Eur Respir J 2001; 17: 157–158
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European Respiratory Journal
ISSN 0903-1936

CORRESPONDENCE

Systemic bioavailability of inhaled steroids: the importance of appropriate and comparable methodology

To the Editors:

Recently, the systemic bioavailability of mometasone furoate (MF) *via* the Twisthaler™ (Schering Corp., Kenilworth, NJ, USA) has been reported to be <1% in healthy subjects [1]. This unusual result, however, was based on a study with sparse data, a low dose (*i.e.* 400 μg) and a relatively insensitive assay (lower limit of detection of 50 pg·mL^{-1}). Plasma concentrations were said to be undetectable in 10 of the 24 subjects in whom this assay was used.

The absolute systemic bioavailability for an inhaled drug is calculated by comparing the area under the plasma concentration-time curve for inhaled dosing, with that obtained following intravenous dosing. To obtain a reliable estimate, the administered doses need to be large enough to produce measurable plasma concentrations. Therefore, an estimate of the true systemic bioavailability of MF cannot reliably be made based on incomplete data and an insensitive assay, and certainly not compared with other inhaled steroids. This can be illustrated by performing similar calculations for another inhaled steroid with similar *in vitro* potency [2] (*i.e.* fluticasone propionate (FP)). The systemic bioavailability of FP in healthy subjects delivered *via* the Diskus™ (GlaxoWellcome, Research Triangle Park, NC, USA) is ~17% [3]. However, this result is based on data from a study where FP plasma levels were measured following a 1,000 μg dose, with an assay limit of detection of 25 pg·mL^{-1}. Since inhaled dosing produces plasma concentrations close to the limit of detection, had this study been performed using an assay with a 50 pg·mL^{-1} detection limit and with a 400 μg dose, the ability to detect FP would have been dramatically reduced and the estimated bioavailability would interestingly have also been ~1%. Figure 1 demonstrates that if FP and MF systemic exposure and bioavailability are compared using similar methodology to that described by THONOOR *et al.* [1], where values below the assay limit of detection are assumed to be zero, similar and misleadingly low values would be obtained for the two drugs.

Three further pieces of information support the similar systemic bioavailability of MF and FP and question the estimated systemic bioavailability of MF of <1%. Firstly, plasma concentrations of MF are readily quantifiable at higher inhaled doses in asthmatic patients [4] resulting in a mean *C*max of 243 pg·mL^{-1} after 28 days *q.i.d.* dosing of MF (1,200 μg·day^{-1} *via* Twisthaler™). The corresponding mean *C*max after 4 weeks *b.i.d.* dosing of FP (1,000 μg·day^{-1} *via* Diskus™) was 97 pg·mL^{-1} [5]. Secondly, doses of MF 800 μg *b.i.d. via* a metered dose inhaler (MDI) cause significant hypothalamic-pituitary-adrenal (HPA) axis suppression (*i.e.* ~30% compared with placebo) in patients with mild-to-moderate asthma, which was not reported to be significantly different from that obtained following FP 1,000 μg *b.i.d. via* an MDI in the same study [6]. Finally, an intra-nasal study comparing MF and FP 800 μg three times daily for 4 days, demonstrated no significant difference in systemic exposure of the two drugs based on either pharmacokinetics or cortisol levels [7]. If MF did have a very low systemic bioavailability, but still produced significant HPA-axis suppression as shown in these two studies, then one possible explanation is that MF has at least one active metabolite. In fact MF has a number of active metabolites with corticosteroid activity, including the 6-β-hydroxy metabolite and the free mometasone moiety [8]. A true estimate of the systemic bioavailability of MF must, therefore, include measurements of MF and all its active metabolites. In addition, MF and FP have similar physicochemical properties, including lipophilicity. The latter is generally well correlated with absorption characteristics and this is, therefore, further evidence that MF and FP probably have a similar potential for pulmonary absorption and systemic bioavailability.

In conclusion, the stated low systemic bioavailability of mometasone furoate is questionable based on the methodologies used to make this measurement, the significant hypothalamine-pituitary-adrenal axis suppression seen with mometasone furoate in patients with

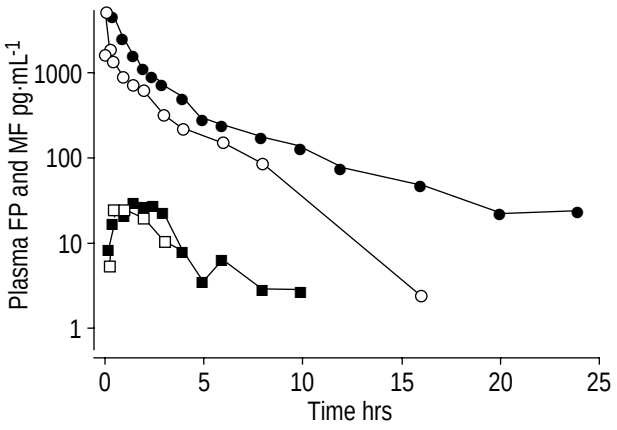

Fig. 1. – Mean plasma concentration-time profiles for inhaled and intravenous fluticasone propionate, dose normalised from 1,000 mcg and with substitution of zero for values below 50 pg·mL^{-1} and mometasone furoate following 400 mcg doses of assay with a lower limit of detection of 50 pg·mL^{-1}. □: fluticasone propionate (FP) inhaled using Diskus™; ○: FP intravenously; ■: mometasone furoate (MF) inhaled using Twisthaler™; ●: MF intravenously.

asthma and the comparable systemic exposure and cortisol effects seen with intranasal mometasone furoate and fluticasone propionate. This estimate of systemic bioavailability has potentially important safety implications for patients and should be repeated using appropriate and comparable methodologies as soon as possible.

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