oil was subjected to preparative TLC on silica gel $HF_{254+366}$ (ethyl acetate). The higher $R_f$ band gave 0.042 g. of an oily product, which was characterized as phenol on the basis of IR and UV spectra as well as TLC. The lower $R_f$ band gave the desired product, IX, as an oil, 0.21 g. (82%). The IR spectrum showed bands at 3472, 3333, and 1681 $cm.^{-1}$. There was no UV absorption in the 240–290-nm. region.

*Method B*—Compound VII (0.60 g., 1.89 mmoles) was subjected to hydrolytic conditions identical to those outlined in Method A. The product obtained following workup was identical to the one obtained by the previous method (0.42 g., 85%).

***cis*-Hexahydro-4-(4-cyanobutyl)-2-cyclopentimidazolone (X)**—A solution of 0.25 g. (5.0 mmoles) of sodium cyanide in 1.0 ml. of water was added to a solution of 0.13 g. (0.5 mmole) of the bromo derivative IX in 5.0 ml. of methanol. The reaction was refluxed for 20 hr., the solvent was evaporated to dryness, and the oily residue was purified by preparative TLC (25% methanol in chloroform). The nitrile was obtained as a colorless oil (0.097 g., 94%). The IR spectrum showed bands at 3472, 3247, 2247, and 1681 $cm.^{-1}$.

**Hexahydro-4-(4-carboxybutyl)-2-cyclopentimidazolone (Carbobiotin) (XI)**—Compound X (0.21 g., 1.0 mmole), dissolved in a mixture of 15 ml. of methanol and 8 ml. of 3 *N* aqueous potassium hydroxide, was heated on the steam bath for 5 hr. The reaction mixture was concentrated to one-third of its original volume and acidified with 10% hydrochloric acid (Congo Red). The white precipitate was filtered and dried, affording 0.19 g. (83%) of crude product, m.p. 187–195°. Several recrystallizations from 95% ethanol gave colorless crystals of XI, m.p. 211–213°. The IR spectrum (mineral oil) showed bands at 3257 and 1695 $cm.^{-1}$.

*Anal.*—Calc. for $C_{11}H_{18}N_2O_3$: C, 58.40; H, 8.02; N, 12.38. Found: C, 58.48; H, 7.89; N, 12.47.

## REFERENCES


(1) J. A. Glasel, *Biochemistry*, **5**, 1851(1966).

(2) M. Caplow, *ibid.*, **8**, 2656(1969).

(3) H. C. Wormser, *J. Pharm. Sci.*, **58**, 1038(1969).

(4) *Ibid.*, **59**, 1732(1970).

(5) M. N. Donin, S. L. Burson, J. H. Müller, C. Chen, W. E. Behnke, and K. Hofmann, *J. Amer. Chem. Soc.*, **73**, 4286(1951).

(6) J. H. Müller, M. N. Donin, W. E. Behnke, and K. Hofmann, *ibid.*, **73**, 2487(1951).

(7) R. Duschinsky, L. A. Dolan, D. Flower, and S. H. Rubin, *Arch. Biochem.*, **6**, 480(1945).

(8) F. J. Pilgrim, A. E. Axelrod, T. Winnick, and K. Hofmann, *Science*, **102**, 35(1945).

(9) L. D. Wright and H. R. Skeggs, *Proc. Soc. Exp. Biol. Med.*, **56**, 95(1944).

(10) R. Hertz, *ibid.*, **52**, 15(1943).

(11) D. Perlman, *Amer. J. Bot.*, **35**, 36(1948).

(12) V. R. Williams and E. A. Fieger, *Ind. Eng. Chem., Anal. Ed.*, **17**, 127(1945).


## ACKNOWLEDGMENTS AND ADDRESSES


Received January 18, 1972, from the *College of Pharmacy, Wayne State University, Detroit, MI 48202, and the †School of Pharmacy, University of Wisconsin, Madison, WI 53706

Accepted for publication March 17, 1972.

Abstracted in part from a thesis submitted by Sangthong Israsena to Wayne State University in partial fulfillment of the Master of Science degree requirements.

The chemical portion of this work was supported in part by a grant-in-aid from Wayne State University. The biological portion was supported in part by a grant from the Graduate School Research Committee, University of Wisconsin, and by an allocation from the General Research Support Grant FR 5056 to the School of Pharmacy from the Department of Health, Education, and Welfare, National Institutes of Health.



▲ To whom inquiries should be directed.


# *COMMUNICATIONS*

## Effect of Volume of Distribution on Plasma Levels of Total Radioactivity


**Keyphrases** □ Volume of distribution—effect on plasma levels of total radioactivity, intravenous haloperidol-$^3$H, man □ Plasma profile of radioactivity—atypical appearance after intravenous haloperidol-$^3$H administration, man, effect of volume of distribution □ Haloperidol-$^3$H, intravenous, man—effect of volume of distribution on plasma levels of total radioactivity, atypical profile discussed □ Radiolabeled haloperidol—effect of volume of distribution on plasma levels, atypical profile discussed, intravenous administration, man


*Sir:*

An unusual but, in retrospect, not unexpected pharmacokinetic phenomenon was observed following intravenous administration of haloperidol-$^3$H (generally labeled). Figure 1 shows the mean plasma level profile of total radioactivity obtained in three healthy male subjects following intravenous administration of 2 mg. of haloperidol-$^3$H. The concentration of tritium in each sample was determined using a liquid scintillation counter[1] and internal standards. All samples were counted to less than a 1% counting error. The purity of the haloperidol-$^3$H used was 99+% as determined by solvent extraction and TLC. Heparinized plasma samples were removed at 0 (predose), 10, 20, 40, and 60 min. and at 2, 4, 6, 8, 12, 24, 48, 72, and 96 hr.

The profile of Fig. 1 is not what one would expect following intravenous administration. Instead of the expected maximum at the first sample time followed by a decline, the plasma levels of total radioactivity increased over the 96-hr. period of observation. The cumulative urinary excretion profile (Fig. 2) shows that significant excretion of radioactivity occurred

[1] Beckman LS200 B.

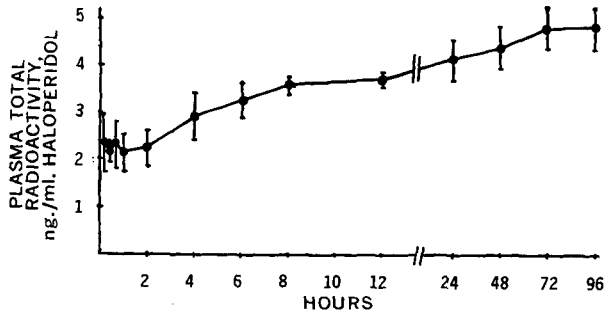


**Figure 1**—*Mean plasma levels (±SE) of total radioactivity, expressed as nanograms per milliliter haloperidol, in three subjects following intravenous administration of 2 mg. of haloperidol-$^3H$.*

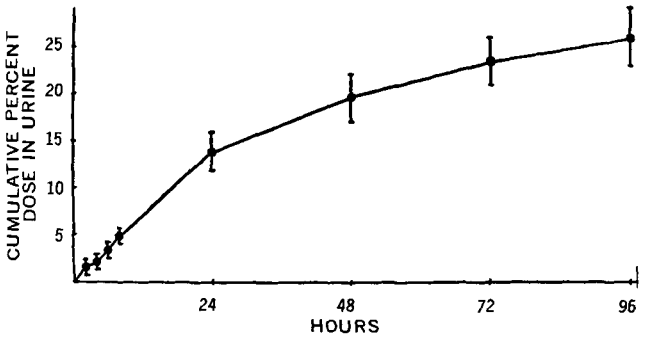


**Figure 2**—*Cumulative urinary excretion of radioactivity (±SE), expressed as percent of administered dose, in three subjects following intravenous administration of 2 mg. of haloperidol-$^3H$.*

during the period of increasing plasma levels. Significant fecal excretion of total radioactivity was also observed by the authors in rats and humans given oral and intravenous doses of haloperidol.

For drugs whose volume of distribution ($V_D$) is larger than the volume of total body water ($V_D$ of haloperidol ~700–1000 l. *versus* ~42 l. for body water), the formation of water-soluble metabolites might be expected to produce a decrease in the apparent volume of distribution of total radioactivity. If these metabolites were excreted more slowly than they were produced (*e.g.*, than haloperidol was metabolized), they would accumulate in the plasma. Because total radioactivity is a nonspecific measure of drug in the plasma, it would be possible, under these conditions, for plasma levels of radioactivity to increase. The increase could occur without further drug absorption and while a significant percent of the radioactivity was being eliminated *via* the urine and/or feces.

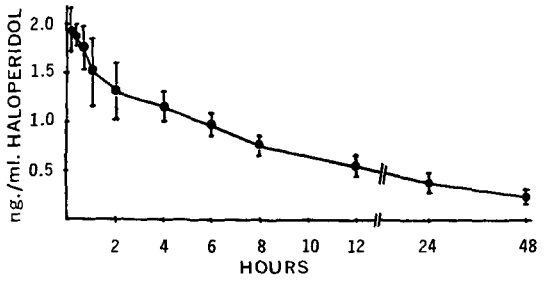


**Figure 3**—*Mean plasma levels (±SE) of haloperidol (haloperidol-like substances) in three subjects following intravenous administration of 2 mg. of haloperidol-$^3H$.*

**Table I**—Volatile Radioactivity (%), Tritiated Water, in Selected Plasma Samples

| Subject | Hours | | | |
|---|---|---|---|---|
| | 0.33 | 1 | 8 | 96 |
| 1 | — | 20 | — | 88 |
| 2 | 0 | — | — | 91 |
| 3 | — | — | 33 | 93 |

The mean plasma levels of haloperidol-like substances (substances extracted from alkaline plasma into ethyl acetate) are shown in Fig. 3. This plasma level profile is more characteristic of that expected following intravenous administration of a drug. Based on the metabolism of haloperidol (1), the theoretical position of the radioactive label, and TLC of selected ethyl acetate samples, these levels (Fig. 3) represent only intact haloperidol, at least at the early time points.

Comparison of Fig. 3 with Figs. 1 and 2 suggests that more than one tritium-labeled metabolite is involved. To produce continued urinary elimination of radioactivity with simultaneous increases in plasma levels, after elimination or metabolic conversion of all plasma haloperidol, at least two metabolites are required. Because of the nature of the radioactive label and the extensive metabolism of haloperidol in animals (1), some tritiated water would be expected as a metabolic end-product. The amount of $^3H_2O$ (volatile radioactivity assumed to be $^3H_2O$) was determined in selected plasma samples by lyophilization. The results are summarized in Table I. The circulating $^3H_2O$ at 96 hr. represents only 5% of the total dose of tritium. However, because of the large volume of distribution difference between haloperidol and body water, the plasma level of radioactivity is higher at 96 hr. than it is at 10 min. At the early sample times (2–72 hr.), the circulating radioactivity is composed of haloperidol-$^3H$, $^3H_2O$, and metabolites. The half-life of haloperidol is too short (3–5 hr.) and the half-life of water is too long (7–14 days) (2–4) to provide, by themselves, the profile observed. This is consistent with the multistep metabolic path for haloperidol (1).

In summary, a plasma profile of radioactivity was obtained following intravenous administration of haloperidol-$^3H$ which, while consistent with established principles of pharmacokinetics, was atypical in appearance. Similar phenomena might be expected with other radioactive drugs which have large volumes of distribution.

(1) G. A. Braun, G. I. Poos, and W. Soudijn, *Eur. J. Pharmacol.*, **1**, 58(1967).

(2) W. G. McTaggart and D. Cardus, in "Organic Scintillation and Liquid Scintillation Counting," D. L. Horrocks and C. Peng, Eds., Academic, New York, N. Y., 1971, pp. 621–634.

(3) J. M. Foy and H. Schnieden, *J. Physiol.*, **154**, 169(1960).

(4) E. A. Pinson, *Physiol. Rev.*, **32**, 123(1952).

W. A. CRESSMAN▲
N. L. RENZI
A. C. BARTHOLOMAY
McNeil Laboratories, Inc.
Fort Washington, PA 19034

Received December 2, 1971.
Accepted for publication March 17, 1972.
▲ To whom inquiries should be directed.