GASTRIC EMPTYING AND DRUG ABSORPTION

The absorption of drugs from the human gastrointestinal tract has received relatively little attention from clinical pharmacologists. Yet the great majority of drugs are given orally, and it has been known for years that there may be enormous intra- and inter-individual variations in the rate and completeness of absorption of drugs. For example, we have observed an eighty-fold range in plasma paracetamol concentrations in fasting hospital patients 1 h after an oral dose, and a seven-fold variation in the amount of tetracycline absorbed by fasting healthy subjects. Anomalous results and inconsistencies in individuals tend to be swept under the carpet in favour of tidier absorption curves based on mean values. Few clinicians (and by no means all clinical pharmacologists) would think of drug absorption as a cause of therapeutic failure.

The lid of Pandora's box has been lifted and recent studies have shown that drug absorption is by no means as simple or predictable as we have been led to believe. Unfortunately, preoccupation with the problems of bioavailability has tended to divert attention from advances in the understanding of the basic mechanisms involved in drug absorption. The traditional theory of pH-dependent absorption of weakly acidic or basic drugs in the unionized lipid-soluble state does not always apply in practice (Pottage, Nimmo & Prescott, 1974). In addition, a change in pH may not produce the anticipated result because changes in drug dissolution and solubility may have an opposite effect on absorption. More is known now of the metabolism of drugs by the gastrointestinal mucosa and gut bacterial flora, biliary excretion and enterohepatic circulation, drug absorption interactions and reduction in the 'systemic availability' (i.e. the proportion of a dose reaching the general circulation intact) by the so-called 'first pass' effect of uptake or metabolism of drugs by the gastrointestinal mucosa or liver during the absorption phase.

The rate of gastric emptying is another important factor. Drug absorption from the stomach is very slow whereas absorption from the upper small intestine is usually rapid, presumably because it has a much greater surface area. Thus ethanol and acidic drugs such as aspirin, paracetamol, warfarin and barbiturates are absorbed much more rapidly from the intestine than from the stomach, and the rate of paracetamol absorption is directly related to the rate of gastric emptying (Heading, Nimmo, Prescott & Tothill, 1973). Unless absorption is normally very slow, gastric emptying is likely to be a rate limiting step in the absorption of drugs regardless of whether they are weak acids, weak bases of neutral compounds. Gastric emptying may account for much of the observed individual variation in drug absorption since it is influenced by many factors such as emotional state, pain, posture, autonomic and hormonal activity, food, the volume, pH, composition, viscosity and temperature of the contents, surface active agents, bile salts and many commonly used drugs including ethanol (Barboriak & Meade, 1970; Levine, 1970). Gastric emptying may also be abnormal in a great many disease states (Rimer, 1966). Paracetamol absorption is very slow in patients with pyloric stenosis, and in a recent report sixty-one enteric coated aspirin tablets (650 mg) were discovered in the stomach of a woman with rheumatoid arthritis who developed pyloric stenosis (Harris, 1973). Drugs such as L-dopa, methyldigoxin and pencillins are metabolized or inactivated in the stomach, and if emptying is delayed they may be ineffective because less unchanged drug is available for absorption (Bianchine, Rivera-Calimlim, Morgan, Dujuvne & Lasagna, 1971).

Many drugs have intrinsic effects on gastrointestinal motility and can modify the absorption of other drugs taken at the same time. Thus compounds with anticholinergic activity such as atropine, tricyclic antidepressants (Consolo, Morselli, Zaccala & Garattini, 1970), trihexyphenidyl (Rivera-Calimlim, Castaneda & Lasagna, 1973) and propantheline (Nimmo, Heading, Tothill & Prescott, 1973) can slow down or reduce the absorption of other drugs while stimulation of gastric emptying by metoclopramide may have the opposite effect. On the other hand, the absorption of drugs or formulations with slow dissolution characteristics and compounds actively absorbed from a limited area of the small intestine may actually be enhanced if the gastrointestinal transit time is reduced by propantheline (Manninen, Apajalahti, Melin & Karesoja, 1973)—presumably because they remain longer at the sites of maximum absorption. Most investigators assume that metoclopramide and propantheline influence the

absorption of other drugs by altering the rate of gastric emptying. However, the associated changes in gastrointestinal motility *per se* may be more important because of effects on drug dissolution rate or the thickness of the 'unstirred' fluid layer in contact with the absorbing epithelium.

A simple rapid method for measuring the rate of gastric emptying would obviously be of great value. Unfortunately, currently available techniques all have disadvantages since they require the passage of a naso-gastric tube, administration of non-absorbable radio-isotopes, or multiple venepunctures. In this issue, Finch, Kendall & Mitchard describe a most ingenious approach to the problem. The assumption was made that the rate of ethanol absorption is determined by the rate of gastric emptying, and the appearance of ethanol in the blood was monitored by a 'breathylser' technique following ingestion of a standard dose. Expired (alveolar) air was sampled automatically and the ethanol concentration determined by an automated gas chromatographic system in about 3 minutes. Serial estimations over a period of 2.5 h yielded impressively smooth blood ethanol curves with only about a 10% intra-subject variation in peak levels. Studies were also carried out following administration of metoclopramide and propantheline. As expected, the rate of ethanol absorption was increased by metoclopramide and decreased by propantheline. Although ethanol itself may influence gastric emptying and drug dissolution and absorption, this simple and painless technique should have wide application in the study of the effects of drugs on gastric emptying.

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