Response to letter from Dr J. De Vries and Dr M. Drent. Respir Med Editorial 2000; 94: 187–189

De Vries and Drent address important aspects of the differences between and the problems with ‘quality of life’ (QOL) and ‘health-related quality of life’ (HRQOL) measurement. I agree on the necessity to strengthen focus on the differences between the disease specific and the generic instruments.

The letter from De Vries and Drent, especially the references, makes one happy to learn how far the Dutch have come in the process of validating disease-specific questionnaires, especially since this is in a relatively small language and culture, concerning the size of the population. What was stressed in the editorial was the fact that we have developed some very useful generic and disease-specific instruments, but this has been achieved by fiery souls from different academies only. The present status is that we have sufficient knowledge to conduct studies with HRQOL and QOL measurements, and what was stressed in the editorial was the fact that HRQOL questionnaires have been developed for a minority of diseases only and only in few languages and cultures. In my opinion, this is the major factor limiting the propagation of HRQOL measurements, and that was why the paper by De Vries et al. (1) was welcomed. It pointed to alternative methods e.g. the focus group, in cases where no specific questionnaire exists.

I can fully agree with De Vries and Drent on the necessity of cultural appropriateness, or in other words, cultural translation of questionnaires. In fact I found this aspect so important that it was focused on in the editorial title (2). At present we do have HRQOL questionnaires for several diseases, often in the English or American languages. But we need instruments for the investigation of minorities concerning language, e.g. Dutch or ethnicity, for examples, Inuit, and the task to produce these instruments seems tremendous. That is why alternatives are needed and proposals are welcome. This also holds for the specifications we have to demand from our generic questionnaires and that is why the SF-36 has an advantage, probably being the one questionnaire validated and translated into most languages and cultures, thus facilitating transcultural comparisons of results.

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References


Re: Dose proportionality of fluticosone propionate hydrofluoroalkane pressurized metered dose inhalers (pMDIS) and comparability with chlorofluorocarbon pMDIS [Respir Med 2000; 94 (Suppl. B): S10–S16]

I read with interest the recent article by Kunka et al. which concluded that HFA and CFC formulations of fluticasone propionate pMDI produced similar lung deposition and no difference in systemic exposure at microgram equivalent doses (1). The conclusion of similar lung deposition with the 125 µg formulation, on the basis of lung bioavailability, is not supported by the ratio of HFA: CFC for plasma fluticasone propionate concentration as area under curve: 0.67 (90% CI 0.57–0.79). For the same 125 µg formulation, despite the difference in plasma fluticasone propionate concentration, there appeared to be no difference in the uncorrected 24-h urinary cortisol excretion, where the ratio was found to be 1.04 (95% CI 0.82–1.32). It is conventional practice to report 24-h urinary cortisol corrected for creatinine excretion. It also seems bizarre that the investigators have gone to all the trouble of collecting the serial 24-h plasma fluticasone propionate concentration, but appear to have omitted collecting blood samples over the same time profile for 24-plasma cortisol, as this would have permitted proper pharmacokinetic/pharmacodynamic modelling.

Furthermore, fluticasone propionate was administered as single doses, and since it has a large volume of distribution, with preferential partitioning in to the systemic tissue compartment rather than blood (due to its high lipophilicity), it would be more clinically relevant to evaluate what happens with chronic dosing at steady-state, where there would be a much greater degree of adrenal suppression due to equilibration between the two compartments (2). After-all, in real life, patients take fluticasone repeatedly twice daily, not as a single dose. In this situation it is more likely that differences between the two formulations would become evident, as suggested by differences between the pharmacokinetic profiles for the 125 µg formulation in the study by Kunka.

In this respect, a previous evaluation was made in healthy volunteers, where steady-state twice daily administration of HFA and CFC fluticasone propionate (250 µg formulations) were given in doses of 500, 1000 and 2000 µg daily,
and placebo (3). These results showed that the lung bioavailability of CFC fluticasone propionate was greater ($P < 0.05$) than the HFA formulation for both overnight urinary cortisol corrected for creatinine: 1-9-fold (95% CI 1.2–3.2) as well as for early morning urinary cortisol corrected for creatinine: 1-8-fold (95% CI 1.1 – 2.8). Moreover, for all three doses together there were significantly ($P < 0.001$) more individual low values for overnight urinary cortisol excretion < 10 nmol h$^{-1}$ with the CFC formulation (31%) compared with the HFA formulation (15%), or compared to placebo (0%). It is also curious that Kunka et al. chose not to cite this article in this paper in their list of references, particularly as our results contradict their own findings.

In view of the discrepancies between the single dose pharmacokinetic and pharmacodynamic data of Kunka et al., along with previous chronic dosing data suggesting differences in lung bio-availability between the HFA and CFC formulations, one would have to cast serious doubts on the validity of the conclusions of Kunka et al. that the two formulations exhibit similar lung deposition and no difference in systemic exposure at microgram equivalent doses.

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References


Dear editor,

Response to letter from Professor B. J. Lipworth Re: Paper by Kunka et al. [Respir Med 2000; 94 (Suppl. B): S10–S16]

Dr Lipworth’s comments focus on urinary cortisol data he presented in a letter to another journal (1). We are not surprised that findings based on cortisol do not agree with our measurements based upon plasma fluticasone propionate (FP) AUC data (2). This is due to a number of factors including the nonlinear sigmoid relationship between these two variables (3). Consequently, it has been shown that cortisol measurements alone cannot be used to reliably quantify the systemic exposure to corticosteroids and direct pharmacokinetic measurements should always be used (4). In addition the type of cortisol data cited by Dr Lipworth (1) was not based on robust methodology. Early morning and overnight urinary cortisol requiring correction for creatine are indirect measurements and have not been validated as a means of comparing the bio-availability of corticosteroids in healthy subjects (5,6). The imprecision and variability in these parameters is high and they have not been shown to accurately predict the degree of corticosteroid systemic exposure as assessed by direct pharmacokinetic measurements (4). Correction for creatinine is applied to account for incomplete urine collections, but was not required in our study because urine was collected for a full 24-h period in closely supervised institutionalized subjects (2). Furthermore, since the relationship between systemic exposure to corticosteroids and changes in cortisol is described by a sigmoid curve, the dose range selected determines the position on the curve and whether the change in cortisol is smaller or larger than the accompanying change in corticosteroid plasma AUC (4). The consequence of this is that in comparing the relative effects on cortisol for two inhaled formulations the difference observed is highly dependent on the doses selected and the study design. This is illustrated in the data cited by Dr Lipworth (1) where cortisol measurements were not able to detect a difference when the dose doubled from 250 µg b.i.d. to 500 µg b.i.d. There were also no significant differences found between the HFA and CFC formulations at two of the three dose levels (250 µg b.i.d. and 2000 µg b.i.d.) and little evidence of dose proportionality. Although the study was described as placebo-controlled and single-blind (1) it is difficult to see how this could be accomplished without the use of placebo inhalers and using an escalating-dose design. In the other reference cited the studies were of similar design, creatinine-corrected overnight cortisol excretion and morning cortisol were used to support conclusions that also do not agree with pharmacokinetic data. Lung deposition was claimed to differ by five-fold for FP MDI plus spacer compared to a dry powder inhaler and two-fold for FP MDI plus spacer compared to FP MDI without spacer (7). These conclusions are unlikely for the following reasons. Firstly, although a spacer removes larger particles of FP and reduces oropharyngeal deposition, the respirable FPM dose is essentially unchanged (8). Secondly, the absolute bio-availability for the FP Diskus® dry powder inhaler has been reported as 17% (95% CI: 14-20%) based on pharmacokinetic data (9). Therefore, a five-fold increase would imply that 100% lung deposition could be attained with an MDI plus spacer, whereas only 20% deposition has been reported (10). The conclusions from our study (2), of similar lung deposition and systemic exposure for FP CFC and HFA MDIs, have been confirmed in another report (11) that compared FP plasma...