

Follow-Up of Hymenoptera-Sensitive Patients Without Active Immunotherapy

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ABSTRACT

Presently there is no definitive guideline for the treatment of adult patients suffering from generalized insect sting reactions limited to skin manifestations or purely respiratory compromise who have not been treated with immunotherapy. Previous studies in adults demonstrate that the majority of patients with insect sting anaphylaxis have a decreased reactivity to re-sting with time, suggesting the insect allergy itself may be self-limiting. In this study, we evaluated 63 patients with initial insect sting manifestations limited to the skin and the respiratory system and noted the incidence and degree of natural re-sting reactions to these patients who had not undergone venom immunotherapy. In those patients with mild systemic reactions limited to the skin, none experienced an increase in severity. A local reaction was found on repeat sting in three of five patients in this group, and two of five had an equivalent cutaneous response (i.e., urticaria/angioedema). In five patients who had an initial respiratory reaction, four of the patients had a local reaction while one patient repeated the same respiratory manifestations. None of the patients with cutaneous or respiratory symptoms demonstrated a more severe reaction upon re-sting. This demonstrates that there is a natural progression of tolerance to insect stings in the adult population. (Allergy Proc 15:65-68, 1994)

Insect sting anaphylaxis has remained a source of some controversy since the death of Egyptian phar-

aoah Menes in 2621 BC. Purified insect venoms have been available since 1979, providing us with the ability to diagnose and treat patients with insect sting reactions. Early studies with insect venoms noted that a patient population exists which responds primarily with anaphylactic reactions, but on subsequent re-sting, presents without a reaction.¹ Studies done on the pediatric population (patients < 16 years) noted that children are especially prone to a more benign course despite lack of immunotherapy.² However, studies have not revealed definitive guidelines for treatment of adult patients with limited insect sting reactions who were not treated with immunotherapy.

PROCEDURE

For the purposes of the current study we adopted the following grading criteria for insect sting reactions:

- Grade I involved local reactions;
- Grade II involved cutaneous reactions limited to urticaria or angioedema;
- Grade III involved respiratory compromise; and
- Grade IV involved vasomotor collapse.

A telephone survey was conducted to evaluate 98 patients initially assessed for Hymenoptera sensitivity who met the additional criteria:

1. Age > 16 years.
2. Grade II cutaneous mild systemic reaction or more severe.
3. Did not receive immunotherapy.

Data was obtained regarding age, number of re-stings, reactions observed, time interval between re-sting, insects involved, and treatment, if any, undertaken. All patients were skin tested initially. Of these initial 98

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patients, only those who were skin test positive and who could identify the initial insect sting were included for continued analysis.

RESULTS

Sixty-three (64.3%) of 98 patients were contacted and asked about their history of insect re-sting since their last evaluation. Table 1 describes the sample population. Twelve of 14 patients were able to specifically identify the insect involved in their initial reactions several years previously. Of these, 12 patients were re-stung after their initial evaluation, with 10 (83.3%) giving a history of being stung with the same insect. No immediate therapy was received after re-sting, preventing any masking of symptoms. The characteristics of these reactions are noted in Table 2.

Further analysis of the patients experiencing cutaneous Grade II (urticaria/angioedema) or Grade III (respiratory/bronchospastic) reactions of their initial sting reactions was done.

In those patients who experienced a mild Grade II reaction, none underwent an increase in the severity upon a re-sting. Three patients (60%) had a local reaction, and two had an equivalent cutaneous response.

In those five patients (re-stung with the same insect) who initially had a Grade III or respiratory reaction, four had a local reaction and one repeated the equivalent of a Grade III respiratory-type reaction.

Neither cutaneous nor respiratory reactions demonstrated a more severe response upon re-sting.

DISCUSSION

There is a distinct difference between the adult population (>16 years) and pediatric population (<16 years) in their allergic response to insect stings. In adults, it has been estimated that approximately two thirds of reactions involve symptoms related to the cardiorespiratory system and in children, considerably less (1/3). The fact that immunotherapy with purified venoms has decreased the risk of reactions to subse-

TABLE II

Characteristics of Reactions		
	GRADE II	GRADE III
Total evaluated	5	5
Age (mean, range)	31.7 yrs (16-67)	39.4 yrs (19-71)
Total re-stings	10	16
Interval to re-sting	2.8 yrs (1-4)	4.0 yrs (3-7)
Re-sting reactions		
GRADE I	3 (60%)	4 (80%)
GRADE II	2 (40%)	0
GRADE III	0	1 (20%)
GRADE IV	0	0

quent stings has made this mode of therapy paramount in the treatment of life-threatening reactions.

Treatment in the adult population has been used to prevent the approximately 50% re-sting reactions.¹ The predominance of cardiorespiratory symptoms in this age group has reinforced the use of venom immunotherapy. As noted, previous studies have indicated that in the pediatric population, immunotherapy is unwarranted in those patients with initial reactions limited to cutaneous manifestations.²

Further, our data advocates the similar treatment of adult patients who initially manifest with cutaneous symptoms. Our data suggest that patients with Grade II cutaneous reactions were noted to have equivalent or weaker responses on re-sting. Thus, these adult patients also do not require immunotherapy.

Patients with a Grade III respiratory response were also noted to display a progression toward tolerance in our study. However, as one patient was noted to display a similar respiratory response, we currently advocate recommending immunotherapy for these patients. Other studies have argued this natural progression of re-sting tolerance.^{3,5} Since we discriminate between Grade III (respiratory) and Grade IV (cardiovascular compromise), differences with other centers may include our definition of reactions.

The time interval between stings has been thought to influence the degree of reactivity following insect re-stings. Previous investigators have shown that reactivity decreases with intervals of greater than 5 years.^{4,6}

Our study population demonstrated a mean interval of <4 years, which agrees with Parker et al., who showed that this interval is unrealistic and not predictive of re-sting incidence or severity.⁷ Recently, Reisman et al. noted a large group study where the time interval between the initial sting reaction and subsequent re-sting was not a factor in predicting future sting reactions.⁸

TABLE I

Sample Population	
Total patients evaluated	=63
Age first sting, range	
# identifying first insect	
Initial reaction	
Grade II	=5
Grade III	=5
Total re-stung	=14 (22.2%)
# re-stung same insect	=10/12 (80%)
Interval to re-sting mean	=3.3 years
Range	=1-7 years

TABLE III

Bee Sting Protocol				
Reactions	Classifications	Venom Test	Treatment	Comments
GRADE I	Local Reactions	NO	Ice Antihistamines	Watch for cellulitis
GRADE II	Cutaneous Reaction <16 years old	NO	Ice Antihistamine ? Epipen	Evaluate individually
	>16 years old	?	Ice Antihistamines Epipen	Exposure Medical Status Severity of reaction
GRADE III	Respiratory Reaction <16 years old	?IT YES	Ice Antihistamine Epipen *IT	
	>16 years old	YES	Ice Antihistamine Epipen *IT	Recommend *IT
GRADE IV	Vasomotor collapse <16 years old	YES	"	"
	>16 years old	YES	"	"

*IT: Immunotherapy

Limitations of our study included the small number of patients in the study population secondary to the requirement that the patient was re-stung by the same insect. Those who could not positively identify the insect, or who were stung with a different insect, were disqualified from the study.

CONCLUSIONS

Based on our clinical observations, we have made the following recommendations (Table 3):

1. For Grade I (local) and Grade II (cutaneous) reactions without evidence of respiratory or cardiovascular embarrassment.
 - A. Children (<16 years):

Diagnostic skin tests—not required
Treatment: Avoidance precautions, local wound care, steroids as needed
 - B. Adults (>16 yrs):

Diagnostic skin tests—Not required
Treatment: Avoidance precautions, antihistamines, steroids as needed, epinephrine standby (Possible testing and immunotherapy under special circumstances, e.g., outdoor workers, farmers)

2. For Grade III (respiratory) and Grade IV (vasomotor collapse) reactions.

A. Children (< 16 yrs):

Diagnostic skin tests—Required

Treatment: Local wound care, antihistamines, steroids as needed, epinephrine standby, and immunotherapy

B. Adults (>16 yrs):

Diagnostic skin tests—Required

Treatment: Local wound care, antihistamines, steroids as needed, epinephrine standby, and immunotherapy

In conclusion, this study presents further data which may be useful in developing accepted guidelines for treatment of both pediatric and adult patients who display sensitivity toward Hymenoptera stings.

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¶ The clinical relevance of these data has not been demonstrated. Impact force testing vs. Beconase, Nasacort, and VANCENASE Nasal Inhaler. In vitro testing was performed using an aerosol Spray Force Tester developed by Continuum Dynamics which measured the spray force of each product at a distance of 1½ inches from the end of the actuator. Data on file.

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BRIEF SUMMARY (For full Prescribing Information see package insert)

INDICATIONS AND USAGE VANCENASE AQ Nasal Spray is indicated for the relief of the symptoms of seasonal or perennial allergic and non-allergic (vasomotor) rhinitis. Results from two clinical trials have shown that significant symptomatic relief was obtained within three days. However, symptomatic relief may not occur in some patients for as long as two weeks. VANCENASE AQ Nasal Spray should not be continued beyond three weeks in the absence of significant symptomatic improvement. VANCENASE AQ Nasal Spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

VANCENASE AQ Nasal Spray is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of systemic corticosteroid with VANCENASE AQ Nasal Spray can be accompanied by signs of adrenal insufficiency.

When transferred to VANCENASE AQ Nasal Spray, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE AQ Nasal Spray treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS **General:** During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude and depression. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with VANCENASE AQ Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping VANCENASE AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE AQ Nasal Spray may suppress HPA function.

VANCENASE AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE AQ Nasal Spray to be effective in the treatment of nasal polyps, the spray must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE AQ Nasal Spray should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of VANCENASE AQ Nasal Spray into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes. Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone dipropionate.

Adverse reactions reported in controlled clinical trials and open studies in patients treated with VANCENASE AQ Nasal Spray are described below.

Mild transient nasopharyngeal irritation following the use of beclomethasone aqueous nasal spray has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the inhaler. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea or lightheadedness following the use of VANCENASE AQ (beclomethasone dipropionate, monohydrate) Nasal Spray. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, and tearing eyes.

Extremely rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see **PRECAUTIONS**).

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy. The oral LD₅₀ of beclomethasone dipropionate is greater than 1 g/kg in rodents. One bottle of VANCENASE AQ Nasal Spray contains beclomethasone dipropionate, monohydrate equivalent to 10.5 mg of beclomethasone dipropionate; therefore, acute overdosage is unlikely.

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BRIEF SUMMARY (For full Prescribing Information see package insert)

INDICATIONS AND USAGE VANCENASE POCKETHALER Nasal Inhaler is indicated for the relief of the symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional treatment.

VANCENASE POCKETHALER Nasal Inhaler is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies in seasonal and perennial rhinitis have shown that improvement is usually apparent within a few days. However, symptomatic relief may not occur in some patients for as long as 2 weeks. Although systemic effects are minimal at recommended doses, VANCENASE treatment should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. VANCENASE treatment should not be used in the presence of untreated, localized infection involving the nasal mucosa.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE POCKETHALER Nasal Inhaler can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients, previously treated for prolonged periods with systemic corticosteroids, are transferred to VANCENASE POCKETHALER Nasal Inhaler. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, VANCENASE POCKETHALER Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS **General:** During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Extremely rare instances of nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE POCKETHALER Nasal Inhaler.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE POCKETHALER Nasal Inhaler may suppress HPA function.

VANCENASE treatment should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

For VANCENASE POCKETHALER Nasal Inhaler to be effective in the treatment of nasal polyps, the aerosol must be able to enter the nose. Therefore, treatment of nasal polyps with VANCENASE Nasal Inhaler should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of the VANCENASE product into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using VANCENASE treatment over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

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Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE POCKETHALER Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with the nasal mucous membranes. Adverse reactions reported in controlled clinical trials and in long-term open studies in patients treated with VANCENASE Nasal Inhaler are described below.

Sensations of irritation and burning in the nose (11 per 100 patients) following the use of VANCENASE Nasal Inhaler have been reported. Also, occasional sneezing attacks (10 per 100 patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children.

Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *Candida albicans* have occurred rarely. (See **PRECAUTIONS**.)

Transient episodes of epistaxis or bloody discharge from the nose have been reported in 2 per 100 patients. Ulceration of the nasal mucosa has been reported rarely.

Extremely rare instances of nasal septum perforation have been reported following the intranasal application of aerosolized corticosteroids. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm have been reported following the oral and intranasal inhalation of beclomethasone.

Increased intraocular pressure has been reported rarely. (See **PRECAUTIONS**.)

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome could occur.

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, VANCENASE POCKETHALER Nasal Inhaler should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

The oral LD₅₀ of beclomethasone dipropionate is greater than 1 g/kg in rodents. One canister of VANCENASE POCKETHALER Nasal Inhaler contains 8.4 mg of beclomethasone dipropionate; therefore acute overdosage is unlikely.

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