# Short- and Long-Term Effect of Oral Salbutamol on Growth Hormone Secretion in Prepubertal Asthmatic Children

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**Salbutamol, a $\beta_2$-adrenergic agonist, is being extensively used in Venezuela as a brochodilator in the treatment of asthma in children. Previous reports have shown oral salbutamol either to inhibit or not to affect growth hormone (GH) secretion. We evaluated the effect of oral salbutamol (0.1 mg/kg every 6 hours for 3 months) on GH secretion in eight prepubertal short children with mild asthma. Levels of GH during sleep (samples taken every 30 minutes from 9 PM to 6 AM) and after GH-releasing hormone ([GHRH] 1 μg/kg intravenously [IV]) were measured before, at 24 hours, and at 3 months of salbutamol treatment. Overnight integrated concentrations of GH and peak GH levels following GHRH diminished significantly after 24 hours of salbutamol therapy (from 4.5 ± 1.3 to 3.4 ± 0.8 μg/L and from 46.6 ± 47.3 to 16.2 ± 7.9 μg/L, respectively, $P < .05$). However, GH levels after 3 months of salbutamol were not different from basal levels (4.5 ± 1.3 *v* 5.1 ± 5.1 ± 2.9 μg/L during the overnight studies and 46.6 ± 47.3 *v* 37.8 ± 30.4 μg/L after GHRH). Our data suggest an inhibition of both spontaneous and stimulated GH secretion following short-term oral salbutamol ingestion, but this suppressive effect is not maintained with its long-term use.**



SALBUTAMOL, a $\beta_2$-adrenergic agonist, is being extensively used in Venezuela as a bronchodilator in the treatment of bronchial asthma in children both in its oral and inhaled forms.

Previous data on the effects of salbutamol on growth hormone (GH) are quite limited. Studies in experimental animals or in adults have found short-term oral or intravenous (IV) salbutamol either to decrease GH secretion, probably through hypothalamic somatostatin stimulation,[1,2] or not to affect GH secretion at all.[3-5] Inhibition of GH release after GH-releasing hormone (GHRH) treatment and during overnight GH testing has been recently described in type I diabetic children following short-term oral administration of salbutamol.[6,7] The effect of more-prolonged salbutamol use on GH secretion apparently has not been previously evaluated.

To our knowledge, the short- and long-term effects of oral salbutamol on the GH secretion of asthmatic children have not been previously studied. We have evaluated a group of prepubertal, mildly asthmatic children to determine the effect of short- and long-term oral salbutamol treatment on these parameters.

## SUBJECTS AND METHODS

Eight otherwise healthy, prepubertal children with mild asthma (in no respiratory distress, with last asthmatic crisis at least 3 months before beginning this protocol) on no other medication were studied. They had a mean ± SD chronological age of 7.9 ± 2.9 years (range, 5.0 to 12.4 years) and were slightly below the 5th percentile in height and weight, but had a normal growth velocity (≥5 cm/yr). All patients were evaluated at the pediatric and endocrine clinics of the Hospital Central "Dr. Carlos Arvelo" after obtaining both parental consent and study approval from the Hospital Clinical Studies Committee.

Overnight GH concentrations, as well as GH levels following short-term GHRH stimulation, were obtained before salbutamol ingestion. Patients were admitted 4 hours before the overnight sampling; they had a balanced dinner at 6 PM, and the lights were turned off at 9 PM after insertion of a venous catheter. A special effort was made to avoid stress and to encourage normal activity in this period between 6 and 9 PM before overnight sampling. Two milliliters of blood were obtained every 30 minutes between 9 PM and 6 AM of the following day through an indwelling venous catheter. One hour after completing the overnight sampling, 1 μg/kg GHRH (GRF; Serono Laboratory) was injected IV, and blood samples were obtained at 0, 30, 60, 90, and 120 minutes for GH determination.

Oral salbutamol treatment at a dose of 0.1 mg/kg every 6 hours was begun in the next few days and administered for a total of 3 months. Twenty-four hours, and then 3 months after beginning salbutamol treatment, patients were again hospitalized for measurement of overnight GH and GH levels following IV GHRH stimulation, as described above.

Blood samples were stored at −20°C. Specific radioimmunoassay techniques were used for the determination of plasma GH levels using the Pharmacia hGH RIA Kit (Uppsala, Sweden). The level of detection of this assay was less than 0.4 mU/L, and the interassay and intraassay coefficients of variation were 5.1%, 2.9%, 2.5%, and 4.5% at GH concentrations of 2.3, 8.4, 21.8, and 43.8 mU/L, respectively (2 mU/L = 1 μg/L). All blood samples were processed in duplicate. Comparisons of GH values obtained before, at 24 hours, and at 3 months of salbutamol therapy were performed using ANOVA. Standard measures of integrated GH secretion were used via the Cluster GH pulse analysis program. Total GH output was estimated by measuring the area under the curve versus the 9-hour time curve. Results are reported as the mean ± SD.

## RESULTS

Overnight GH concentrations, as well as GH levels following short-term GHRH stimulation, were significantly inhibited in our patients by 24 hours of salbutamol therapy. Overnight integrated GH concentrations decreased from a basal level of 4.5 ± 1.3 μg/L (mean ± SD) to 3.4 ± 0.8

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**Table 1. Overnight GH Levels Before, at 24 Hours, and at 3 Months of Salbutamol Treatment**

| Salbutamol Treatment | IC (μg/L) | Peak GH (μg/L) |
|---|---|---|
| Before | 4.5 ± 1.3 | 28.0 ± 18.8 |
| 24 hours | 3.4 ± 0.8* | 19.2 ± 10.1* |
| 3 months | 5.1 ± 2.9 | 30.0 ± 21.3 |

NOTE. Values are the mean ± SD.

Abbreviation: IC, overnight integrated GH concentrations.

*$P < .05$ (values at 24 hours *v* before and at 3 months of salbutamol treatment).

μg/L after 24 hours of salbutamol ($P < .05$; Table 1). The number of overnight GH pulses decreased, although not significantly, from 3.0 ± 1.0 to 2.3 ± 0.8, and mean peak overnight GH levels and total basal GH output (area under the curve ± SD/9 h) decreased significantly (from 28.0 ± 18.8 to 19.2 ± 10.1 μg/L and from 367 ± 214 to 277 ± 167 U, respectively). Basal and peak GH levels after GHRH stimulation also decreased significantly (from 3.3 ± 3.8 and 46.6 ± 47.3 μg/L to 2.1 ± 3.1 and 16.2 ± 7.9 μg/L, respectively, $P < .05$; Table 2).

However, overnight integrated GH concentrations and GH levels following IV GHRH did not change after 3 months of salbutamol treatment. Overnight GH was 4.5 ± 1.3 μg/L before salbutamol and 5.1 ± 2.9 after 3 months of therapy (NS; Table 1), and the number of overnight GH pulses, mean peak overnight GH levels, and total basal GH output were also similar in these two periods (3.0 ± 1.0 *v* 2.5 ± 0.8, 28.8 ± 18.8 *v* 30.0 ± 21.3 μg/L, and 367 ± 214 *v* 385 ± 321 U, respectively). Peak GH levels following IV GHRH were 46.6 ± 47.3 μg/L before and 37.8 ± 30.4 after 3 months of salbutamol (NS; Table 2).

Overnight GH concentrations before, at 24 hours, and at 3 months of salbutamol treatment can be seen in Table 1. Peak GH levels following stimulation with GHRH before, at 24 hours, and at 3 months of treatment can be seen in Table 2 and Fig 1.

Oral salbutamol was well-tolerated by our patients, with no side effects or respiratory distress occurring during therapy.

## DISCUSSION

The effects of salbutamol on the GH secretion of experimental animals and adults have been variable. Goldberg et al[1,2] reported in 1974 and 1975 that GH secretion in healthy adults was not affected by IV salbutamol. However, Mazza et al[3] and Ghigo et al[4] recently found GH secretion to be inhibited by short-term IV salbutamol treatment in a large

**Table 2. GH Levels After GHRH Stimulation Before, at 24 Hours, and at 3 Months of Salbutamol Treatment**

| Salbutamol Treatment | Peak GH (μg/L) |
|---|---|
| Before | 46.6 ± 47.3 |
| 24 hours | 16.2 ± 7.9* |
| 3 months | 37.8 ± 30.4 |

NOTE. Values are the mean ± SD.

*$P < .05$ (values at 24 hours *v* before and at 3 months of salbutamol treatment).

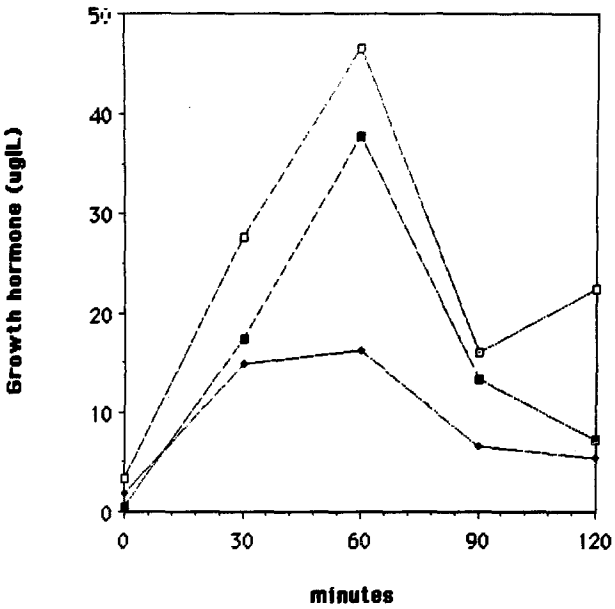


**Fig 1. GH levels after IV GHRH before, at 24 hours, and at 3 months of salbutamol treatment. (□) Basal, (◆) short-term, (■) long-term.**

number of healthy adults, so that GH release decreased significantly from an area under the curve of 324.3 ± 99.7 μg/L/h after IV GHRH alone to 112.7 ± 48.8 after combined IV GHRH and salbutamol ($P < .02$). Studies by Schaub et al[5] in 1983 had already found 0.025 or 0.05 μg/kg intramuscular salbutamol or 0.01 μg/kg IV salbutamol to inhibit GH secretion in rhesus monkeys.

Studies in children that evaluate GH levels following therapy with salbutamol are scarce. Umbilical cord blood concentrations of GH at birth after maternal treatment with oral salbutamol were compared with those of a group of matched patients who had not received betamimetic agents, by Desgranges et al.[8] Cord blood levels of GH were found to be significantly increased at birth after maternal treatment with an oral betamimetic agent, and they concluded that these unexpectedly elevated GH concentrations could reflect either fluctuating fetal blood glucose levels in response to episodic betamimetic administration or direct fetal pituitary production through adrenergic stimulation.

Martina et al[6] and Bartolotta et al[7] recently studied the effect of oral salbutamol on GH secretion in type I diabetic children. They analyzed the effect of a single dose of oral salbutamol on GH release induced by IV GHRH and that of a slow-release form of oral salbutamol administered for 3 days on spontaneous overnight GH secretion and found GH to be inhibited in both instances, most likely due to stimulation of hypothalamic somatostatin. Pituitary GH secretion is modulated by the stimulatory influence of GHRH and the inhibitory influence of hypothalamic somatostatin.[9] One microgram per kilogram of IV GHRH induces a maximal GH release that was clearly inhibited by salbutamol in these subjects, suggesting that this inhibitory effect on GH could be secondary to increased somatostatin secretion or to an increase in somatostatinergic tone.

To our knowledge, the possible changes induced by oral salbutamol on the GH secretion of asthmatic children have not been previously evaluated. Since this medication is being extensively used as a bronchodilator for the treatment of asthma in Venezuelan children, its short- and long-term effects on the GH secretion and growth velocity of these children need to be studied. Our data suggest an inhibition of both stimulated and spontaneous GH secretion following short-term oral salbutamol ingestion, but with normalization of these parameters after more-prolonged salbutamol use. Short-term stimulatory or inhibitory effects on hormones, but without a sustained long-term effect, have been noted with the use of other medications. Such is the case with oral clonidine, which has been proven to stimulate GH release acutely,[10] but with no apparent long-term stimulatory effects on GH secretion.[11]

Other medications routinely used in the treatment of asthma, such as systemic glucocorticoids, clearly inhibit both GH release and the peripheral action of somatomedin. The effects of inhaled glucocorticoids on the GH release and growth velocity of children are still somewhat controversial, although high-dose inhaled budesonide seems to decrease the growth velocity of asthmatic children.[12] We cannot report on the effects of oral salbutamol on the growth velocity of our patients, since the follow-up period was too short to allow us to reach meaningful conclusions.

In summary, oral salbutamol seems to inhibit GH secretion acutely, but this suppressive effect is not maintained with its long-term use. Although our data seem to indicate that the use of oral salbutamol produces no chronic deleterious changes in GH secretion, larger long-term studies using both oral and inhaled salbutamol are clearly indicated to evaluate its effect on the GH secretion and growth velocity of asthmatic children.

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