

vaccine recipients had IgE antibody to gelatin. Animal gelatin has long been used as a stabilizer in not only live virus vaccines but also inactivated vaccines; it was believed to have no antigenicity to human beings. To prevent gelatin anaphylaxis on vaccination, alternative stabilizers that have no antigenicity to human beings should be explored. For treatment of anaphylaxis, children should stay at the clinic for 30 minutes after vaccination. Prior questioning of vaccine recipients and their parents about allergic symptoms associated with ingestion of gelatin-containing foods may be help to prevent anaphylaxis in some children.

We thank the physicians and the vaccine manufacturers for help in serum sampling. We also thank Akira Tanaka and Hiroko Tomiyama, Kabi Pharmacia Diag-

nostics, Tokyo, for measurement of specific IgE to gelatin, and Mie Kato for technical assistance.

REFERENCES

1. Businco L. Measles, mumps, rubella immunization in egg-allergic children: a long-lasting debate. *Ann Allergy* 1994;72:1-3.
2. Fasano MB, Wood RA, Cooke SK, Sampson HA. Egg hypersensitivity and adverse reactions to measles, mumps, and rubella vaccine. *J Pediatr* 1992;120:878-81.
3. Kelso JM, Jones RT, Yunginger JW. Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin. *J ALLERGY CLIN IMMUNOL* 1993;91:867-72.
4. Ogura H. Allergic disease: egg allergy and vaccination [in Japanese]. *J Pediatr Pract* 1993;56:2209-16.
5. Businco L, Grandolfo M, Bruno G. Safety of measles immunization in egg-allergic children. *Pediatr Allergy Immunol* 1991;4:195-8.

Inhaled beclomethasone and bone metabolism in young asthmatic children: A six-month study

Muriel Le Bourgeois, MD,^a Catherine Cormier, MD,^b
Catherine Kindermans, MD,^b Jean-Claude Souberbielle, MD,^b
Michèle Garabédian, MD,^c Jacques de Blic,^a and Pierre Scheinmann, MD^a
Paris, France

Inhaled corticosteroids (ICs) are established as first-line treatment of chronic severe asthma. Because of their pharmacokinetics, ICs have a high local antiinflammatory potency with minimal systemic side effects. Numerous studies agree that moderate doses of ICs do not inhibit long-term linear growth. However, doubt remains about the effects of ICs on bone metabolism in children. Data are scarce for very young children. The aim

Abbreviations used

BDP:	Beclomethasone dipropionate
ICs:	Inhaled corticosteroids
25(OH)D:	25 Hydroxy vitamin D
1,25(OH) ₂ D:	1,25 Dihydroxy vitamin D
PTH:	Parathyroid hormone

From ^aPediatric Pulmonology Department, ^bPhysiology Department, and ^cCentre National de Recherche Scientifique, Unité de Recherche Appliquée 583, Hôpital Necker Enfants Malades, Paris.

Reprint requests: Muriel Le Bourgeois, Service de Pneumologie et Allergologie Pédiatriques, Hôpital Necker-Enfants Malades, 149 rue de Sèvres, 75743 Paris Cedex 15, France.

J ALLERGY CLIN IMMUNOL 1995;96:565-7.

Copyright © 1995 by Mosby-Year Book, Inc.

0091-6749/95 \$5.00 + 0 1/54/65640

of this study was to assess the effects of ICs on bone turnover in very young asthmatic children.

METHODS

Eleven asthmatic infants (4 girls) with a mean age of 21.7 months (range, 9 to 53 months) were studied from November 1992 to February 1993. All the infants had had at least three episodes of wheezing dyspnea in the previous 12 months. Severity was assessed by at least one monthly episode during the previous 3 months or daily

TABLE I. Changes in biochemical markers of bone metabolism in infants with asthma during BDP treatment

Biologic parameters	Normal values*	Day 0	Month 6	P Value
Serum total calcium (mmol/L)	2.25-2.55	2.47 ± 0.092	2.48 ± 0.115	NS
Serum ionized calcium (mmol/L)	1.19-1.3	1.32 ± 0.025	1.32 ± 0.034	NS
Serum intact PTH (pg/ml)	10-65	28.72 ± 15.99	23.54 ± 11.02	NS
Serum 25(OH)D (ng/ml)	5-30	16.45 ± 11.88	13.91 ± 5.02	NS
Serum 1,25 (OH) ₂ D (pg/ml)	20-80	43.27 ± 21.8	50.27 ± 20.11	NS
Urinary calcium/creatinine (mmol/L/mmol/L)	<0.3	0.17 ± 0.14	0.26 ± 0.37	NS
Serum osteocalcin (ng/ml)	8-28	20.04 ± 7.41	25.45 ± 3.61	0.048
Urinary pyridinoline/creatinine (nmol/L/mmol/L)	272-550	174.84 ± 109.45	158.74 ± 65.64	NS
Urinary deoxypyridinoline/creatinine (nmol/L/mmol/L)	39-97	23.05 ± 13.67	22.46 ± 10.37	NS

Results are expressed as means ± SD.

NS, Not significant.

*Normal values are given for the range of age 9 months to 4 years.

symptoms for the previous 2 weeks. None had ever received ICs. Eight of the 11 infants had received one or more short courses oral corticosteroids in the last 3 months, the lastest of which was within the last 2 weeks. Beclomethasone dipropionate (BDP) was administered twice daily through a spacer device (Volumatic 750 ml; Glaxo, France) with a face mask. Each puff was followed by 7 to 10 respiratory cycles. The mean daily dose administered was 597 µg (range, 500 to 860 µg) for a mean duration of 5.8 months (range, 4.5 to 7.5 months). No infant needed oral corticosteroids during the study.

Biochemical markers of bone metabolism were measured on day 0 before BDP administration was started and at the end of the study. Morning blood samples and second-void urinary samples were collected. The paired Student's *t* test was used for statistical analysis.

The markers used were serum total and ionized calcium (ion-selective electrode, ICA₂; Radiometer, Copenhagen, Denmark), 25 OH and 1,25 (OH)₂ D₂ (radiocompetitive binding assays after extraction) intact parathyroid hormone (PTH) (one-step immuno-radiometric assay, Allegro intact PTH; Nichols Institute Diagnostics, Calif.), osteocalcin (OST K-PR cis; Bio International, Gif sur Yvette, France), and urinary calcium/creatinine, pyridinoline/creatinine, and deoxypyridinoline/creatinine parameters. Urinary pyridinoline and deoxypyridinoline were measured by fluorimetry after purification by hydrolysis, column extraction, and high-performance liquid chromatography. Osteocalcin is a marker of bone formation; urinary pyridinoline and deoxypyridinoline are markers of bone and cartilage resorption and are more bone-specific than hydroxyprolinuria.

RESULTS

All values were within normal limits on day 0 except for the urinary pyridinoline/creatinine ratio, which was lower than normal for this age group (Table I). There was no significant change in total and ionized calcium, 25 OH, 1,25(OH)₂D, intact PTH, urinary calcium/creatinine, pyridinoline/creatinine, and deoxypyridinoline/creatinine after 6 months of treatment with BDP. Serum osteocalcin levels were significantly higher after 6 months compared with day 0 (25.45 ± 3.61 ng/ml vs 20.04 ± 7.41 ng/ml, *p* = 0.048). This increase was more marked in the eight infants who had received oral corticosteroids within the preceding fortnight (25.62 ± 3.85 ng/ml vs 18.2 ± 7.89 ng/ml, *p* = 0.03).

DISCUSSION

A decrease in osteocalcin has been described in healthy adults receiving high doses of ICs.¹ Studies of biochemical markers of bone turnover in asthmatic children report either the absence of any effect at doses of 300 to 800 µg of BDP per day for 25 months² and 800 µg of BDP per day for 2 weeks,³ or a reduction of bone formation at doses of 400 to 800 µg of budesonide per square meter of body surface area per day for 5 months.⁴

Our study demonstrates that there is no significant change in bone metabolism after 6 months of treatment with BDP at moderate doses (597 µg/

day) as assessed by markers of bone formation and bone resorption. Furthermore, the stabilization of asthma with ICs reduced the requirement for oral corticosteroids. It may have contributed to the restoration of bone formation, as suggested by the increase in serum osteocalcin, whereas during this period of life a physiologic decrease would have been expected.⁵

Conclusion

Treatment with BDP is effective and does not seem to have any effect on bone metabolism at moderate doses when given to asthmatic infants for 6 months without interruption. This is reassuring, given the growing use of ICs for treatment of asthma in infants. However, it is important to control asthma with the lowest dose of ICs possi-

ble, and further studies of longer term treatment in infants would be useful.

REFERENCES

1. Toogood JH, Jennings BH, Hodsman AB, Baskerville J, Fraher L. Effects of dose and dosing schedule of inhaled budesonide on bone turnover. *J ALLERGY CLIN IMMUNOL* 1991;88:572-80.
2. König P, Hillman L, Cervantes C, et al. Bone metabolism in children with asthma treated with inhaled beclomethasone dipropionate. *J Pediatr* 1993;122:219-26.
3. Wolthers OD, Ris BJ, Pødersen S. Bone turnover in asthmatic children treated with oral prednisolone or inhaled budesonide. *Pediatr Pulmonol* 1993;19:341-6.
4. Sorva R, Turpeinen M, Juntunen-Backman K, Karonen SL, Sorva A. Effects of inhaled budesonide on serum markers of bone metabolism in children with asthma. *J ALLERGY CLIN IMMUNOL* 1992;90:808-15.
5. Delmas P, Chatelain P, Malaval L, Bonne G. Serum GLA-protein in growth hormone deficient children. *J Bone Miner Res* 1986;1:333-8.