The clinical pharmacologist

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Summary

Differences in formulation are of greater clinical importance in the case of sparingly soluble drugs, those with small therapeutic doses, in replacement therapy and in the control of serious clinical conditions with compounds having a low therapeutic index: this subject should receive specific attention in medical teaching and in clinical trials.

THE controversy over prescribing drugs by their trade or approved names is a source of embarrassment to teachers of therapeutics like myself who have, for many years, taught medical students and young doctors to prescribe by approved names, leaving the choice of preparation to the pharmacist, on the assumption that 'the drug is the same'. Today we have to eat our words and recognize, in Sir Philip Rogers' words (1972/3) that 'the same constituents of a drug made up in a different way may have a different effect on the patient'.

For the clinical pharmacologist in a teaching hospital, the issue may be considered from three different aspects, namely (a) clinical practice, (b) teaching, and (c) research.

Clinical practice

Although the importance of differences in bio-availability from various formulations of drugs on their therapeutic efficacy is still being evaluated, it appears that it will be most evident in the following circumstances.

(a) Sparingly soluble drugs such as digoxin, where there is a close relationship between dissolution rate and steady-rate plasma level, and where formulation with similar disintegration times may show marked differences in their dissolution rates (Johnson *et al.*, 1973).

(b) Drugs with small therapeutic doses of up to 1 mg where variation in tablet content or availability might be expected to produce more marked effects. Individual tablet assay in quality control is desirable for drugs whose doses are 1 mg or less.

(c) In replacement therapy, such as for thyroid and adrenal cortical deficiency and in diabetes mellitus. It was in this situation, in fact, that one of

the first observations of importance in this subject was made. Whittet and his colleagues (Whittet, 1971) at University College Hospital, London, noted that patients with Addison's Disease, whose symptoms were well controlled on a particular brand of cortisone, developed signs of adrenal cortical insufficiency when given tablets of cortisone prepared from another source, even though samples of the latter had been found to comply with pharmacopoeal standards including assay and disintegration time. Further studies showed that when particles, into which the tablets disintegrated, were examined microscopically, those of the second formulation contained large aggregates which did not disintegrate on prolonged treatment with a gastric digest solution followed by a pancreatic digest solution, and the investigators concluded that this explained the poor clinical response obtained from these tablets compared with the first.

The clinical effects of small changes in bio-availability of replacement drugs in conditions such as hypothyroidism and Addison's Disease may develop only slowly and insidiously, and may not, therefore, be easily recognized until a serious condition has developed.

(d) In the control of serious clinical conditions in which optimum drug blood levels fall within a narrow range, such as anticonvulsant and anti-dysrhythmic therapy. Changes in formulation of the anticonvulsant drug phenytoin, for example, have resulted in the development of phenytoin intoxication due to enhanced absorption of the drug (Tyrer *et al.*, 1970).

(e) Where the drug has a very narrow therapeutic ratio so that relatively small changes in plasma concentration may lead to failure of therapeutic effect or to the development of signs of toxicity. Digoxin, phenytoin and oral anticoagulants provide examples of such a situation.

In teaching

There is little doubt that many doctors find it easier to remember drugs by their proprietary names, which are often indicative of their supposed therapeutic effect, than by their approved names

which may be long and difficult to pronounce. It must, therefore, be presumed that many of our medical students will be tempted to prescribe drugs in this way in the future unless they can be convinced of the desirability to use another name because of important therapeutic or economic considerations.

Teaching of clinical pharmacology and therapeutics to medical undergraduates and postgraduates should include specific instruction in the matter, with assistance from pharmacist colleagues, setting out the case for ensuring continued administration of one particular formulation of a drug in the clinical situations already discussed, or at least ensuring that an alternative formulation has the same bio-availability characteristics. This is particularly important when patients are transferred from the care of a hospital to that of their General Practitioner, or from one practitioner to another, when a change of pharmaceutical supply is almost always involved.

In research

The most important implication of this subject in clinical pharmacological research probably concerns the formulation and therapeutic efficacy of drugs used in clinical trials. Freestone (1969) has drawn attention to the fact that conclusions in double blind trials of drugs are drawn from their comparative efficacy and incidence of side-effects. The test drugs, produced in special identical galenical forms for the purposes of a clinical trial, which differ

from other preparations of the drugs, may reveal either inferior results or an excessive incidence of side-effects. Similarly, results may be biased unfairly in favour of, or against, the standard drugs if their availability is different from that of the commercially available preparations. In addition to purely quantitative changes, the speed and general pattern of absorption may be altered with clinically significant results. For these reasons it is important to ensure that the availability of any standard drug used in a clinical trial is not different from that of the most commonly used commercial preparation. This will almost always require preliminary studies before beginning the formal investigation.

An increasing amount of time in clinical pharmacology units will undoubtedly be devoted to evaluating the relative bio-availability of different products for therapeutic and research purposes.

References

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Discussion

Mr John Fingerhut, Merck Sharp & Dohme, was delighted that clinical trials had been emphasized by Professor Turner; this problem had previously been ignored. The first clinical trials carried out on a compound are now the usual basis for the subsequent usage and popularity of the drug; he suggested that in the original formulation of a new drug, there might be a small dose of impurity which had an effect on the disease while the drug itself was inactive; it would then be necessary to continue to use the same formulation, using the trade name, in order to maintain the effectiveness of the product.

Dr T. M. Jones, Boots, Nottingham, wondered how the general practitioner wanted information on equivalence of products, in the form of graphs based on chemical and clinical observation or as a statement from a licensing authority. Dr Venables preferred the statement of a licensing authority to the effect that if a certain approved name is written on a prescription, no matter which pharmacy dispenses, the patient will receive a product with the same

therapeutic efficacy. In this event, approved names could safely be used.

Mr Grainger wondered why there was such great faith in the capacity of licensing authorities to produce this information. If objective standards could be achieved at all, they should be achieved and published in a compendium which should be available for inspection by every manufacturer, every doctor and any other interested person—they should be in a pharmacopoeia. Submissions to the licensing authority are unsatisfactory for this purpose; they are confidential, based on particular preparations, not comparative between one formulation and another, and available only to the manufacturer and the licensing authority. We need either baseline pharmacokinetic data or *in vitro* tests which can be made standards in the same way as there are chemical and physico-chemical standards for the chemical constituents of a product.

Professor A. H. Beckett regretted that standard *in vitro* tests could not be produced to cover different

formulations with different additives, which would be suitable for inclusion in a pharmacopoeia as a guide to therapeutic activity.

Dr A. Herxheimer, London Hospital Medical College, suggested that manufacturers should publish or at least make available quality control data on their products.

If *in vitro* tests were of so little value, on what basis were preparations selected by committees awarding regional contracts for supply to hospitals, where prescribing would be by approved names? Mr J. A. Baker admitted that the basis of such decisions in the past was unsatisfactory, in that they

were based largely on price. He agreed that the problem was a lack of data on which rational selection could be made and thought that committees tended to play safe and stick to last year's brand, often an expensive proprietary product, and avoid the risk of buying something much cheaper with no information on bio-availability. Mr J. G. Roberts, Regional Pharmacist, Liverpool Hospital Board and President of the Guild of Hospital Pharmacists, did not agree that price was the only criterion used by committees selecting drugs. He hoped that the basis of such decisions was sounder than that of most doctors writing a prescription.