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Bioavailability of the quaternary ammonium compound thiazinamium methylsulphate (Multergan) after oral and intramuscular administration

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Thiazinamium methylsulphate is a phenothiazine derivative with a quaternary ammonium group and is used against bronchial asthma because of its anticholinergic and antihistamine properties. Although on the market since the early sixties, biopharmaceutic and pharmacokinetic data on this drug are almost completely lacking (Multergan, Note technique, 1961).

Because some recent clinical observations raised doubt about the efficacy of oral thiazinamium therapy and because in general the absorption after oral administration of quaternary ammonium compounds is poor, (Levine, Blair & Clark, 1955; Levine, 1966) we decided to study the bioavailability of the drug after oral and intramuscular administration in man.

We first developed a sensitive and specific method for the determination of the drug in biological fluids. It is based on ion-pair extraction (Schill, Modin & Persson, 1965; Persson & Schill, 1966) with iodide as counter-ion, followed by gas-chromatography of the extract utilizing an alkali flame ionization detector, sensitive for nitrogen (Donike, Jaenicke & others, 1970; Goudie & Burnett, 1973). The detection limit was 2 ng ml^{-1} plasma, whereas accurate quantitation can be done at levels of 20 ng ml^{-1} and up. Recovery was 83% $\pm$ 6·8 s.d. (n = 17).

Bioavailability studies were done in outpatients of the Clinic for Lung Diseases of the University Hospital. After intramuscular injection of 25 mg thiazinamium methylsulphate in 1 ml aqueous solution the drug is taken up in the blood very rapidly. Within 6 min a rather high maximum appears in the plasma-concentration-curve, followed by a rapid decline during the next 10–20 min. This portion of the curve resembles that of an intravenous injection. Then a second maximum is reached between 20 and 30 min after injection, followed by a decline at a much slower rate. The shape of the latter part of the curve is more typical for an i.m. injection. These observations may be explained by the fact that the quaternary ammonium compound is very water-soluble, resulting in a rapid uptake by the bloodstream of at least part of the dose. It indicates that one has to be careful in establishing the i.m. dose of such compounds because the high plasma levels shortly after injection may cause unwanted side effects (tachycardia).

Bioavailability studies after oral administration were done twice, with doses of 300 mg and 900 mg respectively (Multergan-forte tablets). Plasma levels were determined and the areas under the curve were compared with those after i.m. injection. In both cases (300 and 900 mg) the relative bioavailability after oral administration as compared to i.m. injection was only 2–3% (corrected for the dose). This indicates a rather poor and passive absorption process of the drug so that it may be difficult to establish an optimal oral thiazinamium therapy.

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