

Effect of orally administered beclomethasone dipropionate on calcium absorption from the gut in normal subjects

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Abstract

Background—There is evidence that patients with chronic obstructive airways disease and asthma who take inhaled steroids have a low bone density. As most of a drug given from a metered dose inhaler is actually swallowed, the possibility that swallowed beclomethasone dipropionate acts topically in the gut to impair calcium absorption was investigated. Such an effect, if sustained, may be a causative factor of long term bone loss.

Methods—A two week randomised, double blind, placebo controlled, crossover trial was performed in 12 normal volunteers. Subjects were randomly allocated to swallow beclomethasone dipropionate capsules (500 µg twice a day) or placebo for one week. The alternate capsule was given throughout the second week. At the end of each week, calcium absorption was assessed by a strontium absorption test. Serum parathyroid hormone, plasma calcium, and plasma phosphate concentrations were determined on the last two days of each week. Twenty four hour urinary calcium, hydroxyproline, and cortisol concentrations were measured for four successive days in each week.

Results—All subjects completed the study. There was a 12% reduction in strontium absorption during the beclomethasone dipropionate ingestion week. There was also a 23% reduction in 24 hour urinary cortisol excretion during the same week.

Conclusions—Calcium absorption (measured by a strontium absorption test) was reduced by oral administration of beclomethasone dipropionate for one week. Decreased calcium absorption due to swallowed corticosteroid may contribute to side effects of inhaled steroids and further long term studies are needed.

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Patients with asthma and chronic obstructive airways disease are a group at special risk of osteoporosis as shown by several studies reporting subnormal bone density or exces-

sive fractures in such patients.¹⁻⁹ Many of these studies have examined selected subject groups who were dependent on oral corticosteroids. Some included subgroups, however, who had received little or no oral corticosteroids, but who also had subnormal bone densities.^{2,3} Thus other causative factors need to be considered, such as inhaled corticosteroids.³

About 90% of a metered dose of beclomethasone dipropionate given by inhalation is deposited in the mouth and oropharynx, and then swallowed, and less than 10% reaches the lungs.¹⁰ First pass metabolism in the liver and gut should attenuate any systemic effect of swallowed beclomethasone dipropionate.¹¹⁻¹³ Most studies of systemic effects of inhaled beclomethasone dipropionate in adults found little or no effect below 1000 µg/day.¹⁴ Hence, exclusively swallowed beclomethasone dipropionate may have a higher systemic threshold effect than the inhaled drug. A possible topical effect of the swallowed drug on the intestinal mucosa has not, however, been assessed to our knowledge.

Patients receiving oral corticosteroids may be predisposed to osteoporosis in various ways but especially by impaired calcium absorption in the gut.¹⁵⁻¹⁷ Glucocorticoids are known to influence the transport of calcium by an effect on calcium channels,¹³ and to affect intestinal calcium absorption by various mechanisms.¹⁸ Thus it is possible that swallowed beclomethasone dipropionate, and especially its potent, stable metabolite beclomethasone-17-monopropionate,¹⁹ could directly reduce calcium absorption in the small intestine. A topical gut effect of the swallowed fraction or a systemic effect could further reduce calcium absorption. We studied this possibility in subjects swallowing beclomethasone dipropionate for one week. Subjects swallowed beclomethasone dipropionate to avoid inter and intra subject variation in inhaler technique. We chose a dose of 1000 µg/day as this approximates to the oral dose of the drug in patients taking high dose inhaled steroids.¹⁰

Methods

We studied 12 normal volunteers, who were hospital staff aged 24 to 60 years (six men; table 1). Subjects were paired roughly for age

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Table 1 Particulars of subjects

| Sex | BDP (week 1) | BDP (week 2) |
|--------|--------------|--------------|
| | Age | Age |
| Men: | 25 | 25 |
| | 40 | 26 |
| | 42 | 39 |
| Women: | 24 | 27 |
| | 35 | 30 |
| | 39 | 60 |

BDP—beclomethasone dipropionate.

and sex and randomly allocated to swallow beclomethasone dipropionate capsules (500 µg twice a day) or placebo capsules for one week. The alternate capsule was given throughout the second week in a cross over design.

All capsules were made of fast dissolving gelatin. In vitro capsule dissolution time in a gastric acid bath was five minutes. Placebo capsules contained lactose powder and had an appearance and taste that neither subject nor experimenter could distinguish from the beclomethasone dipropionate capsules. Each subject's usual dietary calcium was assessed by a dietitian, and subjects were advised not to deviate from their usual calcium intake, commencing one week before the study period, and continuing throughout the study. Due to the matched study design, there could be no influence of intersubject dietary calcium variation on within subject changes in strontium absorption.

ASSAYS

Strontium absorption tests were performed on the morning of days 7 (last day of week 1) and 14 (last day of week 2). Such tests are a validated measure of calcium-45 absorption in humans and previously published methodology was used.²⁰⁻²² Briefly, 2.5 mmol of strontium chloride in 200 ml distilled water was given with a standardised breakfast that contained only 1.2 mmol elemental calcium. (Breakfast comprised two slices of white bread, 10 g honey, 10 g butter, 100 g tinned peaches, and 50 ml peach juice.) Subjects had no dairy products with the preceding evening meal, and had no oral intake other

than water from 8:00 pm the previous evening until the breakfast. A morning snack was given two hours after breakfast and comprised two dry biscuits and 250 ml orange or mango juice. Blood was taken for strontium assay four hours after breakfast. For the day 14 strontium absorption tests, baseline plasma strontium concentrations were subtracted from the four hour plasma strontium concentration to obtain the percentage of the ingested dose in the extracellular fluid for that day's test. This repeated test would not be affected by saturation of active gut absorption or of clearance mechanisms as a result of the initial week's test.²⁰

Serial 24 hour collections of urine for measurement of calcium, hydroxyproline, and cortisol concentrations were taken throughout days 3 to 7 (week 1), and again during days 11 to 14 (week 2). Twenty four hour urinary cortisol assays were used as a measure of the systemic effect of the swallowed beclomethasone dipropionate. Serum parathyroid hormone, plasma calcium and plasma phosphate concentrations were determined on days 6 and 7 (week 1), and again on days 13 and 14 (week 2).

ANALYTICAL TECHNIQUES

Plasma strontium was assayed by atomic absorption spectrophotometry (coefficient of variation (CV) = 3.5%); serum parathyroid hormone by the mid-molecule radioimmunoassay of Incstar (CV = 16%); plasma calcium and phosphate by Technicon SMAC (CV = 1.6% and 2.6% respectively); urinary hydroxyproline by the spectrophotometric method of Bergman and Loxley²³ (CV = 5%); urinary cortisol radioimmunoassay with an Amersham Amerlex kit (CV = 8.2%); and urinary calcium by absorption spectroscopy (CV = 2.1%).

The study was performed with approval of the institute's ethics committee. Statistical analysis was by a two tailed paired *t* test with Systat 5.2 software.

Results

All 12 subjects finished the study, and all strontium tests were completed. Eighty seven collections of urine and 139 of 144 blood assays were completed. The few failed tests resulted from errors of subject compliance and were not biased to any particular subject group. Subjects did not have side effects during the study. Table 2 shows the results for all assays for all 12 subjects with the beclomethasone dipropionate week compared with the placebo week. Table 3 shows the results for the two separate subject groups of six (placebo to beclomethasone dipropionate and beclomethasone dipropionate to placebo). There was a lower strontium absorption in 11 of 12 subjects during the beclomethasone dipropionate week compared with the placebo week (mean reduction 12%, $p < 0.01$; fig 1). There was also a lower mean 24 hour urinary cortisol concentration in 12 subjects during the beclomethasone

Table 2 Mean (SD) results of assays for all 12 subjects; beclomethasone propionate week compared with placebo week

| Study factor | BDP week | P week | <i>p</i> |
|---------------------------------------|-------------|-------------|----------|
| Strontium test (% of dose in ECF) | 9.7 (2.1) | 11.0 (2.0) | <0.01 |
| Plasma calcium (mmol/l) | 2.38 (0.08) | 2.38 (0.07) | NS |
| Plasma phosphate (mmol/l) | 1.16 (0.14) | 1.10 (0.14) | NS |
| Serum parathyroid hormone (pmol/l) | 43.9 (8.4) | 44.3 (7.5) | NS |
| Urinary cortisol (nmol/day) | 147 (45) | 191 (40) | <0.0005 |
| Urinary hydroxyproline (µmol/day) | 210 (61) | 222 (111) | NS |
| Urinary calcium (mmol/day) | 2.79 (0.66) | 3.00 (0.92) | NS |

BDP—beclomethasone dipropionate; P—placebo; ECF—extracellular fluid.

Figure 1 Strontium absorption as % of dose in extracellular fluid (ECF) four hours after breakfast at the end of each week for the 12 subjects (six placebo in first week, six beclomethasone dipropionate in first week).

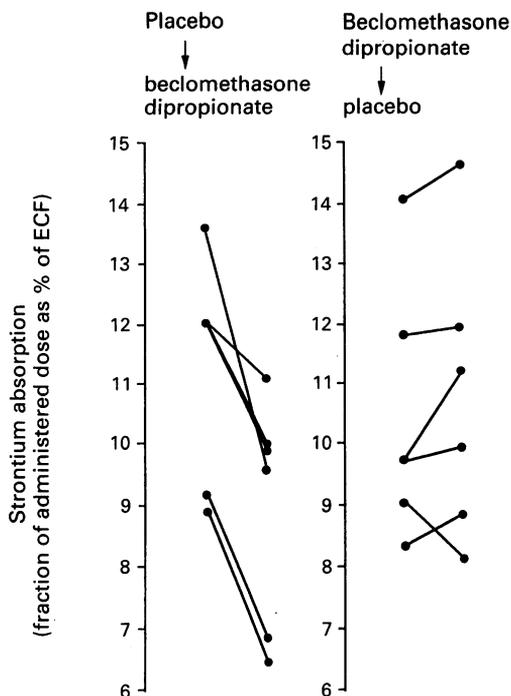
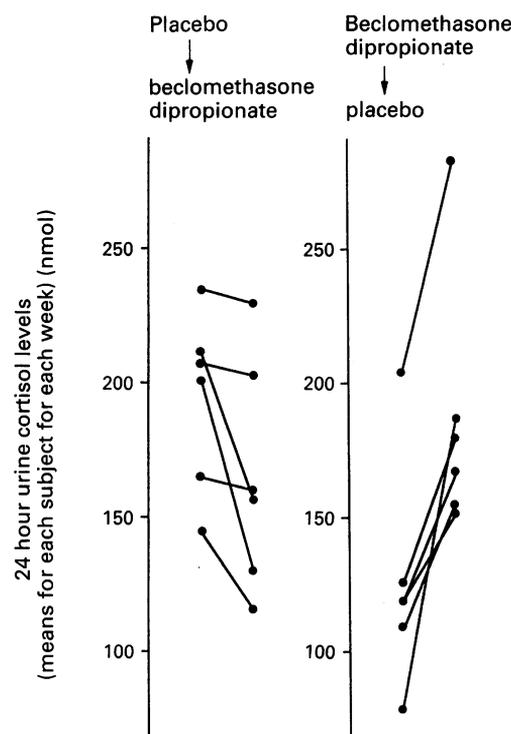


Figure 2 Urinary cortisol concentrations/24 hours averaged over each week for the 12 subjects (six placebo in first week, six beclomethasone dipropionate in first week).



dipropionate compared with the placebo week (mean reduction 23%, $p < 0.0005$; fig 2).

In the six subjects proceeding from placebo to beclomethasone dipropionate, there was a mean reduction of 20.3% in strontium absorption during the second week, with all six subjects having lower strontium absorption when compared with values for the placebo week ($p < 0.005$). In subjects proceeding from beclomethasone dipropionate to placebo, there was a mean increase of 3.2% for strontium absorption in the second (placebo) week, but this was not significant. No other assays showed a significant difference between the beclomethasone dipropionate and placebo weeks, apart from an increased plasma phosphate concentration during the first week of beclomethasone dipropionate ingestion.

Discussion

Inhalation from a metered dose inhaler results in a much greater deposition of topical corticosteroid within the intestine than in the lungs.¹⁰ Topical corticosteroids may have potent actions on mucosal surfaces.²⁴ Within the intestinal lumen, beclomethasone dipropionate is hydrolysed to beclomethasone-17-propionate, which has much greater glucocorticoid receptor affinity.¹⁹ Thus hydrolysis is an important activation step within the intestine, and increases the possibility of a topical effect of the swallowed drug on calcium absorption in the intestine.

The lower strontium absorption during the beclomethasone dipropionate week suggests that intestinal strontium absorption is reduced by beclomethasone dipropionate, as there is no apparent reason for the drug to directly affect strontium clearance. The 20.3% reduction in strontium absorption in the placebo to beclomethasone dipropionate group was not mirrored by an increase of similar magnitude in the other cross over group (fig 1). This may be due to an inadequate washout period after beclomethasone dipropionate in the first week. Beclomethasone dipropionate is unaffected by gastric fluid in vitro, and is slowly metabolised to the more potent beclomethasone-17-monopropionate within the

Table 3 Mean (SD) results of assays for the two separate study groups

| Study factor | P to BDP group | | | BDP to P group | | |
|------------------------------------|----------------|-------------|--------|----------------|-------------|--------|
| | P | BDP | p | BDP | P | p |
| Strontium test (% of dose in ECF) | 11.3 (1.8) | 9.0 (1.9) | <0.005 | 10.4 (2.1) | 10.7 (2.4) | NS |
| Plasma calcium (mmol/l) | 2.41 (0.07) | 2.39 (0.05) | NS | 2.37 (0.10) | 2.36 (0.07) | NS |
| Plasma phosphate (mmol/l) | 1.13 (0.14) | 1.13 (0.17) | NS | 1.18 (0.10) | 1.07 (0.10) | <0.05 |
| Serum parathyroid hormone (pmol/l) | 40 (41) | 41 (3.9) | NS | 47 (11) | 49 (8) | NS |
| Urinary cortisol (nmol/day) | 194 (33) | 166 (43) | NS | 127 (42) | 188 (48) | <0.005 |
| Urinary hydroxyproline (μmol/day) | 269 (145) | 228 (77) | NS | 193 (39) | 173 (30) | NS |
| Urinary calcium (mmol/day) | 2.73 (1.07) | 2.62 (0.80) | NS | 2.96 (0.48) | 3.24 (0.73) | NS |

BDP—beclomethasone dipropionate; P—placebo; ECF—extracellular fluid.

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intestine. Beclomethasone-17-monopropionate is a stable product and only very slowly metabolised within the intestine.¹⁹ The parent compound is sparingly soluble and is poorly absorbed by the intestine.¹¹ A combination of these factors could therefore account for a prolonged and potent glucocorticoid effect on intestinal mucosal calcium absorption, and thus may explain an inadequate washout in the beclomethasone dipropionate to placebo group.

The decrease in urinary free cortisol during beclomethasone dipropionate ingestion suggests that a systemic effect of the orally ingested drug occurred despite (a) the weak systemic potency of beclomethasone dipropionate reported in previous studies,¹⁴ and (b) its expected high rate of first pass metabolism when swallowed. Hence, we cannot be sure to what degree the reduction in strontium absorption is topical rather than systemic. Whatever the mechanism, reduction of calcium absorption secondary to beclomethasone dipropionate may be clinically important to bone health, as long term suppression of calcium absorption is known to be associated with parathyroid mediated bone resorption,^{17 25-29} and low calcium absorption is a major determinant of mineral density loss in vertebral bone.³⁰ Our study assessed the effect of only one week of ingestion, however, and not the effects longer term. The effect of oral corticosteroids on calcium absorption and parathyroid concentrations is sustained,^{17 28 29} and therefore a sustained effect remains possible with swallowed beclomethasone dipropionate; this requires further evaluation.

Our study was on normal volunteers but there is no known reason why a suppressive effect on calcium absorption would not also apply to patients with asthma or chronic obstructive airways disease; again further research is needed.

Inhaled corticosteroids affect various indices relevant to bones,³¹⁻³⁴ but a reduction in calcium absorption secondary to treatment with beclomethasone dipropionate has not, to our knowledge, been reported previously.

More research is required to assess the possibility of chronic suppression of calcium absorption in patients rather than healthy volunteers. Effects on other bone indices, particularly bone density, also require further assessment.

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