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Adverse effects during specific oral tolerance induction: in-hospital "rush" phase

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Key words

Food allergy, specific oral tolerance induction (SOTI), adverse reactions, nebulized epinephrine.

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Summary

Background: *specific oral tolerance induction (SOTI) is a promising approach in the treatment of severe food allergies. Different protocols have demonstrated its efficacy. Nevertheless, SOTI is still considered an experimental method and should be limited to highly controlled settings.* ***Aims:*** *to define the incidence and severity of adverse reactions, possible risk factors, and the safety and effectiveness of nebulized epinephrine as a first-line treatment of respiratory reactions during in-hospital SOTI for cow's milk allergy.* ***Materials and methods:*** *a retrospective study was conducted by reviewing the medical records of patients admitted for SOTI beginning in 2001. Reactions were classified as mild, moderate and severe on a partially modified Clark scale. Adverse reactions were treated following the International Guidelines with the introduction of nebulized epinephrine for level four reactions.* ***Results:*** *of 209 patients, 17 were excluded due to the absence of objective reactions. The remaining 192 were classified as follows: Mild Reactions (Clark Scale 1 to 3): 100 patients received either no treatment, oral antihistamines or nebulized steroids; Moderate Reactions (Clark Scale 4): 87 patients treated with nebulized epinephrine and, depending on their symptoms, oral antihistamines, corticosteroids (nebulized, oral or IV) or nebulized beta 2 agonists; Severe Reactions (Clark Scale 5): 5 children, 4 of whom initially underwent one nebulization of epinephrine and eventually required an IM dose. The fifth patient was immediately treated with IM epinephrine due to hypotension.* ***Discussion:*** *adverse reactions during this in-hospital SOTI protocol were frequent but easily manageable. Nebulized epinephrine can play a relevant role in the treatment of respiratory reactions.*

Introduction

Specific oral tolerance induction (SOTI) is a promising approach in the treatment of severe food allergy. Recent reports have demonstrated the efficacy of different oral desensitization protocols in the treatment of cow's milk (CM) allergy (1-5). Nevertheless, the number of children who have undergone these protocols is still small and SOTI is considered an experimental approach to be limited to highly defined settings. Data regarding the incidence and severity of adverse reactions during SOTI show a wide range varying from infrequent, mild reactions (6,7) to frequent, severe ones (8). This was likely due to the variation in the patients' specific IgE levels or the variation in the increase of the CM dose from patient to patient during the protocols.

SOTI has been applied at the Burlo Garofolo Hospital since January 2001. The rush phase was a hospital based SOTI, with an estimated 10 day hospitalization period. It was applied to children with a positive oral food challenge test for less than a single dose of 4 ml or with a history of severe reactions occurring within the previous year and requiring emergency room care, and with high specific IgE levels (greater than 70 kUA/l). Once the patients were released, the protocol was continued at home.

Aims

To define during the in-hospital rush phase of SOTI, the incidence and severity of adverse reactions, the possible risk factors related to the patients and the protocol, and lastly, the safety and efficacy of nebulized epinephrine as a first-line treatment of respiratory reactions.

Materials and method

Consensus and ethical committee approval: informed consent was obtained from all parents. The ethical committee of the I.R.C.C.S. Burlo Garofolo, Trieste, approved the study.
Definition of cases: children who had a positive double blind placebo controlled food challenge (DBPCFC) or presented with an objective symptom during the course of in-hospital SOTI were included in the study. Children in this latter group were enrolled without DBPCFC for any of one or more of the following reasons: a positive open challenge, a history of recent severe reactions requiring emergency room care within the previous year, specific IgE level greater than 70 kUA/L, or refusal of the parents to allow the child to undergo a DBPCFC.
Method of evaluating the RAST classes: the RAST was determined through the CAP system from Pharmacia and Upjohn AB Diagnostics, Uppsala, Sweden. The specific IgE levels were reported as both a mean number of RAST specific IgE levels (kUA/L) and as a median RAST class because the laboratory did not define the value of more than 100 kUA/L in the sixth class.
Evaluation of patients: prior to beginning the in-hospital phase of SOTI, all patients underwent spirometry. In 2008, a nitric oxide test and a standard ECG were also included in the protocol in order to reveal possible hidden arrhythmias. During the course of a bronchospasm SOTI was delayed and in the case of poorly controlled asthma, a

Table 1 - In hospital treatment schedule.

Days	Dilution	Dose	Cow Milk Proteins (in grams)
1	1 drop of CM in 10 ml of water every hour	1 drop, 4 drops, 12 drops, 1 ml, 2 ml, 4,5 ml	0.000008, 0.000032, 0.000096, 0.00016, 0.00036, 0.00072
2	4 drops of CM in 20 ml of water every 2 hours	1 ml, 3 ml, 6 ml, 10 ml	0.00032, 0.00096, 0.00192, 0.0032
3	20 drops of CM in 20 ml of water every 2 hours	1 ml, 3 ml, 6 ml, 10 ml	0.0015, 0.0045, 0.009, 0.015
4	3 ml of CM in 20 ml of water every 2 hours	1 ml, 3,5 ml, 7,5 ml, 11 ml	0.004, 0.014, 0.03, 0.044
5	10 ml of CM in 20 ml of water every 2 hours	4 ml, 6 ml, 8 ml	0.04, 0.06, 0.08
6	10 ml of CM in 10 ml of water every 2 hours	4 ml, 6 ml, 8 ml	0.064, 0.096, 0.128
7	pure milk every 2 hours	1 ml, 3 ml, 6 ml	0.032, 0.096, 0.192.
8	pure milk every 2-3 hours	4 ml, 7 ml, 11 ml	0.128, 0.224, 0.352.
9	pure milkevery 3 hours	10 ml, 12 ml, 15 ml	0.32, 0.384, 0.48.
10	pure milkevery 3 hours	13 ml, 16 ml, 20 ml	0.416, 0.512, 0.64.

treatment with nebulized steroids, nebulized beta-2 agonists or oral anti-leukotriene antagonists [according to the National Asthma and Prevention Program Guidelines (9)] was promptly started. A 24 gauge cannula, inserted following the application of anesthetic cream, was kept in place during the entire hospitalization period and checked each day for patency.

In hospital CM administration protocol: the 10 days protocol for CM administration was developed based on small initial doses (7) (Tab. 1). The increase in CM was regulated according to the patient's symptoms and reactions. The increase was stopped whenever a grade four reaction occurred and/or in the case of diffuse severe urticaria. The day after the grade four reaction, the corresponding daily doses were halved. In this way, the dose which provoked the initial reaction was re-introduced the following day. For example, a child who reacted on day 8 to 7 ml of CM would have received on day 9,4 ml, 6 ml and 8 ml respectively. While on day 10, the first CM dose was begun at 7 ml. As a rule, the number and severity of reactions did not change the length of admission, but might have changed the amount of single CM dose reached at discharge (the more severe the reactions, the slower the increase and lower the dose of CM at discharge). Patients who did not experience any adverse symptoms during the first few days of SOTI were given increasing doses of CM until symptoms were provoked. In these cases, admission could last less than ten days, and the patient was discharged with a higher tolerance of CM, resulting in a larger initial dose during the home phase.

Definition and treatment of adverse reactions during the hospital phase: adverse reactions were classified according to the Clark scale (10) which was modified by introducing significant gastric pain as an additional reaction (Tab. 2). This was defined as abdominal pain lasting more than 15 minutes, interfering with the child's activities, forcing the child to remain in bed, and associated with an increase in heart rate or pallor. Adverse reactions were treated according to EAACI guidelines (11). However, nebulized epinephrine was introduced as a first-line treatment for respiratory reactions. Acute gastric pain was managed with oral beclomethasone (400 mcg), while oral cromolyn (250 mg) was administered 30 minutes before each CM dose as prophylaxis for recurrent gastric pain episodes. EAACI guidelines were further modified by discouraging the use of oral or intravenous (IV) steroids unless strictly necessary, due to the possible masquerading effect on the reactions in the following days.

Epinephrine was the only drug administered via intramuscular (IM) injection. During the home phase, the use of steroids was recommended for class four reactions without a complete resolution after nebulized epinephrine.

Administration of nebulized epinephrine: nebulized epinephrine was administered using a nebulizer (Nebula® Markos, Italy) at a dose of 0.1 mg/kg (maximum dose 3 mg) and was initially diluted in either 3 ml of standard saline solution or in 800 mcg of beclomethasone. Since 2008, the protocol has been modified and nebulized epinephrine is always diluted in beclomethasone, since it enhances the local anti-inflammatory effect. Beginning in 2006, nebulized epinephrine was repeated after an interval of 15 to 20 minutes (a maximum of two times), in cases where the initial nebulization did not resolve the symptoms. In addition to epinephrine, the other drugs used to manage the reactions were nebulized beta-2 agonists, oral antihistamines, and nebulized or oral corticosteroids.

Analysis of adverse reactions: reactions were classified as mild (Clark scale 1-3), moderate (Clark scale 4) or severe (Clark scale 5). Oral itching and mild gastric pain (lasting less than 15 minutes) were considered slight adverse reactions. However, since they were so common and difficult to evaluate objectively, they were not included in the analysis.

The following characteristics were considered: the amount of CM triggering a reaction, the symptoms, the interval between CM administration and a reaction, the treatments required, the interval of the resolution of symptoms (in relation to onset of symptoms and onset of treatment), and the vital parameters (heart rate, blood pressure, peripheral oxygen saturation rate) before and after the treatment with nebulized epinephrine.

Collection of in hospital phase data: all data regarding the reactions during the hospital phase were systematically recorded on the patients' medical records. Continuous data was reported as mean and SD or as median and interquartile range. Categorical data was reported as number and percentage.

Statistical analysis of in hospital phase data: includes Mann-Whitney U test for mean comparison between two groups, a median test for assessing the difference in the median between the two groups; Fischer exact test for categorical data. All analysis were performed using Stata 9 software.

Results

The study involved 209 patients with history of severe CM allergy who presented to the Pediatric Department of the "Burlo Garofolo" hospital in Trieste, Italy between January 2001 and December 2008.

Of the 209 patients, 17 were excluded due to the absence of objective reactions. Two of these patients eventually experienced clinically significant reactions during the home phase of SOTI with higher CM doses, but were not included in the analysis.

The remaining 192 patients presented with the following reactions during hospitalization:

Mild reactions (Clark scale 1 to 3): 161 reactions in 100 children treated with oral antihistamines or oral betamethasone (in some cases depending on the gravity and type of reaction, treatment was not given).

Moderate reactions (Clark scale 4): 139 reactions in 87 children who were given nebulized epinephrine as a first line treatment, in some cases followed by oral antihistamines, corticosteroids (nebulized beclomethasone or IV methylprednisolone) or nebulized beta 2 agonists.

Severe reactions (Clark scale 5): 5 reactions in 5 children treated with IM epinephrine. Four out of the five patients received nebulized epinephrine once, before the IM injection. Two out of five had already presented with reactions requiring nebulized epinephrine.

For every group common variables were considered:

- Amount of CM eliciting a reaction, time of onset and the time required for the resolution of the symptoms, length of admission, and CM amount at discharge (see table 2).
- Symptoms and treatments required (Tab. 3).
- Vital parameters before and after nebulized epinephrine in moderate and severe reactions (see table 4).
- Time required for the resolution of symptoms after epinephrine inhalation (Fig. 1).

Since 2006, the option of applying a second epinephrine nebulization was introduced in the protocol if there was not a satisfactory resolution of symptoms.

The IM epinephrine use in the period between 2001 to 2006 was compared with the IM epinephrine use in the period between 2006 to 2008. From 2001 to 2006, IM epinephrine was used five times in 83 SOTI procedures. However, after 2006, it was never used in any of the 126 SOTI procedures. There was no change in the SOTI protocol in the two periods and there while continued the immediate use of epinephrine nebulizations, also repeated.

Actually since 2006, 6 children have been treated with two consecutive epinephrine nebulizations and one child with three nebulizations (after 15 to 20 minutes).

Discussion

Using the Burlo Garofolo SOTI protocol, in-hospital SOTI was managed with an acceptable rate of side effects, even in children with very high levels of specific IgE and a history of recent severe reactions. The literature

Table 2 - Clarke scale modified and treatments

Reaction	**Treatment**
Throat and/or tongue transient itching perioral urticaria	No treatment
Throat and/or tongue persistent itching Rhinitis and/or conjunctivitis Generalized urticaria	Antihistaminic per os (cetirizine)
Abdominal pain	Oral beclomethasone 800 mcg
Laryngospasm or hoarse voice Inspiratory dyspnoea Asthma All the symptoms that fail to respond to previous treatment	Nebulized adrenaline (1 ml/10 Kg of adrenaline in 2 ml of saline solution or in 800 mcg beclomethasone) in association with one or more of the following drugs: - Nebulized adrenaline repeated - Nebulized salbutamol (0,05-0,15 mg/kg) - Steroids per os (bethametasone 0,1 mg/kg or prednisone 2 mg/kg) or iv (metilprednisone 1 mg/kg) - Antihistaminic per os or iv (clorfenilamine 0,2 mg/kg)
Reaction perceived immediately as severe and systemic, hypotension	Adrenaline im (0,01 mg/kg)

Table 3 - Common data for mild, moderate and severe reactions in hospital.

	Mild Reactions (Clark scale 1 to 3)	Moderate Reactions (Clark scale 4)	Severe Reactions (Clark scale 5)
Number of reactions/ patients	161/100	139/87	5/5
Mean Ages (*) (min-max)	7 yrs (3-20)	6 yrs (3-22)	6 yrs (3 -8)
Mean RAST value (SD)	45.5 kUA/L (40,8)	70.8 kUA/L (39,1)	82.9 kUA/L (38,4)
Median RAST class (**) (% of patients in 6th class)	4 (24%)	5 (45%)	5.5 (80%)
Percentage of patients with asthma/ viral wheezing (***)	52%	63%	80%
Median eliciting CM dose (min-max)	0.9 ml (0.04-40)	3 ml (0.49- 60)	0.9 ml (0.39 -1.3)
Mean time until the onset of the reaction (interquartile range)	27 minutes (15-60)	30 minutes (10-45)	32 minutes (11-75)
Mean time until the resolution of the main symptoms of the reaction (interquartile range)	64 minutes (32-94)	20 minutes (10-30)	19 minutes (10-25)
Mean length of admission (min-max)	8 days (5-10)	10 days (10-11)	10 days (10-11)
Mean dose of CM at discharge (min-max)	25 ml (12-60)	15 ml (****) (1.5-20)	1.6 ml (****) (0-3)

(*) The mean age difference between mild and moderate reactions is non-significant (p 0.04)
(**) The median RAST class difference between the mild and the moderate group is significant (p 0.006)
(***) The presence of asthma when comparing the mild group versus the moderate group is significant (p 0.01)
(****) In the moderate and severe group, 6 patients received sublingual SOTI.

on adverse reactions during SOTI is still limited. Meglio(4) and Patriarca(1) reported a very low incidence of severe reactions, in 21 and 59 children respectively , with a mean IgE of 3.9 kUA/L and 32 kUA/L. The number of severe reactions were 3/21 and 9/54 respectively. Skripak et al. (12) during the initial-in-hospital build up phase treated with IM epinephrine 2 out of 13 patients with a mean specific IgE level of 34.8 kUA/L.

Nieto et al. (8) described a near fatal reaction in a patient with RAST rating of 6 for CM. In this case, the patient was given 2.5ml of pure CM on the second day of SOTI, despite the fact that the patient had required IM epinephrine one hour earlier due to a reaction to the previous CM dose. The authors used a fast paced protocol with a higher dosage of CM in a shorter time when compared to the Burlo-Garofolo SOTI protocol. In this case a 2.5ml dose of pure CM was administered on the second day of SOTI. One hour earlier the patient had already reacted to the previous CM dose requiring IM epinephrine.

There are some important differences which should be highlighted between the above protocols and that which was used at the Burlo Garofolo during the in-Hospital hospital phase. The patient is treated with a daily dose of antihistamine and the CM dose begins with minute amounts raised slowly over the 10 day period. This approach is prudent, and mirrors the symptoms of the patients in question.

Furthermore, the protocol is always suspended on the day of a reaction requiring epinephrine treatment, and restar-

Table 4 - Symptoms and pharmacological treatments used in mild, moderate and severe reactions in hospital.

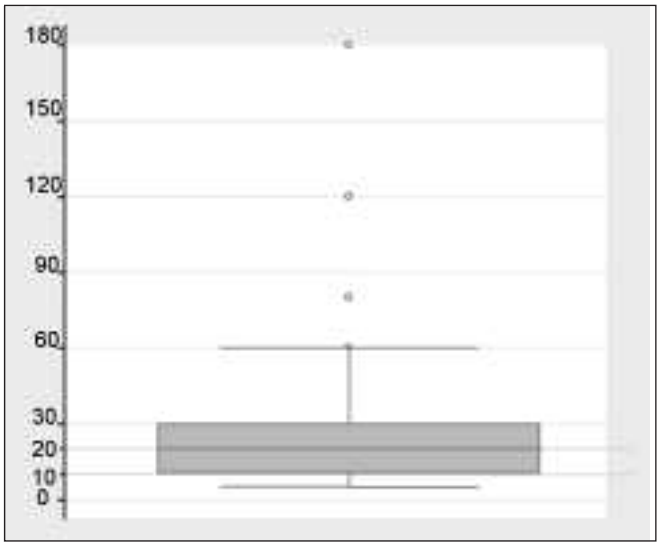
	Mild Reactions (161 reactions/100 patients)		Moderate Reactions (139 reactions/87 patients)		Severe Reactions (5 reactions/5 patients)	
Type of symptoms (% of reactions)	Gastrointestinal	43%	Gastrointestinal	40%	Gastrointestinal	20%
	Mild urticaria	71%	Diffuse urticaria	56%	Diffuse urticaria	20%
	Rhinoconjuntivitis	13%	Rhinoconjuntivitis	17%	Rhinoconjuntivitis	20%
			Cough	35%	Cough	60%
			Sore throat	24%	Sore throat	40%
			Wheezing	50%	Wheezing	100%
			Laryngospasm (Dysphonia)	20%	Laryngospasm	40%
			Rhinitis	25%	Hypotension	20%
Type of drugs and way of administration (% of treated reactions) (*)	Nebulized Beclomethasone (**)	2%	Nebulized epinephrine	100%	IM epinephrine	100%
	Oral beclomethasone	23%	Nebulized beta 2 agonists	87%	Nebulized beta 2 agonists	40%
	Oral antihistamine	37%	Oral antihistamine	86.2%	Oral betamethasone	20%
			IV chlorfeniramine	13.8%	Nebulized epinephrine (***)	80%
			Oral betamethasone	64%	IV methylprednisolone	20%
			Nebulized beclomethasone /epinephrine	73.1%	Fluid bolus	20%
			IV methylprednisolone	0.9%		

(*) During the study none of the patients received IM corticosteroids since they all had an IV line ready for use.

(**) Nebulized beclomethasone alone was used mainly for rhinoconjuntivitis.

(***) Nebulized epinephrine was administered before IM epinephrine.

Figure 1 - Moderate reactions: time required for the resolution of symptoms (in minutes) after nebulized epinephrine administration.



ted the following day with the previously tolerated CM dose, eventually ending with the dose that evoked the symptoms. From the third day of the protocol onward, a minimum interval of two hours is kept between each CM administration, and on the ninth day of the protocol, the interval is increased to three hours.

A slow initial phase characterizes the Burlo Garofolo in-hospital protocol. The smallest amount of CM provoking a reaction was 0.014 gr (the second dose of the fourth day). This suggests that the protocol can be shortened by using slightly larger doses in the initial period. This approach was chosen to maximize safety, and to allow the beginning of a mucosal "mast cell desensitization". A further important difference between this protocol and the others is reflected in the change of the CM increase according to reactions. In this protocol CM ingestion after moderate reactions or severe diffuse urticaria is always discontinued for that day, restarting the following day from the previously tolerated dose.

In this series 67 (34%) patients had a class 6 RAST (specific IgE greater than 100 kUA/L) and 100 (52%) presented with

Table 5 - Vital parameters before and after nebulized epinephrine.

	Before nebulized epinephrine	After nebulized epinephrine
Mean Systolic blood pressure mmHg	108.7	106.5
(interquartile range)	(96-128)	(87-115,6)
Mean Diastolic blood pressure mmHg	58.4	49.1
(interquartile range)	(46-65)	(42-56)
Mean Heart rate in beat/minute	103.8	94.7
(interquartile range)	(84-129)	(78-118)
Mean Peripheral oxygen saturation in percentage	94.5	98
(interquartile range)	(86-99)	(95-100)

a history of associated asthma. As expected, there was an association between the incidence of moderate to severe reactions, and RAST class and history of asthma. Even though the total numbers of reactions were considerable, they were easily manageable, responding well to nebulized epinephrine. This protocol reveals that nebulized epinephrine can play a pivotal role in the management of these patients. Prior to 2006, when only one epinephrine nebulization was administered, 5 patients out of 209 required IM epinephrine. Since 2006, when a second epinephrine nebulization was introduced (after a 15 to 20 minutes interval in cases where the first nebulization did not resolve the symptoms) not a single patient required IM epinephrine. The same treatment protocol can be adopted either during the oral food challenge performed in a day hospital setting or during the home phase of SOTI with similar results. In a different setting, Jarvinen et al. (13) administered IM epinephrine during an oral food challenge to 14 of 50 patients, while Narisety et al. (14) treated 4 of 25 patients with IM epinephrine, during the home phase of SOTI, with a total of 6 injections. In these cases, it is possible that nebulized epinephrine may have reduced the possibility of unnecessary IM epinephrine use.

In the International Guidelines (11), nebulized epinephrine has only recently been introduced as a second line treatment, following IM injection for persistent respiratory symptoms. However, it is well known that respiratory symptoms during anaphylaxis are more prevalent in children than systemic symptoms, such as hypotension that is typical of adults (15). Therefore, it is reasonable to hypothesize that, even with a low level of epinephrine in the blood, the local anti-edema action and the alfa 1-adrenergic effect provided by nebulization plays a major role in the control of symptoms and may arrest the negative chain of respiratory events. The positive effects of nebulized epinephrine were outlined by Hourihane and Warner in 1995 (16) who reported that in 20 years of practice the use of IM epinephrine was replaced by nebulized epinephrine. In their study Simons and Estelle (17), (18) have shown that most children are unable to inhale epinephrine from a pre-measured dosage nebulizer. However, a thorough search of the literature has not revealed evidence comparing continuous nebulization to pre-measured dosages.

The data presented in this article requires cautious interpretation and should not be transferred to any other study or taken out of context. All the reactions occurred in a safe and controlled hospital environment. Nebulized epinephrine should only be used in cases of provoked anaphylaxis, as the event is expected and the epinephrine is ready to be used. Nebulized epinephrine should not be used to replace IM epinephrine in the case of spontaneous anaphylaxis. Even though the possibility and utility of performing a prospective randomized trial comparing the use of nebulized epinephrine versus IM epinephrine should be considered.

The specific protocol for the in-hospital SOTI used at the Burlo Garofolo hospital reveals that patients with high specific levels of IgE were able to undergo SOTI successfully with an acceptable rate of side effects. To the best of our knowledge this study reports the largest series of SOTI related reactions in literature. More research is needed in order to compare the different protocols of CM administration and treatment in order to establish the safest and most cost effective protocol.

Acknowledgements

The authors are really greateful to Miss. Nathalie Leone for the helpful support in the revision of the manuscript.

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