DEPARTMENT OF HEALTH,
P.O. BOX 5013,
WELLINGTON.
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CLINICAL SERVICES LETTER NO. 28

TO MEDICAL PRACTITIONERS

Dear Doctor,

DRUGS AND PREGNANCY[1]

As the tragic experience with thalidomide (Distaval) indicates, the "trying out" of newly promoted drugs in place of established remedies is always potentially dangerous in clinical practice. To determine the effectiveness of a remedy is a difficult undertaking, and to anticipate the range, incidence, and severity of harmful effects is impossible even with carefully controlled trials.

For these reasons the physician should employ the greatest reserve in using new drugs, particularly when the risk of unknown toxicity is not offset by proved and significant superiority over older, standard remedies. As the thalidomide injuries also make clear, drugs should be tested for possible harmul effects upon the embryos of several species of animals at all stages of gestation before any experimental or clinical trial in man is contemplated.

In general, pregnant women should be given as few drugs as possible and, except for urgent indications, all drugs should be withheld during the first trimester. Complete records should be kept of drugs given during pregnancy and they should be reviewed in the light of any abnormalities observed at birth or later. It is noteworthy that the first observations of the toxicity of thalidomide were made by general practitioners; early pharmacological and clinical studies had given no indication whatsoever of the grave risk in the use of this drug by pregnant women.

SUSTAINED OR LONG-ACTING PREPARATIONS[2]

The therapeutic value of preparations of penicillin, insulin, and vasopressin which are designed to prolong their action after parenteral administration is widely accepted. The prolonged action of these preparations depends on a slow and prolonged absorption of the active drug from the site of injection.

In recent years many attempts have been made to apply this principle of slow and continuous action to drugs which are administered by mouth. It has been argued that orally administered sustained-action preparations by ensuring a continuous action throughout the day and night would provide more effective and consistent relief of symptoms and substantially reduce the need for frequent administration of tablets or capsules. Various methods have been developed by which one or several drugs are incorporated in a formulated product from which they are said to be slowly released in the alimentary tract. These depend on (a) coating the active drug with substances that are resistant to gastric juice but

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[2]Reprinted from British *Prescribers' Journal*, Vol. II, No. 2, by kind permission of the Editor.

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slowly soluble in the intestinal secretions, (b) making use of ion exchange resins which bind the active drug(s), (c) forming chemical complexes from which the drugs are slowly dissociated, and (d) embedding the drug in a matrix of fats and waxes or of powdered plastic from which it is gradually leached out by the gastrointestinal fluids. Capsules and multilayer tablets have been prepared which contain a mixture of granules of embedded drug and active drug to provide an immediate as well as a sustained action.

It is unlikely that any sustained release preparation containing a single ingredient will disintegrate in the same way in different patients or in the same patient at different times. In view of the known differences in absorption mechanisms of various drugs, it is also obviously more difficult to produce properly sustained release of all the ingredients of a complex mixture.

Many ingenious techniques have been devised to provide in vitro and in vivo tests of the reliability of these preparations in releasing their active constituents. These tests are of course necessary to ensure uniformity of manufacture, but the therapeutic value of the preparations can only be assessed by appropriate clinical trials. In comparison with the large number of such preparations now marketed there is little published evidence of controlled clinical trials to support the claims made for them.

The sustained-action preparations so far available have not been formulated with drugs where precise and adequate doses are vital to the well-being and life of the patient. The drugs incorporated are nitrites, antihistamines, amphetamine and related drugs, antispasmodics, cough suppressant drugs and sedatives.

The use of sustained-action preparations can be justified only if it can be shown that they produce a significantly longer duration of effect than the unmodified drug or mixture of drugs with which they are formulated, and that this is a distinct advantage to the patient for whom they are prescribed. If distressing or annoying side-effects of a drug cannot be satisfactorily reduced or eliminated by an adjustment of dose consistent with the desired therapeutic effect, the use of a sustained-action preparation which achieves this would also be justified. Unfortunately there is at present a paucity of reliable and acceptable evidence to encourage the view that the sustained-action preparations are likely to meet these requirements. Until such time as evidence of this kind becomes available it does not seem justifiable to recommend the use of these preparations.

Yours faithfully,

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