Phenazepam: More information coming in from the cold.

Phenazepam is a 1-4 benzodiazepine that was developed in 1975 in the former USSR and is used clinically as an anxiolytic [1], anticonvulsant, hypnotic and for the treatment of ethanol withdrawal [2]. Outside of the former soviet bloc there has been evidence of the abuse of phenazepam around the world since 1999 [3], with reports of overdoses, driving under the influence of drug (DUID) cases and also deaths [4-8]. As with other benzodiazepines the deaths have usually involved other drugs as well as phenazepam rather than phenazepam in isolation [9]. This has led to the control of phenazepam around the world. Due to the apparent persistence of phenazepam as a drug of abuse it is important to have knowledge of the pharmacokinetics, in relation to forensic toxicology, to determine the maximum length of time the drug could be detected after death. Also, the possibility of redistribution of the drug, which could affect the postmortem concentrations. The active metabolite of phenazepam, 3-hydroxy phenazepam and the parent drug are both full γ-aminobutyric acid type A ($GABA_A$) receptor agonists [1] and are detectable in a variety of body fluids including subclavian, femoral and cardiac blood, urine, vitreous humour and tissues (thalamus, liver and psoas muscle) [9]. Due to phenazepam being developed in the former USSR there is limited information about it in the English literature with some publications being difficult to obtain. The current knowledge of phenazepam has been extensively reviewed in two fairly recent publications [1,8]. The limited information about the pharmacokinetics of phenazepam cited in these publications was only determined using two subjects (oral doses of 3mg and 5mg [10]) and intravenous/intramuscular injection in six subjects with a single dose of 2mg [11]. These studies gave a limited insight into the pharmacokinetics but was missing important information (such as the volume of distribution) and gave unclear results about the half-life (t½) with a range of 15h (via injection) and 60h (oral) [10, 11] . The authors recently obtained the Russian book “Phenazepam: 25 Years in Medical Practice” [12] containing a thesis based upon the pharmacokinetics of phenazepam which has allowed us to obtain further information [13]. In the thesis they describe a study where six patients were administered a single oral dose between 3 - 5mg and serial blood samples were taken and measured over 301 hours [13]. This new data has allowed us to update the information about phenazepam pharmacokinetics, particularly the information on the volume of distribution (V), half-life ($t_{1/2}$), oral plasma clearance (CL) and absorption half-life ($t_{1/2}$), which we have summarised below in table 1. It is interesting to note that the t½ of phenazepam appears to be significantly greater than 60 h reported in a previous study [10] with the new study giving a t½ (mean) of 140 h (range 48.8 – 301.0 h) [13]. This may account for the long duration of side effects observed in previous overdose cases [14]. This revised information will allow for more accurate interpretation of the drug in both the clinical setting for back calculations, which would be useful in jurisdictions that have blood levels for DUID offences such as Norway and the forensic setting in terms of postmortem phenazepam levels.

Table 1 Pharmacokinetics of phenazepam in Humans

IV – Intravenous injection, IM – intramuscular injection, oral – oral administration

Parameter	Value	Dose/route	Number of cases (n) [REF]
Volume of Distribution (V)	1.01 - 2.15 L/kg	3 – 5 mg (oral)	6 [13]
Absorption Half-Life ($t_{1/2}$)	0.26 – 1.18 h (median: 0.61 h)	3 – 5 mg (oral)	6 [13]
Elimination Half-Life ($t_{1/2}$) – Injection	14.9 h (IV), 15.6h (IM)	2 mg (IV or IM)	6 [11]
Elimination Half-Life ($t_{1/2}$) - Oral	49 - 301h (median: 103 h)	3 – 5 mg (oral)	6 [13]
Bioavailability (F)	0.82	2 mg (IV or IM)	6 [11]
Maximum plasma concentration (C_{max})	0.024 µg/mL (3mg), 0.038 µg/mL (5mg)	3 or 5 mg (oral)	2 [10]
Time to maximum plasma concentration (T_{max})	~2 - 4h	3 or 5 mg (oral)	2 [10], 6 [13]
Absorption rate constant (K_a)	0.024 min^{-1} (3 mg), 0.044 min^{-1} (5 mg)	3 or 5 mg (oral)	2 [10]
Elimination rate constant (K) – Oral	0.0002 min^{-1}	3 and 5 mg (Oral)	2 [10]
Elimination rate constant (K) – Injection	0.044 min^{-1} (IM), 0.047 min^{-1} (IV)	2 mg (IV or IM)	6 [11]
Plasma clearance (CL) – Injection	220.43 ml/hr (IV), 267.93 ml/hr (IM)	2 mg (IV or IM)	6 [11]
Plasma clearance (CL) – Oral	2.53 - 27.90 ml/kg/h (Median: 10.1 ml/kg/h)	3-5 mg (oral)	6 [13]
Constant Steady State (C_{ss})	157.29 µg/L	Repeated 1mg (IM)	6 [11]

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