

BIOAVAILABILITY OF ORAL PROPOFOL IN HUMANS

Victor Contreras, MD¹, Pablo O. Sepúlveda, MD², Steven L. Shafer, MD³

Universidad de Concepción, Chile¹, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile² Columbia University, New York, New York³

Summary: Propofol has negligible oral bioavailability in humans. It may be possible to administer systemic propofol with an oral transmucosal delivery system that bypasses hepatic first-pass metabolism.

Background: Although propofol is only administered intravenously in the practice of anaesthesia, it has been suggested that alternative routes could be utilized, such as nebulized inhalation, transmucosal or upper gastrointestinal, or rectal. The hepatic extraction ratio of propofol is in the range of 0.8 to 0.9. Thus, the a priori expectation is that the oral bioavailability of propofol is no greater than 20%, and plasma levels following oral ingestion should be very low. However, were propofol orally bioavailable in humans, there could be therapeutic utility for the treatment of epilepsy, migraine headache, chronic pain, pruritis, and nausea and vomiting. In this pilot study we evaluated bioavailability of orally administered 1% propofol emulsion.

Methods: With approval from the institutional research and ethics committee (School of Medicine, Clínica Alemana, Universidad del Desarrollo, Santiago, Chile), and after obtaining written informed consent, we enrolled six healthy male volunteers in this open label, unblinded pilot study. The first three volunteers received 20 mls of oral propofol 1% (Fresenius Kabi). The second three volunteers received 40 mls of oral 1% oral propofol emulsion. Venous blood samples were collected at 2, 4, 8, 16, 30 and 60 min after oral ingestion of propofol emulsion.

Volunteers were monitored using a blood pressure cuff and pulse oximetry. The level of sedation, based on the Observer Assessment of Alertness and Sedation (OAA/S), was assessed at 2, 4, 8, 16, 30, and 60 minutes after oral ingestion.

Propofol assay

As recently described, the blood samples were kept on ice and centrifuged within the first 2 h after collection, and the plasma was extracted. The plasma was stored at 22 degrees C until analysis. High-performance liquid chromatography to measure propofol plasma concentrations was performed using the method described by Seno and colleagues. The lower limits of detection and quantification were 0.01 and 0.1 µg/ml, respectively.

Pharmacokinetic analysis

The area under the curve was measured using linear trapezoids. The orally absorbed dose was calculated as $AUC_{oral} \times Clearance$. Clearance was calculated based on the equations of Schnider et al: $Clearance (L/min) = 1.89 + 0.0456 * (Weight - 77) - 0.0681 * (LBM - 59) + 0.0264 * (Height - 177)$. Lean Body Mass was calculated using the James equation:

$$LBM = 1.1 \text{ Weight (kg)} - 128 \left(\frac{\text{Weight (kg)}}{\text{Height (cm)}} \right)^2$$

Results: All subjects completed the study. There were no adverse events. The demographics, including the calculated clearance, are shown in table 1.

The propofol concentrations are shown in table 2. In subjects 2,3, and 6 the propofol concentrations were uniformly below the limits of quantitation.

The propofol concentrations were above the lower limit of quantitation at 2, 4, and 8 minutes in subject 5. The AUC was 7.8 mg • min • L⁻¹. Based on this subject's calculated systemic clearance of 1.41 L/min, the total systemic dose of propofol was 11 mg, and the oral bioavailability was 2.7%.

The propofol concentrations at 60 minutes (last sample) were 0.1 µg/ml and 0.2 µg/ml in subjects 1 and 4 respectively. Using standard formulae one can estimate the absorption half-life that would result in the first measurable propofol in the 60 minute sample, assuming 100% bioavailability. The absorption half-life would be 493 minutes for subject 1, and 509 minutes for subject 4. The peak plasma concentration would be 0.1008 at 83 minutes for subject 1, and 0.202 at 87 minutes

for subject 4. The calculated absorption half-lives for both subjects exceeds 6 hours, which is implausible for a lipophilic drug like propofol. Since two samples are at the limit of quantitation of the assay, they likely represent assay error (e.g., assay imprecision).

No volunteer experienced sedation. No volunteer had any hemodynamic or ventilatory depression. There was no change in the oxygen saturation of any volunteer.

Discussion: The absorption of orally administered propofol is trivial. In 5 of 6 volunteers the propofol concentrations over the first hour were at or below the limits of quantitation. In one volunteer a trivial dose of 11 mg was absorbed following oral ingestion of 400 mg. This is consistent with the complete absence of clinical symptoms during the study in any volunteer.

The clearance of propofol typically exceeds hepatic blood flow. The hepatic extraction ratio of propofol is greater than 80%,^{2,3} and thus the expected bioavailability of orally administered should not exceed 20%. Raof and colleagues found that gut microsomal preparations had similar propofol metabolic capacity to liver microsomal preparations. The combined first-pass effects of gut metabolism and hepatic metabolism likely explains the very low concentrations and complete lack of clinical effect from oral consumption of 200 and 400 mg of propofol in this study.

These results agree with the observations of Cozanitis et al, who estimated the bioavailability of rectally administered propofol at less than 1% in piglets.¹ Patents published by Xu et al also indicate propofol bioavailability less than 1% in monkeys and dogs, and rats.

The results are also consistent with the data reported online by Huixian and colleagues in mice. These investigators documented an ED₅₀ of 208 mg / kg for loss of blink reflex following orally administered propofol. Glen and Hunter documented that the hypnotic dose of propofol in the mouse was 12.8 mg/kg. Thus, 208 mg/kg is 16 fold higher than the required intravenous dose. Inversely, this implies an oral bioavailability of approximately 6% in the mouse. It should be noted that a 200 mg/kg dose represents 20 mls/kg of propofol. The equivalent dose for a 70 kg adult would be 1.4 litres.

A more definitive mouse study was reported by Glen and colleagues, who noted that “An oral dose of 100 mg/kg propofol produced no behavioural effect other than a slight reduction in locomotor activity. At an oral dose of 300 mg/kg propofol produced sedation. ptosis, ataxia, slight tremor, reduced locomotor activity, a reduced respiratory

rate and a reduction in body temperature. Righting reflex was not lost in any animal at this dose.” The same investigators noted that the median intravenous hypnotic dose of propofol on the mouse was 12.8 mg/kg.¹³ Thus, propofol is at least 23 times less potent when administered orally in mice than when administered intravenously. These findings indicate that the plasma concentrations following oral administration are no greater than 4.2% of the plasma concentrations following intravenous administration.

Orally administered propofol in humans has trivial bioavailability, likely reflecting the combined effects of gut metabolism and high first pass extraction. This is expected from fundamental pharmacokinetic principles of first pass metabolism. It is also consistent with the extremely low bioavailability reported in mice, rats, piglets, dogs, and monkeys. As a result, oral propofol emulsion is unsuitable for clinical use. The lack of clinical effect also precludes the possibility that oral propofol emulsion has abuse liability. However, the bioavailability of ~3% in one subject suggests that some modest fraction of ingested propofol is able to cross the oral mucosa and bypass first pass hepatic metabolism. Were a suitable lozenge or other delivery system developed, oral transmucosal propofol might demonstrate clinical utility.

Volunteer	Sample times (minutes)					
	2	4	8	16	30	60
1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.1
2	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
3	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	No Sample
4	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.2
5	1.93	0.5	0.4	< 0.1	< 0.1	< 0.1
6	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1

Table 1: Demographics. Height, Lean Body Mass (LBM), and Systemic Clearance were calculated as described in the text.

Volunteer	Sample times (minutes)					
	2	4	8	16	30	60
1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.1
2	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
3	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	No Sample
4	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.2
5	1.93	0.5	0.4	< 0.1	< 0.1	< 0.1
6	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1

Table 2: Propofol Concentrations. The limit of quantitation of the assay was 0.1 µg/ml. Samples less than this are reported as < 0.1.

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