The absorption and distribution of isopropamide iodide in the rat

In our continuing investigations of drugs that are absorbed as the charged molecular species (Fiese & Perrin, 1969; Perrin & Vallner, 1970) we have recently conducted preliminary studies on the absorption and distribution of the monoquaternary ammonium compound, isopropamide iodide in the rat. As much as 40% of a dose placed directly into the duodenum was absorbed within 1 h and a mydriatic effect was noticed within 15 min. None of the drug, however, could be detected in the blood, and after an intravenous injection, no drug was found in the blood when samples were taken at 5, 10, 15, and 30 min, even though a mydriatic response was observed in less than 30 s. Tissue samples were taken and significant levels of drug were found only in the liver and kidneys.

Male albino rats (12) (300–350 g) were fasted overnight before being used for the intestinal absorption studies. After the animals had been anaesthetized with sodium pentobarbitone (35 mg kg^{-1}, i.p.), a midline abdominal incision was made and the duodenum exposed. Isopropamide iodide (Smith, Kline and French Laboratories, Philadelphia, PA) spiked with its [^{14}C]isotope was injected directly into doubly ligated duodenal segments. Solutions of 1×10^{-3}M isopropamide iodide were prepared in pH 6·6 sodium phosphate isotonic buffer and a total of 1·0 ml was injected.

Whole blood was withdrawn (0·5 ml) by cardiac puncture at intervals of from 5 to 60 min, digested, and decolourized using 1·0 ml of Soluene (Packard) and 0·5 ml of 30% hydrogen peroxide respectively, the process being carried out at 20° for 30 min. The samples were then counted by liquid scintillation. The efficiency for the samples was approximately 30%; colour quenching by the blood resulted in a 25% decrease in the counting rate.

Intestinal absorption was determined by calculating the amount of drug that disappeared from the tied-off loop after 1 h. Correction was made for the amount of drug (%) bound to the mucosa; no intraluminal dilution of the drug occurred. Results obtained indicated that the net amount absorbed within 1 h was slightly more than 40% of the administered dose.

Blood samples taken at intervals during the 1 h absorption period indicated that no radioactivity was present above a background level. Further studies were therefore made by injecting six rats (300–350 g) with [^{14}C]isopropamide iodide (0·1 μCi) intravenously via the tail vein and blood samples taken at 5, 10, 15, and 30 min. A mydriatic response was seen in less than 30 s.

The rats given intravenous isopropamide iodide were killed and tissue samples were assayed. No significant quantities of drug were found in the blood, skeletal muscle, fat, gastrointestinal tissue, or the eye. Large amounts were found in the liver and kidney.

Isopropamide thus appears to be rapidly and effectively removed from the blood by the liver and kidneys. The pharmacological response to this drug is sustained and this may mean that the liver acts as a storage depot for the drug or that the drug is slowly metabolized in the liver and that the metabolite is pharmacologically active.

Similar observations of concentration in the liver have been made when other quaternary ammonium compounds such as oxyphenonium (Levine & Clark, 1957), procainamide ethobromide (Meijer, Bos, & VandeLaan, 1970), decamethonium (Christensen & Holm, 1969), and various tropane alkaloid compounds (Albanus, Sundwall & Vangbo, 1969; Echigoya, Matsumoto & others, 1972) were used. The bisquaternary compound hexafluorenium has been reported by Meijer, Vermeer, & Kwant (1971) to have an initial plasma half-life of 15 min and a secondary longer half-life of 240 min, indicating tissue storage or binding. Not all quaternary am-

monium compounds show this rapid clearance and storage phenomena; for example, neostigmine after oral administration is absorbed slowly and to the extent of about 50%, and blood levels of radio-labelled drug are readily detectable (Roberts, Thomas & Wilson, 1966).

These observations suggest that quaternary ammonium compounds behaving like isopropamide should, in pharmacokinetic terms, be regarded as having the liver as an extravascular compartment, and due attention should be paid to the first-pass effect (Gibaldi & Feldman, 1972).

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October 9, 1972

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Footnote:

Whilst this note was in the press, D. J. Back and T. N. Calvey (*Br. J. Pharmac.*, 1972, **46**, 355-357) have shown that edrophonium is cleared from the blood in a manner similar to that reported above for isopropamide.

Stereospecific requirements for hallucinogenesis

Although many of the known hallucinogens possess centres of optical assymetry, in most cases they have been evaluated only in their racemic state. An exception is the highly potent psychotomimetic (+)-LSD, which has two assymetric centres. The absolute configuration about each has been established (Leemann & Fabbri, 1959) as 5-*R*; 8-*R* (I). Two diastereoisomeric diethyllysergamides exist with the opposite configuration at C5; vis., (−)-LSD (5-*S*; 8-*S*) and (−)-isoLSD (5-*S*; 8-*R*). Both are reported to be without hallucinogenic effect in man (Rothlin, 1957).

Many optically active stimulants and anorexogenic agents are of established absolute configuration, and when compared with the phenyl-C_{10}-C_5-N_6 chain of (+)-LSD are of the opposite, or *S* configuration. Examples are (+)-amphetamine III (Karrer & Ehrhardt, 1951) and (−)-ephedrine (Portoghese, 1967). Both (+)-benzphetamine and (+)-phendimetrazine may be derived from the above compounds and so maintain this configuration.

A number of compounds chemically related to the phenethylamines resemble (+)-LSD in their pharmacology (Shulgin, Sargent & Naranjo, 1969). These substances are α-methylphenethylamines and have an assymetric carbon centre analogous