Biopharmaceutics of rectal administration of drugs in man

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SUMMARY

These investigations in man described in this thesis were designed to study the factors responsible for the transport of drugs from rectal dosage forms into the rectum lumen. This was performed by determining their absorption profile measuring plasma concentrations and/or the urinary excretion rates.

In paper 1 sodium benzoate and benzoic acid are introduced as test drugs to study the biopharmaceutics of rectally administered dosage forms in man by measuring benzoate and hippurate concentrations in urine or plasma. After rectal administration of sodium benzoate in solution form, absorption was fast and complete. In appeared that the driving force in absorption is the concentration used in the micro-enema. Compared with oral administration the extent of absorption was about the same, however the pH in the rectal lumen and the limited absorption surface in the rectum may limit the rate of benzoate absorption.

After rectal administration only negligible amounts of unchanged benzoate could be detected in plasma and urine, indicating that the supposed advantage of the rectal route to bypass the liver is doubtful.

Paper 2 describes the influence of some physiocochemical parameters on the rate and extent of benzoate absorption from fatty suppositories in man. It appeared that depending on the water solubility of the drug the rate of absorption is strongly affected by particle size of the drugs under study. In the case of the water soluble sodium benzoate particles, particle size reduction reduced release rate from the suppository and also absorption rate, whereas in case of benzoic acid, which is slightly soluble in water, there was no such effect.

It was suggested that the pressure of the rectum wall promotes the spreading of the suppository, and that the resulting spreading of drug particles favours the absorption process. Benzoic acid was absorbed from a fatty base more rapidly and with less inter-individual variation than its sodium salt.

Dependent on whether the drug was suspended in the form of single crystals or was present as aggregates of very fine particles, the chemical composition of the fatty vehicle used might also influence the release rate and consequently the absorption rate in man.

These parameters, which may largely influence the release rate from rectal dosage forms, were studied by using some analgesics and anti-epileptic drugs with different physicochemical properties.

Paper 3 deals with the rate and extent of rectal absorption of paracetamol from aqueous dosage forms. Compared with oral administration rectal absorption could be equally rapid, but this depended on the volume of the administered suspension. This volume effect was probably related to differences in absorption surface involved in the rectal absorption process after administration of this dosage form.

Probably due to the limited water solubility of paracetamol, no substantial difference in absorption rate occurred when different amounts of paracetamol were rectally administered in the same volume of aqueous dosage form. The pH of the micro-enema turned out not to be a critical factor with respect to the uptake rate of paracetamol, in line with the consideration that the pK_a of paracetamol is high relative to the prevailing pH in the rectum lumen. Relative bioavailabiliy was found to be in the same range for the oral and rectal route of administration. The possibility that first pass metabolism in the liver is dependent upon the rate of uptake of paracetamol from the gastrointestinal tract and consequently differences in absorption rate may result in the unequal bioavailability was hypothetised.

Paper 4 shows that rectal absorption rate of paracetamol, suspended in fatty suppositories, is markedly increased by particle size reduction of the drug.

Although reduction in particle size had only a small influence on the *in vitro* release rate of paracetamol, *in vivo* small particles may, due to the pressure of the rectum wall, be spreaded over a larger part of the lipid/water interface than large ones, thereby influencing the release surface and consequently the rate and extent of paracetamol absorption. It was concluded that agglomeration of paracetamol particles in the fatty base was not a relevant phenomenon for the *in vivo* release of paracetamol from suppositories. In view of the similar plasma concentration profile of paracetamol after administration of suppositories prepared with Witepsol H 15 or Cocoa butter, it was suggested that in contrast to the *in vitro* situation no essential differences in spreading occurred during the absorption process *in vivo*. In agreement with the studies on rectal administration of aqueous suspensions (paper 3) rectal absorption rate of paracetamol was dependent on the volume of fatty vehicle, rather than on the suppository concentration of the drug used.

Paper 5 reports on the absorption rate and bioavailability of glafenine after rectal and oral administration. After oral administration only negligible plasma concentrations of free glafenine could be detected, probably due to a substantial first pass effect. Peak concentrations of the main metabolite glafenic acid were reached within one hour after administration. The plasma concentration profile indicated that glafenic acid kinetics are more complicated than previously supposed.
Rectal absorption of glafenine occurred very slow, probably since the water solubility of the drug at the prevailing pH in the rectal lumen is extremely poor (1 in 60.000). After oral administration glafenine may become protonated in the relative acid medium of stomach and duodenum, resulting in sufficient dissolution rate for absorption.

Paper 6 underlines the importance of the pH of an aqueous rectal dosage form, in relation to the pK_a of the drug used: after rectal administration of acetylsalicylic acid it appeared that the rate of acetylsalicylic acid uptake from a micro-enema (10 ml) with pH 4.0 was significantly more rapid than from a micro-enema (10 ml) with pH 7.0. In accordance with this observation rectal absorption of calcium acetylsalicylate was very slow.

If a volume of 20 ml of the acid micro-enema was used, the resulting plasma concentration-time curve of acetylsalicylate was similar to the one after oral administration of a solution of the drug under study. In the case of fatty suppositories the use of smaller particles favoured the rate of acetylsalicylic acid absorption. However, absorption proceeded significantly slower compared with oral administration. It was concluded that the volume of the fatty vehicle in which acetylsalicylic acid is suspended, rather than the concentration of the drug under study, determines absorption rate.
For all rectal dosage forms the extent to which acetylsalicylic acid reached the general circulation intact, was smaller than after administration of the oral dosage form.
Paper 7 deals with the absorption rate and bioavailability of phenobarbital and its sodium salt after rectal and oral administration. In the case of the rectally administered aqueous dosage forms of phenobarbital no distinct difference in absorption rate occurred whether the sodium salt or the free acid was used.
Compared with the oral route of administration, rate of uptake from the micro-enemas was slower; in the case of the sodium salt the rate of uptake is probably limited as the result of dissociation of the drug in the rectum lumen. On the other hand rectal absorption of the free acid is probably dissolution rate limited.
If fatty suppositories were used, the rate of absorption of the sodium salt was equally fast and the absorption rate of the free acid much slower compared with the corresponding aqueous rectal dosage forms.

The in vitro release of phenobarbital from fatty suppositories using a coarse powder (125-250 µm) of sodium phenobarbital and with a fine powder (<20 µm) of phenobarbital showed marked differences. The rectal absorption profile of the aqueous and fatty dosage forms of sodium phenobarbital in vivo was quite similar. A much slower absorption rate and a relatively large intersubject variation was found for the suppository with the fine particles of phenobarbital.

Paper 8 shows that absorption of sodium valproate from an aqueous micro-enema is complete and not much slower than after oral administration. From fatty suppositories the free acid was absorbed more rapidly than its sodium salt. It is concluded that in spite of a higher concentration of the sodium salt in the rectum fluid, due to a fast release, the pH conditions are less favourable than after application of the free acid dosage form and consequently a rapid release *in vitro* is not reflected in rapid absorption *in vivo*. Rectal absorption rate of the free acid increased with the dose of the drug, dissolved in the fatty vehicle. It is concluded that the viscosity of the fatty mass is not a relevant factor for the *in vivo* release of valproic acid from suppositories, stressing the importance of the rectal wall pressure. It was suggested that this pressure in the rectum lumen is variable, being dependent on the body position of the human subject. If spreading is important the absorption process may be more irregular in human subjects in lying position compared with sitting position.