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Safety of Inhaled and Intranasal Corticosteroids

Lessons for the New Millennium

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Abstract

Although inhaled and intranasal corticosteroids are first-line therapy for asthma and allergic rhinitis, there has recently been an increasing awareness of their propensity to produce systemic adverse effects. The availability of more potent and lipophilic corticosteroids and new chlorofluorocarbon (CFC)-free formulations has focused attention on these safety issues.

The main determinant of systemic bioavailability of these drugs is direct absorption from the lung or nose, where there is no first-pass inactivation. Consequently, the systemic bioavailability of inhaled corticosteroids is greatly influenced by the efficiency of the inhaler device. Thus, when comparing different inhaled corticosteroids it is imperative to consider the unique drug/device interaction.

The pharmacokinetic profile is important in determining the systemic bioactivity of inhaled and intranasal corticosteroids. For highly lipophilic drugs, such as fluticasone propionate or mometasone furoate, there is preferential partitioning into the systemic tissue compartment, and consequently a large volume of distribution at steady state. In contrast, drugs with lower lipophilicity, such as triamcinolone acetonide or budesonide, have a smaller volume of distribution. The systemic tissue compartment may act as a slow release reservoir, resulting in a long elimination half-life for the lipophilic drugs.

For intranasal corticosteroids, a high degree of lipophilicity diminishes water solubility in mucosa and therefore increases the amount of drug swept away by mucociliary clearance before it can gain access to tissue receptor sites. This may reduce the anti-inflammatory efficacy in the nose, but might also reduce the propensity for direct systemic absorption from the nasal cavity.

The hydrofluoroalkane (HFA) formulations of beclomethasone dipropionate are solutions and exhibit a much higher respirable fine particle dose than do the CFC formulations. Dose-response studies with one of the HFA formulations have shown therapeutic equivalence at half the dosage, with little evidence of adrenal suppression at dosages up to 800 μg/day. A lack of similar studies for another of the available HFA formulations has led to a discrepancy in the recommendations for equivalence. Although *in vitro* studies have pointed to a similar fine particle distribution for the HFA and CFC formulations of fluticasone propionate, this is not supported by *in vivo* data for lung bioavailability, suggesting that care will be required when switching these formulations.

Prescribers of inhaled and intranasal corticosteroids should be aware of the

potential for long term systemic effects. The safest way to use these drugs is to 'step-down' to achieve the lowest possible effective maintenance dosage.

The use of topically potent corticosteroids delivered via the inhaled or intranasal route has revolutionised the treatment of asthma and allergic rhinitis, respectively. Inhaled and intranasal corticosteroids are now widely recognised as being first-line anti-inflammatory therapy for allergic airway disease and have a much better therapeutic ratio than the corresponding dose of oral corticosteroid required to produce the same clinical response.[1,2]

The past decade has seen the availability of newer, more potent topical corticosteroids for inhaled and intranasal use such as fluticasone propionate and mometasone furoate. It has been reported by the manufacturers of these drugs that they have a superior therapeutic ratio due to enhanced potency in combination with lower systemic bioavailability. However, for these more potent drugs there has been a considerable amount of systemic safety data suggesting that the enhanced potency may be a double-edged sword, along with an increasing awareness of direct systemic absorption from the nose and lung which avoids the first-pass effect.[3] There has also been a large body of published data looking at the sensitivity of systemic effect markers such as adrenal suppression for detecting potential systemic bioactivity with both new and older corticosteroids.[4]

Despite greater understanding of the systemic bioavailability of inhaled and intranasal corticosteroids, there remains a surprising lack of awareness amongst prescribers as to their potential for systemic adverse effects, and how the newer drugs compare with older drugs such as beclomethasone dipropionate, triamcinolone acetonide and budesonide.

There are several prerequisites which will determine an optimum profile for an inhaled or intranasal corticosteroid. These include: (i) a high level of glucocorticoid receptor affinity and potency; (ii) prolonged retention within the airway; (iii) adequate deposition at the site of airway glucocorticoid receptors; (iv) a high degree of hepatic first-pass inactivation; (v) rapid systemic elimination; (vi) low systemic tissue distribution and retention; (vii) low systemic bioactivity at therapeutic doses; and (viii) low oropharyngeal deposition. Of course, in real life there is no drug which fulfils all of these criteria and any increase in therapeutic efficacy may be partially offset by an increase in adverse effects. Furthermore, these criteria may differ slightly for the inhaled and intranasal routes of administration; for example, a slow dissolution/absorption rate due to high lipophilicity (e.g. fluticasone propionate or mometasone furoate) is likely to be favourable in the lung but not in the nose, where there is rapid mucociliary clearance. There may be other factors which determine the therapeutic ratio, for example, the tissue specific esterification of budesonide to conjugates in the lung, which may prolong its duration of action.[5]

This review article provides a brief overview of the present state of knowledge of the systemic safety of inhaled and intranasal corticosteroids, as developed over the past decade, and what lessons can be learned for the new millennium. It is not intended to be a systematic review or meta-analysis of systemic safety studies, as this has recently been published in detail elsewhere.[6,7] Rather, its aim is to present our current opinions, provide a stimulus for further discussion and generate ideas for future clinical studies.

1. Glucocorticoid Potency

The available corticosteroids differ in their degree of topical glucocorticoid potency which is conventionally evaluated using the Mackenzie vasoconstrictor assay, and show rank order of potency as follows: fluticasone propionate > mometasone furoate > budesonide > beclomethasone dipropionate > triamcinolone acetonide.[8] Indeed, there seems to be a similar rank order for *in vitro* human lung glucocorticoid receptor affinity, although beclomethasone-17-monopropionate, an active metabolite of beclomethasone dipropionate, exhibits a similar glucocorticoid receptor affinity to momet-

asone furoate.[8] It is worth pointing out that *in vitro* studies evaluating glucocorticoid potency may be biased by the static experimental set-up not seen in real-life clinical practice, where therapy is always dynamically pulsed. It has been shown that while continuous incubation of a glucocorticoid sensitive cell line shows a 6-fold difference in potency between fluticasone propionate and budesonide, this difference was actually reversed following pulse exposure.[9]

Other *in vitro* potency data have shown the rank order for inhibition of anti-IgE–induced histamine release by basophils as: fluticasone propionate > mometasone furoate > budesonide > beclomethasone dipropionate = triamcinolone acetonide; with a similar order for inhibition of interleukin-5–induced eosinophil viability.[10] In contrast, fluticasone propionate and budesonide have an equipotent effect on eicosanoid release, while fluticasone propionate is more potent than budesonide at inhibiting cytokine release.[11,12]

This hierarchy for *in vitro* glucocorticoid potency would be expected to relate to the effects of these compounds on allergic airway inflammation in patients with allergic rhinitis or asthma. However, in real life it is difficult to show a similar hierarchy of corticosteroid potency in clinical studies. Many factors other than *in vitro* potency will affect the clinical response. For example, the dose-response curve for antiasthmatic efficacy *in vivo* is rather flat at higher dosages, and many studies with inhaled corticosteroids have evaluated responses on the plateau part, rather than on the initial steep part, of the curve.[7] The likelihood is that for patients with mild to moderate asthma or allergic rhinitis, who comprise the bulk of the patient population, the effects of increasing potency are minimal as the doses used in clinical practice are often on the plateau part of the dose-response curve. A more sensitive way of assessing relative therapeutic potency is to perform back-titration to establish the minimal effective maintenance dose. In such a study, fluticasone propionate and budesonide given via dry powder inhaler devices (Diskhaler® and Turbuhaler®) were found to be therapeutically equivalent on a microgram nominal dose basis for their minimal maintenance doses.[13]

It is also important to appreciate that as the curve for therapeutic efficacy becomes flat, the dose-response curve for systemic adverse effects becomes steep.[7] In general, for antiasthmatic efficacy the curve becomes flat at a dosage of beclomethasone dipropionate equivalent to or above 800 μg/day in adults and above 400 μg/day in children, whereas systemic activity dose-response becomes steep above these doses. The threshold doses for benefit versus risk will depend on the individual patient's glucocorticoid receptor sensitivity as well as the severity of asthma.

In this respect, as glucocorticoid receptors are ubiquitous throughout the body, one would predict that increased glucocorticoid potency might translate into greater systemic adverse effects on the steep part of the systemic dose-response curve.[7] In effect this means that increased glucocorticoid potency might translate into a worse therapeutic ratio, at least for patients with less severe asthma or allergic rhinitis. For patients with more severe disease it is therefore conceivable that enhanced glucocorticoid potency might be therapeutically desirable and that any potential increase in systemic effects might be an acceptable trade-off. In more severe disease it is also possible that being able to use a lower effective maintenance dosage of a higher potency corticosteroid might ameliorate the therapeutic ratio.

It is well recognised that in real-life practice most patients do not have their dosage of inhaled or intranasal corticosteroid tapered to achieve minimal effective maintenance requirements, and so this makes it even more likely that, for patients who are receiving higher potency corticosteroids, there is a greater potential for a worse therapeutic ratio, as compared with lower potency corticosteroids. This is particularly the case as current guidelines now recommend initiating therapy with a high dosage of inhaled corticosteroid followed by step-down, although in our experience the latter is rarely achieved in either primary or secondary care. Nonetheless, it is important for prescribers to be aware that

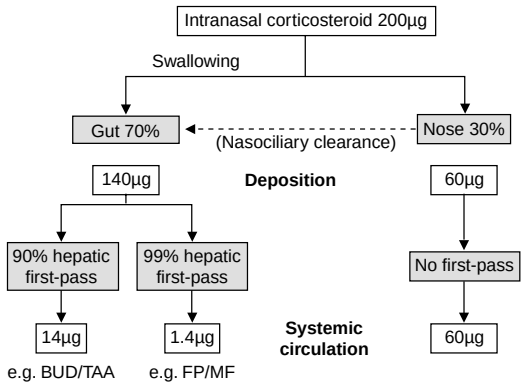

Fig. 1. Schematic diagram depicting systemic bioavailability of a 200µg nominal dose of 4 different intranasal corticosteroids: mometasone furoate (MF), fluticasone propionate (FP), budesonide (BUD) and triamcinolone acetonide (TAA). This scheme depicts the total systemic absorption of unchanged drug for drugs with a 90% hepatic first-pass such as BUD and TAA (total systemic bioavailability 74µg) as compared with the total systemic absorption of unchanged drug for drugs with a 99% hepatic first-pass such as MF and FP (total systemic bioavailability 61.4µg). This is based for schematic purposes on a similar degree of intranasal deposition for all 4 drugs (30%), although in reality this may vary between formulations. However mucociliary clearance (broken line) may also occur from the nose to the oropharynx to a varying degree depending on the lipophilicity of drug, which in turn may reduce the mucosal exposure and bioavailability.

increased glucocorticoid potency may be a double-edged sword in that it is the same glucocorticoid receptor in the airway as in systemic tissue, and consequently this may represent a case of 'no gain without pain'.

2. Systemic Bioavailability

2.1 First-Pass Metabolism

For the inhaled route of administration with conventional pressurised metered dose inhalers (pMDI), of the ex-actuator dose which is delivered to the patient most is deposited in the oropharynx and subsequently swallowed (approximately 80%) and only a small amount reaches the lungs (approximately 20%).[3] The fate of the swallowed dose is then determined by the extent of first-pass hepatic metabolism. This degree of hepatic first-pass inactivation varies between the available inhaled corticosteroids with values of 99% first-pass for fluticasone propionate and mometasone furoate, approximately 90% for budesonide and 80 to 90% for triamcinolone acetonide.[14-19]

The situation for beclomethasone dipropionate is more complicated because it is metabolised not only to inactive compounds in the gut, such as beclomethasone alcohol and beclomethasone-21-monopropionate, but also to the active beclomethasone-17-monopropionate.[19] Surprisingly, no data are yet available on absolute oral availability of either beclomethasone dipropionate or its active beclomethasone-17-monopropionate metabolite. Charcoal block studies with beclomethasone dipropionate have indicated approximately 60 to 70% overall first-pass inactivation, at least in terms of the systemically bioactive moieties producing adrenal suppression.[20] The first-pass metabolism of beclomethasone-17-monopropionate to beclomethasone alcohol is as prominent in the lung as in the gut. Thus, whether beclomethasone dipropionate enters via the lung or the gut, an equal amount of beclomethasone monopropionate is inactivated at first-pass to beclomethasone alcohol.[21,22] This may explain why the systemic bioactivity of hydrofluoroalkane (HFA)-beclomethasone dipropionate is comparable to that of chlorofluorocarbon (CFC)-beclomethasone dipropionate, despite there being much greater lung deposition with the HFA formulation.[23]

At first sight it would therefore appear that drugs with almost complete first-pass hepatic inactivation (i.e. fluticasone propionate and mometasone furoate) would have a markedly superior safety profile in terms of the relative proportions of systemically bioavailable drug from the gut. This only takes into account one side of the equation, as there is also direct systemic absorption of the active unchanged drug from the lung or nose, where there is no first-pass metabolism (except for beclomethasone dipropionate).[24] It is evident that the larger component of systemic bioavailability arises from the nose or lung with the gut contributing a much lower proportion of the total systemic absorption of the un-

changed active drug (figs. 1 and 2). However, for drugs with a high degree of lipophilicity (e.g. fluticasone propionate and mometasone furoate) there may be greater mucociliary clearance from the nose to the throat, which may reduce the amount of nasal retention and consequently nasal absorption (fig. 1). Again, the situation for beclomethasone dipropionate is more complicated since, as in the gut, there is partial biotransformation to active and inactive metabolites in the lung, although whether or not there is first-pass metabolism in the nose is unknown.

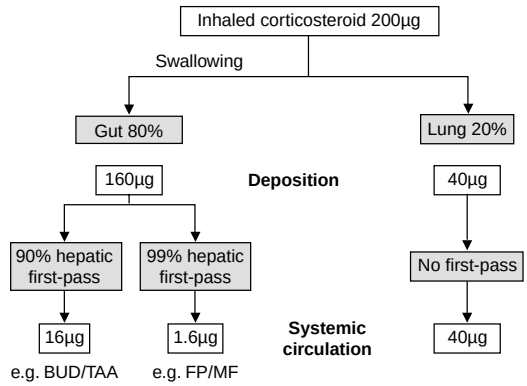

Fig. 2. Schematic diagram depicting systemic bioavailability of a 200µg nominal dose of 4 different inhaled corticosteroids: mometasone furoate (MF), fluticasone propionate (FP), budesonide (BUD) and triamcinolone acetonide (TAA). This scheme depicts the total systemic absorption of unchanged drug for drugs with a 90% hepatic first-pass such as BUD and TAA (total systemic bioavailability 56µg) as compared with the total systemic absorption of unchanged drug for drugs with a 99% hepatic first-pass such as MF and FP (total systemic bioavailability 41.6µg). This is based for schematic purposes on a similar degree of lung deposition for all 4 drugs (20%), although in reality this may vary between formulations.

2.2 Delivery Devices

Inhaler devices with low or high efficiency for lung delivery would be expected to have a commensurate effect on the systemically bioavailable dose, and there are many examples in the literature to substantiate this claim. Pharmacokinetic studies with budesonide using a charcoal block method have dissected out the lung versus gut components of systemic bioavailability.[25] These data showed that for budesonide the dose delivered to the lung was approximately 2-fold greater with the dry powder Turbuhaler® (30%) than the pMDI (15%), whereas the gut deposition after swallowing was approximately 45% for Turbuhaler® versus 75% for pMDI. Given that there is 90% first-pass inactivation for the swallowed dose but no first-pass in the lung, the total (gut + lung) systemic absorption for a 1000µg nominal dose via Turbuhaler® and pMDI would amount to 345µg for Turbuhaler® (lung 300µg + gut 45µg) and 225µg for pMDI (lung 150µg + gut 75µg). Thus for budesonide the ratio of the lung dose to the total systemic availability is higher with an efficient device such as Turbuhaler® (ratio = 87%) compared with pMDI (ratio = 66%).

There is also the theoretical potential for direct systemic absorption without first-pass from the oropharyngeal cavity, particularly with pMDIs where there is a high degree of buccal deposition. Using a mouth rinsing technique with activated charcoal it has been shown that direct buccal absorption of fluticasone propionate pMDI is negligible, as assessed by the degree of detectable adrenal suppression.[26] This presumably reflects the relatively short exposure time in the buccal cavity prior to swallowing, along with the relatively small absorptive surface area.

The effect of adding in a large volume spacer device is to reduce the oropharyngeal deposition whilst at the same time increasing the respirable lung dose. Thus, for a drug such as beclomethasone dipropionate which has a relatively lower degree of oral first-pass inactivation, the overall effect of adding in a large volume spacer will be to reduce the total systemic bioavailability. For drugs with a higher degree of hepatic first-pass inactivation, the net effect will be to increase the systemic bioavailability due to the predominant effect of lung absorption. This has been shown with budesonide and fluticasone propionate delivered by pMDI where the addition of a large volume spacer results in a 2-fold increase in adrenal suppression.[27,28] When comparing the same nominal dose of fluticasone propionate delivered via pMDI plus large volume spacer versus dry powder Diskus® device, there

was a 5-fold difference in systemically bioavailable drug as assessed by adrenal suppression on the steep part of the dose-response curve for both devices.[29] This confirms the findings of *in vitro* studies where the respirable fraction of fluticasone propionate pMDI alone is 2-fold greater than the dry powder device, while the use of a spacer doubles the lung delivery of the pMDI in turn.[30,31] A difference amounting to 7-fold greater adrenal suppression has been observed when comparing the same nominal dose of fluticasone propionate delivered via pMDI with a primed spacer versus a high efficiency breath enhanced jet nebuliser (Pari LC Plus).[32] This reflects the relative inefficiency of many nebulising systems for delivering inhaled corticosteroids, as a large proportion of drug is wasted or left as dead space in the nebuliser.

The systemic bioavailability of different inhaler devices should not be considered in isolation, as the overall therapeutic ratio will also be determined by antiasthmatic clinical efficacy. Hence, one might predict that increased systemic absorption due to improved lung delivery might be associated with a concomitant improvement in antiasthmatic efficacy, especially for inhaler devices which produce greater deposition in the smaller peripheral airways, as the latter represents the largest surface area of inflammation. A good example of this from a dose-response study is the 2-fold increase in dose potency for cortisol suppression when adding in a large volume spacer to budesonide pMDI, which was associated with a commensurate 2-fold increase in antiasthmatic efficacy.[27] This finding would suggest that the large volume spacer resulted in a 2-fold improvement in peripheral airway deposition of budesonide, which is in keeping with *in vitro* findings of a 2-fold increase in the respirable fine particle fraction when using the large volume spacer device.[31] It is, however, conceivable that much greater levels of peripheral deposition might not result in a commensurate improvement in antiasthmatic efficacy, but merely result in increased systemic absorption from the alveoli. It is likely that a balance is necessary in terms of peripheral deposition of corticosteroid and fine particle dose in order to achieve an even distribution to large and small airways.

In a study of patients with asthma given fluticasone propionate at dosages of 500 or 2000 μg/day via Diskhaler® dry powder device, there were significant differences between dosages in systemic bioactivity markers including serum cortisol level and peripheral blood eosinophil suppression, whereas for airway parameters such as methacholine and adenosine monophosphate bronchial challenge or sputum eosinophilia, there was no significant difference.[33] These findings suggested that the therapeutic ratio for fluticasone propionate dry powder inhaler declined sharply above a watershed dose of 500 μg/day.[34] This may be due to the particular performance properties of the Diskhaler® dry powder device, which delivers a 2-fold lower respirable fine particle dose than the fluticasone propionate pMDI.[30] Consequently, increasing the dose of fluticasone propionate dry powder may result in proportionately more large particles being delivered to the central airways and a less than expected impact on small airway inflammation. In other words, increasing the dose may not be as important as optimising the fine particle delivery. In another study, a difference in lung bioavailability between fluticasone propionate formulations was found where the relative ratio for plasma drug concentration between pMDI versus Diskus® dry powder was 1.56, with the relative ratio for cortisol suppression being 1.44.[35]

2.3 Patients versus Healthy Volunteers

There has been considerable controversy as to whether healthy volunteers can be used to evaluate the relative systemic bioactivity profiles of 2 different drugs as a surrogate for what happens in patients with asthma. When comparing fluticasone propionate and budesonide given via their respective pMDIs, the relative ratio for suppression of 8am serum cortisol level was found to be 3.1 in healthy volunteers and 3.5 in patients with asthma.[36,37] For fluticasone propionate and budesonide given via their respective dry powder inhalers, the relative ratio

for suppression of serum cortisol level [measured as area under the curve (AUC)] amounted to 1.7 in healthy volunteers versus 2.1 in patients with asthma.[38,39] Steady-state administration of 2000 μg/day (nominal ex-valve dose) of fluticasone propionate pMDI resulted in 60% suppression of overnight urinary cortisol/creatinine excretion in patients with asthma compared with 53% suppression in healthy volunteers,[36,40] whereas for triamcinolone acetonide pMDI with spacer at a dose of 1600 μg/day (ex-actuator dose) the steady-state suppression of overnight urinary cortisol/creatinine was 30% in both patients with asthma and healthy volunteers.[41,42] These studies indicate that healthy volunteers and patients with asthma are broadly equivalent in terms of their systemic response to inhaled corticosteroids.

However, intuition suggests that with increasing severity of asthma there would be a proportionate reduction in lung absorption from smaller peripheral airways. This is turn might mean than patients with severe asthma would in effect be protecting themselves from the systemic adverse effects of high doses of inhaled corticosteroids because of a reduction in lung bioavailability. All of the above studies evaluated patients with asthma of mild to moderate severity and so it is also important to look at the effects of more severe airflow obstruction on lung bioavailability and systemic adverse effects. In one study with a single 500μg dose of fluticasone propionate dry powder in patients with asthma of varying degrees of severity there was a highly significant linear correlation between the absolute magnitude of adrenal suppression and the lung function expressed as percentage predicted forced expiratory volume in 1 second (FEV_1).[43] This is consistent with pharmacokinetic data where there was 62% lower plasma fluticasone propionate concentrations (as AUC) in patients with moderately severe asthma (FEV_1 = 54% predicted) than in healthy volunteers receiving inhaled fluticasone propionate 1000 μg/day at steady state via pMDI with spacer.[44] Another study found no difference between healthy volunteers and patients with mild asthma in plasma fluticasone propionate or budesonide concentrations after inhalation of 1000μg of both drugs following single or repeated administration.[45] Thus, fluticasone propionate may behave differently in terms of its bioavailability in patients with mild versus severe asthma.

Other data have also shown greater suppression of urinary cortisol metabolites in healthy volunteers compared with patients with asthma after steady-state administration of fluticasone propionate dry powder 1500 μg/day, and there were more patients with asthma with plasma fluticasone concentrations below the limit of quantification compared with healthy controls.[46] In the same study there were no significant differences between healthy individuals and patients with asthma receiving budesonide dry powder 1600 μg/day. This apparent disparity in lung bioavailability between fluticasone propionate and budesonide dry powder inhaler devices in healthy individuals and those with asthma may reflect the higher respirable fraction and smaller particle size from the Turbuhaler® compared with Diskus®,[30] which would tend to overcome the effects of reduced airway calibre in patients with asthma.

An alternative explanation might be that the higher lipid solubility of fluticasone propionate would result in a shorter dwell time in bronchial mucosa than budesonide, and consequently facilitate proximal mucociliary clearance. Hence, a more central deposition of fluticasone propionate dry powder along with a greater propensity for mucociliary clearance might conceivably result in a lower degree of lung bioavailability in patients with asthma compared with healthy individuals. Possibly, the more peripheral uptake via the fluticasone propionate pMDI device, particularly in conjunction with a spacer, will be less affected by mucociliary clearance and hence less affected by asthma severity.

Likewise, for patients with allergic rhinitis it is important to consider whether the inflammatory disease process itself will influence the absorption from the nose. The mucosal swelling might conceivably reduce access to the available absorptive surface area within the nasal cavity, whilst it is unclear whether

there are inherent differences in absorption across inflamed compared with healthy mucosa. One might predict that bioavailability would, if anything, tend to be decreased in patients with allergic rhinitis compared with healthy volunteers. This has been prospectively addressed in a study where the pharmacokinetic profile of intranasal triamcinolone was not different comparing patients with allergic rhinitis versus healthy volunteers.[47] However, further studies are required to investigate whether more severe disease, particularly in association with nasal polyposis, might reduce the potential bioavailability of intranasal corticosteroids.

Following intranasal delivery there is rapid mucociliary clearance from the nose into the throat and consequently a large proportion of the dose is swallowed. The nasociliary clearance will vary depending on the lipophilicity of the drug, which in turn may reduce the mucosal exposure and systemic bioavailability (fig. 1). This is why patients can usually taste the corticosteroid formulation within the first 30 seconds after administration. A high degree of lipophilicity diminishes water solubility and therefore increases the amount of drug swept away by nasociliary clearance before it can get access to the receptor sites. Thus, high lipophilicity may be an unfavourable property for the efficacy of an intranasal corticosteroid as the drug has to be dissolved and absorbed into the target cells in the nasal mucosa in order to bind to the receptor. Indeed, a number of studies indicate that the less lipophilic drugs show a higher clinical potency in allergic rhinitis than either fluticasone propionate or mometasone furoate, and that low doses of intranasal budesonide are as effective as fluticasone or mometasone.[48-50] The moderate clinical efficacy of fluticasone propionate and mometasone furoate may be attributable to the high degree of nasociliary clearance. Because of nasociliary clearance, drugs with a lower degree of hepatic first-pass metabolism for the swallowed fraction (e.g. beclomethasone or betamethasone) may have a greater propensity for systemic adverse effects than drugs with a higher degree of hepatic first-pass inactivation.

There are also differences in systemic bioavailability between the available intranasal delivery devices. In one study comparing delivery of intranasal budesonide formulations, the systemic bioavailability with reference to the metered dose was 29% for aqueous pump spray, 20% for dry powder Turbuhaler® and 13% for pressurised aerosol.[51] It is therefore likely that the higher degree of bioavailability with aqueous nasal sprays may translate in to a greater propensity for systemic adverse effects, although this has not been prospectively evaluated in clinical studies to date. However, as with inhaler devices, it is possible that enhanced efficiency of intranasal delivery may translate into greater clinical efficacy in allergic rhinitis and offset any increase in systemic adverse effects, and consequently an ability to use a lower effective maintenance dosage.

3. Pharmacokinetics

Once the corticosteroid has been absorbed from the lung or the nose, its distribution and elimination will have an important influence in terms of exposure and duration of systemic tissues to the drug. One of the most important determinants of the pharmacokinetic profile is the lipophilicity, with fluticasone propionate exhibiting much higher lipophilicity than drugs such as budesonide or triamcinolone acetonide. Although no data on lipophilicity of mometasone furoate are yet available, the pharmacokinetic behaviour of this drug would suggest a lipophilicity similar to that of fluticasone propionate. Pharmacokinetic studies with the intranasal or inhaled route of administration with mometasone furoate or fluticasone propionate have shown low plasma drug concentrations after single dose administration, and very low bioavailability relative to the same reference dose given via the intravenous route of administration. For example, pharmacokinetic studies with single doses of inhaled and intranasal mometasone furoate have shown a bioavailability of less than 1% in terms of the measurable concentration of mometasone furoate in plasma.[52,53] However, in our opinion some of these studies require closer scrutiny, both in terms of their pharmacokinetics (discussed in this section)

and of the pharmacodynamic effects elicited by such apparently low concentrations (discussed in section 5).

In one such study a single 400μg dose of mometasone furoate dry powder (Twisthaler®) was compared with the same reference dose given intravenously to 24 healthy adult volunteers.[52] The conclusion from this study was that the total systemic bioavailability of mometasone furoate was less than 1% using this device. However, closer inspection of the data reveals that mean plasma mometasone furoate concentrations were consistently below the limit of quantification of 50 ng/L with the inhaled (fig. 3) but not the intravenous route. This limit of quantification for mometasone furoate was rather high as compared with that in similar studies with fluticasone propionate (3 ng/L).[55] Consequently, we believe that it is not meaningful to draw any valid conclusions as to the bioavailability from the mometasone furoate dry powder inhaler device from these data, because the assay was insensitive below the limit of quantification.

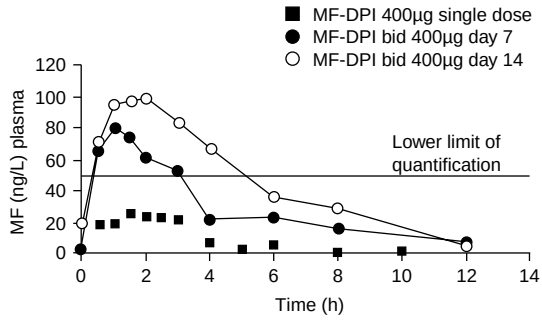

Fig. 3. Plasma concentration versus time data after single and repeated 400μg twice daily (bid) administration of inhaled mometasone furoate (MF) via Twisthaler® dry powder (DPI). The data show clear evidence of accumulation between days 1, 7 and 14. This is a composite of data from Thonoor et al.[52] and Affrime et al.[54] The points are means for n = 24 for the single dose study[54] and n = 16 for the repeated dose study;[52] individual values below the limit of quantification were recorded as zero.

Indeed, assuming no first-pass metabolism in the lung, one could argue that if the inhaled bioavailability was less than 1% this infers that the lung deposition from the mometasone furoate Twisthaler® must also be less than 1%, because there is almost complete first-pass metabolism for the swallowed dose. This is clearly not the case, because *in vitro* performance studies of the mometasone furoate Twisthaler® using a modified Andersen cascade impactor revealed that approximately 35% of the claimed delivered dose was in the particle size range considered to be optimum for inhalation aerosols.[56] Indeed, it was evident that 12.6% of claimed delivered dose for mometasone furoate Twisthaler® 200μg per inhalation was less than 2μm. Particles less than 2μm are more likely to penetrate the acinar airways in the periphery of the lung and would be absorbed directly into the systemic circulation without any first-pass metabolism. (In passing, the relevance of assessing unchanged mometasone furoate can be disputed, as mometasone furoate may form pharmacologically active metabolites.[57]) By comparison, in a pharmacokinetic evaluation of a single 1000μg dose of fluticasone propionate Diskhaler® dry powder, the systemic availability was 15.6% of the nominal dose, using a sensitive assay with a lower limit of quantification of 3 ng/L.[55] Given that the performance of the mometasone furoate Twisthaler® is at least as good as that of the fluticasone propionate Diskhaler®, the bioavailability of inhaled mometasone furoate would be expected to be more similar to that of fluticasone propionate.

Similar to fluticasone propionate, our interpretation is that inhaled mometasone furoate exhibits considerable accumulation during repeated administration, which suggests that mometasone furoate is at least as lipophilic as fluticasone propionate. In a parallel group study of adult patients with mild to moderate asthma, a steady-state pharmacokinetic profile was evaluated over 28 days of treatment with mometasone furoate Twisthaler® 400 or 800μg twice daily.[54] The pharmacokinetic data showed an increase in the AUC comparing the pro-

file after 7 versus 14 days of treatment (fig. 3), suggesting a delayed accumulation effect, possibly due to slow equilibration between the tissue and plasma compartments between these 2 time-points. Indeed, unlike previous data with a single dose of mometasone furoate Twisthaler® 400μg,[52] mean plasma concentrations of mometasone furoate over the first 4 hours were consistently higher than the lower limit of quantification of 50 ng/L, suggesting a greater bioavailability from the lung with this device than suggested from the single dose study (fig. 3). Steady state appeared to have been reached after 14 days in this study.[54] This is clear evidence that marked accumulation of inhaled mometasone furoate occurs. Consequently, estimates of lung bioavailability for mometasone furoate after administration of a single dose will be greatly underestimated as compared with steady-state administration, and indeed the latter are more relevant as in real life patients do not actually take a single dose but take the drug repeatedly once or twice daily over extended treatment periods for prophylactic therapy.

A similar study in patients with mild to moderate asthma administered mometasone furoate pMDI 400 and 800μg twice daily.[58] Close inspection of the pharmacokinetic profile for plasma mometasone furoate shows that in this study the maximal plasma concentration (C_{max}) was approximately half that seen in a previous study in a similar type of patient who received the same dosage of mometasone furoate via the dry powder Twisthaler® device.[54] For example, after 14 days of treatment with 800μg twice daily the C_{max} of mometasone furoate was approximately 80 ng/L with pMDI as compared with a value of approximately 160 ng/L at the same time-point with mometasone furoate dry powder. After 14 days of treatment with mometasone furoate pMDI 400μg twice daily, plasma mometasone furoate concentrations were consistently below the lower limit of quantification of 50 ng/L, whereas at the same time-point with the same dose of mometasone furoate Twisthaler®, values were consistently above the limit for the first 4 hours after inhalation. Taken together, these pharmacokinetic data suggest that the lung bioavailability and consequently lung deposition of mometasone furoate pMDI is approximately half that of the dry powder Twisthaler® device.

For highly lipophilic drugs, such as mometasone furoate or fluticasone propionate, measuring the concentration in the water soluble plasma compartment is only looking at a relatively small proportion of the systemically distributed drug (fig. 4). It is likely that mometasone furoate partitions preferentially into the lipid soluble systemic tissue compartment where most of the drug resides, resulting in a large volume of distribution, similar to that of fluticasone propionate. The volume distribution of fluticasone propionate is 850[55] versus 103L for triamcinolone acetonide.[59] This is why highly lipophilic drugs exhibit particularly low plasma concentrations, in contrast with much higher plasma concentrations with drugs such as budesonide or triamcinolone acetonide which are less lipophilic. An analogy is to think of a wet sponge with the constant drip representing the plasma compartment, and the total body exposure as the amount of drug which comes out once the sponge is squeezed.

Consequently, measuring only the low concentration in the plasma compartment will greatly underestimate the total body exposure with lipophilic compounds. Furthermore, the equilibration between the systemic tissue and plasma compartments for drugs also results in a long elimination half-life, with the systemic tissues in effect acting as a slow-release reservoir. For example, estimates for fluticasone propionate using a sensitive drug assay have shown an elimination half-life of between 11 to 14 hours, as compared with between 2 to 3 hours for budesonide or triamcinolone acetonide and 6.5 hours for beclomethasone-17-monopropionate.[14,25,55,59-61]

Similar arguments apply to pharmacokinetic data evaluating the intranasal route of administration for mometasone furoate. The elimination half-life was estimated at 4.5 hours after an intravenous bolus of 400μg, whereas after a single 400μg intranasal dose the majority of plasma samples were consistently below the lower limit of quantification at 50 ng/L.[52,53] The estimated systemic bioavailability for the intranasal route of administration

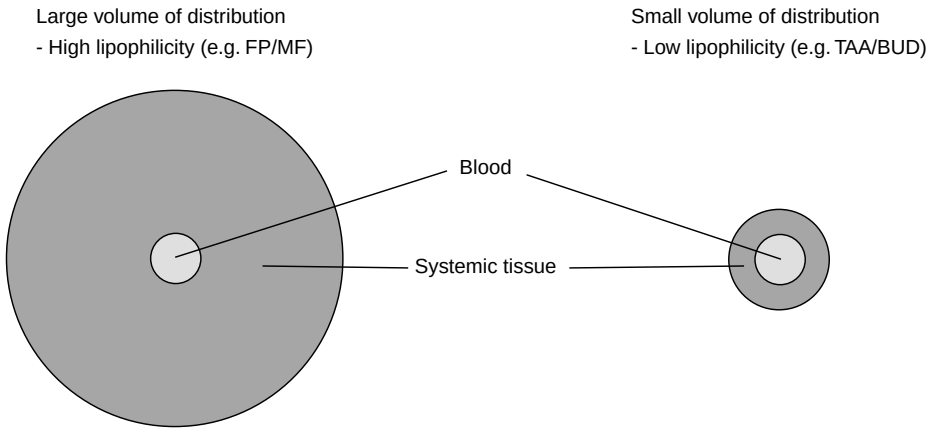

Fig. 4. Schematic diagram depicting the difference between drugs with a high [e.g. fluticasone propionate (FP) and mometasone furoate (MF)] and low [e.g. triamcinolone acetonide (TAA) and budesonide (BUD)] degree of lipophilicity in terms of partitioning between the hydrophilic (water soluble) blood compartment and the lipophilic (fat soluble) systemic tissue compartment, and the consequent differences in total volume of distribution. Therefore, only measuring the concentration in the blood compartment will greatly underestimate the total systemic exposure at steady state for lipophilic corticosteroids.

was estimated at 0.1%, although the same methodological criticisms with respect to the sensitivity of the assay as with the inhaled bioavailability data are applicable. Moreover, with the intravenous route of administration with mometasone furoate, plasma concentrations after 20 hours were below the limit of quantification, making an estimation of the terminal elimination phase inaccurate.[52] If the elimination half-life of mometasone furoate was truly 4.5 hours, then it would not be consistent with the known degree of accumulation which occurs between single dose and steady state.

Pharmacokinetic data in healthy adults using intranasal mometasone furoate and fluticasone propionate administered at 12 times the clinical dose for 4 days (2400 μg/day) showed apparently low systemic bioavailability (<1%) using an assay with a detection limit of 20 ng/L for both drugs.[62] This would not explain the pharmacodynamic data showing detectable systemic bioactivity and, particularly, evidence of peripheral glucocorticoid receptor down-regulation at conventional doses of 200 μg/day of fluticasone propionate.[63] This apparent discrepancy between bioavailability and detectable systemic bioactivity may be explained by extensive tissue binding due to a large volume of distribution.

Pharmacokinetic studies with intranasal corticosteroids in children are sparse. In one study, children with allergic rhinitis receiving 4 times the recommended dose of intranasal triamcinolone acetonide (440 μg/day) showed maximal concentrations of plasma triamcinolone acetonide at 0.95 hours after administration, whereas after 24 hours concentrations were undetectable, in keeping with the short elimination half-life of this drug.[64] This is consistent with the pharmacokinetic profiles in adult patients with allergic rhinitis.[47]

4. Systemic Bioactivity

One of the most readily accessible and sensitive measurements of potential systemic bioactivity is suppression of endogenous cortisol secretion from the adrenal cortex.[4] There are 2 types of measurement, namely those of basal adrenocortical secretion and those which measure dynamic function of the hypothalamic-pituitary-adrenal (HPA) axis to test the level of adrenal reserve. In measuring basal adrenocortical secretion it is important to appreciate that there is a normal circadian rhythm with highest levels early in the morning and lowest levels towards midnight. Measuring a spot sample of early morning plasma cortisol is also of limited value, particularly when there is a variable sampling window between 8 and 10am, which introduces a large variability and markedly reduces the sensitivity of the test. However, this method is often adopted in large multicentre clinical studies because of its simplicity.

The most sensitive measures of basal adrenocortical function are those which integrate either 24-hour or overnight cortisol output in plasma or urine. The collection of serial plasma cortisol samples over a 24-hour period is extremely labour intensive, requiring prolonged patient confinement, and it is therefore impractical for everyday use. Likewise, compliance with a 24-hour urine collection to measure free cortisol excretion is often unrealistic in real-life, at least for outpatient studies. It is also important to point out that corticosteroids with different pharmacokinetic profiles may affect the HPA axis at differing time-points during the dosing interval.

This again emphasises the importance of measuring integrated cortisol output throughout the whole dosing interval, particularly when comparing drugs with different elimination half-lives.

The influence of dosing schedule has also been investigated in patients with asthma. In a study with budesonide, there was less suppression of plasma cortisol and serum osteocalcin when the same dose was administered in the morning as compared with dividing the does in the morning and evening.[65] There are no data directly comparing adrenal suppression with once versus twice daily fluticasone propionate in patients with asthma. However, in another study, there was significantly more suppression of 8am plasma cortisol and overnight urinary cortisol (24h after the last dose) with fluticasone propionate 750μg compared with budesonide 800μg given once daily at 8am.[66] This difference may be explained by the longer elimination half-life of fluticasone propionate than budesonide.

Fractionated collections or urinary-free cortisol excretion have therefore been employed, particularly overnight and early morning collections, coinciding with the period when cortisol output is at its highest. The measurement of urinary cortisol excretion can be further refined by correcting for creatinine excretion and is expressed as the urinary cortisol/creatinine ratio. The use of fractionated overnight or early morning measurements of urinary cortisol/creatinine excretion has been shown to be as sensitive as a full 24-hour urine collection in detecting adrenal suppression due to inhaled corticosteroids.[67] Furthermore, measurement of fractionated overnight or early morning fractionated urinary cortisol/creatinine excretion is as sensitive as integrated 24-hour or fractionated overnight plasma cortisol, measured over the same time period.[68] For example, significant suppression of overnight and early morning fractionated urinary cortisol/creatinine excretion was detected in healthy volunteers receiving a high dose of triamcinolone acetonide (1600 μg/day), without any detectable suppression of 8am serum cortisol with or without 0.5μg corticotropin (adrenocorticotrophic hormone) stimulation.[41] The use of 500 μg/day (nominal dosage) of fluticasone propionate pMDI in patients with asthma produced significant suppression of overnight urinary cortisol/creatinine excretion which amounted to 43% compared with placebo, whereas there was only 14% suppression of 8am plasma cortisol at the same dose level.[36] A 500μg daily dose of fluticasone propionate given via dry powder inhaler to patients with asthma resulted in 33% suppression of 24-hour uncorrected urinary cortisol excretion as well as a 71% reduction in peripheral blood lymphocyte glucocorticoid receptor mRNA

expression, both of which were significant effects.[69]

There are also studies with the intranasal route of administration showing detectable adrenal suppression. In a study of healthy volunteers, significant suppression of uncorrected overnight urinary cortisol excretion (43% reduction) was observed with intranasal fluticasone propionate 200μg once daily compared with placebo, whereas the effect of once daily triamcinolone acetonide 220μg was not significant (23% suppression).[70] In another study in patients with allergic rhinitis, intranasal triamcinolone acetonide 220μg once daily, intranasal budesonide 200μg once daily or 200μg intranasal mometasone furoate once daily had no significant effects on 24-hour or fractionated cortisol profiles in blood or urine.[71]

Detectable systemic bioactivity with intranasal fluticasone propionate 200μg once daily has also been shown after 2 weeks of treatment with a 37% fall in 8am serum cortisol level and a 24% fall in uncorrected 24-hour urinary cortisol.[63] In this study, after 2 weeks of intranasal fluticasone propionate there was an associated 45% fall in serum osteocalcin level, a biochemical marker of bone formation, and a 28% fall in peripheral lymphocyte glucocorticoid receptor mRNA expression. What is particularly interesting from these data was that even after a 1-week washout period there was persistent suppression of peripheral lymphocyte glucocorticoid mRNA expression (a 33% reduction) which would suggest prolonged systemic retention of fluticasone propionate with sustained release into the blood compartment. This is consistent with the large volume of distribution of fluticasone propionate due to its lipophilicity, with much higher tissue than plasma concentrations. In the same study, twice the dosage of intranasal budesonide was also found to exhibit significant effects on systemic bioactivity markers, although there was no persistent suppression of mRNA as was observed with fluticasone.

In adult patients with allergic rhinitis, intranasal fluticasone propionate 200μg once daily produced a 38% fall in peripheral blood eosinophil count and a 13% fall in uncorrected 24-hour urinary cortisol excretion, although only the former achieved statistical significance.[72] The apparent lack of adrenal suppression with 800 μg/day of intranasal fluticasone propionate using a 250μg corticotropin 6-hour infusion test[73] may be explained by the known insensitivity of the test as 250μg represents a supraphysiological dose, whereas much lower doses of corticotropin (0.5 to 1μg) are as effective at producing a stimulated cortisol response and appear to correlate well with the insulin stress test.[4] It is well recognised that the low dose corticotropin test is more sensitive in detecting more subtle insufficiency of the HPA axis in patients receiving exogenous corticosteroids in whom there is a suspicion of adrenocortical atrophy.[74] (Indeed, a normal stimulated cortisol response to 250μg corticotropin either as a bolus or 6-hour infusion may provide false reassurance to the physician in terms of predicting whether it is safe to withdraw corticosteroids or provide corticosteroid cover during stressful situations, in terms of precipitating acute adrenal insufficiency.)

There are few studies that have evaluated adrenal suppression using the low dose corticotropin test in patients receiving inhaled or intranasal corticosteroid. In a study with children and adults with asthma who were taking long term beclomethasone dipropionate or budesonide in a median daily dose of 500 μg/m^2, an impaired cortisol response to stimulation with corticotropin 0.5μg was observed in 24% of study participants who were found to have a normal response to corticotropin 250μg.[75] Furthermore, the suppression of urinary cortisol excretion correlated well with the impaired response to low dose corticotropin. In another study, children with asthma were randomised to receive either sodium cromoglycate, fluticasone propionate 500 μg/day for the first 2 months and 200 μg/day thereafter or budesonide 800 μg/day followed by 400 μg/day, with a low dose corticotropin test being performed before treatment and at 2, 4 and 6 months later.[76] The low dose corticotropin test was abnormal after both the high and low doses of inhaled corticosteroid in 23% of the children. At 4 months there

were slightly more abnormal tests in the budesonide group (9 of 30) than in the fluticasone propionate group (5 of 30). At that time the stimulated serum cortisol level was significantly lower in the budesonide group compared with the sodium cromoglycate group, whilst both budesonide and fluticasone propionate produced significant suppression compared with pretreatment baseline. However, these data should be interpreted with caution as it was an open study and compliance was not checked. Furthermore, when allowing for the difference in dose and delivery method between drugs, it is likely that the deposited lung dose of fluticasone propionate in these children was about 25% of that of budesonide (see Olsson[30]).

There are also data in adults with nasal polyposis who were treated with betamethasone dose drops twice daily, which showed significant blunting of the cortisol response to low dose (1μg) corticotropin stimulation after 6 weeks of treatment.[77] This suggests that betamethasone drops should be regarded as systemic corticosteroid therapy and is consistent with case reports of Cushings' syndrome associated with this treatment in children.[78]

The results of a meta-analysis of 22 dose-response studies showed that the slope for dose-related adrenal suppression using a variety of sensitive endpoints, was significantly steeper with fluticasone propionate in comparison with either beclomethasone dipropionate (2.1-fold, $p < 0.01$), budesonide (2.5-fold, $p < 0.001$) or triamcinolone acetonide (3.6-fold, $p < 0.01$).[7] In a further more refined meta-analysis of 21 studies focusing on urinary cortisol suppression, a similar hierarchy for relative systemic potency was found in terms of the slope of the dose-response curve for fluticasone propionate versus beclomethasone dipropionate (1.9-fold, $p < 0.05$), triamcinolone acetonide (3.7-fold, $p < 0.05$) or budesonide (4.3-fold, $p < 0.001$).[6] It was also shown for suppression of 8am plasma cortisol level from a meta-analysis of 13 studies that inhaled fluticasone propionate and oral prednisolone exhibited equal potency when both drugs were compared on a putative 1 : 10mg equivalent basis.[5] As differences between fluticasone propionate and other inhaled corticosteroids were not parallel across the dose range, this indicated that a difference in glucocorticoid receptor potency was probably not the only reason for the greatest systemic bioactivity exhibited by fluticasone propionate, but rather result from other effects such as lipophilicity and systemic tissue retention (fig. 4).

There are numerous case reports of adrenal insufficiency, growth suppression and Cushings' syndrome in patients treated with inhaled corticosteroids.[79-88] Many of these cases have been associated with the use of inhaled fluticasone propionate and it would seem that there may be some patients who are particularly susceptible to developing systemic adverse effects even at conventional doses, whereas other patients seem to be relatively resistant even at high doses. In one case treatment with high dose inhaled fluticasone propionate over 2 years resulted in classical features of Cushings' syndrome with an associated depressive psychosis and evidence of osteoporosis with a thoracic vertebral wedge fracture.[85] Indeed, this patient first presented to an endocrinologist because of osteoporosis and it was not initially appreciated that an inhaled corticosteroid could cause such marked Cushingoid features. In another case, overt acute adrenal insufficiency occurred in a child who was switched from inhaled fluticasone propionate to budesonide and who was found to have growth retardation and a blunted cortisol response to a low dose corticotropin test whilst receiving fluticasone propionate.[86]

Although in most cases adrenal suppression with inhaled corticosteroids is probably not clinically relevant, it may be prudent to measure overnight urinary cortisol excretion at baseline and whilst receiving treatment in order to assess whether there is any 'potential' for systemic adverse effects. In this respect it is known that suppression of urinary cortisol correlates with skin bruising.[89] It is not unreasonable to expect that changes in collagen turnover in one tissue such as skin might relate to altered collagen turnover in other tissues such as bone. Effects of inhaled corticosteroids on biochemical bone markers such as osteocalcin probably re-

flect short term changes in bone metabolism and, consequently, patients receiving long term high dose inhaled corticosteroid therapy should have at least 1 measurement of bone mineral density to assess whether they are at potential risk of osteopenia or osteoporosis. Clinicians therefore need to be aware of the potential in susceptible patients for developing serious adverse effects, particularly with the higher potency inhaled corticosteroids such as fluticasone propionate, and to try and step down to the lowest possible effective maintenance dose.

It is not within the scope of this review to provide a detailed appraisal of corticosteroid effects on bone, growth or ocular tissue, as these have been extensively reviewed elsewhere.[6] Effects of inhaled corticosteroids on adrenal suppression may be less sensitive than effects on growth. Preliminary data has suggested that using budesonide at a mean dose of 450 μg/day for up to 11 years in children resulted in achievement of expected final adult height.[90] Children whose mothers were receiving budesonide during early pregnancy showed no increase in congenital malformations.[91] A systematic literature review found that doses of inhaled beclomethasone dipropionate or equivalent above 1500 μg/day were associated with a significant reduction in bone density. Long term high dose inhaled corticosteroid (>1500 μg/day of beclomethasone or equivalent) exposure increases the risk of posterior subcapsular cataract and to a lesser degree ocular hypertension. Skin bruising is most likely to occur with long term high dose exposure and is a visible sign of altered collagen metabolism elsewhere in the body. More recently, in a cross-sectional study of young adults taking inhaled corticosteroids (80% were taking beclomethasone) for a median of 6 years and in a median cumulative dose of 876mg, there was a negative association between cumulative dose and bone mineral density.[92] This equated to a 0.16 standard deviation decrease in lumbar bone density for a doubling in dose. The size of effect on bone density means that a patient taking 2000 μg/day of inhaled corticosteroid for 7 years (5110mg cumulative dose) will be 1 standard deviation lower than that in a patient taking 200 μg/day for 1 year. This emphasises the importance of always reducing to the lowest possible maintenance dose of inhaled corticosteroid and to consider the use of second-line nonsteroidal therapy such as theophylline, leukotriene-antagonists or long-acting β_2-agonists to facilitate dose sparing.[93]

5. New Corticosteroids and Formulations

There has been considerable interest in the newer potent corticosteroids such as mometasone furoate, particularly in view of claims of negligible systemic bioavailability with both the intranasal and inhaled route of administration based on pharmacokinetic evaluation, as discussed in section 3. It is therefore important to also appraise the available pharmacodynamic data looking at systemic safety end-points such as adrenal suppression for inhaled and intranasal delivery of this drug.

In a single dose study in healthy volunteers, administration of 20 times the recommended daily dose of intranasal mometasone furoate (4mg) had no detectable effect on 24-hour plasma cortisol level (as AUC) compared with placebo.[94] However, in our opinion the methodology for sampling of the 24-hour plasma cortisol profile was deficient in that there was gap of 7 hours between drug administration at 11pm and the first sampling point at 6am. This 7-hour period coincides with the nocturnal and early morning corticotropin spurts and associated peak cortisol production throughout the night. Given that there is no first-pass inactivation of intranasal mometasone furoate, we find it difficult to believe that such a high dose would not be absorbed from the nose and so we feel that these data must be viewed with a degree of scepticism. Also, the volume needed to administer 4mg is probably too large to be accommodated and retained in the nose. In a separate study, adult patients with allergic rhinitis were exposed to 36 days of treatment with once daily mometasone furoate at a dosage of 200 to 400μg once daily, with no evidence of any suppression of 250μg corticotropin stimulated plasma cortisol compared with placebo.[95] There are also data in children with allergic rhinitis show-

ing no effect of once daily intranasal mometasone furoate 50, 100 or 200μg compared with placebo for 7 days on the 250μg corticotropin response.[96] However, given the known insensitivity of the supraphysiological 250μg dose of corticotropin, no valid conclusions can be made regarding the lack of adrenal suppression in either adults or children, and further studies are required using more appropriate end-points.

Studies have also been performed with mometasone furoate dry powder (Twisthaler®) in patients with asthma. In a parallel group study of 64 adult patients with mild to moderate asthma, a steady-state pharmacokinetic profile and plasma cortisol 24-hour profile was evaluated over 28 days of treatment with mometasone furoate Twisthaler® 400 or 800μg twice daily, prednisone 10mg once daily (positive control for HPA suppression) or placebo.[54] The pharmacokinetic data from this study have been discussed in detail in section 3, but recall that there was evidence of marked accumulation of mometasone furoate with repeated administration. The pharmacodynamic profiles for 24-hour plasma cortisol showed significant suppression with mometasone furoate 400μg twice daily after 7, 14 and 21 days of treatment, with a degree of suppression amounting to between 19 and 25%, as compared with placebo values. There was also significant suppression compared with placebo with mometasone furoate 800μg twice daily throughout the whole 28-day treatment period, with the degree of suppression amounting to between 21 and 40%. In the same study, prednisone 10mg once daily also produced significant suppression amounting to between 64 and 72% over the 28-day period. However, these data were confounded by baseline values being appreciably lower in the patients who received mometasone furoate 800 compared with 400μg twice daily, and so a direct comparison is difficult to make. Nonetheless, the presence of significant adrenal suppression with mometasone furoate Twisthaler® 400μg twice daily clearly indicates to us that the drug is bioavailable from the lung (as it has almost complete oral first-pass metabolism) and so we find it difficult to understand the claim (section 3) that this drug has less than 1% systemic bioavailability when given via its dry powder inhaler device.

In a similar study in patients with mild to moderate asthma, mometasone furoate pMDI (400 and 800μg twice daily) was compared with fluticasone propionate pMDI at 880μg twice daily and placebo.[58] Again, the pharmacokinetic data are discussed in section 3, but the salient point is that lung deposition and bioavailability from mometasone furoate pMDI is approximately half that of the dry powder device. Nonetheless, at a dosage of mometasone furoate pMDI 800μg twice daily there was significant suppression of the plasma 24-hour cortisol profile after 14, 21 and 28 days of treatment, with between 22 and 30% suppression compared with placebo. In the same study fluticasone propionate pMDI at 880μg twice daily also significantly decreased 24-hour plasma cortisol over the 28-day period with suppression of between 44 and 56%. The greater numerical degree of suppression with fluticasone propionate pMDI than mometasone furoate pMDI at comparable doses is perhaps not surprising, given the high efficiency for lung delivery with the fluticasone propionate pMDI device. Indeed, it has been shown in *in vitro* studies that the respirable dose fraction with fluticasone propionate pMDI is approximately 2-fold greater than with fluticasone propionate dry powder Diskhaler®.[30] This in turn suggests that the difference in lung deposition between mometasone furoate pMDI and fluticasone propionate pMDI would be about 2-fold. It is therefore likely that if fluticasone propionate and mometasone furoate were compared via their respective dry powder inhaler devices (i.e. Diskus® *vs* Twisthaler®), mometasone furoate might produce adrenal suppression to a greater degree than fluticasone propionate at steady state, as the lung deposition of the Twisthaler® would be 2-fold greater than the Diskus®.

6. Hydrofluoroalkane Formulations

The impending transition from CFC to HFA pMDIs has led to uncertainty in terms of switching between available products. For example, there are 2 HFA formulations of beclomethasone dipropion-

ate pMDI, with one formulation (Qvar®, 3M Healthcare) being recommended for use at half the dose of the CFC pMDI, whilst the other formulation (Beclazone®, Norton Healthcare) is recommended on a microgram equivalent nominal dose basis. Both of these HFA formulations use a solution in contrast with the older suspension CFC formulations, and consequently result in a much higher fine particle dose being delivered.[97] Pharmacokinetic data for the Qvar® formulation of HFA beclomethasone have shown that the systemic bioavailability is 2-fold greater than with the CFC formulation.[98]

Pharmacokinetic data in children with asthma with 200µg of HFA-beclomethasone (3M Healthcare) via the breath activated Autohaler® device with or without activated oral charcoal (to block gut absorption) have shown that the oral component comprises 25% (as C_{max}) of total early systemic bioavailability (fig. 5).[22] In this respect, C_{max} may serve as an approximate surrogate for early absorption from the lung. In the same study the early systemic bioavailability (as C_{max}) of 200µg HFA beclomethasone Autohaler® with charcoal was 1.5-fold greater than CFC beclomethasone 400µg via large volume spacer, suggesting that the relative lung dose in children is 3-fold higher with the HFA formulation than with the CFC formulation when comparing 200µg HFA Autohaler® with 200µg CFC via a spacer.

Properly designed dose-response studies comparing the 3M Healthcare formulation of HFA beclomethasone have shown equivalent antiasthmatic efficacy from dose-response studies when compared with CFC beclomethasone at a 2.6-fold lower dose.[99] However, there is confusion regarding the Norton formulation of HFA beclomethasone in view of recent pharmacokinetic data also showing 2-fold greater early systemic bioavailability as compared with the CFC formulation, suggesting that it has twice the lung dose and so should also be used at half the nominal dose.[100] Indeed, studies which suggested microgram equivalent antiasthmatic efficacy between the Norton HFA formulation and CFC formulation were flawed because they did not evaluate the dose-response

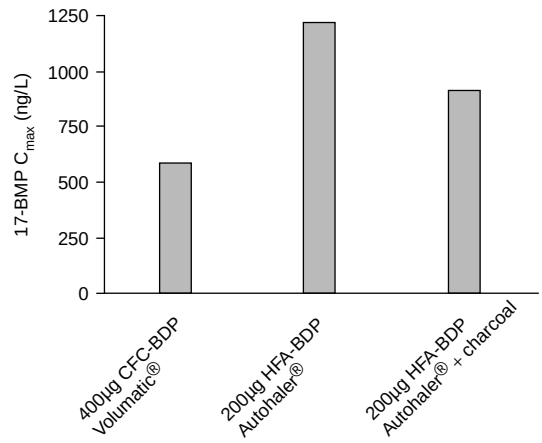

Fig. 5. Pharmacokinetic profiles for early systemic absorption [as maximal plasma concentration (C_{max})] of beclomethasone-17-monopropionate (17-BMP) in children with asthma receiving single inhaled doses of chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) formulations of beclomethasone dipropionate (BDP).[22]

effect.[101,102] On the basis of 2-fold higher lung bioavailability with the Norton HFA formulation, it is therefore likely that similar dosage recommendations should be applied to this product as with the 3M Healthcare formulation, in terms of being able to use a 2-fold lower nominal dose.

One might expect with these HFA formulations, as a consequence of their 2-fold increase in systemic bioavailability, that this would be associated with a commensurate increase in detectable systemic bioactivity. However, extensive studies on adrenal suppression with the 3M Healthcare HFA beclomethasone formulation have shown that the greater systemic bioavailability does not seem to translate directly into increased systemic bioactivity.[103] This may be due to the metabolism of beclomethasone-17-monopropionate to beclomethasone alcohol which occurs to an equal degree in the lung as in the gut. Alternatively, it may simply be because the detectable systemic bioactivity parameters such as adrenal suppression are on the shallow part of the dose-response curve at doses below 800 µg/day of HFA-beclomethasone dipropionate (800

μg/day is the maximum recommended dosage of Qvar® in adults). Another possibility is that the more rapid absorption phase with the HFA formulation may result in the HPA axis being less responsive to increasing plasma concentrations as compared with the more delayed absorption with the CFC formulation. Whether or not this translates into an improved therapeutic ratio, in terms of greater therapeutic efficacy with the HFA formulation without an increase in systemic adverse effects, requires further prospective dose-response studies looking at efficacy and systemic activity at the same time using appropriately sensitive end-points. Nonetheless, the use of the HFA formulation of beclomethasone with its higher fine particle dose within the acinar range (<2μm) offers the possibility of improved drug delivery to the smaller airways, which has not been possible before with conventional portable inhaler devices.[97] This allows, for the first time, specific targeting of topical corticosteroid therapy to the inflammatory process in the distal airways.

The HFA formulation of fluticasone propionate is a suspension unlike the solution formulation of HFA beclomethasone dipropionate. *In vitro* studies from GlaxoWellcome have suggested a similar profile for particle size comparing HFA and CFC formulations of fluticasone propionate pMDI and consequently has resulted in a recommendation for direct switching between formulations on a microgram equivalent basis.[104] Studies comparing antiasthmatic efficacy have not performed proper dose-response evaluations with both formulations, and so it is difficult to assess whether they are truly equivalent. In a dose-response study comparing HFA and CFC formulations of fluticasone propionate pMDI in dose of 500, 1000 and 2000 μg/day in healthy volunteers, it was found that the CFC formulation was associated with 2-fold greater increase in lung bioavailability, as assessed by sensitive measures of adrenal suppression (fig. 6).[40] This difference was found to be significant at the medium dose of 1000 μg/day after steady-state administration for 1 week, where there was 1.9-fold (95% confidence interval 1.2 to 3.2) greater suppression of overnight urinary cortisol/creatinine excretion with CFC than HFA fluticasone propionate, along with 2-fold more individual low values for overnight urinary cortisol excretion (31 *vs* 15% of values). Other pharmacokinetic data in healthy volunteers have suggested a systemic bioavailability of 26 to 28% for both CFC and HFA formulations as fluticasone propionate.[105] Whether the 2 HFA formulations are identical or if the original HFA formulation has been reformulated is unknown. Further more detailed *in vitro* impactor studies are required to clarify these issues.

As there is almost complete first-pass inactivation of the swallowed dose for fluticasone propionate, it can be concluded that the difference in adrenal suppression is representative of lung bioavailability and consequently a 2-fold reduction in respirable lung dose with the HFA compared with the CFC formulation. It is therefore conceivable that for patients on the steep part of the dose-response curve for clinical efficacy that direct switching on a microgram equivalent basis from CFC to HFA

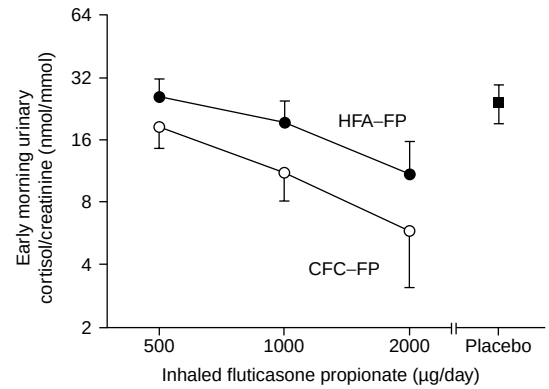

Fig. 6. Dose-response curves for effects of hydrofluoroalkane (HFA) and chlorofluorocarbon (CFC) formulations of fluticasone propionate (FP) as compared with placebo on suppression of early morning urinary cortisol/creatinine excretion. Values are shown as geometric means and 95% confidence intervals. As there is almost complete hepatic first-pass inactivation for the swallowed dose of fluticasone propionate, any detectable adrenal suppression is due to its lung bioavailability, which was significantly lower for HFA-FP and CFC-FP. The lung dose from HFA-FP was approximately half that of CFC-FP.[39]

Table I. Relative pharmacological and pharmacokinetic determinants of systemic adverse effects

Corticosteroid	Glucocorticoid potency	Lipophilicity	Volume of distribution	First-pass inactivation	Elimination half-life	Systemic potency
Beclomethasone dipropionate/ 17-monopropionate	Low/intermediate	Intermediate/high	Intermediate	Intermediate	Intermediate	Intermediate
Budesonide	Intermediate	Low	Low	High	Short	Low
Triamcinolone acetonide	Low	Low	Low	Intermediate/high	Short	Low
Fluticasone propionate	High	High	High	Extensive	Long	High
Mometasone furoate	High	High	Intermediate/high	Extensive	Intermediate/long	High

fluticasone propionate might result in a possibility for clinical relapse as a consequence of halving the respirable lung dose. However, one could also argue that if dose-response studies do indeed show the 2 formulations of fluticasone propionate to be therapeutically equivalent for antiasthmatic efficacy, then the HFA formulation might have a superior therapeutic ratio due to its 2-fold lower propensity for systemic adverse effects, although this requires clarification from thorough large scale dose-response or dose-reduction studies. Similar pharmacokinetic and pharmacodynamic safety studies will be required for other HFA formulations of inhaled corticosteroids which become available over the transition period in order to facilitate rational dosage recommendations for switching between these products.

7. Conclusions and Way Forward

The currently available corticosteroid formulations differ in their pharmacokinetic and pharmacodynamic properties, and a summary of these differences, based on available data presented in this review, is shown in table I. An extensive clinical experience with inhaled corticosteroids, hitherto approximating to 20 billion treatment days, have clearly shown the extremely good tolerability of these agents in a majority of patients with asthma and allergic rhinitis. Also, in children, inhaled corticosteroids have been extremely valuable and found to be surprisingly safe when given at conventional licensed doses.

The past decade of research has produced important insights into the various factors which determine the systemic adverse effect profile of inhaled and intranasal corticosteroids. This emphasises the importance for pharmaceutical companies to conduct properly designed dose-response studies using appropriately sensitive end-points in order to characterise the systemic adverse effect profile across a range of doses, in healthy individuals and patients with asthma. These type of data were not available when fluticasone propionate was first launched and it is only now becoming evident that this drug may produce potent systemic adverse effects, particularly at the high end of the dose range when delivered via high efficiency inhalers in patients with asthma. Also, for the new corticosteroids approaching launch more long term data are needed, and, until such data are available, any risk of clinically relevant adverse effects should be weighed against the expected improvements in asthma.

In particular, the pharmacokinetic profile for the newer more potent lipophilic corticosteroids has shown that they exhibit a large total volume of distribution, with consequent systemic tissue retention and relatively low detectable plasma concentrations. Thus, measuring plasma concentrations after single dose studies for inhaled or intranasal formulations of lipophilic corticosteroids will always underestimate the potential for systemic adverse effects at steady state. This is important to recognise because claims of negligible systemic bioavailability have now been made for mometasone furoate, which has similar pharmacological

and pharmacokinetic properties to fluticasone propionate, and hopefully the lessons have already been learnt in terms of systemic bioavailability and safety issues.

However, a recent study has found no detectable growth retardation in children with rhinitis treated for 1 year with intranasal mometasone furoate.[106] Indeed, the effects of inhaled corticosteroids on growth are reassuring at least when used at conventional doses. The largest cohort study is a follow-up for 4 years of 2355 children, aged 1 to 15 years, in Scotland.[107] Those children receiving doses of beclomethasone or budesonide greater than 400 μg/day who required general practice or hospital services exhibited a significant reduction in their stature. This effect was independent from, but smaller than the effect of socioeconomic deprivation, suggesting that other factors such as nutritional status may be more relevant than any small putative effect of drug therapy. In a prospective cohort study, patients with asthma, of whom 58 were receiving corticosteroids, were compared with 153 age and gender-matched controls.[108] The adult height of the children with asthma adjusted for average parent height, was not significantly different from that of controls and there was no significant overall effect of inhaled or oral corticosteroid exposure. From a pragmatic point of view, it is better to have a child who grows up to be an adult with normal lung function because of optimised inhaled corticosteroid therapy, than worry about being a few centimetres shorter in stature. In 1998, the US Food and Drug Administration applied class labelling to all inhaled and intranasal corticosteroids to include a precautionary note at they may cause growth suppression at conventional recommended doses. Consequently, monitoring of growth is advisable in any child with asthma who is receiving inhaled and/or intranasal corticosteroid therapy. Indeed one could argue that irrespective of corticosteroid therapy, any child with a chronic illness such as asthma should have their growth followed using a stadiometer, as part of good clinical practice.

In many respects, the claims of negligible systemic bioavailability with inhaled and intranasal mometasone furoate are déjà vu with respect to the history of fluticasone propionate, and these are lessons which prescribers should take into the new millennium. It is also behoven on the licensing authorities around the world to take on board these lessons for critically appraising the available data presented to them from pharmacokinetic and pharmacodynamic studies. Similar caution should be applied to appraising the newer HFA formulations of inhaled corticosteroids which will become increasingly available over the new decade, including the profusion of generic HFA substitutes.

In terms of the clinical implications for long term safety, prescribers should also be aware of the potential of an additive systemic burden when using the combination of inhaled plus intranasal corticosteroids. The safest way to use any inhaled or intranasal corticosteroid therapy is to always try and step down to achieve the lowest possible effective maintenance dosage, which will result in the individual patient being exposed to the lowest possible long term systemic burden.

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