# Bioavailability of Organically Bound Iodine

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**Abstract** □ Total serum iodine levels were measured for 24 hr in human subjects following a single, oral, therapeutic dose of organically bound iodine administered as iodinated glycerol. In one volunteer, measurements were taken during continued dosing for 6 days and for 48 hr thereafter. Peak levels were attained 1–2 hr after administration of a single dose, with a gradual fall to almost basal levels by 24 hr. The experiment with continued dosing for 6 days indicated that once peak blood levels were reached, they continued at this concentration until the drug was discontinued; then they progressively dropped to pretreatment figures in about 48 hr. The bioavailability of the iodinated glycerol was demonstrated following aqueous solution, elixir, and tablet formulations. No significant effect on blood thyroxine iodine levels was noted.

**Keyphrases** □ Iodine, organically bound—bioavailability from iodinated glycerol as aqueous solution, elixir, and tablet formulations, humans □ Thyroxine—blood levels following administration of aqueous solution, elixir, and tablet formulations of iodinated glycerol, humans □ Bioavailability—iodine from iodinated glycerol formulated as aqueous solution, elixir, and tablet, humans

Any ingested drug whose pharmacological activity is dependent upon reaching the circulating blood should be detectable in the circulation as a basic step in proving potential therapeutic efficacy. The purpose of the present study was to establish the bioavailability of organically bound iodine as iodinated glycerol[1] when administered as a tablet or in liquid formulation, the latter as an elixir or aqueous solution.

## EXPERIMENTAL

**Study A**—A group of three healthy, human subjects was used for each of the three dosage forms studied. Each subject had blood drawn for total blood iodine after a low-fat breakfast, and the test material was then administered orally at its usual recommended dose.

Group I received 5 ml of iodinated glycerol elixir containing 30 mg of organically bound iodine; blood iodine was determined at 0, 1, 2, 4, 6, 8, and 24 hr. Group II received two iodinated glycerol tablets containing a total of 30 mg organically bound iodine; blood iodine was measured at 0, 1, 2, 4, 8, and 24 hr. Subjects in Group III received 20 drops of iodinated glycerol in aqueous solution containing 25 mg organically bound iodine; blood iodine was estimated at 0, 4, 8, and 24 hr (Fig. 1).

In the case of iodinated glycerol in aqueous solution, both total iodine and thyroxine iodine were determined in three individuals at 0, 4, 8, and 24 hr after a single dose. Mean results are shown in Fig. 2.

**Study B**—In another subject, therapeutic doses of iodinated glycerol in aqueous solution were administered for 7 days (20 drops, four times daily at 8 am, 12 noon, 4 pm, and 8 pm). Total blood iodine levels were determined at the onset of the study and at 4-hr intervals to 192 hr (Fig. 3). Blood was drawn for iodine determination prior to each hour stated in Fig. 3; *i.e.*, the 24-hr iodine determination was made just prior to the first dose of the 2nd day (8 am), the 32-hr determination was made just prior to the 3rd dose (4 pm) of the 2nd day, *etc.* No iodine determinations were made on the 6th and 7th days. Blood was drawn at 8 am on the 8th and 9th days of the study, 12 and 36 hr, respectively, after the last dose of the drug.

Blood thyroxine iodine levels in this subject were measured in the pretreatment sample and at the terminal blood drawing, 48 hr after the last dose of medication (8th day after the study started).

The method used for total iodine determination consisted of wet ashing followed by the ceric ammonium sulfate reaction[2] (1). The thyroxine iodine test (2) was determined by a radioisotope dilution method.

## RESULTS

The results of Study A are indicated in Fig. 1, which shows the total blood iodine levels attained in the serum after the oral administration of a single dose of the various iodinated glycerol formulations. Within the measurements made, all three formulations tested showed peak serum concentration between 1 and 4 hr after administration and demonstrated comparable levels. A progressive decline over 24 hr followed, when an appreciable amount of iodine was still detectable.

In the case of the iodinated glycerol elixir, a mean maximum

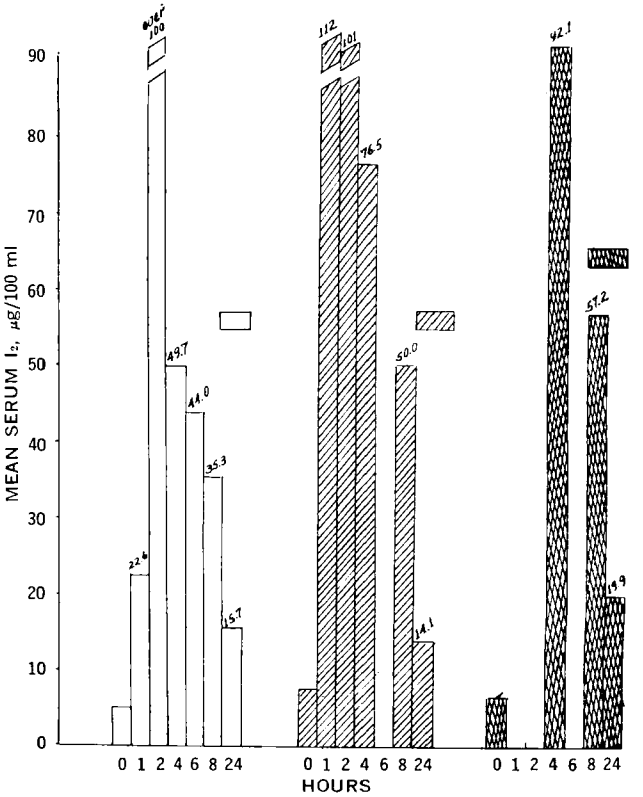


**Figure 1**—*Effect of single doses of iodine-containing products on iodine serum levels in adult subjects over 24 hr. Key:* □, *iodinated glycerol elixir, 30 mg organically bound iodine;* ▨, *iodinated glycerol tablets, 30 mg organically bound iodine; and* ▩, *iodinated glycerol solution, 25 mg organically bound iodine.*

[1] Organidin elixir: 60 mg iodinated glycerol (30 mg organically bound iodine)/5 ml with alcohol 24%; Organidin aqueous solution: 50 mg iodinated glycerol (25 mg organically bound iodine)/ml; Organidin tablets: 30 mg iodinated glycerol (15 mg organically bound iodine)/tablet; Wampole Labs., Stamford, Conn.

[2] Using a Technicon AutoAnalyzer.

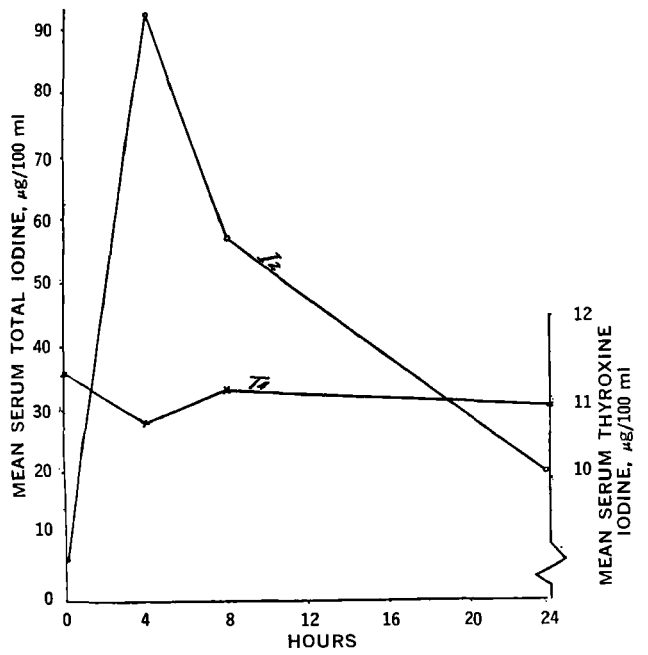


**Figure 2**—*Serum levels of total iodine ($I_2$) and thyroxine iodine ($T_4$) following a single dose of iodinated glycerol solution, 25 mg organically bound iodine.*

level of 100 μg/100 ml was reached in 2 hr, which dropped in progressive steps to 15.7 μg at 24 hr (2.5 × the mean initial level of 5.95 μg). A mean peak level of 112 μg/100 ml was attained after 1 hr when the tablets were used, and within 24 hr the level fell to 14.1 μg (2.4 × the initial level). Following the administration of the aqueous solution, a mean peak level of 92.1 μg was recorded at 4 hr. No blood was drawn in this instance after 1 and 2 hr where the peak undoubtedly occurred, based on experience with the other groups. At 24 hr after medication, levels of iodine in this instance dropped to 19.9 μg (3.3 × the basal level).

There has been some concern that thyroid function tests might be affected by the administration of iodine-containing drugs. Friend (6) found that iodinated glycerol solution administered to a group of healthy subjects in a dose exceeding that recommended as a mucolytic agent did not cause any striking elevation in the protein-bound iodine. The thyroxine iodine test was done to confirm this opinion that iodinated glycerol in the recommended therapeutic dose does not affect thyroid function testing. Figure 2 shows the data along with the corresponding total iodine levels and confirms that there is no effect on thyroxine iodine following administration of a single therapeutic dose of iodinated glycerol solution.

For Study B, the total serum iodine levels following repeated daily doses of iodinated glycerol solution at recommended therapeutic levels is shown in Fig. 3. There was a rapid rise in blood iodine; 4 hr after treatment it reached 65.2 μg from an initial level of 4.9 μg. The iodinated glycerol solution produced a maximum concentration of 100–133 μg, and this level was maintained through 5 days of medication. After administration of iodinated glycerol solution was discontinued on the 7th day, serum iodine levels dropped progressively to pretreatment levels in 36 hr.

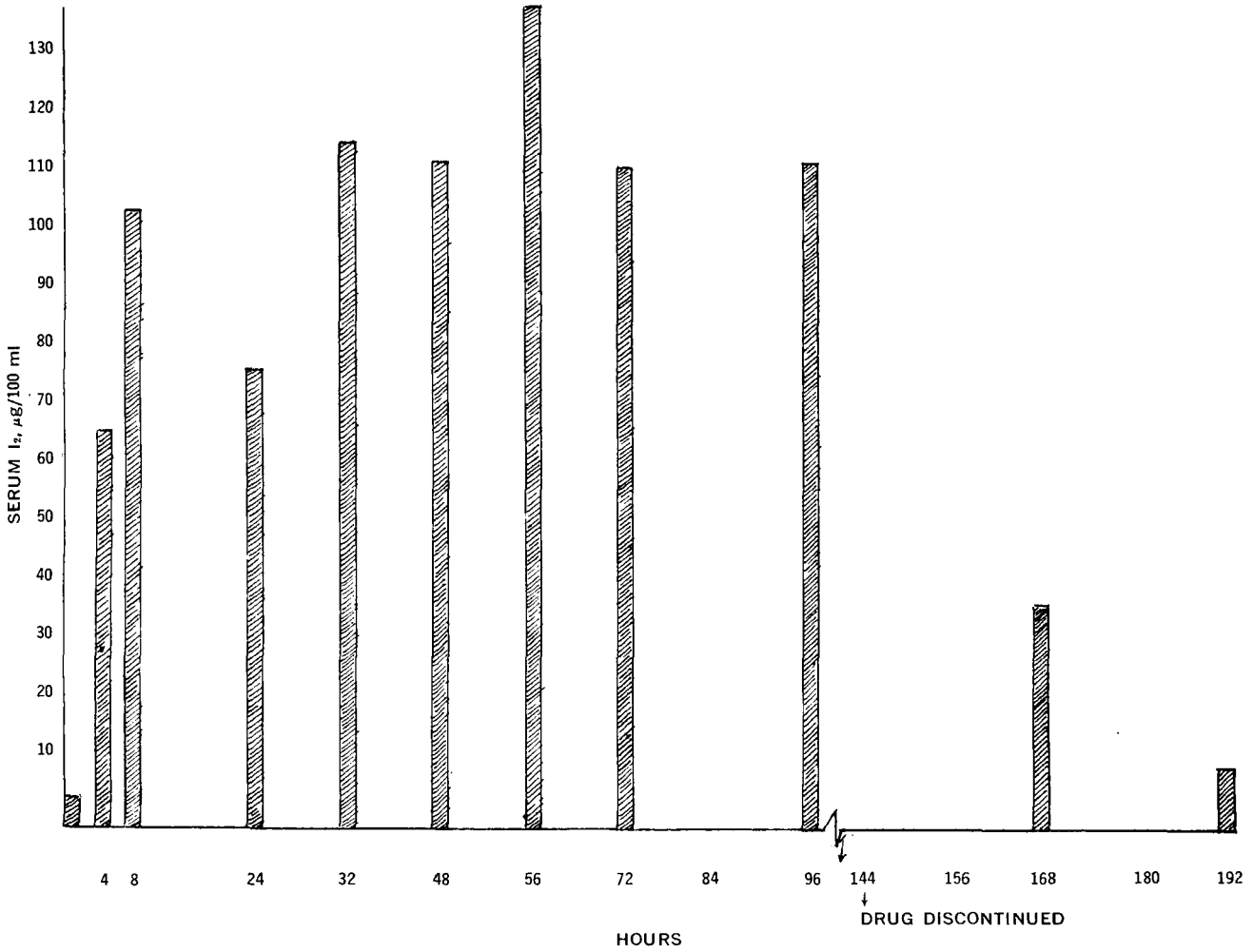


**Figure 3**—*Serum levels of total iodine following repeated therapeutic doses of iodinated glycerol solution, 25 mg organically bound iodine four times daily.*

The thyroxine iodine level was determined at the onset of the 6-day experiment and again 36 hr after discontinuance of the drug, when only a 4% difference in thyroxine iodine level was noted (7.9 μg/100 ml initially *versus* 8.2 μg/100 ml after drug discontinuation); this difference is considered within the normal range.

## DISCUSSION

Organically bound iodine as iodinated glycerol has been widely used as a mucolytic expectorant for over 50 years. It has been reported to be as effective an expectorant as a saturated solution of potassium iodide and to have fewer side effects (3–5), the latter being attributed to the smaller amounts of iodine needed.

Gastric distress is frequently encountered with the use of a saturated solution of potassium iodide and, less commonly, iodism as evidenced by skin rash. Thyroid enlargement is not uncommon with longrange therapy with this drug. On the other hand, Seltzer (3) reported that in 100 consecutive cases treated with iodinated glycerol, there was no instance of thyroid enlargement, iodism, or complaints of gastric irritation. In 100 cases treated with a saturated solution of potassium iodide, he found four cases of iodism and three of thyroid enlargement.

It is self-evident that one must seek that expectorant activity of iodine that can be accomplished with the lowest possible dose and the least side effects, such as can be brought about with organically bound iodine formulations, as long as the formulation is bioavailable. This study has demonstrated that three such formulations containing organically bound iodine are not only bioavailable but are also approximately equiavailable in relation to time and dose.

## CONCLUSIONS

The bioavailability of orally administered organically bound iodine as iodinated glycerol was demonstrated in adult, human, healthy subjects.

Total blood iodine levels following single recommended therapeutic doses of iodinated glycerol showed a rapid rise and a progressive fall over the experimental 24-hr period, at which point there was still an elevated level above initial concentrations. The thyroxine iodine level was not significantly affected after such single doses.

When daily doses of iodinated glycerol were continued for 6 days, it was demonstrated that the total blood iodine rose rapidly, maintained a constant level, and, after discontinuation, returned progressively within 48 hr to preadministration levels. The thyroxine iodine level remained within the normal range after continued medication over this period.

## REFERENCES


(1) Technicon Instruction Manual No. PB/D-1, Technicon Corp., Tarrytown, NY 10591

(2) Tetrasorb-125 (Iodine T-4 diagnostic kit), Abbott Labs., North Chicago, IL 60064

(3) A. Seltzer, *Ann. Allergy*, **19**, 381(1961).

(4) A. Seltzer, *Med. Ann. D.C.*, **30**, 130(1971).

(5) I. A. Fond, *Ann. Allergy*, **19**, 625(1961).

(6) D. G. Friend, *N. Engl. J. Med.*, **263**, 1358(1960).


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# Enhancing Effect of Calcium Ions on Transport of Cholesterol from Aqueous Sodium Taurocholate–Lecithin Micellar Phase to Oil Phase


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**Abstract** □ Experiments on the influence of calcium ions upon the transport of cholesterol from bile salt–lecithin micelles into an oil phase were carried out using previously developed methods. As the calcium-ion concentration is increased, the sterol transport rate increases until a limiting maximum rate is reached at around a 0.03 *M* concentration of calcium ions. This limiting rate corresponds to an interfacial barrier permeability coefficient, *P*, of about $1 \times 10^{-6}$ cm/sec, which is 35–40 times larger than that obtained in the absence of calcium. These results are consistent with the interfacial barrier-controlled mechanism in which the bile salt–lecithin micelle is involved in the rate-determining step at the aqueous–lipid interface.



**Keyphrases** □ Calcium ions—enhancing effect on cholesterol transport from sodium taurocholate–lecithin micelles to oil phase □ Cholesterol transport—from bile salt–lecithin micelles into oil phase, enhancing effect of calcium ions □ Bile salt–lecithin micelles—transport of cholesterol, influence of calcium ions


Recent investigations (1–6) in these laboratories led to the conclusion that the transport of cholesterol and other sterols from aqueous to oil phases may be interfacial barrier controlled rather than bulk phase diffusion controlled. The implications of these findings in biology should be broad, because the understanding of sterol transport is vital to the understanding of sterol absorption in the intestine, of the pathogenesis of atherosclerosis and of cholesterol gallstones, and of the metabolism of sterols generally. That interfacial kinetics rather than bulk diffusion and convection are more important relegates thermodynamics into somewhat of a secondary role as far as transport is concerned. Previous studies (5, 6) showed not only that the kinetics in this situation are interfacial barrier controlled but that the bile salt–lecithin micelle is a key participant in the rate-determining step.

The present report represents a portion of the effort made to understand the mechanistic role of the bile salt–lecithin–cholesterol micelle in the transport of cholesterol at the lipid–aqueous interface. The present data demonstrate a dramatic effect of calci-