

Bioequivalence of inhaled medications

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Expiration of patents on salbutamol, beclomethasone and sodium cromoglycate has resulted in a flurry of activity in both the pharmaceutical industry and the regulatory authorities in an attempt to define bioequivalence for inhaled versions of these products. The situation is accentuated in the United States because of the current size and rate of growth of the market and because the FDA has very precise definitions of bioequivalence which have developed from oral formulations. In the USA, because pharmacists are allowed to substitute products which are established as bioequivalent then, for public safety, careful definition of the term is mandatory. For standard oral formulations bioequivalence is established by carrying out comparative pharmacokinetic studies which are intended to compare the new product and the market leader on the basis of rate and extent of drug absorption. It is argued that such studies are not possible with inhaled products for two reasons. First, dosages are low and, therefore, accurate measurement of blood drug concentration is difficult or impossible. Second, the desired effect is local and, therefore, systemic blood drug concentrations are irrelevant.

It is clearly to the advantage of manufacturers of patented products to argue that only clinical comparisons can establish bioequivalence for these inhaled drugs, thereby delaying the appearance of generic products. This situation is made worse by the fact that, in general, generic manufacturers are not experienced in direct clinical comparisons, and the controversy has been befuddled by a lack of agreement on the appropriate clinical protocol.

In view of the white heat and smoke of this largely political battle, the kinetic approach suggested by

Hindle & Chrystyn (1992) for establishing bioequivalence of salbutamol inhalation products, seems ludicrously simple. They claim, and are probably correct, that the amount of unchanged salbutamol excreted within 30 min of the administration of a salbutamol inhaler is directly related to the amount of drug reaching the lungs. If true, then surely the answer to the assessment of bioequivalence is for inhalers to be compared on two separate occasions in a sufficiently large number of volunteers and to assay a single 30 min urine sample. A comparison of the mean differences in drug content between the two urine samples in a group of volunteers would establish whether the lung deposition for the copy product was bioequivalent to the market leader.

Although this test involves less risk than proposed challenge studies with methacholine and histamine, a simple urine study might be considered too mundane for the rather grand purposes of establishing bioequivalence. At the least this method should provide confidence that a formulation will prove to be clinically equivalent. Considering that the large inter-patient variability in ability to use inhalers is superimposed on relatively large dose-to-dose variation in inhaler function, it seems to be 'gilding the lily' to propose a complicated means of establishing bioequivalence between products. The simple method suggested by Hindle & Chrystyn (1992) should be validated carefully with assessment of intra-subject variability such that estimates can be made of the number of subjects required in a crossover study to be statistically confident that two products are bioequivalent. The possibility of applying a similar technique to other inhaled drugs should also be investigated.

Reference

- Hindle, M. & Chrystyn, H. (1992). Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br. J. clin. Pharmac.*, **34**, 311–315.