WHICH DRUGS SHOULD WE BE TESTING FOR BIOAVAILABILITY?

Evidence of generic non-equivalence between drug products has not created any widespread consternation amongst doctors in Britain and it is still questionable whether it has influenced their prescribing habits. This hesitancy in accepting that generic products which are chemically equivalent may not be biologically equivalent when given to patients is surprising, but it may reflect the recent indoctrination of doctors about the merits of generic prescribing and they cannot easily reconcile the apparent conflict. Those clinicians and pharmacists who recognize the potential hazard of variations in clinical efficacy feel impotent, because they cannot decide which drugs to use; indeed, all of us would like to know the extent of the bioavailability problem.

Our pharmaceutical standards do not measure dissolution of drug products and it is this step which determines the rate and extent of drug absorption rather than the simple disintegration of the dose form. Even if we agree upon the physical determination of dissolution in the laboratory, there are physiological and biochemical problems which will militate against some straightforward correlation with *in vivo* bioavailability studies (Smith, 1974). As soon as we give a drug product to man the active constituent can be metabolized in the gut before it is absorbed or be complexed with food and gut secretions thus hindering absorption. The rate of transit through the gut and concomitant pH changes may influence the absorption of the drug. After its absorption the drug must pass through the liver and this 'first-pass' effect may result in extensive metabolism. All these factors can modify the amount of drug reaching the systemic circulation, which after all is the essential step in getting most drugs to their site of action.

Although we can devise *in vitro* tests of dissolution for most drug products, no laboratory test can take these physiological facts into account and, therefore, we cannot guarantee that the test really reflects what happens in man. It is this difficulty in translating *in vitro* data into clinical advice about relative potency and reliability of drug products which has kept clinicians in a quandary. Therefore, doctors have rightly adopted a wait-and-see policy, and in the meantime decided either individually or by contract purchase in their hospital to stick to one product.

In order to assess bioavailability we need

human studies and the techniques for drug testing in man are being refined, but they are time-consuming and naturally we would prefer to limit the number of tests which we carry out. *In vitro* checks will permit quality control and hopefully some correlation with *in vivo* data will be possible. These laboratory tests would limit *in vivo* assessments of bioavailability, but a more realistic approach would be a critical appraisal of those drugs which need bioavailability testing. After all slight variations may not be important in some situations where the vagaries of everyday dosage produce as much if not more fluctuation in clinical effect than any changes in the product's potency.

Which drugs should we be testing for bioavailability? First, we can categorize compounds into those which have narrow limits between therapeutic efficacy and toxicity, because fluctuations in the amount of drug released must be critical. In this category we would include anticoagulants and cardiac drugs, e.g. digoxin. On the other hand we are not likely to advocate the testing of all products containing aspirin where the toxicity risk is small. Indeed, it would be a huge task and not commensurate with the clinical advantage, if any, of defining the 'best buy'. Second, the drugs which have a pharmacodynamic action must be considered individually. The anti-hypertensives and oral hypoglycaemic drugs might be appropriate choices for thorough bioavailability testing and submission of their profiles by each manufacturer. However, diabetic control is subject to many factors, and variations in bioavailability of oral hypoglycaemic drugs from batch to batch or from one manufacturer to another may be clinically insignificant compared with the fluctuations in glucose load due partly to diet and partly to variations in the rate of gastric emptying. Third, there is a different problem with the antibiotics, because we must achieve a minimum concentration of the drug for inhibition of bacterial growth. Once again an adequate plasma concentration of antibiotic will be maintained by most products despite some variations between them in their bioavailability. We really want to eliminate the bad products and these do exist on the British market as recent evidence about tetracycline (Barnett, Smith, Greenwood & Herrington, 1974) and oxytetracycline (Barber, Calvey, Muir & Hart, 1974) published in this Journal has shown. Thus, it is

necessary to draw up some short-list of drugs which ought to be checked for bioavailability.

In compiling this list of compounds it will be necessary to rely upon world-wide evidence of possible generic non-equivalence. Undoubtedly the problem of bioavailability has received more attention in North America than in Europe, and the main conclusion from published studies is that generic equivalence of drug products is rare. In other words, if we look for it non-equivalence will be demonstrable. This is not so surprising as it may seem. Within the pharmaceutical industry research formulations of one active drug will differ in their bioavailability, so this difference between the proprietary product and those rejected research formulations will inevitably be repeated when another manufacturer decides to formulate the same drug. It is unlikely that he will devise an identical product to that marketed by the innovator, and some may spend less effort on problems of formulation than they ought. For these reasons generic non-equivalence can be expected.

What is the extent of the problem? A recent survey suggests that as many as seventy-three generic compounds are susceptible to variations in bioavailability (Chodos & DiSanto, 1973). Unfortunately, this publication has received less attention than it deserves and, that being so, our awareness of the extent of the problem has been blunted. Individual reports have gained some prominence in Britain, especially when digoxin bioavailability was highlighted by the Scowen Committee's warning, but most bioavailability studies have not appeared in clinical journals and some doctors may not have seen them. Their review (Chodos & DiSanto, 1973) of the problem was not confined to commercially available generic products, but it was based mainly on human studies of bioavailability (sixty-six drugs) and it can be argued that if such fluctuations are possible then some manufacturer either now or in the future will market a poor product. We have got to be on our guard for these bad ones.

If we accept this list of seventy-three drugs, then we can speculate that a few hundred branded generic products on the world market are non-equivalent. Whether these products are dangerous is another question, but it is an unsatisfactory prospect for doctors, pharmacists and patients. Most of the antibiotics are implicated; ampicillin, chloramphenicol, chlor-tetracycline, erythromycin, griseofulvin, lincomycin, nitrofurantoin, methicillin, oxytetracycline, penicillin, various sulphonamides and tetracycline. Likewise, the diuretics display non-equivalence; these include hydrochorthiazide, frusemide, spironolactone and triamterene. These

compounds are a major portion of our therapeutic armamentarium and also the more costly fraction. Therefore, we ought to ensure that we get the 'best buy'.

Until the patents of drugs introduced in the recent past expire, generic products will not appear, but even so the innovator may modify his formulation, albeit unwittingly by some slight modification of adjuvant, and unless there is a bioavailability check it will go unnoticed. In some countries patent laws are disregarded and generic products are already on the market. In Britain we already have a considerable number of generic products in hospital and retail pharmacies which may differ in bioavailability (Chodos & DiSanto, 1973); several antibiotics, steroids (cortisone acetate, dexamethasone, fluocinolone and prednisone) and anticoagulants (dicoumarol, phenyl-indanedione and warfarin). Apart from official warnings about digoxin, these other compounds are purchased without doctors or pharmacists being aware of any bioavailability problem mentioned in scientific literature and without any evidence of drug release from his product being offered by the manufacturer. Fortunately, a dissolution test for digoxin is now agreed and will be included in the British Pharmacopoeia.

What is the immediate prospect for checking drug bioavailability? We can envisage two types of tests being applied. One would be based on the clinical assessment of bioavailability using the most suitable criteria for that particular compound (Smith, 1974). Most commonly this would be based on measurement of drug levels in human volunteers or patients. The other would be a laboratory test fulfilling a secondary role of screening out undesirable products. It may not equate directly with bioavailability in man, but it would separate the good products from the bad. This test would also act as a quality control for batch-to-batch variations. All these checks would need a reference standard and the requirements of the latter have been outlined (Barr, 1972). There are many constraints in devising suitable tests; difficulties in chemical measurement of the active constituent, effects of metabolites (which may or may not be active pharmacologically) on the assay, and logistical problems in human studies with inevitable variations from one subject to another which militate against a perfect study. Nevertheless, our techniques now permit some evaluation of bioavailability for most products.

An increasing problem for drug manufacturers has been the discrepancies in test criteria laid down by different countries. International companies can encounter vastly different requirements on one product, and some 'tests' would fail to detect any bioavailability change, if such existed,

and are both useless and time-consuming. Most manufacturers are attempting to measure bioavailability of their product and to maintain consistency of its effective potency. Such evidence is needed for all new product applications. Unfortunately, once the product licence is granted some change in the manufacturing process or source of raw material cannot be scrutinized so readily with present legislation. Of course, most manufacturers impose batch-to-batch checks on their products, and if these include some *in vitro* test of bioavailability such variations would be detected. Not surprisingly, the industry might resent any directive to announce evidence of their product's bioavailability in comparison with some agreed reference product; in fact, the Committee on the Safety of Medicines (CSM) can obtain this information in confidence from manufacturers. It is questionable whether government agencies should be directly involved in bioavailability tests apart from their supervisory role in ensuring that suitable tests of bioavailability are agreed upon and applied to drug products. When the Medicines Act (1968) was implemented in 1971 about 35,000 finished medicinal products obtained licences of right, because they had been on the market beforehand. They were not subjected to scientific scrutiny, but it was always implied, and the EEC directives now require, that these licences will be reviewed at a later date. In doing this, evidence of bioavailability will be required, but in the meantime bad products exist on the market.

How should we select an effective product? As

already indicated, it would be rational to decide which drugs really require precise investigation of bioavailability. Having done that, the manufacturers could be asked for bioavailability data before placing a contract purchase, but for the time being we are not likely to get such information for most products. The individual doctor and retail chemist have less guidance than hospital committees in choosing products. What can be done? There have been no warnings about suspect products. With the recent publication of evidence about poor tetracycline products on the British Market one might expect that there would be enquiries from official bodies, both professional and governmental, but none were made. If such data raises no queries, we might assume that extensive reviews of world-wide evidence of generic non-equivalence (Chodos & DiSanto, 1973) have gone unheeded too. It appears so. In the USA guidelines for drug-testing have been laid down by the Academy of Pharmaceutical Sciences and efforts are made to inform pharmacists about bioavailability problems. There are no parallel moves in Britain. Doctors and pharmacists are ill-informed, and all this must cause some disquiet within our professions.

R.N. SMITH

*Academic Division of Medicine,
University of Sheffield,
The Royal Infirmary,
Sheffield S6 3DA*

References

- BARBER, H.E., CALVEY, T.N., MUIR, K. & HART, A. (1974). Biological availability and *in vitro* dissolution of oxytetracycline dihydrate tablets. *Br. J. clin. Pharmac.*, **1**, 405-408.
- BARNETT, D.B., SMITH, R.N., GREENWOOD, N.D. & HETHERINGTON, C. (1974). Bioavailability of commercial tetracycline products. *Br. J. clin. Pharmac.*, **1**, 319-323.
- BARR, W.H. (1972). The use of physical and animal models to assess bioavailability. *Pharmac.*, **8**, 55-101.
- CHODOS, D.J. & DiSANTO, A.R. (1973). *Basics of bioavailability*. Kalamazoo, Michigan: The Upjohn Company.
- SMITH, R.N. (1972). Generic equivalence and non-equivalence of drugs. *Lancet*, **ii**, 528-530.
- SMITH, R.N. (1974). The general problem of bioavailability and its assessment in man. *Postgrad. med. J.*, **50**, (Suppl. 6), 7-14.