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Questions and Answers

Question: Is anything known about the effect of the severity of asthma on compliance, in that one might expect patients with more severe disease to be more compliant?

Prof. M.E. Hyland: There are certainly some patients with mild asthma who are less compliant than those with more severe disease. A recent study by Barnes showed that about half of health professionals with asthma took less prophylactic medicine than recommended, but they also had fewer exacerbations than their more compliant colleagues – presumably because of the greater severity of disease in those who were compliant. This kind of noncompliance is usually based on rational beliefs and is not problematical. However, there is also a smaller proportion of patients with severe disease who are poorly compliant, often because of denial of asthma, and these have an unsatisfactory outcome.

Question: What are the factors determining compliance in children? Compliance in younger children is presumably determined by their adult caregivers – are compliance and treatment choices affected by the attitudes of these adults to health and illness?

Prof. Hyland: The factors determining noncompliance in children are many and varied, and change as the child grows older. In very young children, adult caregivers control medication but, as children go through the stages of growing up, they gradually acquire more control themselves. The extent of control varies and depends on the adult caregiver, the age and characteristics of the child, and the advice given. There are two particular problems in children. One is the transfer of control from adult to child. The other, noticeably in adolescents, is the effect of asthma on self-image, most importantly as it affects social life and relationships with members of the opposite sex.

Question: Is there any evidence that fatty acid esterification of budesonide to the much more lipophilic esters leads to tissue accumulation of the drug?

Dr S. Edsbäcker: At steady state, the plasma concentrations of budesonide are somewhat (5 to 20%) higher than after a single dose, indicating slight systemic retention of budesonide due to the esterification mechanism. Retained budesonide may be derived from sites within the airways and lung (where ester concentrations are high) and peripherally (where ester concentrations are much lower).

Question: You have indicated that the hypothalamic-pituitary-adrenal (HPA) axis may be affected more by persistent steady-state concentrations of corticosteroids than by high peak concentrations, which may support once-daily administration of inhaled corticosteroids. Is anything known about concentration-effect relationships for the anti-inflammatory effects of these drugs?

Dr Edsbäcker: There is a less clear concentration-effect relationship for the anti-inflammatory effects than for the HPA axis effects, probably because of the differences in complexity between the 2 actions. Specific anti-inflammatory effects may be rapid (e.g. a change in the distribution of circulating leucocytes and inflammatory markers), but may also be indirect and first detectable after several hours (cytokine release, lung function improvement, etc). Hence, a clear-cut relationship between the corticosteroid concentration in plasma or target tissues and therapeutic effect is not what would be expected. Several clinical studies in patients with mild to moderate asthma have, however, shown that once-daily administration of budesonide is as efficacious as the same daily dose given twice daily. This would imply that the dosage frequency, and hence peak concentrations, are not

critical for the therapeutic outcome in this patient group, given that compliance is high.

Question: You've mentioned compliance issues in patients with mild asthma. Isn't there also a problem with patients admitting that they need to initiate long term treatment for a disease that can be controlled but not cured, and perhaps once-daily treatment might be seen as less invasive in this group?

Dr P.M. O'Byrne: Compliance with regular inhaled corticosteroid treatment is a major problem in all asthma patients requiring such therapy. One of the reasons for this is that when patients become asymptomatic they discontinue their corticosteroid treatment; this will certainly be a problem in patients with mild asthma, most of whom will become fully asymptomatic when treated with inhaled corticosteroids. It is possible that once-daily treatment will be seen as less intrusive and complicated in patients with mild asthma, and this patient population has been shown to be well controlled with once-daily inhaled budesonide. For this reason, once-daily treatment is being used in the START trial evaluating effectiveness in patients with mild asthma.

Question: In terms of treating asthma with the lowest possible dosage of medication, what are likely to be the optimum features of an inhaler/corticosteroid combination for best control with the lowest possible dosage?

Dr O'Byrne: Providing asthma control with the lowest possible dosage of medication requires an easy-to-use inhaler device in combination with an inhaled corticosteroid that can be delivered once daily and that is available in a low dosage per inhalation.

Question: Your group has shown that an initial twice-daily loading dose of budesonide followed by a 'step down' to half the total amount given once daily provides earlier clinical benefit than once-daily therapy from the outset. However, is there a need for this higher initial dosage in your experience? Might the same effect be achieved with a lower dosage given twice daily at the outset and followed, after 4 to 6 weeks, by the same daily dosage given once daily?

Dr L.M. Campbell: As has been shown in several studies, a once-daily regimen is as effective as twice-daily treatment, both in patients already on a twice-daily regimen and in corticosteroid-naive patients. There is some evidence that starting high and dropping down provides faster symptom relief. This is a recommendation of the British Thoracic Society guidelines for asthma management. The significant factor is, therefore, the total daily dose rather than the frequency of administration. It would be reasonable to start with a single daily dose of budesonide 800μg and then lower the dose once control has been achieved.

Question: The evidence favouring once-daily therapy is compelling but, in your experience, is there any advantage to be gained with evening administration over morning administration? Is the degree of control the same or do you see more nocturnal awakenings and lower morning peak expiratory flow rate (PEFR) readings with morning administration?

Dr Campbell: Several studies have examined morning versus evening administration. Some minor differences have been reported but, overall, no significant differences have been found. It must be remembered, however, that these overall results may conceal some individual variation. My normal practice is to recommend night-time administration immediately before tooth brushing, but if for any reason the patient prefers morning administration I see no problem with this.

Question: You suggest that once-daily administration of inhaled corticosteroids is simpler and may promote compliance, but twice-daily administration may be seen as more 'forgiving' in that the effect of a single missed dose is not as great. Have there been any studies of, for example, alternate-day administration that tell us anything about the effects of missed doses of once-daily corticosteroids on asthma control?

Dr C. Möller: My clinical impression is that occasional missed doses of inhaled corticosteroids given once daily do not affect treatment efficacy.

There are, to my knowledge, no studies of inhaled corticosteroids given every other day; I should like to perform such a trial, although compliance could be a problem, particularly with alternate-day therapy.

Question: Turning now to the choice of a particular inhaled corticosteroid and inhaler device for children, you've mentioned the value of high lung deposition and we've read elsewhere in this supplement that lung deposition seems to be a function of the drug, the inhaler device and the propellant (if any) as a system. Would you consider high lung deposition and ease of use to be the major factors when choosing an inhaled corticosteroid for children?

Dr Möller: The value of high lung deposition depends on the corticosteroid used. A high lung deposition means lower doses, which has both tolerability and economic implications. If we use an inhaled corticosteroid with a very insignificant risk of adverse effects, we can increase the dose until the required efficacy is achieved. Thus, one major factor is the risk of adverse effects at an effective dose; ease of use is another major issue.

Question: In your experience with nebulised budesonide, is there a more rapid clinical improvement with twice-daily administration at the outset of treatment before dropping back to once-daily administration? As we have already read, this appears to be the case with the dry powder inhalation device in adults, but is it your impression that the same applies for nebulised therapy in young children?

Dr G.G. Shapiro: Since use of the nebuliser suspension in the US is confined to young children with fairly severe disease whose families can acquire the medication outside of the country, my clinical experience is skewed. I always start with twice-daily therapy and taper to once daily when I am convinced that the patient's clinical course has stabilised. It is likely that success with once-daily therapy will be greater when the patient's airway inflammation has abated to some degree as a result of more aggressive twice-daily therapy for a period of time.

Question: In young children who do not appear to satisfactorily accept treatment with budesonide via a pressurised metered dose inhaler (pMDI) plus spacer, can you give some advice on dosage selection for transferring to nebuliser administration, e.g. if the child was on 200μg twice daily with a pMDI, what dosage, given once daily, would you start him/her on with the nebuliser solution?

Dr Shapiro: My usual approach is to start therapy at 0.5mg twice daily. I will increase or decrease the dosage depending on the patient's response. If the patient is doing well, I will usually wait 3 to 6 months before adjusting downward. If the patient continues to have exacerbations, I will respond quickly with an increase in dosage.