

Reintroduction failure after negative peanut challenges in children

Francine C. van Erp¹, Jenneke Boot¹, André C. Knulst², Suzanne G. M. Pasmans², Cornelis K. van der Ent¹ & Yolanda Meijer¹

¹Department of Paediatric Pulmonology and Allergology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands; ²Department of (Paediatric) Dermatology and Allergology, University Medical Centre Utrecht, Utrecht, The Netherlands

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Correspondence

Francine C. van Erp, Department of Paediatric Pulmonology and Allergology, Wilhelmina Children's Hospital, University Medical Center Utrecht, PO Box 85090, 3508 AB Utrecht, The Netherlands
Tel.: +31 (0)88 75 53201
Fax: +31 (0)88 75 54747
E-mail: f.c.vanerp@umcutrecht.nl

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Abstract

Background: A negative double-blind placebo-controlled food challenge (DBPCFC) should normally be followed by reintroduction of the food. However, reintroduction fails in a subset of children. The observed reintroduction problems could be due to refusal of the food that long has been avoided, to other behavioural/psychological factors or to false negative DBPCFC outcome. This study analyses the frequency, causes and risk factors for reintroduction failure in children after negative peanut DBPCFC.

Methods: A retrospective study of children with a negative DBPCFC for peanut was performed. During follow-up after DBPCFC, parents were systematically interviewed about the current diet, symptoms and problems during reintroduction, and reactions to peanut after the reintroduction period. Successful reintroduction was defined as eating peanut or products containing peanut as ingredient on a regular basis.

Results: Follow-up data were obtained in 103 children with a negative peanut challenge. In 70 (68%) children, reintroduction was successful (54 children tolerated peanut, 16 children tolerated peanut as ingredient). Reintroduction failed in 33 (32%) children. Food refusal (45%) and peanut-related symptoms (33%) were the most reported reasons. Risk factors for reintroduction failure were an elimination diet for more than three other foods ($p = 0.019$), a long elimination diet for peanut ($p = 0.048$) and peanut-related symptoms at home ($p = 0.002$).

Conclusion: Reintroduction failure is a common problem in children after negative peanut challenge. To guide reintroduction and identify potential peanut-related symptoms at home, careful follow-up after negative DBPCFC is advised. When symptoms occur or persist, food challenge outcome needs to be reconsidered.

Children suspected of peanut allergy often present with a long-lasting elimination diet. To maintain this diet, parents of peanut allergic children change their way of life. They cautiously read labels, have to be alert when buying food and cooking and have to arrange a safe environment at school, being at family and friends or during holidays. Children are faced not only with dietary but not infrequently also with social restrictions (1). In line with this, the majority of parents of children with suspected food allergy show high levels of anxiety about a potentially life treating reaction (2). Moreover, quality

of life in adults and children suffering from food allergy is impaired (3). To prevent unnecessary (psychosocial) burden on families with food allergic children, it is therefore important to diagnose the culprit foods accurately. To confirm food allergy, a double-blind placebo-controlled food challenge (DBPCFC) is considered to be the gold standard (4). If no objective symptoms or severe or long-lasting subjective symptoms to one of the active doses occur, a food challenge is considered negative and reintroduction of the challenged food is advised. However, there is evidence that reintroduction fails in a subset of children. Failure rates up to 25% were reported and even higher rates in children with previously suspected peanut allergy were found (5, 6). The observed reintroduction problems could be due to refusal of the food that long has been

Abbreviations

DBPCFC, double-blind placebo-controlled food challenge; OAS, oral allergy syndrome; sIgE, specific IgE; SPT, skin prick test.

avoided or other behavioural/psychological factors. On the other hand, failure of reintroduction (especially when symptoms occur) could indicate lack of diagnostic accuracy and false negative outcome of the food challenge. There are limited data on the success rate of reintroduction and risk factors for failure in a large and unselected group of patients with negative DBPCFC for peanut. We studied the variety of problems observed after reintroduction and aimed to identify risk factors of failure in children with negative peanut challenge outcome.

Methods

Study population

We performed a retrospective study of children who underwent a DBPCFC for peanut in our tertiary allergy centre from 2008 to 2010. DBPCFCs were performed in all eligible children except for children with reactions requiring previous admission to an intensive care unit. Suspicion for peanut allergy was based on sensitization [a raised specific IgE (sIgE) or positive skin prick test (SPT) to peanut] together with a history of (i) symptoms after ingestion of peanut, (ii) no previous known ingestion of peanut due to severe eczema or other food allergy or (iii) allergic reaction with unknown origin. Children with a negative DBPCFC and available follow-up data were selected for this study. Data were collected as part of regular patient care, obtained by chart review and used in strictly anonymous form, according to the code of conduct for medical research approved by the hospital's medical ethical committee.

Peanut challenges

The DBPCFC protocol was described earlier by Flinterman et al. (7). In short, increasing amounts of defatted peanut flour (50% peanut protein) from 0.01 to 3000 mg were given with time intervals of 15–30 min with randomly dispersed placebos. An open challenge of 10 g peanuts was the last step in the protocol. Patients were observed for at least 2 h. Challenges were discontinued and considered positive in case of objective symptoms or if suggestive subjective symptoms occurred at three subsequent doses or a severe subjective symptom lasted for more than 45 min. Oral allergy symptoms (OAS), abdominal pain and nausea were referred to as subjective symptoms. Objective symptoms were classified according to the Sampson classification (8). All signs and symptoms during challenge were recorded on a food challenge score sheets including timing and administration of doses. Twenty-four hours after negative food challenge, families were contacted by telephone. If no late symptoms occurred, parents were told to reintroduce peanut by means of a reintroduction schedule with increasing amounts of peanut (Table 1). The reintroduction schedule was used to assist parents and children in the reintroduction process and not (as physicians explicitly explained to parents) because peanut allergy was still suspected. After finishing the reintroduction schedule, parents were advised to quit label reading regarding

Table 1 Reintroduction schedule

Day	Product
1	Traces allowed*
2	Traces allowed*
3	1/2 sandwich with peanut butter
4	1 sandwich with peanut butter
5	2 sandwiches with peanut butter
6	5 peanuts
7	10 peanuts

*Product labelled with 'May contain peanuts' or 'Manufactured on a shared line with products containing peanut'.

peanut and administer products containing peanut whenever they wanted.

Follow-up after DBPCFC

Up to 4.5 yr after the negative DBPCFC, parents were systematically interviewed by their physician based on a pre-defined questionnaire. The telephonic questionnaire contained questions about the current and previous diet concerning peanut and other allergens, timing and success of reintroduction and symptoms after peanut ingestion (Fig. S1). Successful reintroduction of peanut was defined as the child eating peanut (e.g. whole peanuts, peanut butter) or products with peanut as ingredient (e.g. cookies or snacks) on a regular basis, and no food labels were checked. We considered reintroduction as failed when children did not introduce peanut or only introduced products labelled with 'May contain peanut' or 'Manufactured on a shared line with products containing peanut', as in this case, it is unclear whether there is actual consumption of peanut.

Statistical analysis

Analyses were performed using SPSS for Windows (version 20.0; SPSS Inc., Chicago, IL, USA). Patient and reintroduction characteristics between children with successful and children with failed reintroduction were compared using univariable and multivariable logistic regression analysis. Variables significantly associated with failure in the univariable model were entered in a multivariable model to determine independent risk factors for reintroduction failure. A *p*-value < 0.05 was considered significant.

Results

During the study period, a total of 219 peanut challenges were performed; 110 children had negative food challenge outcome. Follow-up data were obtained by telephonic interview in 103 (94%) children. Patient characteristics of included children are shown in Table 2. Time between interview and food challenge ranged from 1.4 to 4.4 yr, with a mean (s.d.) time of 3.0 (0.90) years. Median age of children at food challenge was 7.1 yr (range: 3.4–17.3 yr). The study population consisted of predominantly boys (75%), and another food allergy was often

Table 2 Characteristics of children at time of challenge and during follow-up, n = 103

	Total (103)	Failure (33)	Success (70)	p-value	Adjusted p-value*
Median age [IQR] at food challenge in years	7.1 [4.8–9.4]	7.6 [5.0–9.8]	6.8 [5.4–9.7]	0.740	
Mean time ($\pm$ s.d.) between FC and Q in years	3.0 $\pm$ 0.90	2.7 $\pm$ 0.81	3.2 $\pm$ 0.91	0.019	0.039
Male	77 (75)	24 (73)	53 (76)	0.745	
Atopy					
Eczema	84 (82)	56 (80)	56 (80)	0.554	
Hay fever	44 (43)	14 (42)	30 (43)	0.967	
Asthma	35 (34)	12 (36)	33 (33)	0.726	
Other food allergy	78 (76)	25 (76)	53 (76)	0.996	
Median sIgE to peanut [IQR] in kU/l	0.68 [0.35–2.44]	1.30 [0.38–2.80]	0.60 [0.38–2.80]	0.409	
Ara h2†	0.09 [0.03–0.42]	0.91 [0.04–2.64]	0.06 [0.02–0.18]	0.132	
Ara h8†	0.18 [0.01–1.26]	0.08 [0.01–1.59]	0.19 [0.00–1.19]	0.925	
Positive SPT‡	49/69 (71)	14/17 (82)	35/52 (67)	0.358	
History of peanut allergy					
No previous known ingestion	60 (59)	19 (58)	41 (59)	Ref	
Previous reaction mild/moderate	30 (29)	11 (33)	19 (27)	0.636	
Previous reaction severe	13 (13)	3 (9)	10 (14)	0.543	
Duration peanut-free diet before FC					
0–2 yr	19 (18)	2 (6)	17 (24)	Ref	
>2 yr	84 (82)	31 (94)	53 (76)	0.026	0.048
Elimination diet for other food					
None	27 (26)	5 (15)	22 (31)	Ref	
1–2 other foods	53 (52)	16 (49)	37 (53)	0.152	
>3 other foods	23 (22)	12 (36)	11 (16)	0.015	0.019
Current elimination diet for tree nuts	46 (45)	19 (58)	27 (39)	0.070	
Symptoms during food challenge§	39 (38)	16 (49)	23 (33)	0.129	
Refusal during challenge	9 (9)	3 (9)	6 (9)	0.931	
Reintroduction schedule used¶	45/97 (46)	16/33 (49)	29/64 (45)	0.767	
Reported symptoms after challenge	21 (20)	13 (39)	8 (11)	0.003	0.002
Current diet					
No traces of peanut	3 (3)	3 (9)	–	–	
Products with traces of peanut**	30 (29)	30 (91)	–	–	
Products with peanut	16 (16)	–	16 (23)	–	
Peanut	54 (52)	–	54 (77)	–	

FC, food challenge; s.d., standard deviation; sIgE, specific IgE; SPT, skin prick test; IQR, interquartile range.

Boldface variables were significantly related to reintroduction failure and entered in the multivariable logistic regression model.

*After multivariable logistic regression analysis.

†Missing n = 62 (60%).

‡Missing n = 34 (31%).

§Transient subjective symptoms (not feeling well, change in behaviour).

¶Missing n = 6 (6%).

**Product labelled with 'May contain peanuts' or 'Manufactured on a shared line with products containing peanut'.

present (76%). The majority of children had a long elimination diet for peanut (82%) and no previous history of peanut-related symptoms (59%).

Outcome of reintroduction

Parents of 45 (46%) children confirmed that they used the reintroduction schedule during follow-up. Overall, 70 (68%) of children successfully reintroduced peanut in their diet, including 54 (52%) children who consumed peanut and 16 children (16%) who consumed products with peanut as ingredient. The latter did not tolerate whole peanuts due to the taste/structure

of peanut. Reintroduction failed in 33 (32%) children, and parents of those children were still reading food labels for peanut. Thirty children (29%) with introduction failure did introduce products with (possible) traces of peanut, and three children (3%) also eliminated those products.

Reasons for reintroduction failure

Despite the instructions after DBPCFC, reintroduction was not started at all in 7 (7%) children. In 26 (25%) children reintroduction failed in the weeks after starting. Reported reasons for reintroduction failure are shown in Table 3.

Table 3 Reported reasons for reintroduction failure, n = 33

	Not started reintroduction (7)	Started reintroduction (26)	Total (33)
Fear of a reaction	1	1	2 (6)
Not convinced by test	1		1 (3)
Allergy family	2		2 (6)
Refusal	2	13	15 (45)
Habituation to the peanut-free diet	1		1 (3)
Symptoms after ingestion of peanut		11	11 (33)
Autism child		1	1 (3)

Refusal of peanut (n = 15) was the most reported reason for failure. Further comparison of children with and without refusal revealed no significant differences with respect to patient characteristics, level of sIgE to peanut, severity of previous reaction, duration of previous peanut-free diet, presence of other elimination diets or the presence of symptoms during challenge.

Peanut-related symptoms after negative food challenge

During follow-up, 21 (20%) parents reported peanut-related symptoms. Based on the type of reported symptoms (Sampson grade 1–grade 5), time between ingestion and reaction (0–30 min) and confirmation that the food contained peanut as ingredient, we suspected 13 of 21 children for having allergic reactions to peanut during follow-up. In those children, reactions were often recurrent and the median number [IQR] during follow-up was 5 [3–10]. Severity of reactions ranged from Sampson grade 1 (oral allergy or localized angio-oedema) up to Sampson grade 4 (dyspnoea). The estimated peanut dose ingested did never exceed the maximum dose given during

peanut DBPCFC. Symptoms developed most often at home in presence of parents. Parents of six of 13 children treated symptoms with antihistamines; in one case, they also visited a doctor for dyspnoea. Allergic reactions to peanut were reason to avoid (products with) peanut in nine of 13 children. Parents of four of 13 children continued to administer their child (products with) peanut. Reasons not to avoid peanut were the presence of mild symptoms only (n = 2) or absence of symptoms after specific products containing (small amounts) peanut as ingredient (n = 2). No significant differences in patient characteristics, severity of previous reaction to peanut or level of sIgE were found between children with and without suspected peanut allergic reactions after challenge. Details of children with suspected peanut allergic reactions are shown in Table 4. In eight of 21 children, reported symptoms were considered non-specific due to the type of symptoms (abdominal pain, eczema), time between ingestion and reaction (>60 min) or the ingestion of food without a substantial amount of peanut (traces). Nevertheless, parents of three of eight children avoided (products with) peanut due to the non-specific symptoms.

Potential risk factors for reintroduction failure

Univariable logistic regression analysis of patient characteristics showed that several patient- and diet-related factors were associated with reintroduction failure (Table 2). In the multivariable model, time between food challenge and questionnaire (in years) p = 0.039, an elimination diet for more than three other foods (vs. 0–2 eliminated foods) p = 0.019, a longer than 2 yr elimination diet for peanut (vs. 0–2 yr elimination) p = 0.048 and the presence of peanut-related symptoms during follow-up p = 0.002 were significantly associated with reintroduction failure. Children with reintroduction failure also tended to have an accompanying nut-free diet more often although no significant association could be found. Other patient characteristics as age, atopic diseases, sensitization or

Table 4 Children with suspected peanut allergic reactions, n = 13

Pt	Reactions (nr)	Symptoms	Grade*	Timing (min)	Label of food ingested	Location	Action taken	Current diet
12	20	Ang	1	5	Peanut as ingredient	Home	AH	Traces
13	2	Dys	4	–	Peanut	School	AH + doctor	Traces
30	3	Urt	2	2	Peanut	Home	AH	Traces
44	8	Abd, OAS	1	30	Peanut	Home	None	Peanut
47	30	OAS	1	10	Peanut as ingredient	Home	None	Traces
52	14	OAS	1	5	Peanut	Home	None	Peanut
68	–	OAS	1	10	Peanut as ingredient	Home	None	Peanut as ingredient
69	4	OAS	1	1	Peanut	Home	None	Traces
75	8	Ang, Dys, OAS, Thr	3	1	Peanut	Home	AH	Traces
77	3	Ang, Ecz, OAS	1	5	Peanut as ingredient	Home	AH	Traces
83	4	Thr,	3	5	Peanut as ingredient	Home	AH	Peanut as ingredient
90	–	Urt	2	5	Peanut	Home	None	Peanut as ingredient
91	5	Abd, Con, Rhi	2	10	Peanut	School	AH	Traces

Abd, abdominal pain; AH, antihistamines; Ang, angio-oedema; Con, conjunctivitis; Dys, dyspnoea; Ecz, eczema; Min, minutes; OAS, oral allergy syndrome; Pt, patient; Rhi, rhinitis; Thr, throat tightness; Urt, urticaria;

*Sampson classification of anaphylaxis (8).

occurrence of subjective symptoms during food challenge could not be identified as potential risk factors for reintroduction failure.

Discussion

This study shows that reintroduction failure is a common problem in children after negative peanut challenge. Despite negative challenge outcome and the advice to start reintroduction, one-third (32%) of the children were eliminating products with (traces of) peanut during follow-up. Moreover, parents of 13 (13%) children were suspected of (recurrent) peanut allergic reactions after peanut ingestion at home.

Our study shows that several patient-related factors are associated with reintroduction failure. The presence of an elimination diet for more than three other foods was significantly associated with failure. In addition, children with reintroduction failure had a longer elimination diet for peanut in history. They also tended to have an accompanying nut-free diet more often although no significant association could be found. This is in contrast with a previous small study about follow-up of challenges who could not identify risk factors for failure, possibly because only seven children with negative peanut challenge were included (5). Seven parents did not start reintroduction at all, and a subset was still concerned about the presence of peanut allergy. Practical difficulties, fear and uncertainty about the diagnosis were reported as the main reasons for not starting. These (parents of) patients continued to carefully read labels of products possibly containing peanut, suffer from dietary and social restrictions, and may still have an impaired quality of life. Our results underline that changing dietary habits with regard to peanut avoidance needs more guidance and counselling than a negative challenge outcome and a reintroduction schedule alone, especially in patients with other dietary restrictions. Moreover, prior to the challenge, parents should be questioned about their expectations of the challenge and the reintroduction procedure should be emphasized.

Refusal of the child was the most important reported reason for reintroduction failure. Refusal could not be explained by patient-related factors as young age, a previous long elimination diet or the presence of other dietary restrictions. Although refusal could be a sign of intolerance (e.g. OAS), we did not find differences in level of sensitization, occurrence of subjective symptoms during challenge or peanut-related symptoms during follow-up between children with and without refusal. It is therefore most likely that these children have difficulties with the unfamiliar taste and structure of (products with) peanut. This is also demonstrated by the 16 children with reintroduction success who avoided whole peanuts and only consumed products with peanut as ingredient. It is debatable whether the prolonged peanut-free diet in children with reintroduction failure due to aversion has a negative impact on quality of life as parents might well be satisfied with the negative challenge outcome itself (2, 9). Nevertheless, regular ingestion of (products containing) peanut should be encouraged because previously published data suggest that long-term avoidance of allergen exposure might result in the occurrence of acute allergic reactions (10).

Among the reported reasons for reintroduction failure were also symptoms after the ingestion of peanut at home, possibly representing the presence of peanut allergy despite a negative food challenge. It is unlikely that the ingested amount of peanut during challenge was insufficient as was suggested by previous authors (11), because an open provocation with 10 g whole peanuts was the last step of our DBPCFC protocol. Although all challenges were performed according to international guidelines in an expertise centre, very mild allergies could have been missed and resulted in a false negative food challenge (12). Subtle subjective symptoms during challenge could have been only one end of the range of reactions (the very mild one) in the child's food allergy and therefore do not correspond to reactions observed during reintroduction at home (13). We could, however, not find a significant association between the occurrence of mild transient symptoms during challenge and reintroduction failure. It has also been suggested that symptoms after negative peanut challenge can be caused by recurrence of peanut allergy and that food challenges with increasing amounts may induce specific oral tolerance that is only transient (14–17). We cannot exclude or confirm this, because we do not have information about the exact timing of reactions, amount of peanut ingested during follow-up and (change in) level of sIgE to peanut. Moreover, in the future, these children should be rechallenged to objectify symptoms and verify the presence and severity of a possible recurrent peanut allergy.

When interpreting the results of this study, some limitations have to be discussed. This retrospective study is based on telephonic interviews after a relatively long follow-up time. Due to the retrospective nature, we do not have data on the exact timing of failure. Recall bias cannot be ruled out as parents of children with reintroduction failure may have reported symptoms and reintroduction problems in the past more accurate compared to children with successful reintroduction. Follow-up time was significantly shorter in children who failed to reintroduce peanut (2.7 vs. 3.2 yr). We think, however, that this difference is unlikely to be clinically relevant as the minimum follow-up time of both groups was 1.4 yr, which should be enough to accomplish reintroduction. The questionnaire used in this study was not validated but composed according to daily clinical practice. We cannot rule out that the content and way of asking may have influenced the results or our study. Furthermore, as is mentioned above peanut-related symptoms after negative challenge were parent reported and unfortunately not objectified with rechallenges at the time of writing.

In conclusion, this study shows that despite negative peanut challenge, continuation of the elimination diet occurred in a significant proportion of children. This might be due to patient-related factors as refusal and the presence of other elimination diets or to (parent reported) peanut-related symptoms after challenge. To guide parents and children and monitor the occurrence of symptoms, follow-up after food challenges should be intensified. When typical food allergic symptoms reoccur food challenge outcome needs to be reconsidered.

Conflict of interest

All authors declare that no funding was received, and no conflict of interest is disclosed relevant to this manuscript.

Authors contributions

F.C. van Erp and J. Boot substantially contributed to design, concept, acquisition of data, analysis and interpretation of data, drafting the article

and final approval of version to be published. A.C. Knulst substantially contributed to interpretation of data, drafting the article and revising critically for important intellectual content and final approval of version to be published. C.K. van der Ent substantially contributed to design, interpretation of data and revising critically for important intellectual content and final approval of version to be published. Y. Meijer, and S.G.M. Pasmans substantially contributed to interpretation of data and revising critically for important intellectual content and final approval of version to be published.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Questionnaire after negative food challenge for peanut.

SUPPLEMENTARY MATERIAL

Figure A. Questionnaire after negative food challenge for peanut

Current diet	
1. Which of the following products is included in the diet of your child on a regular basis?	a. Products with peanut as ingredient (visible peanut) b. Products with peanut as ingredient (not visible) c. Products with the label "may contain traces of peanut" d. Products with the label "Manufactured on a shared line with products containing peanut" e. None
2. Do you read labels (regarding peanut) of products in the diet of your child?	a. Yes b. No
3. If products with peanut are ingested, how much and how often?	a. Product (s): b. Frequency: times a week / month c. Amount:
4. Does your child has other diet restrictions due to a (possible) food allergy?	a. Yes, including (allergens): b. No
5. Does anyone in the household of your child has diet restrictions due to a (possible) food allergy?	a. Yes - Family member (s): - Allergen(s): b. No
Challenge and introduction	
6. Did you agree with the original food challenge outcome?	a. Yes, because b. No, because
7. Did you use the reintroduction schedule after food challenge?	a. Yes b. No, because
8. When did you start to reintroduce peanut after the food challenge?	a. Yes days / weeks / months after challenge b. I did not start introduction
9. Why didn't you start to reintroduce peanut?	- o I fear an allergic reaction - o My child fears an allergic reaction - o My child doesn't want to eat peanut - o I don't feel it necessary to introduce peanut - o I do not agree with the challenge outcome - o Other
10. Do you feel the reintroduction was successful?	a. Yes, because b. No, because
Symptoms after food challenge	
11. Did your child developed symptoms after the ingestion of peanut during follow-up?	a. Yes, ... times b. No

12. Details of symptoms

When:

Time between ingestion and symptoms:

Product (s) eaten:

Product label contained peanut / may contain peanut / peanut not mentioned?

How much of the product? was ingested?

Where did the symptoms occur?

13. What did you do after the symptoms (multiple answers possible)?

- ☐ Administer medication:
 - a. Auto-injector
 - b. Antihistamines
 - c. Other:
- ☐ Visit a doctor
- ☐ Called 911

14. If your child developed one or more symptoms, please fill out this form (multiple answers are possible)

- ☐ Itchy red / thickened / dry skin (eczema)
- ☐ Localized urticaria
- ☐ Localized flushing
- ☐ Generalized urticarial
- ☐ Generalized flushing
- ☐ Angioedema
- ☐ Itchy mouth / throat
- ☐ Abdominal pain
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Itchy nose, rhinorrhea, nasal congestion, sneezing
- ☐ Red itchy eyes
- ☐ Throat hoarseness
- ☐ Cough
- ☐ Dyspnea
- ☐ Expiratory / Inspiratory stridor
- ☐ Change in activity level
- ☐ Lightheadedness
- ☐ Loss of consciousness