Oral and Rectal Absorption of Chloral Hydrate and Its Betaine Complex

MICHAEL SIMPSON and EUGENE L. PARROTT ˣ

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Abstract □ Chloral hydrate and its betaine complex were administered orally and rectally to nine healthy male subjects. The urinary excretion, which was a reflection of absorption, of a metabolite, trichloroacetic acid, was determined. No statistically significant difference was found between the oral absorption of chloral hydrate and its betaine complex and between the rectal absorption of chloral hydrate and its betaine complex. A statistical difference was found between the oral and rectal absorption of chloral hydrate and between the oral and rectal absorption of chloral betaine.

Keyphrases □ Chloral hydrate—oral and rectal absorption, compared to chloral betaine □ Chloral betaine—oral and rectal absorption, compared to chloral hydrate □ Absorption—oral and rectal, comparison of chloral hydrate and chloral betaine

The solubility, diffusivity, and lipid–water partition coefficient of drug complexes can differ significantly from these properties of the respective free drug. Therefore, some drug complexes may not penetrate biological membranes and thus have no biological activity (1). Conversely, if a complex is highly dissociated when diluted in biological fluids, complexation has little effect on absorption.

Several derivatives of chloral hydrate have been prepared and tried clinically to reduce or eliminate its bitter taste and gastric irritation (2, 3). Chloral betaine is a 1:1 complex of chloral hydrate and betaine (4). The purpose of this study was to determine if complexation influenced the absorption of an equivalent weight of chloral hydrate and chloral betaine by the oral and rectal routes. The availability of chloral hydrate and chloral betaine from rectal and oral administrations also was compared.

EXPERIMENTAL

Preparation—Chloral betaine was prepared by mixing 135.2 g of betaine monohydrate[1] with 200.2 g of chloral hydrate[2] and warming the mixture on a water bath at 60° (4). The pasty mixture was stirred continuously at 60° for 30 min. The solid residue was crystallized three times from a minimum of distilled water and was stored in a desiccator.

The crystals were compared to the NF reference standard[3] and to NF specifications (5). The melting point of the chloral betaine was determined[4] to be 121.5–123°. With sodium hydroxide TS, the chloral betaine produced chloroform, which was recognized by its odor (5). Measurement[5] of the IR spectra showed that the NF reference standard and the chloral betaine were similar. Differential thermal analysis[6] of the NF reference standard and the chloral betaine showed a single melting point at the same temperature.

The chloral betaine contained 7.97% of moisture by Karl Fischer titration; the NF specification is 5.9–7.5% (5). The excessive moisture was considered in the dose administered, so 881.5 mg of chloral betaine was equivalent to 500 mg of chloral hydrate in this study. The content of chloral hydrate in the chloral betaine assayed as 57.71%, within the NF specification of 56.0–59.5% (5). The amount of betaine was 41.54%, within the NF specification of 40–44% (5).

In the preparation of capsules, each compound was passed through a 60-mesh screen; then 500 mg of chloral hydrate and 881 mg of chloral betaine were placed in 00 and 000 hard gelatin capsules, respectively. Each capsule was stored in a coded, amber, screw-capped bottle.

The suppository base consisted of 24% beeswax[7] in cocoa butter[8] prepared by the fusion method. The base was stored in a cool room for 4 weeks prior to use. In the preparation of suppositories, each compound was passed through a 60-mesh screen; then equivalent weights of chloral hydrate and chloral betaine were manually incorporated in 2.5 g of the base. Each suppository was wrapped in aluminum foil with an inner lining of Parafilm and stored in a screw-capped bottle in a refrigerator until 10–15 min before insertion.

Protocol—All dosage forms were coded and were distributed by a crossover design with overnight fasting; 2 weeks elapsed between the administration of each dosage form. Three subjects did not continue the study after the first dose so the study was completed utilizing nine male subjects from 23 to 39 years of age and weighing 60–73 kg.

Upon arising, the bladder was voided, and a capsule was ingested with 300 ml of water. With rectal administration, the bladder was voided upon arising, the bowel was evacuated, a suppository was inserted high in the rectum, and 300 ml of water was ingested. At least 2 hr was allowed to elapse before food was eaten. Subjects were instructed not to ingest alcoholic beverages and coffee and not to operate machinery during the day.

Urine samples were collected at 2, 4, 6, 8, 10, 12, 16, and 24 hr after drug administration. Volumes were measured, and aliquots were retained in amber vials for analysis. No attempt was made to control the urinary pH. The urinary pH was determined at the time of each sample collection; for a given subject, the fluctuation of pH did not exceed 1.2 pH units.

Analytical Method—Since chloral hydrate has a very short half-life in the body and is not excreted as such, the urine was analyzed for trichloroacetic acid, one of the metabolites. The trichloroacetic acid excreted in the urine was determined by the method of Cabana and Gessner (6).

Statistics—The significance of the difference between the means was calculated using the Student t test, two tail ($p = 0.05$).

RESULTS AND DISCUSSION

Chloral hydrate is rapidly and completely absorbed after oral administration (7, 8), and relatively high concentrations of trichloroacetic acid are found in the blood coincident with the appearance of trichloroethanol after oral administration (9). After rectal administration, chloral hydrate is also converted to trichloroacetic acid and trichloroethanol (10). It appears that chloral hydrate is converted to its metabolites during the first pass through the liver (10), and chloral hydrate is not detectable in the blood at levels as low as 0.5 μg/ml 10 min after administration (10, 11). Chloral hydrate is biotransformed and is excreted as trichloroacetic acid, trichloroethanol, and trichloroethanol glucuronide. Trichloroacetic acid is also formed from trichloroethanol and is excreted in the urine (8, 10, 12).

Since the biotransformation of chloral hydrate is complex with a wide biological variation, a comparative study of chloral hydrate and chloral betaine administered by oral and rectal routes was based on the urinary excretion of trichloroacetic acid with the assumption that in a given subject this biotransformation would be essentially the same. In the crossover study, 500 mg of chloral hydrate or an equivalent weight of chloral betaine was administered in a hard gelatin capsule and in a cocoa butter suppository to nine male subjects. Plots of the milligrams excreted against time to each subject are not given; however, the individual plots

[1] Lot 26C-0292, Sigma Chemical Co.
[2] USP, lot AAZ50, City Chemical Co.
[3] Lot 69140.
[4] Thomas-Hoover melting-point apparatus, A. H. Thomas.
[5] Model 267 IR spectrophotometer, Perkin-Elmer.
[6] Model 900, DuPont Instruments.
[7] White wax USP, Fisher.
[8] USP, Ruger.

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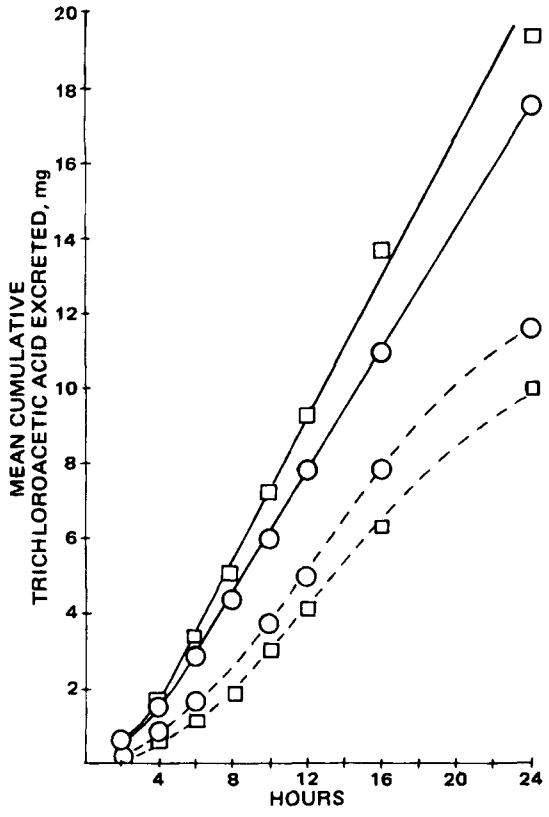

Figure 1—*Mean cumulative milligrams of trichloroacetic acid excreted by nine subjects in 24 hr after administration of 500 mg equivalent of chloral hydrate and chloral betaine in a capsule and in a suppository. Key: —, capsule; – –, suppository; ○, chloral hydrate; and □, chloral betaine.*

follow the general pattern shown in Fig. 1 for the mean cumulative amount of trichloroacetic acid for nine subjects as given in Table I.

It has been observed that complexes may alter absorption (1). Perhaps the most often observed complex formation is between various drugs and macromolecules such as gums, cellulose derivatives, and high molecular weight polyols. The nonabsorbable nature of this type of interaction (amphetamine with carboxymethylcellulose sodium; phenobarbital with polyethylene glycol 4000) provides ample explanation for the nonabsorbable character of the drug complex. With other types of complexes, the dilution of the drug complex in the biological fluids after administration may result in its complete dissociation so that the complexation has little or no effect on absorption. Soci and Parrott (13) noted that methylcellulose and carbomer complexed with nitrofurantoin *in vitro* but that this complexation did not interfere with GI absorption in humans. It was of interest to consider the influence of complexation by comparing the excretion of trichloroacetic acid after the administration of chloral hydrate and its betaine complex.

The significance of the difference between the means in Table I was calculated using the Student *t* test. There was no significant difference between the oral administration of an equivalent weight of chloral hydrate and chloral betaine. Likewise, there was no statistically significant difference between the rectal administration of an equivalent weight of chloral hydrate and chloral betaine (Fig. 1).

Table I—Mean Cumulative Milligrams (±*SD*) of Trichloroacetic Acid Excreted in 24 hr after Oral and Rectal Administration of 500 mg Equivalent of Chloral Hydrate and Chloral Betaine

	Oral		Rectal	
Hours	Chloral Hydrate	Chloral Betaine	Chloral Hydrate	Chloral Betaine
2	0.63 ± 0.52	0.69 ± 0.39	0.29 ± 0.20	0.18 ± 0.17
4	1.52 ± 0.87	1.65 ± 0.63	0.86 ± 0.51	0.51 ± 0.38
6	2.87 ± 0.97	4.44 ± 1.61	1.65 ± 0.81	1.07 ± 0.86
8	4.28 ± 1.74	5.06 ± 1.87	—	1.87 ± 1.45
10	6.01 ± 2.16	7.17 ± 2.55	3.76 ± 1.67	3.04 ± 2.34
12	7.41 ± 2.91	9.31 ± 3.48	4.92 ± 2.08	4.16 ± 3.20
16	11.49 ± 4.58	13.76 ± 4.92	7.84 ± 4.18	6.31 ± 4.53
24	17.17 ± 7.67	19.48 ± 7.15	11.62 ± 6.30	10.04 ± 7.17

Chloral hydrate may be administered rectally, especially in infants and children, to avoid bad taste and gastric irritation (14); however, it may be irritating to the rectal mucosa. The Student *t* test and the data in Table I indicated a significant difference between the oral and rectal administration of chloral hydrate. As shown in Fig. 1, more trichloroacetic acid was excreted after the oral administration of 500 mg of chloral hydrate than after rectal administration by means of a suppository.

There was also a significant difference between the oral and rectal administration of chloral betaine. As shown in Fig. 1, more trichloroacetic acid was excreted after oral administration than after rectal administration. Thus, although the chloral betaine complex is absorbed rectally, it appears that the rectal dose required is somewhat greater than the oral dose.

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