Morning serum cortisol concentrations after 2 mg inhaled beclomethasone dipropionate in normal subjects: effect of a 750 ml spacing device

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Abstract

Large spacing devices have been shown to provide more selective delivery of an inhaled steroid to the lung but the effect on the hypothalamo-pituitary-adrenal suppression associated with high dose inhaled corticosteroids has been little studied. The effect of a large spacing device (Volumatic; 750 ml) on suppression of 0900 h cortisol after 2 mg inhaled beclomethasone dipropionate was therefore investigated in normal, healthy volunteers. Twenty four subjects (12 male, 12 female) took part in a randomised, double blind, placebo controlled cross over study in which a single dose of 2 mg beclomethasone dipropionate was taken at 2300 h on two occasions seven days apart, once from a metered dose inhaler alone and once from a metered dose inhaler attached to a 750 ml spacing device. The 0900 h serum cortisol concentration was the same on the morning before each administration (468 nmol/l, 95% confidence interval (CI) 390-561 nmol/l, day 1 *v* 479 nmol/l, 95% CI 463-494 nmol/l, day 8). The 0900 h serum cortisol concentration the following morning, however, was lower when 2 mg beclomethasone dipropionate was given by metered dose inhaler alone (182 (95% CI 128-264) nmol/l) than when it was given by a spacing device (363 (95% CI 281-475) nmol/l). These results suggest that a large spacing device attached to a metered dose inhaler may decrease the risk of hypothalamo-pituitary-adrenal suppression by high dose inhaled steroid treatment.

Inhaled topically active corticosteroids are an important treatment of asthma. Inhaled beclomethasone dipropionate in doses of up to 2 mg a day is widely used but may be associated with systemic side effects, the most important being hypothalamo-pituitary-adrenal suppression.^{1,2} Large spacing devices are advocated for patients who have poor coordination of actuation and inhalation with conventional metered dose inhaler delivery systems. They also provide more selective delivery of inhaled steroid to the lower airway.^{3,4} We tested the hypothesis that the use of a spacing device (750 ml, Volumatic, Allen and Hanburys Ltd) may reduce systemic absorption and hypothalamo-pituitary-

adrenal suppression caused by high dose inhaled corticosteroids.

Methods

In a double blind, crossover study 24 normal healthy volunteers (12 female and 12 male, aged 20-42 years) inhaled a single 2 mg dose of beclomethasone dipropionate (eight puffs of Becloforte) on each of two days one week apart. Beclomethasone dipropionate was inhaled from a metered dose inhaler alone or from a metered dose inhaler attached to a 750 ml spacer. The mode of delivery was alternated on the two visits, the order was randomised, and on each occasion placebo was given by the alternate delivery method. Serum for cortisol estimation was taken at 0900 h on the morning before and the morning after administration of inhaled beclomethasone dipropionate.

All subjects had a good inhaler technique (assessed by the investigators) and had never received regular oral, inhaled, or topical corticosteroids. They first took eight puffs from a metered dose inhaler alone and then immediately afterwards eight puffs from a metered dose inhaler attached to the spacer. All inhalations were performed over a 20 minute period. To minimise drug deposition on the spacing device only one puff of beclomethasone dipropionate was delivered to the spacer at one time. The subjects inhaled through the spacer for a timed period of two minutes after each puff.

Subjects gave written informed consent and the approval of the ethical committee was obtained.

SERUM CORTISOL ASSAY

For serum cortisol estimations we used a commercial kit (Farnos Diagnostica, Finland). The coefficient of variation of the assay for mid (440 nmol/l) and high control (725 nmol/l) was 3.7-3.8% both within and between batches. For low control (57 nmol/l) the within batch coefficient of variation was 7.2% and the between batch coefficient of variation 9.1%. The assay was 100% specific for cortisol, showing less than 0.1% sensitivity for dexamethasone or beclomethasone dipropionate. The sensitivity of the assay was 5 nmol/l for cortisol estimation.

STATISTICAL ANALYSIS

Geometric means (GM) and 95% confidence intervals (CI) are shown for log transformed data. Suppression of 0900 h cortisol was

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Serum cortisol
($\times 100$ nmol/l)

Basal (0900 h) serum cortisol concentrations the morning before and the morning after inhalation of 2 mg beclomethasone dipropionate at 2300 h from either a metered dose inhaler alone or a metered dose inhaler and spacer combined. Bars represent geometric means and 95% confidence intervals. The open symbols indicate the subjects with greater cortisol suppression after using the metered dose inhaler with spacer than on its own.

calculated as Δ cortisol = 0900 h cortisol concentration on morning before – 0900 h cortisol concentration on morning after inhalation of steroid. Values for the two modes of delivery were compared (within subjects) by using paired Student's *t* test. The effect of delivery method on suppression of 0900 h cortisol, with account taken of the order in which each mode of delivery was used, was determined by calculating the difference in suppression of 0900 h cortisol for the two administrations of steroid (Δ cortisol

day 1 – Δ cortisol day 8) for each order and comparing the values obtained (between subjects) by unpaired Student's *t* test. Changes were considered significant if $p = 0.05$ or less (two tailed).

Results

Administration of beclomethasone dipropionate by metered dose inhaler alone caused about three times more depression of 0900 h cortisol concentration than administration by metered dose inhaler and spacer combined. Serum cortisol concentrations were the same on day 1 and day 8, the mornings before administration of the inhaled steroid—468 nmol/l (day 1, 95% CI 390–561 nmol/l) and 479 nmol/l (day 8, 95% CI 463–494 nmol/l; NS). After 2 mg beclomethasone dipropionate by metered dose inhaler alone the 0900 h cortisol fell by 268 nmol/l (95% CI 186–322 nmol/l). When beclomethasone 2 mg was administered by metered dose inhaler and spacer combined 0900 h cortisol fell by 95 nmol/l (95% CI 4–177 nmol/l; $p < 0.001$). There was considerable between subject variability in the suppression of 0900 h cortisol by 2 mg inhaled beclomethasone dipropionate (range 8–91% including both routes of administration). Of the 24 subjects studied, only three (one of them male)—the subjects indicated open symbols in the figure—showed greater suppression of 0900 h cortisol after beclomethasone had been given by metered dose inhaler and spacer combined than by metered dose inhaler alone. The suppression of 0900 h cortisol was greater when the metered dose inhaler was used alone whether this mode of delivery was used on day 1 (difference 122 nmol/l; 95% CI 28–216 nmol/l, $n = 13$) or on day 8 (difference 202 nmol/l; 95% CI 43–345 nmol/l, $n = 11$, $p < 0.001$). The difference in cortisol suppression between the two forms of administration was not affected by their order of use ($p = 0.34$).

Discussion

The effect of inhaled high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal suppression is related to the degree of systemic absorption of the inhaled corticosteroid. About 10% of steroid delivered by metered dose inhaler alone reaches the lower airway.^{3,4} Orally administered beclomethasone dipropionate causes considerably less hypothalamo-pituitary-adrenal suppression than oral dexamethasone because of the extensive hepatic metabolism of beclomethasone dipropionate to inactive polar metabolites, whereas after dexamethasone up to 80% of the circulating drug is unchanged.⁵

Studies in models³ and in man⁴ show that spacers provide more selective delivery of inhaled corticosteroid to the lung. With large spacing devices the proportion of steroid deposited on the oropharynx decreased to 10% of the delivered dose and the fraction deposited in the lungs was maintained or even increased. About 40% of the delivered dose remains in the spacing device.^{3,4} Spacers would therefore be

expected to increase the steroid dose supplied to the lower airway and reduce hypothalamo-pituitary-adrenal suppression caused by systemic absorption of steroid from the mouth, oropharynx, and gut. The limitations of currently available methods for assessing the effect of inhaled steroid on hypothalamo-pituitary-adrenal suppression have been discussed by Ebden *et al.*² Suppression of 0900 h serum cortisol has been shown to give results concordant with those obtained by measuring urinary cortisol excretion or the response to tetrocosactrin.^{1,2,6}

A study in children has shown that adding a spacing device to a metered dose inhaler increased urinary 24 hour cortisol excretion, implying improved adrenocortical function.⁷ We have shown that the use of a 750 ml spacer to deliver 2 mg beclomethasone dipropionate to normal subjects causes less depression of 0900 h cortisol and again implies less hypothalamo-pituitary-adrenal suppression. There was substantial intersubject variability in suppression of 0900 h cortisol by beclomethasone dipropionate, as has been observed for other topically active corticosteroids.^{2,6} The mechanism for this is not clear but presumably reflects a mixture of influences, including inhaler technique, extent of hepatic metabolism of the adsorbed dose, and variation in feedback sensitivity of the hypothalamo-pituitary axis. These sources of variation will have occurred during both phases of this crossover trial and should not influence the principal findings of the study.

The present study, in which a single dose of corticosteroid was given to normal subjects, does not address the questions of safety and efficacy in asthmatic patients, who inhale steroid regularly and twice daily. Existing

evidence suggests that the use of a spacer for inhalation of high doses of steroid should not result in less effective treatment, and there may be additional benefit from the delivery of more inhaled steroid to the lower airway. A decrease in steroid deposition in the oropharynx may decrease systemic absorption of steroid, with a consequent reduction in the risk of hypothalamo-pituitary-adrenal suppression in addition to a lower risk of oropharyngeal candidiasis.⁸ Further studies of the use of large spacers in asthmatic patients are needed.

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