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ACKNOWLEDGMENTS AND ADDRESSES

Received September 24, 1974, from the *Schools of Medicine and Pharmacy, University of Southern California, Los Angeles, CA 90033*

Accepted for publication January 31, 1975.

Supported by Contract NO1-CM-23241 from the National Cancer Institute, U.S. Public Health Service, Bethesda, MD 20014

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COMMUNICATIONS

Relative Bioavailability of Cyclobarbital Calcium from Aqueous Solution Compared to Tablets

Keyphrases □ Cyclobarbital calcium—relative bioavailability from aqueous solution and tablets □ Bioavailability—cyclobarbital calcium, aqueous solution and tablets

To the Editor:

For biopharmaceutical studies, the aqueous drug solution is generally recommended as the reference dosage form if no comparison can be made with intravenous data (1). The highest relative bioavailability of a drug is expected from the solution since dissolution of the drug in the GI tract seems to be bypassed. The present report on cyclobarbital calcium shows that this supposition is not always true.

The pharmacokinetics and relative bioavailability of cyclobarbital calcium were studied in six healthy volunteers (21–26 years of age). Three preparations were used:

1. Tablets[1], containing 200 mg of cyclobarbital calcium, 60 mg of potato starch, 27 mg of lactose, 7 mg of talc, 3 mg of magnesium stearate, and gelatin *q.s.*
2. Tablets[2], containing 200 mg of cyclobarbital calcium.
3. Aqueous solution of cyclobarbital calcium (300 mg/150 ml), which was prepared within 15 min prior to administration.

After fasting overnight, at 9 am the volunteers were given 300 mg of cyclobarbital calcium incorporated in one of the preparations together with 150 ml of water. Additional water was not supplied when cyclobarbital calcium was given in solution. The volunteers remained in an upright position for 15 min after intake of the drug and then rested supine for at least 3.5 hr.

Blood samples were taken at 0.15 or 0.33, 0.66, 1.0, 1.5, 2.0, 2.5, 3.0, 5.0, 8.0, 12, 24, and 32 hr following drug administration. Each volunteer received the three preparations in a random sequence, with an interval of at least 1 week. Cyclobarbital plasma concentrations were determined after a single extraction step by GC with nitrogen selective detection, following on-column methylation with trimethylanilinium hydroxide. The use of a nitrogen detector for the sensitive assay of barbiturates in biological fluids was described previously for hexobarbital (3).

In Table I the cyclobarbital plasma peak concentrations and times (mean values) are given, as well as the bioavailability relative to Preparation 1. Relative bioavailability was estimated for each individual by comparing the areas under the experimental plasma concentration curves and correcting for the undetermined area to infinity. The elimination of cyclobarbital followed first-order kinetics with an average half-life of 11.6 hr (range of 8–17 hr). The half-lives were fairly constant within the individuals during the three trials.

[1] Prepared by the Dutch Pharmacist's Laboratory, The Hague (2).
[2] Commercially obtained as Phanodorm, Merck/Bayer.

Table I—Plasma Peak Concentrations and Relative Bioavailability of Cyclobarbital following Oral Administration of the Three Cyclobarbital Calcium Preparations

Preparation	Mean t_{max} (Range), hr	Mean C_{max} (Range), mg/liter	Mean F_{rel} (Range), %
1. Tablets	1.2 (0.33—3.0)	8.3 (7.3—10.8)	100
2. Tablets	1.2 (0.66—2.5)	8.7 (7.4—10.3)	101 (89—136)
3. Aqueous solution	0.7 (0.25—1.5)	8.3 (5.8—11.7)	78 (64—100)

Although substantial variations in absorption rate and relative bioavailability were observed between individuals (see range values), the rank order of these values for the three preparations was generally the same for each volunteer. For one subject, absorption was comparatively slow (t_{max} of 3.0, 2.5, and 1.5 hr for Preparations 1, 2, and 3, respectively), but still the drug was absorbed more rapidly and to a lesser extent when given in aqueous solution.

The present findings clearly indicate that the extent of bioavailability of cyclobarbital in humans is lower when its calcium salt is administered in aqueous solution. This finding is unexpected, whereas the highest absorption rate is in accordance with the usual behavior of an oral aqueous drug solution. It may be argued that after oral administration of barbiturate salts, precipitation of the poorly soluble free acid will occur as soon as the acidic medium of the stomach is reached. This precipitation, however, will also occur for the calcium salt incorporated in the tablets. The precipitate formed after administration of the aqueous solution may have unfavorable redissolution properties in comparison to the precipitate formed after tablet administration. If so, this situation only holds for part of the precipitate, since the rapid absorption of cyclobarbital calcium solution also suggests that rapid (re)dissolution occurs.

A similar observation was made in a separate study when comparing absorption of heptabarbital as free acid with heptabarbital sodium, both from solid dosage forms. The salt showed the highest absorption rate; however, bioavailability relative to the free acid was approximately 20% lower (4). Higuchi *et al.* (5) showed that, in general, salts show higher dissolution rates than the corresponding nonionic drug at any pH, even though the final equilibrium solubility of the drug and its salt is the same. Additional *in vitro* experiments with cyclobarbital calcium are required to study the influence of precipitate formation on the redissolution characteristics of cyclobarbital under acid and weak alkaline conditions.

Although barbiturates are weak acids, their major site of absorption is the intestine (6, 7); therefore, another factor involved in the present findings may be the rate of drug transfer from the stomach to the intestine. However, it is hard to see how this factor could explain the discrepancy between the rate and the extent of cyclobarbital calcium bioavailability from the aqueous solution. Its rapid rate of absorption suggests that rapid drug transfer takes place, which, in principle, favors high bioavailability.

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Received April 7, 1975.
Accepted for publication June 13, 1975.

Fluorocarbon Aerosol Propellants VII: Interaction Studies with Human and Bovine Globulins Using Partition Coefficient Method

Keyphrases □ Fluorocarbon aerosol propellants—interaction with human and bovine globulins, partition coefficient method □ Globulins, human and bovine—interaction with fluorocarbon aerosol propellants, partition coefficient method □ Plasma protein binding—interaction of fluorocarbon aerosol propellants with human and bovine globulins, partition coefficient method

To the Editor:

The partition coefficients of some commonly employed propellants between the aqueous phase and the head space have been shown to be higher in plasma–air systems for humans (1, 2) and other species (2) than in the water (or normal saline)–air system. This finding was postulated to be due to the binding or complexation of these propellants to certain constituent(s) in plasma, as was subsequently confirmed by the partition coefficient method using purified human and bovine albumins (3, 4).

The ability of trichloromonofluoromethane to bind to bovine albumin also was recently demonstrated using a fluorescent probe technique, and these results will be published later. The binding or complexation with other tissue components was also hypothesized to account partially for the high apparent volume of distribution of these neutral propellants in dogs (5).