The fate of Drotaverine - Acephyllinate\(^+\) in rat and man
I. Absorption, distribution and excretion in the rat

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SUMMARY

Two different labelled forms were used for the pharmacokinetic investigations: the carbon 1 in the isoquinoline ring (Drotaverine-\(^{14}\)C-Acephyllinate) and the carboxyl group of theophylline-7-acetic acid (Drotaverine-Acephylline-\(^{14}\)C-ate).

Drotaverine-\(^{14}\)C-Acephyllinate was rapidly absorbed from duodenal and ileal segments. Biliary excretion was substantial after oral administration and radioactivity was excreted mostly in the feces.

Absorption of Drotaverine-Acephylline-\(^{14}\)C-ate from the gastrointestinal tract was very poor and radioactivity was therefore excreted for the most part in the feces.

The results of the study were confirmed by whole body autoradiography.

INTRODUCTION

Benzyl-isoquinoline derivatives (Paraverine, Ethaverine, Drotaverine) are well known for their excellent smooth muscle relaxant and cardiovascular properties. Drotaverine-Acephyllinate (Fig. 1), (theophylline-7-acetate of 6,7,3,4-tetraethoxy-1-benzyl-3,4-dihydro-isoquinoline) is a potential new smooth muscle relaxant and geriatric synthesized by Szentmiklosi and Meszaros (1). The clinical studies showed a positive peripheral vasodilating effect (2).

Comparative pharmacology indicated that the duration of action of Drotaverine-Acephyllinate was greater than that of Drotaverine HCl (No-Spa\(^\circ\) Chinoin) and at the same time was 1.6 times less toxic which made it therapeutically more advantageous.

Whole body autoradiography of Drotaverine-\(^{14}\)C HCl was carried out on mice by Magyar (3), absorption and excretion were studied by Simon (4) in the rat.

Comparative blood level studies of Drotaverine-\(^{14}\)C HCl and Drotaverine-\(^{14}\)C-Acephyllinate performed by Szentmiklósí (5) on mice showed higher values for Depogen after intravenous as well as oral administration.

Strolin-Benedetti (6) examined the absorption and excretion of theophylline-7-acetic acid (acephylline) in rats and dogs and found that absorption was very poor, the compound being eliminated for the most part in the feces.

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+ Depogen\(^\circ\) (Chinoin, Budapest).

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Fig. 1: The chemical structure of Drotaverine-Acephyllinate (positions of \(^{14}\)C label).
MATERIALS AND METHODS

Radiochemicals

Drotaverine-1-\textsuperscript{14}C HCl was synthesized by Koltai (7) and this compound was used for the preparation of Drotaverine-\textsuperscript{14}C Acephyllinate (spec. act.: 0.266 GBq/g, 7.255 mCi/g; 169.1 MBq/mM, 4.57 mCi/mM).

Drotaverine-Acephylline-\textsuperscript{14}C-ate was synthesized at the Institute for Drug Research, Budapest (spec. act.: 0.107 GBq/g, 2.88 mCi/g; 67.7 MBq/mM, 1.83 mCi/mM).

Radiochemical purity of the labelled compounds proved to be higher than 95 per cent as checked by thin layer chromatography using the LB 2723 Berthold scanning system.

Experimental animals

For the whole body autoradiographic and balance studies Wistar-H/Riop and for the measurements of absorption and biliary elimination, CFY male albino rats weighing 180-200 g were used. On a small number of animals control studies were carried out and the experimental results proved that there were no strain differences.

Absorption studies by in vivo loop technique

On the small intestine of narcotized animals (40 mg/kg i.p. Nembutal) following upper laparotomy two loops were isolated, the first in the duodenum (8 cm long), the second in the ileum (10 cm long).

Radioactive Drotaverine-Acephyllinate dissolved in 0.3 ml distilled water was injected into the sacs and the abdominal wall was temporarily closed. At the end of the experimental period the sacs were opened, rinsed with 10 ml distilled water and the wall the loop was homogenized. Radioactivity of the rinsing water and homogenate was measured and the missing part was considered to have been absorbed.

Whole body autoradiography

Whole body autoradiography was carried out according to the method described by Ullberg (8) using PMV-450 MP Cryomicrotome (LKB). The X-ray film copies were evaluated by Telechrom OE-976 (Chinoin) videodensitometer.

Biological sampling

After administration of the drug, the animals were placed in individual metabolic cages, urine and feces were collected separately. During the experimental period the rats were given pellet food and water ad libitum. \textsuperscript{14}CO\textsubscript{2} content of the expired air was absorbed in Carbo-Sorb\textsuperscript{R} II. (Packard). At the end of the experimental time the animals were killed by chloroform anaesthesia and total radioactivity of the carcass was measured.

For collecting bile samples the bile duct of Nembutal-narcotized animals was cannulated.

Measurement of radioactivity

200 \textmu l sample of the intestinal wall homogenate, rinsing water or bile was diluted with 800 \textmu l distilled water and 9 ml 1:2 V/V Triton-X 100- toluene cocktail (6 g PPO, 0.4 g POPOP in 1000 ml toluene) was added.

Radioactivity of 50 \textmu l urine samples was measured by adding 10 ml Bray cocktail (4 g PPO, 0.2 g POPOP, 60 g naphthalene, 100 ml methanol, 20 ml ethylene glycol, 1000 ml dioxane).

The feces were dried to constant weight over P\textsubscript{2}O\textsubscript{5} and homogenized, combusted by Oxiscint equipment (9) according to Gács (10). The radioactive CO\textsubscript{2} was absorbed in 2 ml Carbo-Sorb II., 13 ml cocktail was added (4 g PPO, 0.25 g POPOP in 1000 ml toluene).

For the measurement of the expired \textsuperscript{14}CO\textsubscript{2} the above system was used.

The carcass was dissolved in 200 ml conc. sulphuric acid (4-5 days, preliminary experiments proved that no radioactivity bubbled out of the system), 50 mg sample taken, 0.4 ml \textsubscript{3}H\textsubscript{2}O added, after 3 hours 6 ml ethylene glycol monomethyl ether and 10 ml toluene cocktail (6 g PPO, 1000 ml toluene).

Radioactivity was measured by LKB Wallac 8100 equipment, quench correction made by external standardization.

RESULTS

Absorption from intestinal loops

Absorption of Drotaverine-\textsuperscript{14}C-Acephyllinate from duodenum and ileum as a function of time is shown in Table I (dose: 80 \mu g and 600 \mu g per sac). Drotaverine-Acephyllinate was quickly absorbed from the sacs with high absorption capacity; there was no difference between the two intestinal segments.