Biopharmaceutics of rectal administration of drugs in man

6. Absorption rate and bioavailability of acetylsalicylic acid and its calcium salt after oral and rectal administration


ABSTRACT
Rectal absorption of acetylsalicylic acid and its calcium salt was studied in man and compared with oral absorption.

Plasma concentrations of acetylsalicylic acid and salicylic acid were measured by means of HPLC analysis, after a single dose of acetylsalicylic acid (500 mg) and after single rectal doses of acetylsalicylic acid (500 mg) and calcium acetylsalicylate (640 mg) in a cross-over study in 8 volunteers. The rectal dosage forms included fatty suppositories and aqueous solutions.

Compared with oral administration rectal absorption of acetylsalicylic acid can be equally rapid, if the volume and the pH of the aqueous micro-enema was optimized (20 ml, pH 4.0). Rectal absorption of calcium acetylsalicylate occurred very slowly. If fatty suppositories were used smaller particles favoured the rate of acetylsalicylic acid absorption. Compared with oral administration absorption from the optimized suppository dosage form proceeded significantly (P < 0.05) slower. For all rectal dosage forms, the extent to which acetylsalicylic acid reached the general circulation intact, was smaller than after oral administration.


INTRODUCTION
The clinical importance of acetylsalicylic acid as an effective mild analgesic has led to numerous studies concerning pharmacokinetics in man (SMITH and SMITH 1966; ROWLAND and RIEGELMAN 1968; VAN GINNEKEN 1976). The plasma concentration-time curve of acetylsalicylic acid after intravenous administration of 650 mg acetylsalicylic acid was described by a bi-exponential equation. The half-life for the rapid component was 2-5 min, while that of the second component ranged from 13-19 min. The average total body plasma clearance in man was 650 ml/min, while the apparent volume of distribution was found to be less than 10 l (ROWLAND and RIEGELMAN 1968).

After a single oral dose of 650 mg acetylsalicylic acid, dissolved in 250 ml of water, absorption was reported to be rapid and complete. Peak plasma levels of acetylsalicylic acid were reached within 20 min (ROWLAND et al. 1972). These levels then declined rapidly, with only small amounts remaining after 2 h. Plasma levels of the metabolite salicylate rose rapidly and exceeded those of acetylsalicylic acid because of slower elimination rather than differences in distribution (ROWLAND and RIEGELMAN 1968). Maximal plasma levels were reached after about 60 min. The elimination half-life of salicylic acid was about 2.5 h and the volume of distribution was smaller than 10 l (VAN GINNEKEN 1976). Comparison of the area under the acetylsalicylic acid plasma concentration-time curve following intravenous and oral routes indicated that only 68 percent of the oral dose reached the circulation intact. Since the area under the salicylic acid curve was the same following either route of admin-

1In honour of Professor POLDERMAN on the occasion of his retirement.
istration, excluding incomplete absorption from the gastro-intestinal (gi) tract, first pass metabolism by liver or gut wall was supposed to occur (ROWLAND et al. 1967).

Rectal absorption of acetylsalicylic acid has only been evaluated monitoring plasma or urine concentrations of the metabolite salicylate. The influence of the chemical composition of the suppository vehicle on the in vitro release and the in vivo absorption has been studied by many workers (CACCHILO and HASSSLER 1954; SAMELIUS and ÄSTRÖM 1958; NEUWALD and KUNZE 1964; LOWENTHAL et al. 1970; GIBALDI and GRUNDHOFER 1975). In general it was concluded that the composition of the fatty bases was only of secondary importance in vivo, in contrast to the laboratory in vitro tests. Particle size reduction of acetylsalicylic acid did increase the absorption rate (CID 1974; PARROT 1975), although the underlying mechanism of this phenomenon was not established. LOWENTHAL et al. (1970) found that, in accordance with the results of NEUWALD and KUNZE (1964), absorption of acetylsalicylic acid and calcium carbamiprin (a soluble complex of calcium acetylsalicylate with urea, Ascal®) followed similar patterns. When compared with oral administration of an equal dose of acetylsalicylic acid, rectal absorption was reported to be slower (COLDWELL et al. 1969; GIBALDI and GRUNDHOFER 1975; SUPERSTINE et al. 1978), or equally fast (CACCHILO and HASSSLER 1954; SAMELIUS and ÄSTRÖM 1958; PARROT 1971). However, the formulation of the rectal dosage forms used in these studies was rather different and acetylsalicylic acid concentrations in plasma were not measured. No distinction was made between the release from the dosage form and the rectal absorption process, and consequently it remained uncertain whether one of the two processes was rate determining.

The aim of our study was to establish the character of the rectal absorption process of acetylsalicylic acid, by measuring plasma concentrations of acetylsalicylic acid and salicylic acid, in volunteers. In addition rectal absorption of the watersoluble calcium salt was studied. For comparison an orally administered solution of acetylsalicylic acid in water was included.

EXPERIMENTAL

Dosage forms
Acetylsalicylic acid (USP XIX, Aldrich) and calcium acetylsalicylate (Ascal®, ACF Chemiefarma nv) were used.

A coarse (125-250 μm) fraction of acetylsalicylic acid and calcium acetylsalicylate was separated by sieving (Alpine model A 200 LS). A micronised (<20 μm) fraction was prepared by grinding the material in a jet mill. The powders were mixed with a molten base Witepsol H 15 (Interpharm), poured into brass moulds (3 ml) and stored in the refrigerator for at least one night before use. The weight of the suppositories was adjusted exactly to 2.8 g, and they contained 17.14 % w/w acetylsalicylic acid (500 mg) or 22.85 % w/w calcium acetylsalicylate (640 mg).

An acid micro-enema was prepared, containing 500 mg of micronised (<20 μm) acetylsalicylic acid, suspended in 10 ml of a medium, containing 0.5% methylcellulose 400 cP (Ned. Pharm. Ed. vt) in citrate/phosphate buffer (pH = 4.0). The buffer was prepared by dissolving 12.6 g citric acid monohydrate (Merck p.a.) and 28.6 g disodium hydrogen phosphate 12-hydrate (Merck p.a.) in 1000 ml of distilled water. A neutral micro-enema was prepared by dissolving 500 mg of acetylsalicylic acid in 10 ml of a medium, containing 0.5% methylcellulose 400 cP in distilled water. The latter solution was prepared with the aid of 1.312 g sodium hydrogencarbonate (Merck p.a.) and 0.933 g citric acid monohydrate. The pH of this micro-enema was 7.0.

A micro-enema containing 640 mg calcium acetylsalicylate was prepared by dissolving the compound in 10 ml of medium, which consisted of 0.5% methylcellulose 400 cP in distilled water. The pH of the solution was adjusted to pH 7.0 using a 0.1 M solution of sodium hydroxide. The oral dosage form was a 200 ml aqueous solution, containing 500 mg of acetylsalicylic acid.

In vitro determinations
The release of acetylsalicylic acid and calcium acetylsalicylate from the fatty dosage forms at 37°C was determined using a release apparatus with a fixed lipid/water contact area, described by SCHOOENEN et al. (1979). The results are mean values of four runs.

Human experiments
Eight healthy human subjects, female and male, ranging in age from 23-37 years and in body weight from 55-70 kg, participated in the cross-over study at 2-week intervals over a period of 3 months. No drugs were taken prior or during the study. The experiments were initiated in the morning and the volunteers did not take any food during the experiments. They were asked to remain in a sitting