

A COMPARISON OF NEBULIZED BUDESONIDE, INTRAMUSCULAR DEXAMETHASONE, AND PLACEBO FOR MODERATELY SEVERE CROUP

DAVID W. JOHNSON, M.D., SHEILA JACOBSON, M.B., B.CH., PETER C. EDNEY, B.SC., PAT HADFIELD, R.N.,
MARIANNE E. MUNDY, R.N., AND SUZANNE SCHUH, M.D.

ABSTRACT

Background In children with croup, treatment with nebulized budesonide decreases symptoms, but it is uncertain how budesonide compares with dexamethasone, the conventional therapy for croup, and whether either reduces the rate of hospitalization.

Methods We performed a double-blind, randomized trial involving 144 children with moderately severe croup. The children were treated with racipnephine and a single dose of 4 mg of nebulized budesonide (48 children), 0.6 mg of intramuscular dexamethasone per kilogram of body weight (47 children), or placebo (49 children). The children were assessed before treatment and then hourly for five hours after treatment. Physicians who were unaware of the treatment assignments determined the children's need for further treatment and hospitalization.

Results The characteristics of the groups were similar at base line, including the types of viruses identified, the types of croup, and the clinical severity of the illness. The overall rates of hospitalization were 71 percent in the placebo group (35 of 49 children), 38 percent in the budesonide group (18 of 48 children), and 23 percent in the dexamethasone group (11 of 47 children) (unadjusted $P=0.001$ for the comparison of budesonide with placebo, $P<0.001$ for the comparison of dexamethasone with placebo, and $P=0.18$ for the comparison of budesonide with dexamethasone). Children treated with budesonide or dexamethasone had a greater improvement in croup scores than those given placebo ($P=0.03$ and $P<0.001$, respectively), and those treated with dexamethasone had a greater improvement than those treated with budesonide ($P=0.003$).

Conclusions In children with moderately severe croup, treatment with intramuscular dexamethasone or nebulized budesonide resulted in more rapid clinical improvement than did the administration of placebo, with dexamethasone offering the greatest improvement. Treatment with either glucocorticoid resulted in fewer hospitalizations. (N Engl J Med 1998; 339:498-503.)

©1998, Massachusetts Medical Society.

EACH year croup is diagnosed in 3 of every 100 children under six years of age,¹ and approximately 1 percent of children with croup are hospitalized.¹ As a result, it accounts for a substantial proportion of all pediatric hospitalizations (2 percent at Alberta Children's Hospital). A treatment that substantially reduced the hospitalization rate in children with croup would therefore be

expected to decrease health care costs and the social burden of the disease.

Klassen et al. found that among children with croup who were treated in an emergency department, those who received nebulized budesonide were less likely to be hospitalized than those who received placebo.² Though their results suggest that glucocorticoids act rapidly enough to reduce the likelihood of hospitalization, they studied only 54 children, and the difference in hospitalization rates between the two groups was marginal ($P=0.05$). Another study of nebulized dexamethasone, which included 55 children and had a similar design, found no significant reduction in the rate of hospitalizations.³ Thus, it remains uncertain whether glucocorticoid therapy can reduce the need for hospitalization in children with croup.

Numerous studies have demonstrated that inhaled budesonide decreases the symptoms of croup more rapidly than does placebo.^{2,4-6} However, it is unclear how treatment with budesonide compares with conventional therapy with parenteral or oral dexamethasone.⁷ In one study fewer patients were hospitalized at 24 hours in the oral-dexamethasone group than in the nebulized-budesonide group, but the differences between groups were not significant.⁴

We designed a randomized, double-blind, placebo-controlled trial to determine whether the administration of glucocorticoids to children with moderately severe croup evaluated in an emergency department reduces the rate of hospitalization and to compare nebulized budesonide and intramuscular dexamethasone.

METHODS

Study Subjects

Trained study nurses were notified of children with acute onset of audible stridor who were seen between 3 p.m. and 6 a.m. at the emergency departments of the Hospital for Sick Children in Toronto from September 1993 through May 1996 and Alberta Children's Hospital in Calgary from October 1995 to May 1996. Children were enrolled in the study if they were three months to nine years of age, had been given a diagnosis of croup (defined as acute onset of inspiratory stridor associated with a "seal-like"

From the Department of Paediatrics, University of Calgary, Alberta Children's Hospital, Calgary, Alta. (D.W.J., M.E.M.); the Department of Paediatrics, University of Toronto, Hospital for Sick Children, Toronto (S.J., P.H., S.S.); and Astra Pharma, Mississauga, Ont. (P.C.E.) — all in Canada. Address reprint requests to Dr. Johnson at the Child Health Research Unit, Alberta Children's Hospital, 1820 Richmond Rd. SW, Calgary, AB T2T 5C7, Canada.

TABLE 1. THE CROUP SCORING SYSTEM.*

SYMPTOM	SCORE	TOTAL CUMULATIVE SCORE
Stridor		
None	0	
When agitated	1	
At rest	2	2
Retractions		
None	0	
Mild	1	
Moderate	2	
Severe	3	5
Air entry		
Normal	0	
Decreased	1	
Markedly decreased	2	7
Cyanosis while breathing room air		
None	0	
With agitation	4	
At rest	5	12
Level of consciousness		
Normal	0	
Disoriented	5	17

*The scoring system of Westley et al.⁸ was used.

barking cough), and had persistent, moderately severe respiratory distress, defined as a croup score of 3 to 6 (Table 1) after treatment with humidified oxygen for 30 minutes.⁸ Exclusion criteria included symptoms or signs suggesting another cause of stridor, such as epiglottitis, bacterial tracheitis, or supraglottic foreign body⁹; inability of the patients' parents to speak English well enough to understand and give informed consent; or a history of chronic pulmonary disease, severe systemic disease, immune dysfunction,³ stridor or intubation for more than one month, or glucocorticoid therapy in the four weeks before study entry.

The study was approved by the institutional review boards at each hospital. Written informed consent was obtained from each patient's parents before enrollment.

Study Design

Eligible children were randomly assigned to receive a single dose of nebulized budesonide (4 mg; Pulmicort Nebuamp, Astra Pharma, Mississauga, Ont.), intramuscular dexamethasone (0.6 mg per kilogram of body weight; Decadron Injection, Merck Sharp & Dohme Canada, Kirkland, Que.), or placebo. All patients received 0.5 ml of 2.25 percent racemic epinephrine (Vaponefrin, Rhône-Poulenc Rorer Canada, Ville St. Laurent, Que.) and normal saline combined with either the budesonide or placebo suspension (total volume, 8 ml). The suspension was delivered by means of a nebulizer (model 1700 Up-draft Neb-U-Mist, Hudson, Temecula, Calif.) with oxygen from a wall outlet at a rate of 6 to 7 liters per minute through a face mask held tightly to the patient's face over a period of 20 minutes. Study nurses closely supervised nebulizer treatments to ensure compliance.

The placebo suspension, prepared by Astra, was slightly clearer than the budesonide suspension. To make the nebulized study drugs indistinguishable from each other, they were packaged in opaque containers and discharged directly into a colored nebulizer with the racemic epinephrine and normal saline. For ethical reasons, only children who were randomly assigned to dexamethasone received injections. To maintain masking, the study nurse temporarily took the parents away from their child while an emergency staff nurse not otherwise involved in the care of the child injected the dexamethasone into the child's thigh, placed a bandage over

the injection site (all children received a bandage whether or not they received dexamethasone), and initiated nebulization. The nurse was instructed not to inform anyone, including other emergency staff members, about the treatment delivered. At the completion of the observation period for each child, the adequacy of masking was assessed.

Randomization

A blocked randomization code was produced by random-number-generating software (Astra) and provided only to the pharmacy at each hospital. The pharmacies prepared sequential patient packets containing study drugs that were sealed and were identical in appearance and weight. The code was not broken until after the study ended and all decisions regarding data analysis were finalized.

Viral Cultures and Assessment of the Type of Croup

Cultures of nasopharyngeal secretions were obtained at each hospital with the use of standard procedures to test for parainfluenza virus, influenza virus, and respiratory syncytial virus. The children were classified as having spasmodic croup, acute laryngotracheitis, or a mixed presentation. Patients with sudden onset of stridor (<2 hours before presentation), with no fever (temperature, <38.0°C) or upper respiratory tract infection, were considered to have spasmodic croup. Patients with a prodromal upper respiratory tract infection (>12 hours before the onset of stridor) and fever or a history of fever were considered to have acute laryngotracheitis. Patients with symptoms that did not meet either of the previous definitions were considered to have a mixed presentation.¹⁰

Other Treatments and Hospitalization

Emergency physicians made all decisions regarding the need for further treatment with racemic epinephrine and hospitalization on the basis of their clinical judgment. No treatment or admission criteria were imposed, except that physicians were asked not to administer glucocorticoids unless they decided to admit the child to the hospital after the five-hour observation period. All children received mist therapy throughout the observation period. At the Hospital for Sick Children, mist was administered through a plastic hose held by the parents to the child's face, and at Alberta Children's Hospital, mist was administered by a bedside humidifier before the study treatment and with a mist tent thereafter.

Follow-up

Study nurses telephoned the parents of children who were not hospitalized 72 hours after they had been discharged from the emergency department to ascertain whether the children had been reevaluated. Children who remained symptomatic were followed up every 72 hours until they were free of symptoms.

Outcome Measures

The hospitalization rate was the primary outcome measure, and the change in croup score (from base line to five hours after treatment) and the number of additional racemic epinephrine treatments administered (two to five hours after treatment with the study drug) were chosen as secondary outcome measures. A single nurse determined the croup score in each child when the child was in a quiet, alert state, before treatment and then hourly for five hours after treatment or until the child was sent home from the emergency department (Table 1). The nurse also measured oxygen saturation while the child was breathing room air, respiratory rate, heart rate, and blood pressure at these times. The nurses were trained by the principal investigator to use the croup scoring system, and the results were validated throughout the enrollment period by having study physicians independently determine the children's scores at the same time that the nurses made their assessments. Physicians and nurses were unaware of each other's assessments. The respiratory rate was counted for one

minute; the heart rate and oxygen saturation were measured by pulse oximetry while the child was breathing room air.

Statistical Analysis

On the basis of previous experience,³ we estimated that the hospitalization rate in the control group would be approximately 65 percent. In order to allow the detection of a 40 percent reduction in the proportion of children who were hospitalized, we planned to enroll 210 children, with an interim analysis after the enrollment of approximately 150 children. A biostatistician who was not otherwise involved in the study performed the interim analysis using the primary outcome variable, hospitalization rate. The criterion for stopping the study was the finding in an overall test for differences between the three treatment groups of a P value of less than 0.005. To maintain an overall type I error of 0.05, we adjusted the alpha level for the final analysis to 0.048.¹¹

The data were analyzed with SAS software (version 6.08) and VMS/VAX software (version 6.1). The normality of the distribution of variables was assessed by the Wilk-Shapiro test.^{12,13} Proportional variables were analyzed without adjustment by Fisher's exact test and with adjustment for covariates by multiple logistic-regression analysis. The latter analysis allowed us to explore the effect of several base-line prognostic factors (base-line croup score, study center, study nurse, type of croup, and viral-culture results) on the primary and secondary outcome measures.^{13,14} Continuous variables were analyzed without adjustment by one-way analysis of variance and with adjustment by an analysis of covariance with the same covariates that were used in assessing proportional variables.^{15,16} All statistical tests were two-tailed.

An intention-to-treat analysis was performed, in that all children who were randomly assigned to a treatment group were included in the full analysis. In addition, an analysis was performed of all children who completed the study except those with an unintentional deviation from the study protocol.

RESULTS

Characteristics of the Patients

Among 4075 children with a discharge diagnosis of croup during the enrollment period, 3857 were not approached for enrollment in the study. The reasons for exclusion were as follows: disease that was too mild (3206 children); disease that was too severe, stridor that was not due to croup, or the presence of a disqualifying disease (229); previous treatment with glucocorticoids (121); wrong age (19); parents could not speak English well enough to give consent (7); evaluation outside of the study hours of 3 p.m. to 6 a.m. (176); refusal of physician to allow enrollment of child (7); and miscellaneous reasons — for example, the study nurse was not contacted (92). The parents of the remaining 218 eligible children were approached for consent, and 145 consented. All 145 enrolled children were randomly assigned to treatment and evaluated, except for 1 child who had a febrile seizure immediately after informed consent was obtained. A total of 49 children were randomly assigned to the placebo group, 48 to the budesonide group, and 47 to the dexamethasone group. The numbers of children who were evaluated at base line, three and five hours after treatment, and after discharge from the emergency department (among those who were not hospitalized) are shown in Table 2. As planned, an interim analysis was performed

TABLE 2. FOLLOW-UP OF ENROLLED CHILDREN.

TIME OF EVALUATION	PLACEBO GROUP (N=49)	BUDESONIDE GROUP (N=48)	DEXA-METHASONE GROUP (N=47)	TOTAL (N=144)
Base line	49	48	47	144
Three hr after treatment	49	47	46	142
Five hr after treatment	39	23	20	82
After discharge from emergency department*	16	31†	39	86

*The children's parents were contacted by telephone.

†The parents of one child were not reached.

TABLE 3. REASONS FOR DEVIATIONS FROM THE PROTOCOL IN THE CASE OF 25 CHILDREN.

DEVIATION	TREATMENT ASSIGNMENT	NO. OF CHILDREN*
Treatment with dexamethasone before need for hospitalization determined	Placebo, 1; budesonide, 1	2
Failure to meet inclusion criteria		3
Treatment with dexamethasone <4 wk before study	Budesonide, 1	
History of tracheomalacia	Budesonide, 1	
Enrolled twice	Dexamethasone, 1	
Treatment with dexamethasone in emergency department after decision was made to discharge child	Budesonide, 9; dexamethasone, 3; placebo, 5	17
Unmasking of treatment assignment by study nurse or emergency department physician	Budesonide, 1; dexamethasone, 4; placebo, 2	7

*Some of the 25 children had more than one protocol deviation.

after approximately 150 children had been enrolled. The study was terminated because the results of an overall test for differences in the hospitalization rate among the three treatment groups exceeded the pre-established stopping criteria (P<0.001).

Of the 144 randomized children, 25 had an unintended deviation from the protocol (Table 3). The results of a subanalysis of children with each type of protocol deviation and those without it were qualitatively similar to the results of the intention-to-treat analysis. Therefore, only the results of the latter analysis are reported.

There were no significant differences between treatment groups with regard to demographic or clinical variables, including the types of viruses identified and the types of croup (Table 4). There were 100 boys and 44 girls; the mean (±SD) age was 24±18 months; and the mean weight was 12.9±4.5 kg.

The viral cause, study center, and type of croup did not qualitatively alter the differences between

TABLE 4. BASE-LINE CHARACTERISTICS OF THE CHILDREN.*

CHARACTERISTIC	PLACEBO (N=49)	BUDESONIDE (N=48)	DEXAMETHASONE (N=47)
Classification of croup — no.			
Acute laryngotracheitis	18	20	18
Mixed presentation	28	26	28
Spasmodic croup	3	2	1
Viral culture — no.	45	45	43
Parainfluenza 1	10	9	10
Parainfluenza 2	4	3	3
Parainfluenza 3	2	3	2
Influenza A	1	2	0
Influenza B	0	0	0
Respiratory syncytial virus	2	0	2
Previous croup — no.	16	14	10
Prior treatment with rhapinephrine — no.	8	9	9
Duration of symptoms — hr†			
Fever	8 (0–26)	17 (0–36)	10 (0–36)
Cough	24 (12–48)	29 (15–42)	24 (12–48)
Stridor or respiratory distress	7 (3–16)	8 (4–21)	6 (3–18)
Temperature — °C	37.2±0.9	37.4±0.9	37.1±1.1
Croup score	3.8±0.8	3.8±0.9	4.0±0.9
Heart rate — beats/min	144.3±23.9	148.4±20.9	144.4±23.9
Respiratory rate — breaths/min	34.1±8.6	34.9±8.0	35.0±8.0
Oxygen saturation — %‡	95.7±2.7	95.4±2.6	95.8±2.5

*Plus-minus values are means ±SD.

†Median values are given, with the interquartile ranges in parentheses.

‡Oxygen saturation was measured while the patients were breathing room air.

treatment groups for any of the primary or secondary outcomes. Consequently, none of these variables were included in the adjusted analyses as covariates.

Hospitalization

The rates of hospitalization after treatment were highest in the placebo group (33 of 49 children, 67 percent), intermediate in the budesonide group (17

of 48 children, 35 percent), and lowest in the dexamethasone group (8 of 47 children, 17 percent). The need for hospitalization was determined by the time of the five-hour assessment or shortly thereafter in the case of most children (88 percent). Four children, all of whom were in the placebo group, were admitted to the intensive care unit. No child was intubated. Six children who were initially sent home were subsequently hospitalized (two in the placebo group, one in the budesonide group, and three in the dexamethasone group).

The final rates of hospitalization were significantly lower in both glucocorticoid groups than in the placebo group (Table 5). The unadjusted rates of hospitalization in the dexamethasone and budesonide groups were not significantly different from one another (P=0.18). Logistic-regression analyses that included adjustment for base-line croup score and study nurse yielded P values ranging from 0.03 to 0.12.

Clinical Assessments

Study nurses and physicians concurrently determined the croup score in 33 children. The agreement between raters was high (weighted kappa value, 0.9; 95 percent confidence interval, 0.8 to 1.0). The mean changes in the croup score were significantly greater in both glucocorticoid groups than in the placebo group, and the change in the dexamethasone group was significantly greater than that in the budesonide group before adjustment for covariates (Table 5). Adjustment for covariates did not qualitatively alter any of these findings.

The changes in heart rate and respiratory rate from base line to the last assessment in each of the treatment groups mirrored the changes in the croup scores. The placebo group had the smallest mean change in heart rate (−8±25 beats per minute) and respiratory rate (−5±10 breaths per minute), with intermediate changes in the budesonide group

TABLE 5. FINAL HOSPITALIZATION RATES AND CHANGE IN CROUP SCORE.*

VARIABLE	PLACEBO GROUP (N=49)	COMPARISON OF BUDESONIDE WITH PLACEBO	BUDESONIDE GROUP (N=48)	COMPARISON OF DEXAMETHASONE WITH BUDESONIDE	DEXAMETHASONE GROUP (N=47)	COMPARISON OF DEXAMETHASONE WITH PLACEBO
Hospitalization — no. (%)	35 (71)		18 (38)		11 (23)	
Odds ratio for differences between treatments (95% CI)		0.2 (0.1 to 0.6)		0.5 (0.2 to 1.2)		0.1 (0.1 to 0.3)
P value		0.001		0.18		<0.001
Mean (±SE) change in croup score†	−1.3±0.2		−2.0±0.2		−2.9±0.2	
Estimate of differences between treatments (95% CI)		−0.6 (−1.2 to −0.1)		−0.9 (−1.5 to −0.3)		−1.5 (−2.1 to −1.0)
P value		0.03		0.003		<0.001

*Odds ratios and P values are unadjusted. P values are shown for the pairwise comparison of differences between treatments. CI denotes confidence interval.

†The change in scores from base line to the assessment at five hours (or the last assessment for children who were sent home before five hours) is shown.

(-16 ± 23 beats per minute and -7 ± 7 breaths per minute, respectively), and the largest changes in the dexamethasone group (-26 ± 23 beats per minute and -9 ± 8 breaths per minute, respectively). However, the only significant differences between treatments on pairwise comparisons were the change in heart rate for the comparison of dexamethasone with placebo ($P < 0.001$) and for the comparison of dexamethasone with budesonide ($P = 0.005$) and the change in respiratory rate for the comparison of dexamethasone with placebo ($P = 0.03$). The changes in oxygen saturation and blood pressure were similar in all groups.

Other Treatments

In addition to receiving mist therapy, eight children received an additional racementhine treatment within two hours after the administration of the study drug (four in the placebo group, three in the budesonide group, and one in the dexamethasone group). Two to five hours after treatment, 29 children received one or more additional racementhine treatments: 16 in the placebo group, 9 in the budesonide group, and 4 in the dexamethasone group. The unadjusted differences between groups were as follows: $P = 0.16$ for the comparison of budesonide with placebo, $P = 0.005$ for the comparison of dexamethasone with placebo, and $P = 0.23$ for the comparison of budesonide with dexamethasone. Logistic-regression analyses that included adjustment for the baseline croup score and study nurse yielded P values ranging from 0.03 to 0.09 for the comparison of budesonide with placebo and from 0.05 to 0.13 for the comparison of budesonide with dexamethasone.

Adverse Effects

No child had gastrointestinal bleeding or bacterial tracheitis.³

DISCUSSION

In our randomized, double-blind, placebo-controlled trial involving children with moderately severe croup, the hospitalization rate among those treated with glucocorticoids was less than half that among those given placebo. Although the differences in the rates could be due to factors other than the drug therapy, those factors should have been distributed evenly among the treatment groups. Furthermore, the consistency in the differences between groups for all clinical outcomes — croup score, heart and respiratory rates, doses of epinephrine, and admissions to the intensive care unit — suggests that the differences in the rates of hospitalization were due to glucocorticoid therapy.

The rate of hospitalization in the placebo group in our study was substantially higher than that reported by Klassen et al. (71 percent vs. 22 percent),² even though we used a similar croup scoring system.⁸

The most likely explanation for the difference is that our clinical assessments were carried out when the children were quiet and alert, which resulted in the enrollment of sicker children than those in their study.

Treatment with intramuscular dexamethasone led to a significantly greater clinical improvement, as measured by the croup score, than did treatment with nebulized budesonide. It was surprising that dexamethasone was apparently more effective, because the concentration of budesonide in respiratory tissue increases much more rapidly after nebulized administration than does the concentration of dexamethasone after intramuscular administration.¹⁷ However, this finding is unlikely to be due to inadequate delivery of budesonide. The administration of budesonide with racementhine should not have significantly affected delivery.¹⁸ Also, the children were closely observed to ensure compliance, the dose was twice that administered in previous studies,^{2,4-6,19,20} and the low flow rate and type of nebulizer used should have provided reasonably adequate delivery to the upper airway.^{21,22}

There were some deviations from the study protocol. A majority, however, involved the administration of dexamethasone, which, if anything, should have biased the results toward the null hypothesis — i.e., that there was no difference between the treatment groups. In contrast, the unmasking of the treatment assignment might have biased the results toward finding a difference. However, when we excluded these children from the analysis, the results were qualitatively similar to those obtained with the intention-to-treat analysis.

Another noteworthy aspect of our study design was the identification of viral causes and the type of croup. Several reviews have suggested that the failure to identify these factors was a major methodologic flaw in previous studies.^{23,24}

Supported by Astra Pharma, Mississauga, Ontario, Canada.

We are indebted to Joanna Lee for biostatistical support; to research nurses Nancy Bartleman, Carol Cumming, Allyson Link, and Janielee Williamson for their efforts; and to the staff members of the emergency departments of Alberta Children's Hospital and the Hospital for Sick Children for their support.

REFERENCES

1. Denny FW, Murphy TF, Clyde WA Jr, Collier AM, Henderson FW. Croup: an 11-year study in a pediatric practice. *Pediatrics* 1983;71:871-6.
2. Klassen TP, Feldman ME, Watters LK, Sutcliffe T, Rowe PC. Nebulized budesonide for children with mild-to-moderate croup. *N Engl J Med* 1994;331:285-9.
3. Johnson DW, Schuh S, Koren G, Jaffe DM. Outpatient treatment of croup with nebulized dexamethasone. *Arch Pediatr Adolesc Med* 1996;150:349-55.
4. Geelhoed GC, Macdonald WBG. Oral and inhaled steroids in croup: a randomized, placebo-controlled trial. *Pediatr Pulmonol* 1995;20:355-61.
5. Husby S, Agertoft L, Mortensen S, Pedersen S. Treatment of croup with nebulized steroid (budesonide): a double blind, placebo-controlled study. *Arch Dis Child* 1993;68:352-5.
6. Godden CW, Campbell MJ, Hussey M, Cogswell JJ. Double-blind pla-

- cebo controlled trial of nebulised budesonide for croup. *Arch Dis Child* 1997;76:155-8.
7. Geelhoed GC. Croup. *Pediatr Pulmonol* 1997;23:370-4.
 8. Westley CR, Cotton EK, Brooks JG. Nebulized racemic epinephrine by IPPB for the treatment of croup: a double-blind study. *Am J Dis Child* 1978;132:484-7.
 9. Daum RS, Smith AL. Epiglottitis (supraglottitis). In: Feigin RD, Cherry JD, eds. *Textbook of pediatric infectious diseases*. 3rd ed. Vol. 1. Philadelphia: W.B. Saunders, 1992:197-209.
 10. Cherry JD. Croup (laryngitis, laryngotracheitis, spasmodic croup, and laryngotracheobronchitis). In: Feigin RD, Cherry JD, eds. *Textbook of pediatric infectious diseases*. 3rd ed. Vol. 1. Philadelphia: W.B. Saunders, 1992:209-20.
 11. Geller NL, Pocock SJ. Interim analyses in randomized clinical trials: ramifications and guidelines for practitioners. *Biometrics* 1987;43:213-23.
 12. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). *Biometrika* 1965;52:591-611.
 13. Altman DG. *Practical statistics for medical research*. London: Chapman & Hall, 1991.
 14. Stokes ME, Davis CS, Koch GG. *Categorical data analysis using the SAS system*. Cary, N.C.: SAS Institute, 1995.
 15. Norman GR. Issues in the use of change scores in randomized trials. *J Clin Epidemiol* 1989;42:1097-105.
 16. Neter J, Wasserman W, Kutner MH. *Applied linear statistical models: regression, analysis of variance, and experimental designs*. Homewood, Ill.: Richard D. Irwin, 1985.
 17. Loew D, Schuster O, Graul EH. Dose-dependent pharmacokinetics of dexamethasone. *Eur J Clin Pharmacol* 1986;30:225-30.
 18. Roberts GW, Rossi S. Compatibility of nebuliser solutions. *Aust J Hosp Pharm* 1993;23:35-7.
 19. Klassen TP, Watters LK, Feldman ME, Sutcliffe T, Rowe PC. The efficacy of nebulized budesonide in dexamethasone-treated outpatients with croup. *Pediatrics* 1996;97:463-6.
 20. Fitzgerald D, Mellis C, Johnson M, Allen H, Cooper P, Van Asperen P. Nebulized budesonide is as effective as nebulized adrenaline in moderately severe croup. *Pediatrics* 1996;97:722-5.
 21. Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer brand. *Chest* 1996;110:498-505.
 22. Simonsson BG. Anatomical and pathophysiological considerations in aerosol therapy. *Eur J Respir Dis Suppl* 1982;119:7-14.
 23. Cherry J. The treatment of croup: continued controversy due to failure of recognition of historic, ecologic, etiologic and clinical perspectives. *J Pediatr* 1979;94:352-4.
 24. Tunnessen WW Jr, Feinstein AR. The steroid-croup controversy: an analytic review of methodologic problems. *J Pediatr* 1980;96:751-6.