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Gamma scintigraphy: an in vivo technique for assessing the equivalence of inhaled products

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Abstract

Classical bioequivalence testing, based upon equal rates and extents of drug absorption, is inappropriate for showing equivalence of products containing inhaled asthma drugs, which act directly on the airway surface. The non-invasive imaging technique of gamma scintigraphy gives a measure of local bioavailability at the site of action in the lungs, and lung deposition data are strongly correlated with clinical response to inhaled asthma drugs. Therefore if two inhaler products have the same whole lung deposition and the same regional airway deposition pattern, they will be therapeutically equivalent. For assessing the equivalence of inhaled asthma medications, gamma scintigraphy determines in vivo drug delivery more precisely than in vitro testing, and is more incisive than clinical response studies. The approach requires fewer patients than clinical response studies, providing appropriate data in less time, and with the guarantee of strong endpoints. Gamma scintigraphy should therefore become a recognized technique by the regulatory authorities for assessing pulmonary bioequivalence of inhaled products.

Keywords: Drug delivery; Gamma scintigraphy; Inhalers; Bioequivalence

1. Introduction

Many new pulmonary drug products are being developed at the present time, stimulated by a variety of factors including: (i) the introduction of new inhalers that do not use ozone-depleting chlorofluorocarbon (CFC) propellants, (ii) the search for new inhalers that patients will be able to use more easily than established products, (iii) the development of generic brands of bronchodilator and steroid inhalers, and (iv) the increasing prevalence and severity of asthma worldwide (Wolff and Niven, 1994). Companies

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developing such products often intend that novel inhalers or formulations for asthma therapy should behave in the same manner in vivo as the products that are being replaced; in other words, that old and new products will be equivalent in terms their efficacy. Before these products can be marketed, it is incumbent upon manufacturers to demonstrate this to regulatory authorities. This topic has been the subject of several recent reviews (Chrystyn, 1994; British Association for Lung Research Workshop Report, 1995; Derom and Pauwels, 1995; Fuller et al., 1995; Snell, 1997), but there seems to be no clear concensus about the practical choice of assessment methods that should be used to show equivalence for these products. Gamma scintigraphy can determine local bioavailability of inhaled products, and should play a key rôle in the regulatory approval process for new asthma products, helping to facilitate the early introduction of these products to the market.

2. In vivo bioequivalence based on systemic drug levels

Before considering inhaled products, it is instructive to consider the situation applicable to novel products for oral administration, for which equivalence with existing oral products is shown by classical bioequivalence testing. The text-book definition of bioequivalence for two products given orally is that they have identical rates and extents of absorption (Expert Group Report, 1993). These assessments are based upon the plasma levels of drug plotted against time, with the area under the curve (AUC) and maximum plasma level (C_{max}) being the primary metrics. The acceptance of bioequivalence of two products requires that the 90% confidence interval for the ratio of test product to reference product lies within a pre-determined bioequivalence interval; for AUC the generally accepted interval is 0.8–1.25 (Diletti et al., 1991; Metzler, 1991). A wider interval may be appropriate for C_{max}, because of its inherently greater variability (Steinijans et al., 1992). Once bioequivalence of the two products is established, then it is *assumed* that they will be therapeutically equivalent.

Pharmacokinetic data (plasma and urine levels) are sometimes used to infer the delivery of asthma medications to the lungs. However, this approach is not appropriate for showing therapeutic equivalence between asthma medications which act locally on the airway surface, and not from within the systemic circulation (Fuller et al., 1995). Indeed, the Committee for Proprietary Medicinal Products (CPMP) state in their 1996 guidance note on locally acting products that:

> "For locally applied products bioequivalence generally is not a suitable way to show therapeutic equivalence since plasma levels are not relevant for local efficacy, although they may play a rôle with regard to safety" (CPMP Guideline, 1996).

Further, systemic drug levels of inhaled asthma drugs are generally very low, and hence are difficult to quantify accurately. Methods based on the plasma levels (Newnham et al., 1993) or urine levels (Hindle and Chrystyn, 1992) of salbutamol within 1 h of inhalation have been used as indices of lung dose, but require further validation. The 'charcoal block' pharmacokinetic method, in which orally administered charcoal is used to prevent gastrointestinal absorption of swallowed drug, can quantify lung dose from the amount of drug excreted in a 48-h urine collection (Borgström and Nilsson, 1990), but is probably applicable only to a limited range of pharmaceuticals. Hence an alternative method must be sought in order to show equivalence for inhaled asthma products.

3. In vitro equivalence based on particle size distributions

Drug delivery to the lungs can be assessed by in vitro laboratory tests of particle size distribution, giving a measure of 'fine particle fraction' (percentage of drug mass contained in particles smaller than about 5 μm diameter). These tests, while being key to the quality control of new and existing inhaled products, do not accurately predict lung dose in vivo; in fact, the fine particle

fraction, as determined by current particle impactors fitted with simple 90° inlet 'throats', almost always overestimates the actual amount of drug deposited in the lungs (British Association for Lung Research Workshop Report, 1995; Newman, 1998). This situation results primarily from the difficulty of simulating real-life airway anatomy and inhalation techniques with the very simple 'models' found in particle impactors such as the Twin Impinger and Andersen Sampler (Hallworth, 1993; Holzner and Müller, 1995).

Perhaps even more importantly, however, it is becoming increasingly clear that in vitro data not only give potentially misleading information on the absolute level of drug delivery to the lungs, but may also fail to predict accurately the *relationship* between the drug deliveries of two products (Newman, 1998). This discrepancy between in vitro and in vivo data is particularly marked when two inhalers with very different cloud characteristics are being compared. To give an example, a recent study comparing a pressurised metered dose inhaler (which delivers a very rapidly moving spray with a significant 'ballistic' component) with a novel multidose nebuliser (from which the spray is much more slowly moving) showed mean fine particle fractions of 33.3 and 50.3%, respectively (ratio 1.5), but lung depositions of 14.3 and 31.1%, respectively (ratio 2.2) (Steed et al., 1997). These limitations of in vitro particle sizing data for predicting in vivo drug delivery to the lung are broadly analogous to the limitations of dissolution testing for predicting the in vivo behaviour of orally administered dosage forms.

4. Clinical response studies

Clinical efficacy studies currently form the cornerstone of assessment of asthma inhalers, and regulatory authorities generally recommend the demonstration of therapeutic equivalence between two inhaled products. Whilst the provision of efficacy data undoubtedly provides reassurance concerning the clinical performance of the product, there are some serious problems in conducting clinical efficacy studies with inhaled asthma products. Bronchodilators produce a rapid easy-to-measure response, but studies are often conducted close to the top of the dose–response curve, so that both products give a maximal response and any difference between the effects of products is missed. For drugs such as inhaled steroids that do not elicit a rapid easy-to-measure response, it may be necessary to carry out studies in which treatments are administered over periods of several weeks, probably involving parallel groups assigned to different treatments. A patient's clinical stability and compliance can be hard to maintain over a long treatment period. Further, some of the clinical endpoints used in such studies (e.g. extra puffs of beta-agonist and symptom scores recorded on diary cards) are relatively 'weak'.

Perhaps most importantly, the inter-subject variability in clinical response is generally high, so that hundreds of patients may be needed to show a difference between treatments, leading to very expensive and highly unwieldy multicentre trials. It has been estimated by Zanen and Lammers (1995) that between 273 and 1250 patients would be needed to show therapeutic equivalence between two inhaled corticosteroid products whose mean clinical response differed by 5%, bearing in mind the known variability in clinical response as shown in published trials, and using the equivalence criteria normally applied for orally administered products. For these reasons, clinical efficacy measurements can be regarded as a relatively 'blunt instrument', and a more incisive technique is needed to differentiate between products. We believe that gamma scintigraphy fulfils this rôle.

5. Gamma scintigraphy

The non-invasive imaging technique of gamma scintigraphy was developed originally for use in diagnostic tests in nuclear medicine (Belcher and Vetter, 1971; Freeman and Johnson, 1975). Specific radiopharmaceuticals which localise in different organs and which are visualised by gamma camera are used to provide vital information about the structure and function of various body systems. Since about 1980 the technique has been

extended to the evaluation of pharmaceutical dosage forms delivered by the oral, rectal, pulmonary, nasal, ophthalmic and vaginal routes (Davis et al., 1992; Meseguer et al., 1994; Wilson, 1994). When used in this manner, the rationale of gamma scintigraphy is that the drug formulation is radiolabelled with a small quantity of an appropriate gamma-ray-emitting radiotracer, and a gamma camera, coupled to a sophisticated data processing system, is used to quantify the behaviour of the formulation in vivo. This method enables direct visualisation and quantification of where the formulation has been delivered, what it is doing, and whether or not it is behaving according to its proposed rationale. According to a recent comprehensive review of the subject (Meseguer et al., 1994):

> ''Gamma scintigraphy has become the method of choice for investigating the fate of pharmaceutical [dosage] forms in the body''.

The great majority of scintigraphic studies of the respiratory tract have involved two-dimensional 'planar' imaging (Newman, 1993). Three-dimensional single-photon emission computed tomography (SPECT) studies involving asthma inhalers are also possible (Perring et al., 1994), but are less well established as a routine procedure, and are difficult to apply to multidose inhalers, requiring an order of magnitude more radioactivity to be handled and administered.

When gamma scintigraphy is used in the assessment of pulmonary drug delivery, the formulation is usually labelled with the gamma-ray emitting radionuclide ^{99m}Tc, which has an ideal radiation energy (140 keV) for use with a gamma camera (Newman, 1993). The short half-life of ^{99m}Tc (6 h), coupled with a very 'clean' radiation emission profile which contains few beta-particles, results in very low radiation doses, so that satisfactory scintigraphic data can be obtained using only a fraction of the radiation dose required for diagnostic X-ray procedures. Prior to each study, radiolabelling validation measurements are carried out in vitro in order to show that the drug delivery characteristics of the product are unaltered by the labelling process, and that the radiolabel acts as a marker for the drug across the full range of particle size bands (Farr, 1996; Newman, 1996). Once the radiolabelling method has been validated, scintigraphic data can be recorded in vivo, in the knowledge that these data show exactly where the drug itself has been deposited.

Recorded counts from planar images are used to calculate deposition data, being corrected where necessary for attenuation of gamma rays by tissue (Pitcairn and Newman, 1997). It is acknowledged in the scientific literature that planar gamma scintigraphy provides an accurate measure of drug deposition in the lungs expressed as a percentage of metered or delivered dose (Gonda, 1996; Smaldone, 1996). The accuracy of scintigraphic data has been demonstrated by making a comparison with data collected simultaneously by the charcoal block pharmacokinetic technique (Newman et al., 1995). In addition to providing an accurate assessment of whole lung deposition, data analysis enables the amounts of drug deposited in 'central', 'intermediate' and 'peripheral' lung regions (corresponding approximately to large, medium and small airways, respectively) to be quantified. The peripheral zone/central zone deposition ratio enables differences in regional deposition between treatment regimens to be detected (Newman et al., 1989; Steed et al., 1997), and is correlated with the fraction of the lung dose which penetrates to the alveoli (Agnew et al., 1986). Lung deposition assessed by planar gamma scintigraphy is a key piece in a 'jigsaw puzzle' of data relating to inhaled drugs, without which the complete picture of drug delivery cannot be seen (Fig. 1). The method has been used in the evaluation of a wide range of inhaler devices, as listed in Table 1.

Drug deposition data are predictive of both the beneficial clinical effects and the side effects of inhaled asthma medications. The beneficial effects depend upon the amount of drug delivered to the airways. For instance, Newman (1982) investigated the effects of changing systematically the inhaler techniques of asthmatic patients upon both deposition of drug in the lungs, and the effects of an inhaled beta-agonist (terbutaline sulphate) delivered by pressurised metered dose inhaler. There were six inhalation techniques,

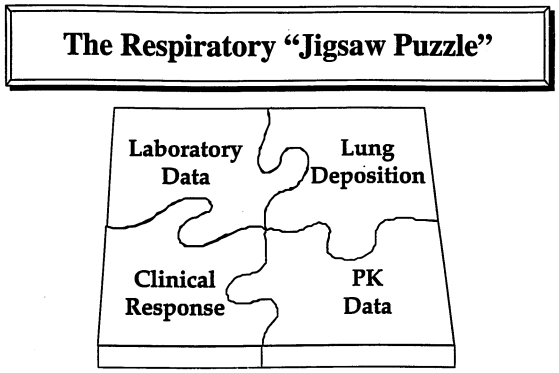

Fig. 1. The respiratory jigsaw puzzle.

involving two breath-holding pauses (4 and 10 s) and the inhaler was fired at three points during the inhalation (beginning, middle or end of the breath). The close correlation between lung deposition and bronchodilator response over the six inhalation techniques is shown in Fig. 2. Optimal inhaler technique gave the best lung deposition and the best bronchodilator response, while sub-

Table 1
Some scintigraphic studies of drug delivery from asthma inhalers

Device	Reference
Metered dose inhalers	Dolovich et al. (1981)
	Newman (1982)
	Spiro et al. (1984)
	Vidgren et al. (1987a)
	Newman et al. (1991a)
Spacer devices	Vidgren et al. (1987b)
	Newman et al. (1989)
	Newman et al. (1991b)
	Newman et al. (1991c)
	Newman et al. (1995)
Dry powder inhalers	Vidgren et al. (1988)
	Newman et al. (1994)
	Pitcairn et al. (1994)
	Borgström and Newman (1993)
	Vidgren et al. (1994)
Nebulisers	Newman et al. (1988)
	O'Doherty et al. (1988)
	Johnson et al. (1989)
	Thomas et al. (1991)
	Steed et al. (1995)
	Newman et al. (1996)

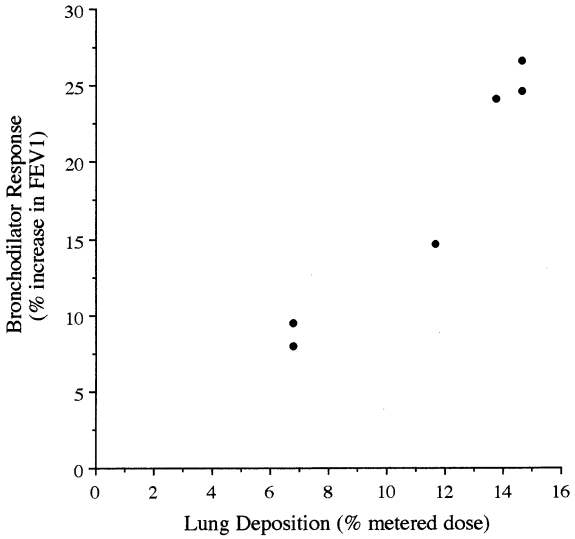

Fig. 2. The correlation between lung deposition and clinical response to an inhaled beta-agonist, for six different inhalation techniques from a pressurised metered dose inhaler. Data from Newman (1982).

optimal inhaler technique gave lower lung deposition and a reduced clinical response. Novel inhaler devices that deposit twice as much drug in the lungs per dose as a pressurised metered dose inhaler appear to be clinically effective, using only half the nominal drug dose. This phenomenon has been demonstrated for the Turbuhaler dry powder inhaler (Löfdahl et al., 1994; Thorsson et al., 1994; Borgström et al., 1996), and for the Respimat, a new multidose liquid spray device (Newman et al., 1996; Maesen et al., 1997). Two recent major reviews concluded that lung deposition data from asthma inhalers have been reflected in the results of most single-dose cross-over clinical efficacy studies (Selroos et al., 1996; Pauwels et al., 1997).

6. In vivo equivalence based on gamma scintigraphy

What is the rôle for gamma scintigraphy in the regulatory approval process for new pulmonary products? This process often requires the demonstration of equivalence (for instance between in-

novator and generic products, between CFC and non-CFC products, or between an established pressurised metered dose inhaler and a novel dry powder inhaler). By accurately quantifying 'lung dose', gamma scintigraphy can establish the equivalence of two inhalers in a simple and convincing manner.

The CPMP guidance note for assessing equivalence of locally acting products (1996) states that:

> "clinical trials are in principle necessary…but other models may be used or developed…local availability studies can be considered provided that all studies used are adequately validated".

Gamma scintigraphy assesses local bioavailability since it enables lung deposition from inhaler devices to be quantified accurately as a percentage of the metered or delivered dose, and the relevance of lung deposition data for clinical effect is proven. An alternative definition of bioequivalence has recently been given as:

> "The absence of a significant difference in the rate and extent to which the active ingredient or active moiety…becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (Nation and Sansom, 1994).

A scintigraphic study of drug deposition assesses the rate and extent to which the drug becomes available at the site of drug action, and hence provides powerful evidence that the two delivery systems are either equivalent or inequivalent in terms of their drug delivery characteristics.

An analogy may be drawn between the use of scintigraphic data for inhaled asthma medications and the use of systemic drug levels for orally administered products, and more specifically between whole lung deposition for an inhaled asthma product and AUC for a product given orally. If gamma scintigraphy shows that two products containing the same amount of the same drug have the same whole lung, and regional lung depositions, then bearing in mind the strong correlation discussed above that exists between lung deposition and clinical response, then it may be safely assumed that they are therapeutically equivalent (Table 2). We believe that this approach is an elegant, logical and practical solution to the much-debated problems of showing equivalence for inhaled products, and that the justification for using data generated by gamma scintigraphy in regulatory submissions is compelling. As stated in the recent British Association for Lung Research Workshop Report, 1995:

> "The technique…enables [bio]equivalence between inhaled products to be determined, since [bio]availability, defined as the extent to which active drug becomes available at the site of action…can be assessed".

An example is cited in Table 3 and Fig. 3, in which a bronchodilator aerosol has been delivered as CFC and non-CFC formulations on different days in a randomised cross-over study to 12 healthy volunteers. The data in Table 3 show identical depositions in the whole lung, in central, intermediate and peripheral lung regions, and in the oropharynx for the two products. The images

Table 2
Therapeutic equivalence for oral products and for inhaled asthma products

Equivalence testing of oral products
Bioequivalence demonstrated
Therapeutic equivalence assumed
Equivalence testing of inhaled asthma products
Equivalence of local bioavailability demonstrated
Therapeutic equivalence assumed

Table 3
Mean (S.D.) deposition data for CFC and non-CFC pressurised aerosols in 12 healthy subjects

Deposition site	Non-CFC	CFC
Lungs (%)	15.1 (5.9)	15.8 (5.1)
Central zone (%)	4.5 (2.1)	4.5 (2.0)
Intermediate zone (%)	5.1 (2.0)	5.2 (1.9)
Peripheral zone (%)	5.5 (2.0)	6.0 (1.4)
Peripheral zone/central zone ratio	1.4 (0.4)	1.5 (0.5)
Oropharynx (%)	66.7 (8.0)	69.5 (4.8)

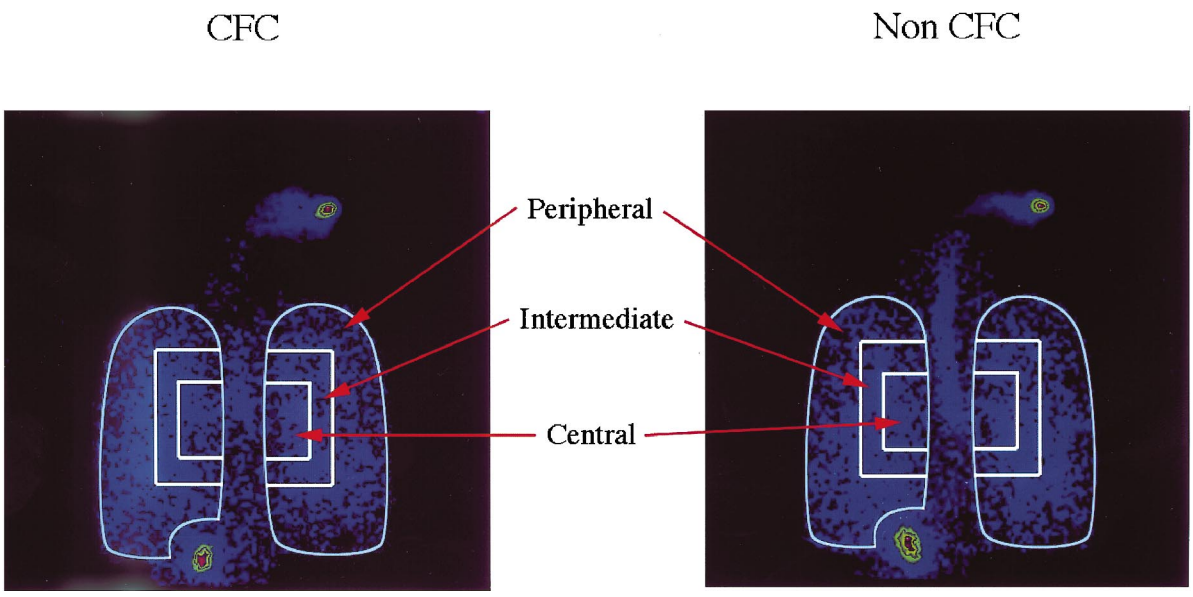

Fig. 3. Scintigraphic images showing identical total and regional depositions for CFC and non-CFC pressurised aerosols. Lung regions: C, central; I, intermediate; P, peripheral.

in Fig. 3 confirm these observations. On the basis of identical delivery of drug to the target site in the lungs, we would expect the two formulations to be therapeutically equivalent.

7. Conclusions

Gamma scintigraphy is able to quantify accurately the amount of drug delivered from an inhaler device to the target site in the lungs, enabling the equivalence of two inhaled products to be determined. The relationship of scintigraphic data to clinical efficacy is well established. For assessing the equivalence of inhaled asthma medications, gamma scintigraphy is more appropriate than classical bioequivalence measurements, more accurate than in vitro data, and more incisive than clinical response studies. The approach requires fewer patients than clinical efficacy studies, and provides appropriate data in less time with the guarantee of strong endpoints. Gamma scintigraphy should become a recognised technique in the regulatory approval process for pulmonary products not just to provide supporting data, but rather as a means of reducing reliance upon clinical efficacy studies, particularly for essentially similar products. There is no clear practical alternative to gamma scintigraphy for assessing the local bioavailability and equivalence of inhaled products.

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