ABSORPTION, EXCRETION AND METABOLISM OF ORAL BROMPERIDOL IN RATS AND DOGS

J. HEYKANTS, W. MEULDERMANS and M. MICHELS
Department of Drug Metabolism, Janssen Pharmaceutica, B-2340 Beerse, Belgium

Received for publication: February 17, 1978

Key words: 3H-Bromperidol; Neuroleptic; Metabolism; Rat; Dog

SUMMARY

After an oral dose of 0.16 mg/kg, the absorption, excretion and metabolism of bromperidol-3H, an analogue of the neuroleptic haloperidol, were studied in dogs. In rats, the tissue distribution, excretion and metabolism were followed.

Plasma levels of unchanged bromperidol in the dog were maximal 4-7 hours after dosing and corresponded to 4 ng/ml. Afterwards, elimination of intact drug was biphasic with a terminal half-life of approximately 30 hours. Levels of radioactivity decreased more slowly, probably due to the presence of tritiated water in the plasma.

The radioactivity in the urine of both rats (35% of the dose) and dogs (46% of the dose within 4 days) consisted mainly of polar acidic metabolites. Inverse isotope dilution demonstrated that the polar urinary fraction was due to the glycine conjugate of p-fluorophenylacetic acid almost completely in the rat but only partly in the dog. Unchanged bromperidol was present in trace amounts in the urine, and only 10% of the dose was excreted with the faeces for both rats and dogs. Oxidative N-dealkylation was the major metabolic pathway in both species and the fate of bromperidol was similar to that of haloperidol.

INTRODUCTION

Bromperidol (R 11 333) is the bromo-analogue of haloperidol, the prototype of the neuroleptics belonging to the butyrophenone series (Figure 1). Although the excretion and metabolism of haloperidol are well documented (1-4), the fate of bromperidol has been reported only in rats after subcutaneous administration. A close resemblance to the metabolic disposition of haloperidol was obvious (1).

This paper deals with the pharmacokinetics of bromperidol in rats and dogs after single oral doses of the tritium-labelled drug.

TECHNIQUES AND METHODS

The structure of tritium-labelled bromperidol (5) is shown in Figure 1. The specific activity of the drug was 154 microcuries/mg and the radiochemical purity was above 98%, as demonstrated by thin-layer chromatography (TLC).

Send reprint requests to: Dr. J. HEYKANTS, Janssen Pharmaceutica, V-2340 Beerse, Belgium.

Fig. 1. - Structures of bromperidol (R 11 333) and haloperidol: T denotes the position of the tritium label in bromperidol-3H.

R = Cl : haloperidol
R = Br : bromperidol (R 11333)

Experiments with rats

Two groups of five male Wistar rats (240-260 g) were kept in metabolism cages. After an overnight fast, each rat received by gastric intubation a dose of 0.16 mg/kg, provided in 2.5 ml of 0.01 M tartaric acid (0.016 mg bromperidol-3H/ml). Rats were allowed access to food two hours after drug administration.

Urine and faeces were collected separately for up to 48 (group I) and 96 hours (group II). At those times, the
animals were sacrificed for the determination of residual radioactivity in some organs and tissues.

Experiments with dogs

Three female Beagle dogs (15.0 ± 3.5 kg) were kept in individual metabolism cages. After an overnight fast, each dog received a dose of 0.16 mg/kg by stomach tube (0.32 mg bromperidol·H/ml). Dogs were allowed access to food and water four hours after drug administration. From each dog 10 ml of blood were drawn in heparinized containers from the jugular vein at various time intervals from 1 to 96 hours after dosing. Urine and faeces (only from dog I) were collected up to 96 hours after drug administration.

Radiochemical and analytical methods

- Aliquots (0.2 ml) of the plasma and urine samples were diluted with 0.8 ml of water and mixed with 10 ml of Instagel® (Packard). Faeces were homogenized (1/8, w/v) in methanol using an Ultra-Turrax TP 18/2 homogenizer. The radioactivity in 0.2 ml aliquots was determined after combustion in a Packard Sample Oxidizer (Model 306). Faeces extracts were prepared by three consecutive extractions with methanol. The residual amounts of radioactive material in rat organs and tissues were assayed as previously described (6). The radioactivity in the samples was measured by liquid scintillation spectrometry using external standardization. (Packard Tri-Carb, Model 3380, equipped with an absolute activity analyzer 544).

- The nature of the radioactive compounds in the excreta of both rats and dogs was investigated by liquid-liquid extraction, following the extraction scheme presented in Figure 2. Possible glucuronides in the urine were hydrolyzed with 1300 Fishman units of β-glucuronidase per millilitre of acetate-buffered urine at pH 5.0 for 24 hours at 37°C (Sigma G-0876, Type H-2).

- Unchanged bromperidol and some expected metabolites were estimated by inverse isotope dilution. Unlabelled bromperidol (250 mg) was dissolved in 10 ml of methanol and added to 1 ml of the urine samples or to 10 ml of the methanolic faeces extracts.

![Image of extraction scheme](image-url)

**Fig. 2.** Extraction scheme for the investigation of the nature of the radioactive compounds in the urine.