The gastrointestinal absorption of drugs in man: a review of current concepts and methods of investigation

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1 The various mechanisms which have been advanced to explain drug absorption are critically reviewed and the limitations of current theories are discussed.

2 Various techniques for investigating drug absorption and transit through the gut are presented, and the results obtained with metoprolol are briefly considered to illustrate the potential of some of these methods.

Keywords gastrointestinal absorption transit time metoprolol

Introduction

The absorption of drugs is a complex process, or more accurately, a combination or succession of complicated processes. After oral administration, the drug leaves the dosage formulation and dissolves in the aqueous digestive fluids. It reaches and crosses the gastrointestinal (GI) mucosal membrane before passing into blood. Simultaneously, drug in solution or in solid form moves along the GI tract with the luminal content at a variable speed. The absorption process itself is influenced by the nature and surface area of the GI mucosal membrane, which varies from the stomach to the rectum, and by the physicochemical properties of the luminal content.

Considerations of GI tract anatomy and the physiology of digestion led to the widely held view that drug absorption occurred primarily from the upper segments of the gut (the duodenum and jejunum). This belief was formalized in the concept of an 'absorption window', which was often postulated in the absence of convincing experimental evidence for its existence. Another common assumption was that absorption was a first-order process, thus allowing plasma concentration data to be analysed using pharmacokinetic models in which absorption was described by a single rate constant and half-life. The absorption mechanism itself continues to be described in terms of a simple pH partition hypothesis, in which absorption is governed by the position of the equilibrium between ionized and non-ionized forms of the drug at the different physiological pH values encountered in the GI tract.

In recent years, the factors which influence and limit drug absorption have received greater attention (Prescott & Nimmo, 1981). Pharmaceutical research is becoming progressively more orientated towards the development of special dosage formulations which release drug slowly throughout the GI tract. However, the pharmacological activity of novel drugs may be restricted by their inability to be absorbed from the GI tract. This review will consider the physiological aspects of drug absorption from the GI tract and will outline experimental techniques for its investigation. It will also attempt to summarize current views on the mechanisms involved.

Physiological aspects*

Gastric emptying

Relatively few drugs are believed to be absorbed from the stomach (Gibaldi, 1981). Most are retained there temporarily, largely in solution, and are progressively delivered to the small intestine where they are absorbed. For this reason gastric emptying is a critical factor in drug absorption.

*The author is indebted to Professor J. J. Bernier (Paris) for information on several of the topics discussed in this section, which are presented extensively in his book *Physiologie de la Digestion chez l'Homme normal et l'Opéré du tube digestif*. Doin Editeur, Paris, 1980.

Liquid is emptied through the pylorus at a rate which is proportional to the volume remaining in the stomach. This constitutes a first-order process which can be characterized by a single half-life value. In one study, a mean of 33 min (range 20–55) was reported in 14 healthy subjects who received a meal of cornflakes and milk (Heading *et al.*, 1971). In another study (Jian *et al.*, 1979) a half-life of 54 min (range 30–89) was estimated for liquid-phase emptying in 15 healthy subjects who received a 'normal' lunch. After a composite meal, various food components were shown to empty at different rates (Johansson, 1973); the half-life was around 23 min for carbohydrates, 32 min for proteins, 40 min for water, and as much as 87 min for lipids. The latter float on the surface of the gastric contents, and pass through the pylorus only after the main part of the meal has been emptied. Many drugs are very lipophilic in their non-ionized form and probably would dissolve in this lipid layer if administered during or after a meal. Such a mechanism could partly explain the time lag in absorption often observed when drugs are given together with food (Melandar, 1978).

When a drug is given in a solid dosage formulation that does not disintegrate in the gastric medium, it may remain in the stomach for a variable but extended length of time. Experiments in which solid and liquid phases of a meal were labelled separately with different radio-isotopes (Jian *et al.*, 1979) revealed that liquids are emptied more rapidly than solids. Other investigations (Malagelada, 1977) suggest a screening effect of the pylorus for solid particles larger than approximately 2 mm. This process is more efficient shortly after food intake but is never 100% efficient so that larger solids may occasionally be emptied soon after a meal. The retention of objects larger than 2 mm may be of considerable significance when enteric-coated or sustained-release tablets are administered with food.

The gastric emptying of drugs, as opposed to food, has been investigated only to a limited extent. In one of the relatively few experiments which have been performed, paracetamol was administered together with a non-absorbable isotopic marker (Clements *et al.*, 1978). Gastric emptying was followed by external scintigraphy, and plasma concentrations of paracetamol were measured simultaneously. Assessments were performed under normal conditions and when narcotic analgesics had been pre-administered. In all cases the plasma concentration profiles were closely related to the emptying pattern, indicating that this is the rate-limiting factor in the absorption of paracetamol.

Indirect evidence of the importance of gastric emptying on the rate of drug absorption has also been provided by studies on the influence of various factors such as concurrent drug treatment on both emptying and absorption (Nimmo, 1976).

In recent years our Research Centre, in collaboration with others, has been involved in the direct measurement of the gastric emptying of metoprolol, a β -adrenoceptor antagonist, in healthy volunteers. The drug was dissolved in a homogenized normal meal and administered together with a non-absorbable marker which permitted volume changes due to gastric secretion to be estimated during the study period. The results of these experiments are reported elsewhere in this issue (Jobin *et al.*, 1985) and show that the drug was not absorbed from the stomach, and that the rate at which it left the stomach and entered the duodenum was a zero-order process until around 65–75% of the administered dose had been emptied. Thereafter the rate became first-order.

Intestinal transit

The intestine exhibits complex motor activity which ensures both the mixing and transfer of its contents. After a meal, the first liquid fractions delivered by the stomach proceed rapidly through the small intestine and may reach the ileum within a few hours. Studies performed with a normal liquid meal containing a non-absorbable marker (Johansson, 1975) revealed that 26% of the marker had reached or passed the upper jejunum 30 min after ingestion of the meal, and that 4% had reached the ileum. These values rose to 77 and 28% respectively after 2 h, to 94 and 61% after 3 h, and to 98 and 88% after 4 h.

Other, more recent investigations have characterized different types of motor activity in the small intestine (Vantrappen *et al.*, 1977). When food is present in the GI tract, the movements of the intestinal wall are irregular but frequent. By contrast, when the gut is empty, i.e. when digestion is completed, there are periods of strong motor activity alternating with periods of quiescence. The periods of activity correspond to bursts of rhythmic waves of contraction that progress slowly down the intestine. As one system of waves reaches the ileum, another develops in the duodenum. This process probably serves to remove remnants of the preceding meal, and for this reason is termed the 'housekeeper' of the small intestine. Housekeeper waves are initiated mostly in the proximal duodenum or in the stomach, but may also arise in the jejunum. In normal subjects,

the mean duration of a complete cycle is around 1.5–2 h. This activity ceases when food is given, and reappears 3.5–4 h after a light meal.

Most patients take drugs during or immediately before a meal so that their GI tracts function in the digestive mode. In this situation drug transit through the gut is likely to be more or less continuous. Under certain circumstances, however, administration may be under fasting conditions and the drug may either be rapidly transferred through the GI tract by a single housekeeper wave or remain motionless for some hours to await the next phase of housekeeper activity.

Water fluxes in the GI tract

In addition to the transport of material through the GI tract, water fluxes due to secretion and reabsorption in the different segments may significantly influence drug absorption. Over a 24 h period approximately 2.2–2.5 l of water enter the stomach (1.5 l from food and beverage, and 0.7–1 l from saliva). Gastric secretion contributes a further 1.5–3.5 l to this volume which together with 0.7 l from bile and 1.5–3 l by pancreatic secretion produces a flow rate into the duodenum of between 6–10 l of fluid per day. Most of this fluid is reabsorbed in the duodenum so that at its distal end the flow rate is reduced to 3–5 l per 24 h. It is further reduced to 1.5–2 l/24 h by the end of the jejunum, 0.7–1.2 l/24 h by the end of the ileum, and is only 0.1 l/24 h at the end of the colon, i.e. in the faeces.

The existing evidence suggests that water crosses the mucosal membrane through pores that are too small in diameter to allow drug molecules to pass. Water fluxes in the gut would therefore be unlikely to have a direct effect on drug absorption. However, the presence of large volumes of water in the duodenum, and to a lesser extent in the jejunum and ileum, may influence the dissolution of sparingly soluble drugs. The considerable water flux in these GI segments may also facilitate intraluminal transport of dissolved drug molecules towards the absorption sites on the mucosa (Ochsenfahrt & Winne, 1972). The secretion and reabsorption of water also modifies the luminal concentration of drug, and therefore its rate of absorption.

Experimental techniques

Drug absorption has been studied extensively in animal models *in vivo*, *ex vivo* and *in vitro*. Drug absorption in man may be investigated

indirectly through a pharmacokinetic approach, or directly by intubation techniques. In addition, specific procedures have been developed to estimate transit times in the various segments of the GI tract.

Indirect methods

Pharmacokinetics permits mathematical models to be constructed which simulate the fate of a drug in the organism to which it is administered. When a drug is given orally, the first step in its fate is absorption. In general, it is not possible to perform a rigorous pharmacokinetic analysis of the absorption process from oral data unless the parameters of the model have first been derived from a separate intravenous experiment. Analysis of the oral data in the same subject then permits the absorption kinetics to be determined. These are generally assumed to be first-order processes with a single compartment representing the whole GI tract, although more complicated models have been proposed (Wagner, 1975).

In practice, the indirect approach is difficult and time-consuming to perform, as it requires intravenous and oral dosing according to a crossover design. Simplified procedures have been developed to overcome this problem. The Wagner-Nelson method (Wagner & Nelson, 1963) is based on an open one-compartment pharmacokinetic model, and estimates the rate but not the extent of absorption. If absorption obeys non-uniform kinetics, the method simply provides an absorption/time plot. The Loo-Riegelman method (Loo & Riegelman, 1968) uses a two-compartment model, but also requires intravenous dosing. It allows the amounts absorbed to be calculated as a function of time. A more recent technique has been reported by Gerardin *et al.* (1983), which may be applied to linear two-compartment models but does not require any prior assumptions concerning the nature of the absorption kinetics.

All indirect methods, however, give only a partial view of absorption since they are concerned only with the appearance of the drug in the circulation; they do not indicate how the drug is removed from the GI tract or where absorption takes place. Despite these limitations, indirect methods are useful for comparing absorption from various dosage formulations and for correlating *in vitro* and *in vivo* data.

Direct methods

A complete investigation of drug absorption must include the determination of the rate of

absorption at the different sites within the GI tract which are reached at various times after drug intake. Different experimental techniques have been developed to measure absorption rates and transit times in the various GI segments.

Absorption rates can be estimated directly from the rate of disappearance of the drug from the gut lumen. This approach presupposes that all the drug removed from the lumen is absorbed, and not lost through other processes including intestinal metabolism, enzymatic or bacterial degradation, and binding to the intestinal mucosa.

The volume of the GI contents is continuously modified by water input (digestive secretions) and output (water reabsorption). Changes in drug concentration in the GI tract cannot, therefore, be taken as a measure of drug absorption, and the use of a non-absorbable marker is required to indicate changes in the volume of GI contents. The use of polyethylene glycol 4000 (PEG) was proposed by Borgstroem and colleagues in 1957 (Borgstroem *et al.*, 1957), and has since been extensively used to investigate digestion. This technique has been refined further by introducing a second non-absorbable marker, ^{14}C -labelled PEG, into the stomach with a meal, while the non-labelled PEG in solution is infused at a constant rate in the upper duodenum (Bernier & Lebert, 1971). In this procedure fine flexible tubes are swallowed by the subjects and located in various parts of the GI tract. The gastric and intestinal contents are then sampled at frequent intervals after administration of the test drug and markers. By determining the concentrations of both markers, suitable corrections can be made for fluid fluxes, and the amounts of drug entering and leaving a particular segment can be calculated.

This intubation technique has been used primarily to investigate the GI absorption of nutrients but has been applied for the first time to drug absorption by our research group. In a study involving metoprolol (Jobin *et al.*, 1985) we were able to show that: (1) the drug is not absorbed from the stomach; (2) most of the amount of drug leaving the stomach is absorbed in approximately 90 cm of the small intestine (roughly two thirds of this amount is absorbed in the duodenum, and one half of the amount leaving the duodenum is absorbed in the jejunum); and (3) the rate of absorption in each intestinal segment is controlled by the rate of delivery to that segment.

Investigation of metoprolol absorption from lower segments of the gut required different

intubation techniques. Absorption from the ileum was studied by means of a 4-channel tube to which a rubber balloon was attached. When the tube was correctly located in the GI tract, the balloon was inflated to isolate the intestinal segment to be studied, and the various secretions coming from the proximal intestine were aspirated continuously. A solution of metoprolol containing PEG was perfused just below the occlusive balloon, and the luminal content aspirated 30 cm below this point. The system was located on the first day in the jejunum, and on the second day in the ileum. With this technique, we were able to demonstrate that the absorption rates of metoprolol are similar in jejunum and ileum (Vidon *et al.*, 1985).

Lastly, absorption in the colon was investigated by a second variant of the intubation technique. A simple tube was used to perfuse a solution of metoprolol first into the jejunum, and then into the colon. Blood was collected at convenient intervals, and the plasma concentration profiles obtained during each treatment were compared. The results which we obtained showed that metoprolol was absorbed from the colon at approximately the same rate as from the jejunum (Godbillon *et al.*, 1985).

This series of experiments illustrates the considerable potential of intubation techniques in permitting the complete characterization of the absorption of metoprolol in all segments of the gastrointestinal tract from the stomach to the colon. However, the technique is complicated and time-consuming, and cannot be used extensively.

Absorption sites and transit times have generally been investigated using less sophisticated techniques. The transit of non-disintegrating solid dosage forms (single tablets, or pellets) containing a radio-opaque compound, such as barium sulphate, can be followed through the GI tract by X-ray examination. However, it is usually necessary to administer a barium sulphate suspension simultaneously to visualize the intestinal tract and difficulties may be encountered in locating the radio-opaque bodies against this background. This technique has generally been used to investigate GI transit, both in normal and pathological conditions, but can also be employed to identify absorption sites (Bozler *et al.*, 1977). In one study, for example, tablets containing the drug and two small stainless steel balls were followed by X-ray examination, the disintegration site being indicated by the movement apart of the two balls. By simultaneously measuring plasma concentrations of the drug the relationship between disintegration and onset of absorption was investigated. A more

sophisticated procedure has recently been reported by Zimmer *et al.* (1981): this makes use of a plastic capsule containing a small latex balloon filled with a solution of the drug and a perforating device that can be operated from outside the body by a high-frequency generator. The capsule is swallowed by the subject and located in the GI tract by radiography. The device is then activated to release its drug content, and the subsequent appearance of drug in plasma is monitored.

Experiments concerned with drug transfer from the stomach to duodenum are generally simpler to perform because they require only the use of enteric-coated dosage formulations and measurement of the lag time until drug appears in the circulation. This technique has been employed to compare the absorption of acetylsalicylic acid from enteric-coated tablets and granules in both fasting and non-fasting individuals (Bogentoft *et al.*, 1978). When taken with food, the tablets remained in the stomach for around 4 h, probably because of the screening effect of the pylorus (see above, under *Gastric emptying*); under fasting conditions they were emptied in less than 1 h. In contrast, granules did not exhibit this difference.

Mouth-to-caecum transit times have been estimated by exploiting a special property of sulphasalazine (salicylazosulphapyridine) (Kennedy *et al.*, 1979): this drug does not appear to be absorbed in the upper segments of the GI tract, but is probably metabolized by the microbial flora in the large bowel to generate sulphapyridine, which is rapidly absorbed. The time lapse before detection of sulphapyridine in plasma gives an estimation of the transit time from mouth to caecum; in normal fasting subjects this is around 3.5–5 h.

Mechanism of drug absorption

The transfer of a drug molecule from solution in the aqueous luminal medium into the bloodstream is a complex process which is far from being clearly understood. The recent use of electron microscopy has provided detailed information on the structure of the mucosa of the small intestine, including that of the absorption cells lining the microvilli. It is now known that most digestive enzymes are located at the surface of these cells and may be directly involved in the absorption of digested nutrients. It seems that drugs, which are absorbed unchanged in most cases, are not transported by such enzyme systems.

At least one concept is now generally accepted: drug absorption is not a simple movement

through the pores of the GI mucosal membrane. The total pore area is negligible in comparison with the entire membrane surface area (Curran & Solomon, 1957). There is also a size restriction since it appears that only lipid-insoluble molecules with molecular weights of less than 100 are able to pass through the intestinal epithelial layer by this mechanism (Hogben, 1960). It must therefore be assumed that most drugs are transferred across biological membranes by passing through the bulk phase.

The passage of drugs through the membrane lipid bilayer can be understood on the basis of the pH-partition hypothesis proposed by Shore and colleagues (1957). This assumes that firstly, there is an equilibrium between the ionized and the non-ionized forms of the drug molecule, which depends on its pKa and on the pH of the medium, and secondly, only the non-ionized form is able to cross the lipid bilayer. Drug absorption is thus a purely passive process, the driving force of which is the difference in concentration, i.e. the chemical potential, across the membrane. The non-ionized hydrophobic molecule is incorporated between the long hydrocarbon chains inside the double layer by a process similar to dissolution, and is transferred into the absorptive cell. The continuous displacement of the equilibrium between the ionized and non-ionized forms, resulting from the disappearance of the latter, permits complete absorption of drug from the GI lumen.

The validity of the pH-partition hypothesis has been demonstrated for many compounds, but more recent studies have shown its limitations (see Prescott & Nimmo, 1981). In some instances it has been found to be necessary to assume the existence of a region with a pH lower than that of the GI lumen, possibly located at the surface of the intestinal epithelium, to account for the observed drug absorption profile (Hogben *et al.*, 1959). The presence of unstirred water layers adjacent to the intestinal epithelium that reduce the permeability coefficient of passively transported substances has also been postulated (Wilson *et al.*, 1971). Furthermore, the pH-partition hypothesis cannot account for the transport of organic anions and cations across the intestinal membrane, albeit at a significantly slower rate than lipid-soluble, uncharged molecules. It is not clear whether this occurs only by passive diffusion (Levine & Pelikan, 1961) or by some more complex mechanism. Finally, there are indications that some drugs can be absorbed by a specialized active transport process if their chemical structures are sufficiently similar to those of naturally transported substrates (Shanker, 1963).

In conclusion, gastrointestinal absorption is the first step in a complex series of events that culminates in the arrival of an orally administered drug at its site of therapeutic action. Variable amounts of the drug may be lost during the different stages of transit through the

body, but the initial absorption process is, in general, the primary determinant of the speed of onset and magnitude of the therapeutic effect. This topic clearly deserves greater scientific investigation in the future.

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