minimum trough level (median value) were 5.4 ± 4.5 h for the EG patients and 12.0 ± 27.4 h for the methanol patients.

As demonstrated in Table 3, the rates of fomepizole elimination were very consistent after the multiple doses within each patient, so the means of the multiple rates of elimination are included in Tables 1 and 2. The mean and median zero-order rates of fomepizole elimination in EG patients (Table 1) were 17.2 and 13.1 μmol/L/h (range 3.8–36.6) and in methanol patients (Table 2), 13.0 and 14.8 μmol/L/h (range 5.2–19.3). The rates of elimination were not significantly different between the EG and methanol patients ($p > 0.05$). To assess whether the presence of EG or methanol might affect the elimination of fomepizole, the EG or methanol concentration that was measured at the beginning of the interval during which the elimination rate was calculated was related to the elimination rate that was determined (Fig. 3). Although there appeared to be a slight decrease in fomepizole elimination rate as the concentrations of either

Table 1 Fomepizole elimination kinetics in ethylene glycol-poisoned patients

Patient	Peak[a]		Trough[a]		V_d[b]	Elimination rate[c]	Blood ethanol[d]
	Level	Time	Level	Time			
	μmol/L	h	μmol/L	h	L/kg	μmol/L/h	mg/dL
1	314	5.3	93	8.75	0.812	NC[e]	41
2	402	0	139	12	0.677[f]	12.65	97
3	273	0.6	NC	NC	0.671[f]	19.86	210
4	442	1	NC	NC	0.418	NC	160
5	338	9.25	86	8.6	0.797	7.27	181
6	273	12	91	3.3	0.984	11.13	122
7	740	11.8	221	4.4	0.324	36.64	8
8	276	0.5	NC	NC	0.590	3.8	0
9	486	19	151	6	0.514[f]	31.27[g]	0
10	251	26.5	56	3.25	0.977	10.26[g]	66
11	230	7.25	74	31	0.668	13.54[g]	76
12	491	0.5	52	5.25	NC	NC	76
13	328	0.3	94	5.3	0.540	NC	49
14	281	0.5	64	4.2	0.680	NC	0
15	379	10.25	148	5.5	0.640[f]	25.40	86
Mean	367	6.9	106	8.1	0.664	17.18	78
SD	133	8.0	50	7.6	0.188	10.79	67
Median	328	5.3	92	5.4	0.669	13.1	76
IQR	169	11.3	79.3	4.5	0.267	17.4	114

[a]The peak fomepizole concentration after any of the multiple doses and the minimum fomepizole concentration at one of the troughs during the multiple dosing—the true minimum would be 0 μmol/L at the end of dosing

[b]V_d calculated from measured C_o unless indicated by footnote f

[c]Apparent elimination rate of fomepizole during the zero-order phase of elimination, which occurred during the periods in which the patients were not undergoing hemodialysis

[d]Blood ethanol level upon admission to the participating hospital—no additional ethanol was administered at these sites. Blood ethanol levels declined to <20 mg/dL in 3–5 h in most cases (<8 h in all)

[e]*NC*, not calculated (because data points or blood sampling times insufficient for proper determination)

[f]V_d calculated from the C_o determined by extrapolation of an initial zero-order elimination phase (preceding or without hemodialysis)

[g]Mean elimination rate determined from several zero-order phases in the same patient (see Table 3)

Table 2 Fomepizole elimination kinetics in methanol-poisoned patients

Patient	Peak[a]		Trough[a]		V_d[b]	Elimination rate[c]	Blood ethanol[d]
	Level	Time	Level	Time			
	µmol/L	h	µmol/L	h	L/kg	µmol/L/h	mg/dL
16	560	28.5	195	4.0	0.505	14.77[e]	151
17	330	6.8	106	4.7	0.573	15.31	104
18	442	24.5	182	12.3	0.987	14.31[e]	11
19	241	0.5	41	6.6	0.663	NC[f]	199
20	272	1.5	128	12.0	0.720	10.70[e]	68
21	321	48.0	61	22.0	0.464	15.14[e]	89
22	192	3.8	NA[g]	NA	0.867	5.21	0
23	173	3.2	NA	NA	0.996	5.99	0
24	207	8.3	0	43.0	0.736	16.15	11
25	482	0.8	60	5.6	0.468	19.31	0
26	187	2.8	0	55.1	0.489	NC	0
Mean	310	11.7	86	18.4	0.679	12.99	58
SD	132	15.4	72	18.5	0.201	4.74	70
Median	272	3.8	61	12	0.663	14.77	11
IQR	250	13	134.5	27.4	0.378	7.38	104

[a]The peak fomepizole concentration after any of the multiple doses and the minimum fomepizole concentration at one of the troughs during the multiple dosing—the true minimum would be 0 µmol/L at the end of dosing

[b]V_d calculated from measured C_o

[c]Apparent elimination rate of fomepizole during the zero-order phase of elimination, which occurred during the periods in which the patients were not undergoing hemodialysis

[d]Blood ethanol level upon admission to the participating hospital—no additional ethanol was administered at these sites. Blood ethanol levels declined to < 20 mg/dL in 3–5 h in most cases (< 8 h in all)

[e]Mean rate of elimination determined from several zero-order phases within the same patient (see Table 3)

[f]*NC*, not calculated (because either data points or blood sampling times were insufficient for proper determination)

[g]*NA*, not applicable (because there was only one dose of fomepizole, so no minimum)

Table 3 Fomepizole elimination rate after multiple doses in methanol and ethylene glycol patients

Subject	Elimination rate (µmol/L/h)			
	Dose 1	Dose 2	Dose 3	Mean
9	38.54	25.34	29.94	31.27
10	9.29	11.22		10.26
11	13.28	13.80		13.54
16	9.50	15.85	18.96	14.77
18	10.84	17.77		14.31
20	11.48	9.92		10.70
21	19.05	14.12	12.25	15.14

EG or methanol increased, neither of these regressions were significant. Because of the nonlinearity of the fomepizole elimination outside of dialysis, the plasma clearance of fomepizole would be variable and was not calculated per se.

The volume of distribution of fomepizole was determined from the plasma concentration(s) after the first dose. During the 30-min loading infusion, little if any of the fomepizole was eliminated (due to the slow elimination rate). The mean and median V_d were 0.66 and 0.67 L/kg for EG patients and 0.68 and 0.66 L/kg for methanol patients (Tables 1 and 2).

During the hemodialysis periods, the kinetic parameters of linear pharmacokinetics (K_e, $T_{1/2}$, and CL_p) were determined (Table 4). The mean and median plasma clearances of fomepizole were 230 and 208 mL/min for EG patients and 200 and 194 mL/min for methanol patients, while the mean and median $T_{1/2}$s were 3.2 and 3.0 h for EG patients and 2.7 and 2.5 h for methanol patients.

By protocol, no patient was given ethanol for therapy at the participating hospital; however, some patients had significant blood ethanol levels on admission, either from a preceding hospital therapy or from co-ingestion (Tables 1 and 2). Although these levels were above 50 mg/dL in 9 of 15 EG-poisoned patients and in 5 of 11 methanol-poisoned patients, ethanol was rapidly eliminated, reaching levels below 20 mg/dL by 3–5 h in most of the patients and by 8 h in all of the patients.
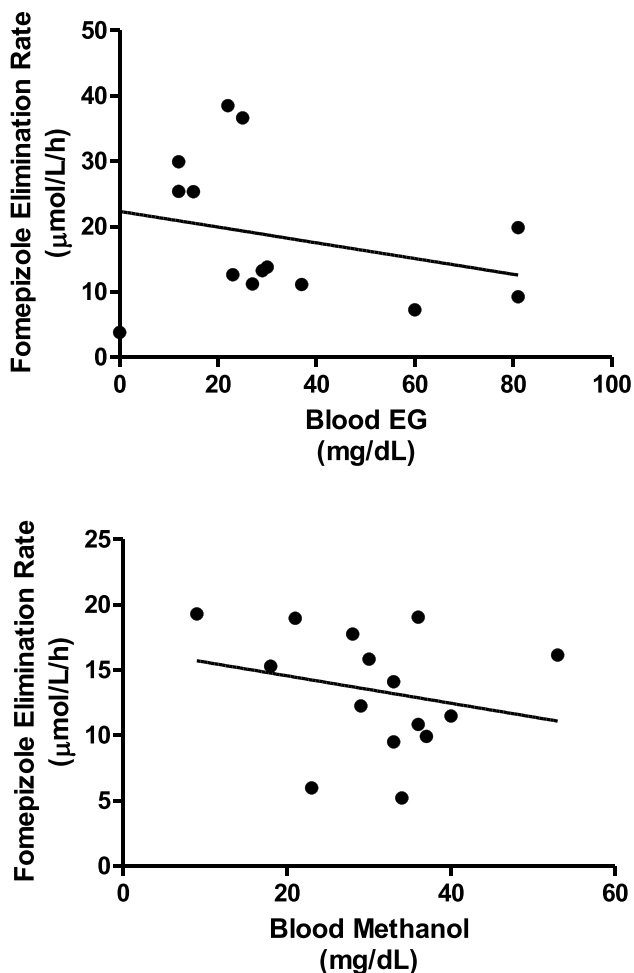
Fig. 3 Relationships between blood ethylene glycol (EG) and methanol concentrations and the fomepizole elimination rate. Data points represent the EG concentrations (top graph) or the methanol concentrations (bottom graph) at the beginning of each respective time period when fomepizole elimination rates were calculated. There are more points than the number of patients in Tables 1 and 2 because all periods were used (see Table 3). The linear regression parameters were as follows: for EG, $y = -0.12x + 22.3$ ($r^2 = 0.073$, $p > 0.05$); for methanol, $y = -0.11x + 16.7$ ($r^2 = 0.056$, $p > 0.05$)

Discussion

Treatment of methanol and EG poisonings has consisted of the administration of an alcohol dehydrogenase inhibitor, either ethanol or fomepizole, of alkali to reverse acidemia, and of dialysis to remove the alcohols and their metabolites. As examined in two large clinical studies [22, 23], both ADH inhibitors appear to have similar therapeutic efficacy, such as reversal of the poisoning syndrome or in survival of patients. However, maintaining therapeutic blood ethanol concentrations is difficult, due to its rapid and also highly variable elimination, and ethanol therapy can often lead to elevated blood ethanol levels and hence to CNS depression [24]. In contrast, fomepizole has been suggested to be more practical in terms of dosing, because of a lesser ability to induce CNS depression and because its pharmacokinetics have been described as being predictable with and without dialysis. Pharmacokinetic results from studies in healthy human subjects have generally predicted the clinical experience in poisoned patients [7, 8]. Such studies [10, 11, 25] have shown that a single dose of fomepizole is eliminated relatively slowly by Michaelis–Menten kinetics with a zero-order phase at therapeutic plasma concentrations. The elimination rates in healthy humans (6–19 μmol/L/h) would predict that dosing every 12 h should be sufficient to maintain therapeutic concentrations (> 10 μmol/L) between doses. The present results showed that the minimal trough concentration averaged 86–109 μmol/L, which is roughly 10 times higher than the minimum therapeutic concentration [12]. In the 21 patients with multiple dosing, only 2 patients had a minimal trough concentration < 10 μmol/L (patients 24 and 26, Supplemental Fig. 5). The time of the minimal trough concentration in both cases was > 42 h, which was late in the duration of therapy and likely less impactful on its efficacy. Thus, the proposed dosing schedule, with and without hemodialysis, did maintain therapeutic concentrations throughout the time course.

Despite the wealth of information on fomepizole kinetics in animals and in healthy human subjects, there is very little information on its kinetics in methanol- or EG-poisoned patients. Nonlinear elimination kinetics have been reported in two separate cases, with zero-order elimination rates of 7 and 17 μmol/L/h [13, 14]. In contrast, there is one report suggesting a first-order elimination of fomepizole after multiple doses with a half-life of about 14 h [15]. Besides this dichotomy in kinetics among the few case studies, there is also the issue as to whether co-exposure to methanol or EG might alter fomepizole kinetics. Therapeutic levels of ethanol (roughly 100 mg/dL or 21.7 mmol/L) have been shown to slow the elimination of fomepizole in healthy humans [16], while a similar effect was observed with methanol in monkeys at blood levels above 250 mg/dL [12]. In the present study, a small range of plasma concentrations after each repeated dose of fomepizole made it difficult to ascertain with confidence whether fomepizole was eliminated by zero-order or first-order kinetics with multiple dosing. Given that zero-order elimination rates have been confirmed at similar doses in healthy subjects [10, 11], it is likely that our data reflect similar kinetics. Therefore, we used a zero-order elimination calculation to compare the elimination rates in the methanol patients and in the EG patients with those determined in healthy human subjects. The elimination rates in methanol patients ranged from 5 to 19 μmol/L/h, while those in EG patients ranged from 4 to 37 μmol/L/h. In healthy subjects, the elimination rates, as represented by the *Vmax*, ranged from about 6 to 30 μmol/L/h [10, 11], which thus encompasses the range in

Table 4 Fomepizole kinetics in methanol and ethylene glycol patients during dialysis

Patient	Ethylene glycol			Patient	Methanol		
	$T_{\frac{1}{2}}$[1]	K_e[1]	CL_p[1]		$T_{\frac{1}{2}}$[1]	K_e[1]	CL_p[1]
	h	h^{-1}	mL/min		h	h^{-1}	mL/min
1	1.98	0.349	340	16	4.17	0.166	203
2	NA[2]	NA	NA	17	2.96	0.234	190
3	NC[2]	NC	NC	18	NA[2]	NA	NA
4	NC	NC	NC	19	2.51	0.276	194
5	5.82	0.119	177	20	NA	NA	NA
6	3.36	0.206	293	21	2.93[3]	0.244[3]	150[3]
7	2.94	0.236	191	22	NA	NA	NA
8	2.97	0.233	174	23	NA	NA	NA
9	NC	NC	NC	24	2.46	0.282	235
10	1.77	0.392	326	25	2.07	0.334	156
11	3.92	0.177	116	26	1.96[3]	0.369[3]	270[3]
12	NC	NC	NC				
13	2.68	0.259	224				
14	NC	NC	NC				
15	NC	NC	NC				
Mean	3.18	0.246	230		2.72	0.272	200
SD	1.27	0.088	81		0.74	0.067	420
Median	2.96	0.234	208		2.51	0.276	194
IQR	1.62	0.142	143		0.89	0.100	79

[1]Elimination rate constant, half-life, and plasma clearance of fomepizole during hemodialysis

[2]*NA*, not applicable (no dialysis); *NC*, not calculated (because data points or blood sampling times insufficient for proper determination)

[3]Mean half-life, elimination rate constant, and plasma clearance determined from several periods of hemodialysis within the same patient (#22 = 2.41 and 3.45 h, 0.287 and 0.201 h^{-1}, 178 and 124 mL/min, respectively; #27 = 2.53, 1.66, and 1.68 h, 0.274, 0.418, and 0.413 h^{-1}, 201, 307, and 303 mL/min, respectively)

our poisoned patients. Likewise, the mean values of 13 and 17 μmol/L/h in our patients are similar to those in healthy subjects (7 and 19 μmol/L/h). Thus, fomepizole appears to be eliminated in the presence of methanol or EG in the poisoned patients at a similar rate and manner to what has been reported previously in healthy subjects. Furthermore, the presence of methanol or EG did not appear to have altered the rate of fomepizole elimination as observed in Fig. 3. One caveat to this conclusion is the relatively low concentrations of methanol (< 55 mg/dL) or of EG (< 85 mg/dL) that were observed during the period of fomepizole elimination. As noted above, it takes about 100 mg/dL ethanol or 250 mg/dL methanol to alter fomepizole elimination [12, 16] and none of our patients had such levels.

One study in healthy subjects indicated that the rate of elimination of fomepizole should increase after about 60 h with repeated dosing every 12 h (as is done clinically) [10]. This increased rate of elimination corresponded to an increased excretion of the primary metabolite 4-carboxypyrazole in the urine, suggesting that the elimination increased due to an increased metabolism of fomepizole, presumably by auto-induction of cytochrome P450s. In the

repeat dose studies in healthy humans after 96 h, the elimination of fomepizole appeared to follow linear, first-order kinetics [10]. In the present studies, few of the patients were treated for such a length of time, such that there was little evidence of a delayed conversion to first-order kinetics.

The volume of distribution in methanol and EG patients averaged 0.68 and 0.66 L/kg, respectively. These values are essentially the same as those determined in healthy subjects, 0.58 [10] and 0.66 [11] L/kg. These results indicate that fomepizole is distributed to total body water and that there are no differences in distribution between healthy subjects and poisoned patients.

The distribution to body water, small molecular weight, and relative neutrality of fomepizole allows it to be readily removed by hemodialysis. In animals, fomepizole can be eliminated with a dialysance that is similar to that of urea [26]. Dialysis in patients has confirmed that fomepizole can be removed with clearance rates from 52 to 127 mL/min [27, 28]. The extraction of fomepizole during intermittent hemodialysis appears to be significantly greater than that during continuous veno-veno HD [24, 28]. Such studies have confirmed the need to replace the

fomepizole that is removed, particularly during intermittent hemodialysis. In the present studies, the elimination kinetics of fomepizole during the periods of hemodialysis were first order. The resulting half-life for methanol and EG patients averaged 2.7 and 3.2 h, respectively. The plasma clearances were generally 150–300 mL/min, which are greater than the hemodialysis clearance rates cited above. Most likely this difference results from the fact that the total plasma clearance included the dialysis component, but also a significant contribution from fomepizole metabolism.

Limitations

One limitation in this study is that we chose to designate the peak maximum concentration from the highest plasma concentration after any dose. In some patients, the peak occurred after the first dose, in which case the times of the peak maximum concentration were very low (<1 h), while in other patients, the peak occurred after multiple doses resulting in times >24 h. When all of the values are averaged in the tables, the values are therefore skewed, for example, resulting in the median times for maximum peak and minimum trough concentrations for EG patients of 5.3 and 5.4 h, respectively.

Another limitation of this study is that all of the dialyzed patients underwent intermittent hemodialysis (IHD), such that the kinetics that are reported here are only valid for such patients. Dialysis modalities today include many types of continuous methods, in which the fomepizole kinetics would be significantly different. It is likely that the removal of fomepizole is much greater during IHD than during continuous methods [29]. Also, there was no analysis of the dialysate samples in these studies, because such samples were not collected as per the study protocol.

The data presented here come from the patients in the clinical trials of the efficacy of fomepizole and as such included patients where its use was not "standardized." Hence, the results may differ from what happens in todays' real life usage of fomepizole, where conditions have been somewhat standardized by 20 years of practice. Although we have presented elimination data from 26 patients, which is significantly more than any case reports or series, this still represents a relatively small number of patients.

Lastly, the blood concentrations of EG and methanol that were encountered in these patients were relatively low. We can state that these levels of EG and methanol did not appear to alter fomepizole elimination, but it is still possible that much higher concentrations of EG or methanol could decrease the elimination.

Conclusions

Pharmacokinetic analysis of the plasma fomepizole concentrations in the 26 methanol- and EG-poisoned patients in the META clinical trials [7, 8] has shown that the rate of elimination of fomepizole is essentially the same in these patients as in healthy human subjects [10, 11]. Fomepizole was rapidly distributed to total body water (V_d of 0.66–0.68 L/kg) and then was slowly eliminated with rates of elimination (averaging 13–17 μmol/L/h) very similar to those reported in human volunteers (7–19 μmol/L/h). These results indicate that the levels of methanol or EG in the patients, as well as the often critical illness of the poisoned patients, did not affect the elimination of fomepizole.

Declarations

Conflicts of Interest In the 1990s, Dr. Brent served on the Speakers' Bureau of Orphan Medical, the manufacturer of Antizol (trade version of fomepizole), and Dr. McMartin has an ongoing royalty agreement with Mericon Investment Group, which sub-licensed the rights to Antizol to Orphan Medical and hence to subsequent drug companies that subsumed Orphan Medical.

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