Pharmacokinetic study on the mechanisms of rectal absorption in man.
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1985

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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SUMMARY

This pharmacokinetic study in man was aimed to investigate the mechanisms of rectal absorption, as well as the factors that may influence this process, in a quantitative way. In order to be able to perform the study a rectal perfusion apparatus was developed, which is described in Chapter I.

With this apparatus a well defined area of the human rectal mucosa can be perfused under single-pass and recirculation conditions. With sodium benzoate as a test drug it was shown that very reproducible absorption values per unit area (μg.min⁻¹.cm⁻²) could be obtained in one subject. After absorption, sodium benzoate is immediately conjugated with glycine to give hippuric acid which is rapidly eliminated (t½ = 0.5 hr). By intravenous injection of hippurate, total body clearance (Cl) was determined in each individual. Rectal perfusion with benzoate was maintained until the steady state plasma concentration (Cₘ) was reached. In steady state the rate of absorption is equal to the rate of elimination (Cl x Cₘ). By measuring the steady state plasma concentration of hippuric acid by HPLC, and knowing the individual clearance value and absorption surface of the rectum, the absorption influx of sodium benzoate per unit area could accordingly be calculated (μg.min⁻¹.cm⁻²). With recirculation perfusion experiments it could be shown that the amount of sodium benzoate which disappeared from the perfusion solution, equaled the amount of benzoic acid that was calculated to be absorbed. Therefore it is concluded that the experimental set-up enables monitoring as well as manipulation of the absorptive conditions in the rectal lumen. From single-pass perfusion experiments in four volunteers, a linear relationship between the concentration of sodium benzoate and the rectal absorption was found. This indicates that absorption probably occurs according to the mechanism of passive diffusion.

One of the characteristics of the passive diffusion absorption process is the influence of the pH-value. Chapter II deals with the study on the influence of the pH on the rectal
absorption of sodium benzoate in man. On successive occasions
three volunteers have been perfused with a sodium benzoate
solution with different pH-values, ranging from pH = 4.2 to
pH = 10.2. The solutions used were either buffered or adjus-
ted to the chosen pH with hydrochloric acid or sodium hydros-
xide. The curves relating the absorption rate of benzoic acid
(\( t_{in} \)) to the pH of rectal perfusion fluid showed two interes-
ting phenomena.

First, although the perfusion experiments had been perfor-
med under single-pass conditions, which means that the offe-
red luminal pH remained constant, a difference was seen in
the absorption rate from the buffered and the non-buffered so-
dium benzoate solutions in the acid region. Because the buffer-
components themselves did not alter the membrane absorption
characteristics (see also Chapter II), this difference was
concluded to be the result of the buffer capacity of the per-
fusion system employed. This implies that the pH of the un-
buffered solutions at the absorptive site can be easily effec-
ted \( \text{in vivo}, \) due to an activity of the rectal mucosa.

Secondly, the relation between the absorption rate and pH-
value showed that in addition to a pH-dependent absorption
of benzoic acid, also a pH-independent component in the total
absorption of benzoic acid seems to be present. This observa-
tion indicated absorption of the anionic form of benzoic acid.
Although rectal absorption of such charged molecules can still
be explained by reversing of the dissociation of benzoic acid
at the mucosal membrane, this latter phenomenon can also be
due to other absorption mechanisms, such as carrier-mediated
or paracellular transport.

With respect to the pH-dependent absorption process, the
experimental data deviated from the pattern that can be anti-
cipated on the basis of the dissociation of benzoic acid and
permeation of the uncharged (lipid soluble) form. Successive
\textit{in vitro} experiments, in which the transport rate of benzoic
acid from an aqueous phase to an organic solvent was studied,
showed that such deviations could be explained by an altera-
tion of the aqueous diffusion layer at the aqueous/lipid in-
terface of such a partition system or alternatively to an
altered partition coefficient induced by the buffer components. These factors may add to the influence of a pH-value at the membrane surface which deviates from the luminal pH, a phenomenon that even occurred despite the use of buffer solutions.

In view of these results, it was of interest to investigate what the influence would be of the buffer composition as well as the buffer capacity on the rectal absorption process. This study is described in Chapter III. On successive occasions three volunteers were perfused each under single-pass conditions with a sodium benzoate solution, adjusted to pH = 5.2 with hydrochloric acid, citrate-phosphate and acetate buffer respectively. Because most of the buffered solutions used were not isotonic, control experiments were performed in order to exclude any influence of hypotonic or hypertonic properties on the absorption rate of sodium benzoate. No influence of tonicity was found for the buffer solutions of various composition used in this study. In accordance with the results of Chapter II, the data on the influence of buffer composition and buffer capacity on the rectal absorption rate of benzoate showed that the absorption rate was enhanced considerably in the case of using a buffer solution instead of a nonbuffered solution. In addition it was shown that it is the buffer capacity rather than the buffer composition of the solutions that determines this effect.

Apart from the buffer capacity of the perfusion solution used, a possible buffering activity of the human rectum itself may greatly influence the absorption process. Therefore a study was performed in order to determine this supposed buffering activity of the human rectum in a quantitative manner (Chapter IV). Six volunteers were perfused under recirculation conditions according to the pH-stat method, which enabled to maintain the pH-value constant by means of titration which either acid or alkali during time of the experiment. The amount of acid or alkali necessary to maintain the pH constant was assumed to correspond with the amount of alkalization or acidification activity of the rectal wall. The change in composition of the perfusate with regard to the electrolytes K⁺, Na⁺, Cl⁻ and HCO₃⁻ was detected by measurements of the ions, before and after
the experiment. First, recirculation perfusion experiments were performed without titration, in order to record the changes of the pH in the acid and alkaline perfusions respectively. From the results it was concluded, that neutralization by the human rectum actually occurs both in the case of the acidified as well as in the alkalized solution. Subsequently perfusion experiments were done in order to determine the alkaline secretion more quantitatively. The results, obtained in five subjects, showed that alkaline secretion is extensive and that this process can be stimulated by H+ as well as Cl- ions. Direct evidence was found, that at least part of this alkalizing activity is the result of HCO3- secretion. In addition to the alkaline secretion measurements, also the acid secretion by the human rectum was determined quantitatively in three subjects. This process is very likely the result of H+ secretion and was shown to be dependent on the extent of pH-deviation. The data indicated that this process is stimulated by Na+ ions. In the future it would be of great interest to investigate whether the alkaline and acid secretion process in the human rectum can be manipulated by pharmacologically active agents in order to enhance rectal absorption of pH-sensitive drugs.

Finally Chapter V deals with a preliminary study on the pH-independent absorption of sodium benzoate in man. An attempt was made to determine whether this pH-independent absorption of sodium benzoate is the result of paracellular ("pore") or carrier-mediated transport. The properties of such processes were considered. Two characteristics of carrier-mediated transport, namely saturability and competition, were studied in three and two subjects respectively. In order to investigate whether the absorption is saturable, three volunteers were perfused with solutions, consisting of increasing concentrations of sodium benzoate at a pH = 9.2. At this pH the dissociation of benzoic acid is essentially complete. A linear relationship between \( \phi_{in} \) and the benzoate concentration was found, which argues against a carrier-mediated transport. Subsequently inhibition experiments in two subjects have been performed with probenecid, as a classical competitive inhibitor of organic acid transport and having a closely related
structure to benzoate. However, again no effect was observed. Although from these results no definite conclusions could be drawn, absorption of the ionized benzoate by the human rectum via paracellular routes was tentatively assumed to be the most likely mechanism. Further studies have to be performed in order to investigate how substantial paracellular transport of drugs actually is in the rectal mucosa.

The absorption studies described in this thesis may contribute to a better insight in the mechanism of drug transport across the rectal wall in man, with special reference to the aspect of the micro-climate of the mucosal surface in the rectal lumen. Future biopharmaceutical studies should be planned to integrate this knowledge in the rational design of rectal dosage forms for drugs. The final aim of such studies should be to obtain a programmable and reproducible absorption profile for various classes of drugs after rectal administration to patients.