Leading article

Where do all the tablets go in 1986?

The surprising answer to this question is that our knowledge of the gastrointestinal transit of commonly prescribed drugs is remarkably patchy. As I will seek to show, however, techniques which allow a detailed description of the gastrointestinal transit, dispersion and dissolution of orally presented drugs now exist. Studies in this area are becoming increasingly important as pharmaceutical scientists develop ever more complex controlled – release formulations. Transit of these drug delivery systems through the gut has until recently been relatively unexplored with, as we shall see, sometimes lethal consequences.

Many drugs are dispensed as liquids, suspensions or rapidly dispersing tablets and their gastrointestinal transit is rarely problematic because liquids and suspensions usually pass rapidly from the mouth to the small intestine, which is where most drugs are absorbed. Pharmaceutical scientists have, however, become increasingly interested in developing solid oral sustained release formulations aiming to provide the convenience of once daily dosage without toxic effects. Various methods have been used¹ such as coating the drug with insoluble semi-permeable membrane, incorporating it into a variety of slowly eroding matrices – for example, waxes, plastics,² or mixing it with a hydrophilic matrix – for example, hydroxypropylmethylcellulose, which on contact with water forms a gel-like coating to act as a diffusion barrier to the subsequent release of drug.³ Another approach is the osmotic pump, in which water diffuses through a semi-permeable membrane and dissolves the drug and an osmotic agent contained in the core of the capsule, the resulting solution then being expelled through a laser drilled 0.1 mm diameter hole.⁴ As 24 hours supply of drug together with the matrix must be incorporated into these drug delivery systems, patients may have to swallow relatively large tablets or capsules – up to 25 mm long, whose gastrointestinal transit and site of dissolution can not always be predicted.

Oesophageal transit

It has been recognised only relatively recently that oesophageal transit could be a major problem, when a number of instances of oesophageal ulceration were reported⁵ apparently because of the impaction of a wax-based slow-release form of potassium chloride. Systematic study of the relationship between transit, pill size, shape, and consistency then followed and it became abundantly clear that large tablets can often lodge in the oesophagus without exciting any subjective discomfort. Ten years ago in a seminal article entitled 'Where do all the tablets go?',⁶ Evans and Roberts showed that an aspirin-sized barium sulphate tablet took longer than 5 minutes to traverse the oesophagus in over half their patients who swallowed the tablet with a small amount (15 ml) of water and then lay flat:

in five subjects transit exceeded 20 minutes! Although delayed transit was twice as common if there was a radiologically abnormal oesophagus, most of those with delayed transit had no radiological features which could have alerted the clinician to the problem. More importantly, only 3% were aware that the tablet had stuck. Once attention had been drawn to the problem, numerous case reports appeared^{7 8} and a more sophisticated study⁹ indicated that within the range of commonly used 'pills', size, shape, standing or lying, and the volume of water swallowed all made significant differences to the incidence of delayed transit. As expected, oval, small tablets passed most easily while about half the large round tablets had delayed oesophageal transit, defined by the authors as > 90 sec, especially when taken with the smaller amount of water in the supine position. The importance of these studies is that they drew attention to a previously under recognised problem and also led to the very practical conclusion that patients should be advised to take their tablets in the upright position, with at least 100 ml of water. Elixirs would seem to be the only sure way of avoiding oesophageal problems in bedridden patients, especially if they have an abnormal oesophagus.

Gastric dispersion

Once a tablet or capsule reaches the stomach its behaviour will depend on its formulation and on the contents and motility of the stomach. In the past great emphasis has been laid on *in vitro* tests of disintegration and dissolution, in which the solid dose is either agitated vigorously in a large beaker of water, or exposed to a rapid flow of water and the rate of disintegration or dissolution assessed.¹⁰ The implication is that tablets which perform satisfactorily in such a test will behave similarly in the human stomach. Early radiological¹¹ and more recently scintigraphic studies,¹² however, clearly indicate that in the fasting state there are long periods during which tablets are subjected to only minimal agitation and they often disperse surprisingly little. The effect of the resulting high local drug concentration was strikingly illustrated in the endoscopic study by Hey and colleagues,¹³ who showed that mucosal adherence and poor dispersion of a drug, in this case encapsulated pivampicillin, was associated with local hyperaemia, bleeding and mucosal erosions, which were not seen if the same drug was given in a more readily dispersing tablet form. These findings explain why in everyday clinical practice pivampicillin tablets produce significantly fewer upper gastrointestinal unwanted effects than pivampicillin capsules.^{14 15} It would seem advisable therefore, to assess *in vivo* dispersion of solid dosage forms during development of drugs. This can now be done non-invasively with minimal irradiation using radioisotope techniques.^{16 17} Under the gamma camera an isotopically labelled tablet can readily be identified and its disintegration assessed from the fall in counts (corrected for radioactive decay) in a region of interest drawn around the tablet image. Disintegration assessed in this way correlates well with appearance of drug in the plasma¹⁸ and the method looks promising. In such studies, however, it is not usually possible to radiolabel the drug itself, therefore the isotope is usually merely adsorbed on to the tablet matrix, or bound to an ion-exchange resin mixed with the matrix, and the data should be interpreted with this in mind. If the gamma camera images

are to be valid representations of drug release one must first show *in vitro* that isotope and drug are released together in conditions simulating those obtaining in the gut.¹⁷ Another important technical point is that as the isotope moves within the gut either towards or away from the camera, counts will rise and fall respectively; it is therefore necessary to use the geometric mean of the anterior and posterior counts to avoid such artefactual changes.¹⁹ Further sophisticated nuclear medicine techniques are now evolving²⁰ and it appears likely that in the near future it will be possible to define even more closely the physical state of the drug by virtue of changes in the angular correlation between sequentially emitted gamma-rays from certain isotopes such as ¹¹¹Indium.

Gastric emptying

By virtue of its vast surface area the small intestine is the main site of absorption for most drugs so that even though many dosage forms become dispersed in the stomach, they still usually have to pass the pylorus before they can exert their desired effect. Thus even for a rapidly disintegrating preparation such as paracetamol, gastric emptying can exert an important influence on its rate of absorption, especially in pathological states.²¹ Gastric emptying is especially important for the absorption of drugs from sustained release formulations which are often of substantial size and designed to disintegrate either slowly – for example, wax based preparations, or not at all – for example, osmotic pumps. During the last two decades there have been substantial advances in our knowledge of the control of gastric emptying, which are highly relevant to this discussion. Experimental animal studies²² and non-invasive radioisotope studies agree that postprandially the stomach of man²³ and dog²⁴ is able to selectively empty liquids, while retaining particulate solids. This capability appears to depend on the presence of either the antrum or the pylorus,^{25 26} whose co-ordinated contractions triturate particulate solids until they reach a certain diameter (usually <2 mm), when they pass the pylorus with the liquid phase.^{27 28} Thus 7 mm diameter plastic spheres fed with a meal are not emptied from the canine stomach until fasting activity returns about eight hours later,²⁹ whereas smaller, non-digestible particles [such as 3×3 mm paper squares³⁰ or plastic spheres <1 mm in diameter²⁸] empty with the meal; within the range of 1–5 mm spheres empty at progressively slower rates.²⁸ The importance of these studies is that while feeding substantially delays the emptying of large single unit preparations, it has relatively little effect on the emptying of smaller units which leave the stomach with the liquid phase of the meal at rates similar to those recorded during fasting. Why large units are retained in the stomach until the fasting motor patterns reappear can be readily explained now that we recognise the important changes in gastric motility which accompany fasting. Regular antral contractions in the postprandial period propel gastric contents toward the pylorus from which small amounts of chyme are expelled into the duodenum, while most of the antral contents, including all the larger particles, are retropelled back into the body of the stomach.^{31 32} By contrast, during fasting the stomach exhibits cyclical motor activity³³: an inactive phase 1 (30–50 min in dogs) followed by a period with irregular contractions (phase 2, 30–50 min), this phase being terminated by the

arrival of phase 3:—a short period (10–15 min.) of intense phasic contractions which sweep towards the pylorus, deeply indenting the gastric outline and virtually occluding the gastric lumen. Such powerful contractions propel all before³² and on reaching the pylorus most of the antral contents, including particulate solids,²⁹ are expelled into the duodenum.

One implication of these findings is that unless administration of drugs is synchronised with the fasting cycle, mouth-duodenum time can be expected to vary by at least the length of the fasting cycle (1–2 h), depending on when in the cycle the drug was swallowed. Furthermore, as man, unlike the trained laboratory dog, tends to have disconcertingly wide inter- and intra-individual variations in the length of the fasting cycle,³⁴ entry of large single unit drug delivery systems into the small intestine can be expected to be highly variable, a prediction which has been borne out by experience.^{12 18} Thus administration of enteric coated sustained release preparations which release active drug only when they reach the pH found in the small intestine have been shown to result in substantial inter- and intra-individual variation in bioavailability.³⁵

The practical relevance of these theoretical considerations is beautifully illustrated in the article by Davis and colleagues³⁶ in this issue of *Gut*. These authors have studied the gastric emptying and colonic arrival of a wide range of isotopically labelled solid dosage forms. During these studies subjects took normal meals, so their results are highly applicable to everyday clinical practice. The authors found that large single units (dimensions 25×9 mm) rapidly leave the fasting stomach (0.2–1.5 h), while after a heavy breakfast emptying of similar units (24×7 mm) is markedly delayed, in most subjects by more than 11 hours. By contrast, but in accordance with the evidence reviewed already, gastric emptying of small pellets (<1.2 mm) was relatively unaffected by feeding, presumably because such formulations mix with the liquid phase of the meal which empties rapidly relative to the solid phase.

Small bowel transit

The authors also found that once through the pylorus there was little evidence of any effect of formulation type or size on small bowel transit, which is perhaps surprising at first sight. This observation agrees with a number of previous studies,^{37 38} however, which have suggested that particle size has little effect on small bowel transit of solids, perhaps because chyme boluses traverse the small bowel sequentially with remarkably little mixing.^{39 40} Animal²³ and human studies⁴¹ have indicated that selective retardation of the gastrointestinal transit of solids is mainly due to antropyloric sieving and once past the pylorus solids and liquids have identical transit rates. Unphysiologically high fluid flow rates produced either experimentally by intestinal perfusion⁴² or in certain disease states⁴³ can produce streaming, which is a more rapid transit of liquids than solids, but this must be considered pathological.

Implications for drug formulation

The implication of these studies is that whatever the formulation, once past the pylorus a sustained release preparation has surprisingly little time in which to release its active principle, mean transit being three to four hours, with a wide range (one to eight hours), so that some individuals have as

little as one hour available for drug absorption. It follows therefore that sustained release during 24 hours can only be achieved from an oral preparation if some method is devised to retain a reservoir of drug in the stomach, from which it can be slowly released. Once past the pylorus, no formulation remains in the small bowel long enough to give 24 hour release and when the drug enters the colon, poor absorption combined with bacterial degradation, makes bioavailability uncertain. The initially attractive idea, that a large single-unit slowly disintegrating tablet could be maintained in the stomach to act as a drug reservoir, seems likely to founder on the rock of intersubject variability and the capricious nature of the human fasting cycle, which together result in highly erratic gastric emptying,¹² as is well illustrated in Davis's report. An alternative strategy is to use multi-unit preparations which dissolve in the stomach to release a large number of coated particles. As Davis and colleagues³⁶ found, gastric emptying of multiple small particles is more uniform and predictable than that of a large single unit, less influenced by fasting or feeding and in a number of reports this system appears to provide for more reliable drug delivery.⁴⁴

Quite apart from variability in effectiveness, it seems likely that in some cases the large single unit preparations can be associated with unique toxic effects related to their high drug load and hence the risk that the mucosa will be exposed to a toxic concentration of drug if the unit is retained for a prolonged period in the gut, either at the site of some local abnormality such as a diverticulum, or in a region where slow transit can be expected, such as the distal ileum,⁴⁵ or colon.³⁷ Such a sequence of events was thought to be responsible for the two deaths caused by ileal and colonic perforation in which intact osmotic pumps, designed to provide sustained release indomethacin (Osmosin), were found at the site of the perforations.^{46 47}

The future

At present pharmacologists are vigorously debating the ideal form of slow release preparations^{44 48 49}; whatever the outcome of this debate, there is now considerable and surely justifiable pressure on pharmaceutical companies to define the gastrointestinal transit of new preparations in man, postprandially and fasting. We can therefore expect, and indeed insist on a considerable increase in our knowledge of the gastrointestinal disposition of drugs as regards their transit and site of dispersion. This should enable us to give our patients rational instructions as to exactly how these new preparations should be taken and what should be the optimum timing of drug ingestion in relation to meals. Although this will involve more development work and slightly longer consultations it may be a valuable investment of time, because it should ensure adequate drug absorption while avoiding the gastrointestinal toxicity which has been all too common in recent years.

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