

A retrospective study of suspected anaphylactic reactions during anesthesia in Belgium

R. VAN DEN EYNDE (*), F. SOETENS (**), I. LEUNEN (**), L. AL TMIMI (*), M. VAN DE VELDE (*)

Abstract : *Background :* Since 2008, Belgian anesthesiologists can report suspected anaphylactic reactions during anesthesia on the website of the Society for Anesthesia and Resuscitation of Belgium (SARB). *Material & Methods :* We analyzed the database retrospectively, covering a period from January 2008 to May 2013.

Results : Out of 97 cases, two were excluded because of insufficient data. Fifty-six % of cases were reported by the 2 hospitals that conducted the survey. The incidence of severe reactions was higher in regional hospitals than in university hospitals. Respiratory symptoms were more frequent in patients with a history of respiratory disease. Mast cell tryptase (MCT) after the reaction was measured correctly in only 54% of cases, and was positive in 66% of cases (MCT > 13.5 µg/L). Basal MCT was measured in 64% of patients. Skin testing was done in 72% and was positive in 51 (75%) of them. Most frequently incriminated agents were neuromuscular blocking drugs (NMBDs) (63%) and antibiotics (18%). Cross-sensitivity between NMBDs occurred in 78% of cases. A complete investigation (MCT at 30-90 min, basal MCT at distance from the reaction, and skin testing) was conducted in 38% of cases.

Conclusion : There was probably severe underreporting of suspected anaphylactic reactions in Belgium. Moreover, in a majority of cases, necessary investigations were carried out incompletely. Underreporting and incomplete investigation increases the risk for new episodes of anaphylaxis during subsequent anesthesia.

Key words : Allergy ; Anaphylaxis ; Anesthesia complications ; Perioperative period.

INTRODUCTION

Anaphylaxis is an uncommon but severe complication during anesthesia (1). The initial diagnosis is based on clinical signs and symptoms, and on the short onset time between contact with the allergen and the occurrence of those clinical features. The etiological diagnosis is crucial to provide safe subsequent anesthesia (2). Since 2008, it is possible for Belgian anesthesiologists to report suspected anaphylactic reactions during anesthesia

on the website of the Society for Anesthesia and Resuscitation of Belgium (SARB) (3). In this article, we analyzed the database and compared the data with the literature.

MATERIALS AND METHODS

Since January 2008, a questionnaire is available on a protected website of the SARB to guide Belgian anesthesiologists in reporting suspected anaphylactic reactions (3). The questionnaire contains questions about the patients' demography, symptoms, treatment, and outcome of the suspected anaphylactic reaction. The questionnaire also provides guidance for patient referral to an allergy center for further investigation and follow-up. One of the questions of the questionnaire insures that both the patient and anesthesiologist give consent to process the data anonymously. We reviewed the database from January 2008 to May 2013. The following items were retrieved from the questionnaire :

— Patient demography: age at the time of reaction, gender, type of intervention or procedure, medical history, and particularly history of a respiratory disease (chronic obstructive pulmonary disease (COPD) or asthma), surgical and anesthetic history, known allergies, and type of hospital where the reaction occurred (university or regional hospital).

Raf Van den Eynde, M.D.; Filiep Soetens, M.D.; Ine Leunen, M.D.; Layth Al Tmimi, M.D.; Marc Van de Velde, PhD., EDRA.

(*) Department of Anesthesiology, University hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.

(**) Department of Anesthesiology, AZ Turnhout, Steenweg op Merksplas 44, 2300 Turnhout, Belgium.

Abstract presented by I. Leunen, M.D., at the Research Meeting of the Belgian Society of Anaesthesia and Resuscitation on the 24th of June 2014.

Corresponding author : Raf Van den Eynde, M.D., University hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. Phone: +32 499261892.

E-mail: raf.vandeneynde@uzleuven.be

— The suspected anaphylactic reaction: drugs and substances used before the onset of the suspected anaphylactic reaction, type of anesthesia (general or regional), time of reaction relative to the induction of anesthesia, first clinical sign, and incidence of cardiovascular, respiratory and cutaneous signs. The severity of the reaction was determined using the classification of Ring and Messmer (Table 1) (4). The difference between grade 2 and 3 was arbitrarily based on the need for adrenaline. For each grade, the incidence of cardiovascular, respiratory and cutaneous signs was calculated. The incidence of respiratory signs in patients with COPD or asthma was compared with patients without COPD or asthma.

— Treatment of the suspected anaphylactic reaction: use and dose of adrenaline, need for endotracheal intubation, and external cardiac compressions.

— Outcome: incidence of cancellation of the intervention or procedure, referral to an intensive care unit (ICU), and subsequent morbidity and mortality.

Table 1

Classification of Ring and Messmer, according to Mertes P. (4)

Grade I	Generalized cutaneous signs: erythema, urticaria, with or without angioedema
Grade II	Non-life-threatening multivisceral involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity
Grade III	Severe life-threatening multivisceral involvement: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm
Grade IV	Cardiac and/or respiratory arrest

Because the questionnaire was completed at the time of the suspected anaphylactic reaction, the results from mast cell tryptase (MCT) in plasma 30 to 90 minutes after the onset of the suspected anaphylactic reaction and 24 hours later, and skin tests performed several weeks later, were not available in the database. To retrieve these results, the responsible anesthesiologist was contacted by mail or phone. MCT sampling is best determined approximately one hour after the onset of the suspected anaphylactic reaction. A baseline MCT must be determined at least 24 hours later to exclude mastocytosis. The incidence of a complete investigation of the suspected anaphylactic reaction was determined. An investigation was considered complete if 1. a MCT plasma level measurement was performed 60 minutes (30 to 90 minutes) after the onset of the reaction, and after 24 hours, and 2. skin tests were performed after 4-6 weeks when the MCT

at 60 minutes was positive, or, in case the MCT was negative at 60 minutes, the suspected anaphylactic reaction was severe (grade 3 or 4). Anaphylactic reactions classified as Ring and Messmer grade 1 and 2 were referred to as mild, while grade 3 and 4 were referred to as severe.

STATISTICAL METHODS

The results were analyzed using SPSS v 25.0 for Mac (IBM, Armonk, NY). The categorical data were analyzed with Fisher's Exact tests and Chi-square tests.

We used a one-way analysis of variance (ANOVA) with Bonferroni adjustment for multiple comparisons to compare MCT levels between mild and severe reactions. Differences among these 2 groups were analyzed using the Mann-Whitney U-test or Student's T-test, when appropriate. We tested for normality using the Shapiro-Wilk test. All tests were 2-sided. The threshold for statistical significance was set at a p-value of < 0.05.

RESULTS

There were 97 medical records in the database. Two files were excluded because of insufficient information.

Most suspected anaphylactic reactions occurred in the fifth (19%), sixth (21%) and seventh (18%) decade of life (Fig. 1). The youngest patient was seven years old, and the oldest 82 years. Fifty-eight percent of patients were female, and 47% had a history of allergy (pollen, penicillin, non-steroidal anti-inflammatory drugs, or contrast). Nineteen patients had a history of asthma or COPD, and 17% of patients never had anesthesia before. Importantly, 44% of the reactions were reported from university hospitals, and 56% of all reactions were reported by the hospitals that conducted the survey: 19% in AZ Turnhout, and 37% in UZ Leuven, respectively.

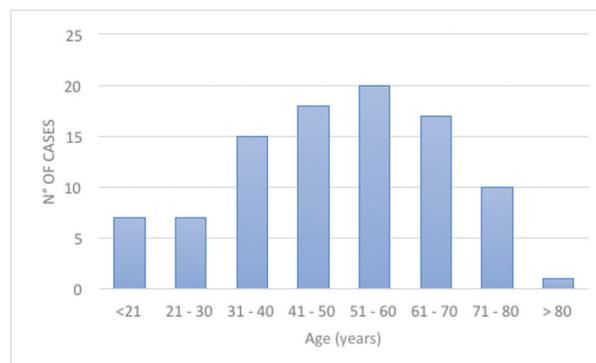


Fig. 1. — Incidence of suspected anaphylactic reactions and age.

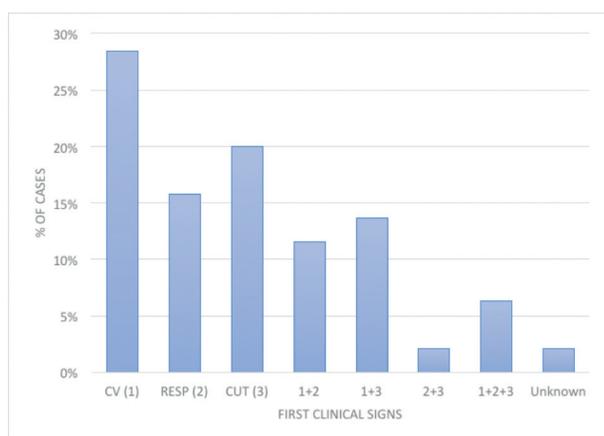


Fig. 2. — Incidence of first clinical signs. CV : Cardiovascular signs (1) ; RESP : respiratory signs (2) ; CUT : cutaneous signs (3).

Most reactions (92%) were reported by Flemish hospitals.

Almost all (95%) of reported suspected anaphylactic reactions occurred during general anesthesia. The time delay between induction of anesthesia and onset of the reaction was less than five minutes in 54% of cases. In 47 out of 95 cases, both the causative agent and the time interval between induction and onset of first clinical signs was known. Neuromuscular blocking drugs (NMBDs) were the culprit in 29 of these 47 cases. In 24 of these 29 cases (83%), NMBDs caused anaphylaxis within five minutes after induction of anesthesia. On the other hand, first clinical signs occurred within 5 min only in 2 out of 5 cases (40%), in which disinfectants were responsible for anaphylaxis. This difference between the onset of first clinical signs between NMBDs and disinfectants was however not statistically significant (83% vs 40% respectively ; Fisher's $p = 0.07$).

Most often, the first clinical signs were cardiovascular (hypotension and/ or tachycardia) (28% of patients), followed by cutaneous (20% of patients), and respiratory signs (bronchospasm and/ or desaturation) (16% of patients) (Figure 2). The incidence of cutaneous, cardiovascular, and respiratory signs during the course of a suspected anaphylactic reaction was 89%, 85% and 60%, respectively. Patients with a history of respiratory disease, as compared to patients without such, had a higher incidence of respiratory signs during a suspected anaphylactic reaction (89% and 52%, respectively ; Fisher's $p = 0.003$), and showed more often respiratory signs as the first clinical sign (58% and 29%, respectively ; Fisher's $p = 0.03$).

Grade 1, 2, 3 and 4 reactions occurred in 9%, 25%, 54%, and 12% of cases, respectively. The incidence of cutaneous signs in grade 1 reactions

tended to be higher than in grade 4 reactions (100% and 72% respectively ; Fisher's $p = 0.22$). There was no statistical difference in the severity of anaphylaxis between patients with a history and patients with no history of respiratory disease (74% and 65%, respectively; Fisher's $p = 0.59$). The incidence of severe reactions (grade 3 and 4) was higher in regional hospitals than in university hospitals (81% and 45%, respectively; Fisher's $p = 0.0004$).

In 62% of patients, adrenaline was administered. The mean dose was 1.6 mg. Cardiopulmonary resuscitation was needed in 13% of patients. Surgery was cancelled in 39% of cases. Forty-seven percent of patients were referred to the ICU. One patient suffered from subsequent respiratory morbidity, not further specified, and one patient from cardiac morbidity (cardiac arrhythmias including atrial fibrillation and ventricular tachycardia). One patient died.

In 77 out of 95 patients (81%), MCT after the suspected anaphylactic reaction was determined. In only 51 patients (54%), sampling was done within the right time frame (30 to 90 minutes after the onset of the suspected anaphylactic reaction). In 26 patients, MCT sampling was not performed within the right time frame (in 8 patients too early, in 11 patients too late, and unknown in 7 patients). In 66% of all patients in which MCT was determined, MCT levels were above the threshold value of $13.5 \mu\text{g/L}^{-1}$.

The MCT level correlated with the severity of the reaction as assessed by the classification of Ring and Messmer (Fig. 3). The ANOVA test demonstrated a statistically significant difference in MCT levels between the 4 patient groups, ranked according to their classification of Ring and Messmer ($p = 0.001$). The Bonferroni test showed that there was a statistically significant difference between MCT levels in grade 4 reactions versus

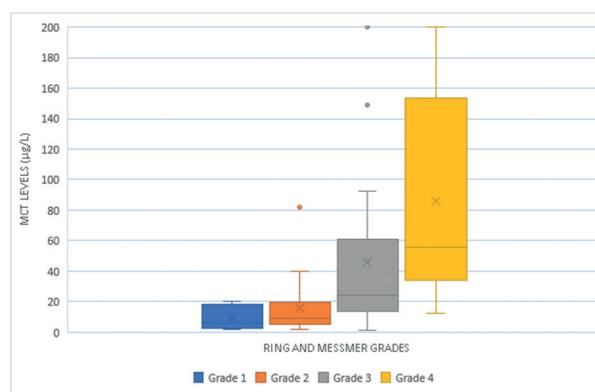


Fig. 3. — MCT level and the severity of the anaphylactic reaction as assessed by the classification of Ring and Messmer.

grade 1 ($p = 0.017$) and grade 2 ($p = 0.002$). There was however no statistically significant difference between grade 1 and grade 2 ($p = 1.00$), grade 1 and grade 3 ($p = 0.51$), grade 2 and 3 ($p = 0.16$) and grade 3 and 4 reactions ($p = 0.128$).

We compared the MCT levels between mild (grade 1 and 2) and severe (grade 3 and 4) reactions. The MCT levels in mild reactions ranged from 1.80 to 93.10 $\mu\text{g/L}$ with a median (interquartile range) of 7.75 $\mu\text{g/L}$ (4.55 to 19.38 $\mu\text{g/L}$), whereas the MCT levels in severe reactions ranged from 1.40 to 200 $\mu\text{g/L}$ with a median (interquartile range) of 29.00 $\mu\text{g/L}$ (15.35 to 70.15 $\mu\text{g/L}$). Because a Shapiro-Wilk test showed that the MCT levels in mild versus severe reactions did not belong to normal distribution, we decided to resort to nonparametric tests. A Mann-Whitney U test to compare MCT levels in mild versus severe reactions showed statistically significant difference ($p = 0.002$).

A baseline MCT was measured in 64% of patients. Skin testing was done in 68 out of 95 patients (72%), and was positive in 51 (75%) of them. Complete investigation was only performed in 38% of cases.

The most frequently incriminated agents were NMBDs (32 patients). In the group of NMBDs, rocuronium (22 patients) was most frequently the culprit, followed by cisatracurium (4 patients), succinylcholine (3 patients), mivacurium (2 patients) and atracurium (1 patient). Twenty-seven of these 32 reactions were severe (grade 3 or 4). Cross-sensitivity with at least one other NMBD occurred in 78% of cases, and with 2 or more NMBDs in 50% (Table 2).

Nine patients suffered from an allergic reaction to antibiotics. Cefazolin was the most frequently involved (7 patients : 1 grade 1 reaction, 4 grade 2 reactions, 2 grade 3 reactions), followed by erythromycin (1 grade 2 reaction) and ornidazole (1 grade 3 reaction).

Anaphylaxis caused by disinfectants occurred in 5 patients. Chlorhexidine was responsible for 3 severe reactions (grade 3 or 4). Povidone-iodine was responsible for one grade 4 reaction, and contact

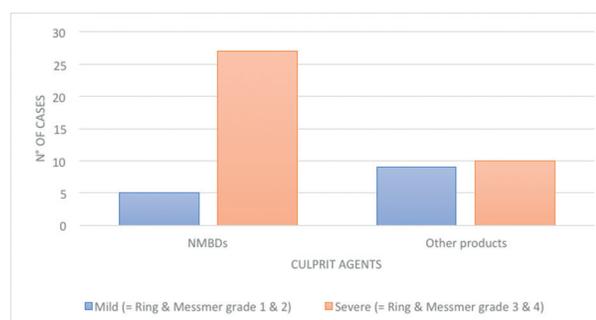


Fig. 4. — Severity of the anaphylactic reaction between NMBDs and other agents.

allergy in another patient.

Lidocaine, propofol, hydroxyethyl starch, and patent blue also caused anaphylaxis, each of them in 1 patient. In one patient, skin tests were positive to morphine derivatives, penicillins and cephalosporins.

Reactions to NMBDs were more severe than reactions to other agents (84% and 53%, respectively; Fisher's $p = 0.02$) (Fig. 4).

Two patients were diagnosed with mastocytosis.

DISCUSSION

Our epidemiological results are in line with other surveys. Most suspected anaphylactic reactions occurred in the fifth, sixth and seventh decade of life and were more likely in females (1,5,6). Intravenous exposure to a culprit substance led to symptoms of anaphylaxis rapidly, as opposed to skin exposure where symptoms were delayed (2). Cutaneous symptoms occurred in most patients, but were absent in some grade 4 reactions. Patients with a history of respiratory disease exhibited more frequent respiratory signs, and those signs were more often the first signs. Data on patient outcome after perioperative anaphylaxis are scarce, but our results resembled recent Australian data that found a need for CPR in 11%, cancellation of surgery in 45%, ICU referral in 47%, and a 0 to 1.4% mortality (7). There was a correlation between MCT levels and reaction severity (8). NMBDs were the culprit

Table 2
Incidence of cross-sensitivity between triggering NMBD and other NMBDs. N/A = not applicable.

	N°	Rocuronium	Vecuronium	Atracurium	Cisatracurium	Mivacurium	Succinylcholine	
Triggering NMBD	Rocuronium	22	N/A	11	1	4	10	5
	Atracurium	1	0	0	N/A	1	0	0
	Cisatracurium	4	1	3	3	N/A	4	0
	Mivacurium	2	0	0	0	0	N/A	0
	Succinylcholine	3	3	2	0	2	1	N/A

agents in the majority of cases of perioperative anaphylaxis. Rocuronium was, of all NMBDs, the most frequently incriminated agent, but we don't have information about the relative use of NMBDs in Belgium (2). Cross-sensitivity between NMBDs is frequent (9).

We made two important observations in this study: there is probably underreporting of suspected anaphylactic reactions in Belgium, and there is a high incidence of incomplete investigation in cases where anaphylaxis is suspected.

Several arguments plead for underreporting of suspected anaphylactic reactions :

1. The incidence of anaphylaxis in the literature is 1/10.000-1/20.000. If we assume that, each year, 1 million of anesthetic procedures are performed in Belgium, the incidence in this study is only 1/56.000.
2. Only 8% of cases were reported from hospitals in Brussels or Wallonia. Geographical variation in the incidence of anaphylaxis has been demonstrated due to differences in sensitization (1, 10). However, we don't think this explains the observed discrepancy. Furthermore, more than 50% of cases were reported by the 2 centers that elaborated the questionnaire. We think these differences are explained by knowledge of the existence of the questionnaire.
3. The incidence of more severe cases was higher in regional hospitals, which gives the impression that there is underreporting of less severe cases by regional hospitals.

The necessary investigation was complete in only 38% of cases. Performance of MCT sampling (both acute and baseline) within the right time frame and skin testing was poor. Patients get in contact with many different products at the same time during induction of anesthesia. Adequate identification of the cause of the anaphylactic reaction based on clinical arguments only, is often wrong (11). Although most of the reactions are caused by NMBDs, simply using another NMBD for a subsequent procedure is dangerous, because of the high incidence of cross-sensitivity between NMBDs.

An investigation can also lead to a wrong diagnosis: if a baseline MCT is not performed, the diagnosis of mastocytosis can be missed. Both underreporting and incomplete investigation potentially expose the patient to a life-threatening anaphylactic reaction during a subsequent anesthetic procedure.

CONCLUSION

Our results are in line with other databases. There is severe underreporting of suspected anaphylactic reactions. Moreover, in a majority of cases, necessary investigations are carried out incorrectly. Underreporting and incomplete investigation increases the risk for a new episode of anaphylaxis during subsequent anesthesia.

References

1. Soetens F.M. 2004. Anaphylaxis during anaesthesia: diagnosis and treatment. *Acta Anaesth. Belg.* 55(3) : 229-237.
2. Harper N.J., Dixon T., Dugué P. and Edgar D.M. et al. 2009. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia.* 64(2) : 199-211.
3. SARB website. [Online] <http://www.bvar.be>.
4. Mertes P.M., Tajima K., Regnier-Kimmoun M.A. and Lambert M. et al. 2010. Perioperative anaphylaxis. *Med. Clin. North. Am.* 94(4) : 761-789.
5. Dewachter P., Mouton-Faivre C. and Hepner D.L. 2015. Perioperative anaphylaxis: what should be known? *Curr. Allergy Asthma Rep.* 15(5) : 21.
6. Mertes P.M., Alla F., Téchet P., Auroy Y., Jouglu E. and Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. 2011. Anaphylaxis during anesthesia in France: an 8-year national survey. *J. Allergy Clin. Immunol.* 128(2) : 366-373.
7. Gibbs N.M., Sadleir P.H., Clarke R.C. and Platt P.R. 2013. Survival from perioperative anaphylaxis in Western Australia 2000-2009. *Br. J. Anaesth.* 111(4) : 589-593.
8. Stone S.F., Cotterell C., Isbister G.K. and Holdgate A. 2009. Elevated serum cytokines during human anaphylaxis: Identification of potential mediators of acute allergic reactions. *J. Allergy Clin. Immunol.* 124(4) : 786-792.
9. Sadleir P.H., Clarke R.C., Bunning D.L. and Platt P.R. 2013. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. *Br. J. Anaesth.* 110(6) : 981-987.
10. Bruschi A.M., Clarke R.C., Platt P.R. and Philips E.J. 2014. Exploring the link between pholcodine exposure and neuromuscular blocking agent anaphylaxis. *Br. J. Clin. Pharmacol.* 78(1) : 14-23.
11. Kroigaard M., Garvey L.H., Menné T. and Husum B. 2005. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? *Br. J. Anaesth.* 95(4) : 468-471.