J. Pharm. Pharmac., 1978, **30**, 284–286 *Received December* 5, 1977

Rectal absorption of homatropine [^{14}C]methylbromide in the rat

M. B. CRAMER*, L. A. CATES AND D. E. CLARKE

College of Pharmacy, University of Houston, Houston, Texas, U.S.A. 77004

Homatropine[^{14}C]methylbromide (HMB-^{14}C) was administered to rats by intramuscular injection, oral gavage and rectal suppository. Plasma concentrations of ^{14}C were measured over the subsequent 12 h. Peak plasma concentrations were higher and achieved more rapidly after rectal administration than by the other routes whether HMB-^{14}C was administered in a water-soluble suppository base or in aqueous solution. Twelve h after the suppositories were inserted and retained 28% of the ^{14}C had been excreted in the urine while 56% remained in the large intestine. Unlabelled HMB, given in rectal suppositories to anaesthetized rats, caused prompt blockade of the effects of vagal stimulation on pulse rate and of intravenous acetylcholine on blood pressure. These results confirm the rapid rectal absorption of the drug.

Quaternary derivatives of antiacetylcholine drugs are commonly considered to be less effective when administered orally than when given parenterally. This difference has been attributed to the poor absorption of quaternary compounds from the gastrointestinal tract (Levine, 1959; Albanus, Sundwall & Vangbo, 1969). Both *in vivo* and *in vitro* a brief early phase of rapid absorption of quaternary ammonium compounds from the small intestine occurs followed by a cessation of absorption at a time when most of the dose is still in the intestinal tract (Levine & Pelikan, 1964; Turnheim & Lauterbach, 1977).

Rectal administration of drugs, while providing for prompt and effective absorption in some instances, often results in slow and erratic absorption (Nowak, Brundhofer & Gibaldi, 1974; Goodman & Gilman, 1975). Rectal suppositories containing the quaternary ammonium drug homatropine methylbromide (HMB) are used for purposes requiring at least some absorption of the drug, e.g. treatment of nausea and vomiting. We have examined whether effective plasma concentrations of HMB could be attained after rectal administration.

MATERIALS AND METHODS

Synthesis of homatropine [^{14}C]methylbromide (HMB-^{14}C)

An excess of homatropine in absolute ethanol was added to [^{14}C]methylbromide in a dry ice-chloroform bath. The mixture was sealed in a glass tube and allowed to reach room temperature with periodic release of pressure. After 1 week at room temperature (20°), white crystals had formed. Methylbromide gas was then bubbled through the solution for 30 min, and the tube re-sealed and allowed to stand for 3 days. Anhydrous diethyl ether was added and caused a dense, white precipitate which was washed several times with anhydrous diethyl ether and stored in a dessicator (yield 81% m.p. 188–191°, Merck Index value: 191–192°). Silica gel thin-layer chromatography, using acetone–0·05 M HCl (4:1) as the eluant, detected one radioactive (as measured by liquid scintillation spectroscopy) spot at $R_F = 0{\cdot}32$ identical with the R_F of HMB in this system. These data, along with a series of extractions of the product with octanol which showed no radioactive component with solubility characteristics different from those of HMB, were evidence of radiochemical purity. The specific activity of HMB-^{14}C was 256 μCi μmol^{-1}.

pondence.

Plasma concentrations

Male albino rats, 220–350 g (Texas Inbred Inc., Houston, TX) were fasted for 24 h, but had free access to 5% dextrose in tap water, before HMB-^{14}C given by intramuscular injection or oral intubation, and for 48 h before rectal administration.

At the beginning of each experiment rats were lightly anaesthetized with diethyl ether. A blood sample of approximately 85 μl was collected from the tail vein for determination of background radioactivity. HMB-^{14}C was then administered by (a) intramuscular injection (25 μCi kg^{-1}) (b) orally, by gavage (50 μCi kg^{-1}) (c) rectally, by 9 mm × 5 mm conical suppository (approximately 50 μCi kg^{-1} in a water-soluble base) (d) rectally, in aqueous solution (50 μCi kg^{-1}). After rectal administration of HMB-^{14}C a glass bead (approx. 6 mm diam.) was inserted into the rectum and the anus closed with wound clips. This procedure resulted in no detectable leakage of rectal contents during the ensuing 12 h.

After drug administration each animal was placed in a restraining cage which permitted access to water. Blood samples (approximately 85 μl each, from the tail vein) and urine were collected at intervals over 12 h at the end of which the rats were killed with anaesthetic. The bladder was removed and its contents added to the final urine sample. In some animals the gastrointestinal tract was removed and rinsed. Radioactivity in plasma, urine and tissues was measured with a liquid scintillation spectrometer. Thin-layer chromatography of plasma samples using two solvent systems capable of distinguishing between unchanged HMB and its hydrolysis products revealed only one radioactive spot which had the same R_F value as pure HMB-^{14}C.

Cardiovascular studies

To demonstrate that absorbed drug possessed the pharmacological activity of HMB, its effect on certain cardiovascular parameters were measured. Rats were anaesthetized with sodium pentobarbitone (35 mg kg^{-1}, i.p.). The left femoral vein was cannulated for injection of acetylcholine iodide. The left carotid artery was cannulated for measurement of arterial blood pressure and pulse rate. Stimulating electrodes were attached to the left vagus nerve and the nerve was cut centrally. Heart rate was measured by inserting needle electrodes under the skin and converting the QRS of the resultant electrocardiogram into rate through a biotachometer. Arterial pressure was measured using a Statham pressure transducer. Pre-drug effects were determined for various intravenous doses of acetylcholine on blood pressure and various frequencies of vagal stimulation on pulse rate. A suppository containing unlabelled HMB in a concentration equivalent to those used in plasma concentration studies was inserted rectally, and the same responses measured.

RESULTS

Absorption and distribution of HMB

Fig. 1 illustrates the plasma ^{14}C concentrations (adjusted for differences in doses) after intramuscular, oral and rectal administration of HMB-^{14}C. After intramuscular administration, peak plasma concentrations were attained within 75 min and began to decline at about 180 min. Absorption by mouth was slower, with a peak plasma value after 4 h that was much lower than from the other routes. After the suppository there was a rapid rise of plasma ^{14}C concentrations to a peak within 45–60 min and then a rapid decline. The variability of plasma ^{14}C concentrations was most pronounced after the suppository.

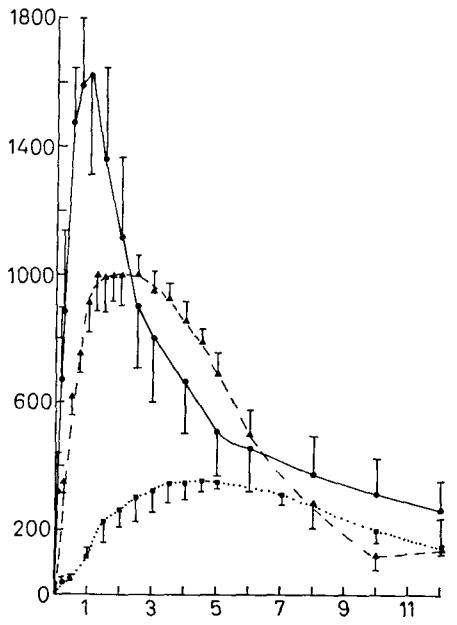

FIG. 1. ^{14}C Plasma concentrations after administration to rats of homatropine [^{14}C]methylbromide by intramuscular injection (▲ – – ▲), gavage (■ . . . ■) and rectal suppository (● —— ●). Each point represents the mean from 5 rats ± standard error. Ordinate: ^{14}C plasma concentration (d min^{-1} ^{14}C ml^{-1} plasma/dose in d min^{-1} kg^{-1}) × 10^7. Abscissa: Time (h) after drug administration.

The possibility that the suppository base itself might be responsible for the rapid absorption of HMB-^{14}C was tested in another experiment summarized in Fig. 2. HMB-^{14}C in aqueous solution was administered rectally in a manner similar to the suppositories, and ^{14}C plasma concentrations measured. Absorption of HMB-^{14}C from solution was as rapid as that from the suppository since the curves obtained were similar (Fig. 2).

Table 1 summarizes the amount of ^{14}C excreted in the urine and remaining in various tissues 12 h after a suppository. Nearly 56% of the ^{14}C remained in the large intestine; another 28% appeared in the urine. The presence of some radioactivity (2·5% of the administered dose) in the small intestine suggests the possibility of excretion of a portion of the absorbed dose into the intestinal tract (Table 1).

Cardiovascular effects of rectally-administered HMB

HMB, given by suppository, blocked cardiovascular responses to vagal stimulation and acetylcholine; 10–20 min after insertion of the suppository the effects of vagal stimulation over a range of 2–16 Hz, 5 V, on pulse rate was virtually abolished and re-

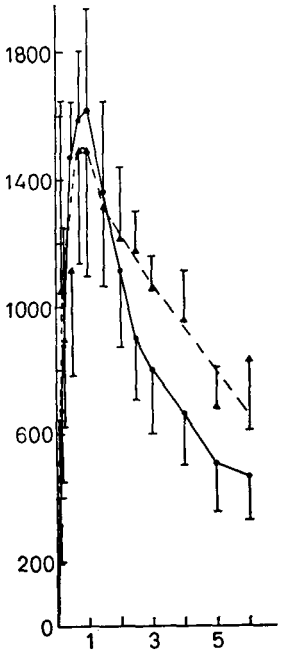

FIG. 2. ^{14}C Plasma concentrations after the rectal administration to rats of homatropine [^{14}C]methylbromide in aqueous solution (▲ – – ▲) or as a suppository (●——●). Each point represents the mean from 5 rats ± standard error. Ordinate and abscissa as for Fig. 1.

mained unchanged at 45–60 min. A control suppository had no effect on the frequency-response relation.

Similarly, at 5–20 min after the suppository the depressor response to intravenous acetylcholine iodide at doses 19·5 ng–19·5 $\mu g\,kg^{-1}$ was almost completely blocked. At 80–95 min, corresponding to the time of declining plasma concentrations in conscious rats, the response to acetylcholine had begun to reappear at doses $>195\,\mu g\,kg^{-1}$ but had not returned to pre-drug values. Administration of a blank suppository had no effect on the dose-response relation.

DISCUSSION

In this study, rectal administration resulted in more rapid peak plasma concentrations than did intramuscular injection. At 12 h after rectal administration of HMB-^{14}C (or 11 h after plasma concentrations began to decline) over half of the administered dose of radioactivity remained in the large intestine. Most of the remainder had been excreted in the urine. These observations are consistent with the model of Turnheim & Lauterbach (1977). There was no significant difference in absorption when HMB-^{14}C was given rectally as a solution or as a suppository.

Direct comparison of the effects of rectal administration of HMB on cardiovascular parameters with plasma concentration data is complicated by the fact that the ^{14}C plasma concentrations were measured in conscious rats subjected to restraint stress while the cardiovascular responses were measured in anaesthetized rats. Nevertheless it is clear that sufficient HMB was rapidly absorbed rectally to exert a measurable pharmacological effect. These findings are compatible with the hypothesis that the absorbed material is indeed HMB.

Table 1. *^{14}C Distribution 12 h after rectal administration of homatropine* [^{14}C]*methylbromide in a suppository to rats.* Urine was collected for 12 h, at the end of which the animals were killed and tissues collected. Liquid samples were dissolved in scintillation cocktail. Tissue samples were homogenized, an aliquot dissolved in tissue solubilizer and, subsequently, in scintillation cocktail. Samples were counted in a liquid scintillation spectrometer.

Sample	% Admin. activity (mean ± s.e.; n = 4)
Stomach + contents	0·069 ± 0·008
Small intestine + contents	2·52 ± 1·30
Large intestine + contents	55·6 ± 1·7
Brain	0·0062 ± 0·0013
Liver	0·805 ± 0·109
Kidneys	0·665 ± 0·365
Urine	28·0 ± 1·9
Total recovery	87·7 ± 1·7

Acknowledgement

This study was supported, in part, by Comatic Laboratories, Inc., Houston, Texas.

REFERENCES

ALBANUS, L., SUNDWALL, A. & VANGBO, B. (1969). *Acta pharmac. tox.*, **27**, 97–111.
GOODMAN, S. & GILMAN, A. (1975). *The Pharmacological Basis of Therapuetics*, 5th edn, p. 7. London: Macmillan.
LEVINE, R. M. (1959). *Archs int. Pharmacodyn. Thér.*, **121**, 146–149.
LEVINE, R. M. & PELIKAN, E. W. (1964). *A. Rev. Pharmac.*, **4**, 69–84.
NOWAK, M. M., BRUNDHOFER, B. & GIBALDI, M. (1974). *Pediatrics*, **54**, 23–26.
TURNHEIM, K. & LAUTERBACH (1977). *Biochem. Pharmac.*, **26**, 99–107.