Causes of perioperative hypersensitivity reactions in the Netherlands from 2002 to 2014

van de Ven, Annick A. J. M.; Oude Elberink, H. J. N. G.; Nederhoed, Vera; van Maaren, Maurits S.; Tupker, Ron; Rockmann-Helmbach, Heike

Published in:
Clinical and Experimental Allergy

DOI:
10.1111/cea.14042

Publication date:
2022

Received: 13 November 2020 | Accepted: 31 October 2021

DOI: 10.1111/cea.14042

RESEARCH LETTER

WILEY

Causes of perioperative hypersensitivity reactions in the Netherlands from 2002 to 2014

To the editor,

Although relatively rare, immediate perioperative hypersensitivity reactions (POH) are important complications of drug administration prior to, during and after surgical and other interventional procedures. Both the incidence of immediate POH and their major culprits are difficult to establish and vary considerably between reports; the incidence may be as high as 1:1250 or almost a tenfold lower.[1] Most studies have a yield of positive allergy test results of 50% to 60%, suggestive of an immunoglobulin E (IgE)-mediated reaction. Neuromuscular blocking agents (NMBA) were shown to be the most common cause of immediate POH in various countries including France and Australia,[2] while other countries (USA, UK, Spain, Denmark) identify antibiotics to be the primary culprit.[1,3,4]

Other frequently and increasingly identified culprits in POH are dyes, non-steroidal anti-inflammatory drugs (NSAID), induction agents and colloid solutions (reviewed in [1]). Dyes such as patent blue are increasingly used during oncologic surgical interventions and accounted for 5%–6% of POH in the UK and France.[2,3] It is particularly important to rule out or identify POH against so-called hidden allergens such as natural rubber latex (NRL) and chlorhexidine, since these allergens carry a high risk of re-exposure.[5] Oligosensitization to two or more substances has been reported in 2%–20% of patients.[3]

A diagnostic evaluation including a detailed history, thorough investigation of the anaesthetic files and additional diagnostics such as skin tests is highly recommended.[6] Until now, no epidemiologic data regarding immediate POH in the Netherlands have been published.

We here describe a retrospective multi-centre study including all patients with a suspected POH referred and tested between 01 January 2002 and 31 December 2014. Clinical data were retrospectively collected from the medical charts. Data that support the findings of this study are available from the corresponding author upon reasonable request.

Clinical severity of POH was classified according to the modified Ring and Messmer four-step grading scale.[6] All drugs to which the patient had been exposed to during and prior to anaesthesia were collected. Skin prick (SPT) and intradermal (IDT) tests were performed in accordance with EAACI/ENDA recommendations, with small adaptations in local protocols.[7] Serum tryptase levels were rarely measured post reaction and therefore not collected; baseline tryptase levels were measured in 122 patients. Four of them had increased tryptase levels, leading to the diagnosis of indolent systemic mastocytosis in one patient.

Specific serum IgE could be measured for chlorhexidine (from 2007 onward), NRL and rocuronium using ImmunoCAP® System fluorescence enzyme immunoassay. Results of all performed drug provocation tests (DPT, including antibiotics, NSAIDs, colloids, local anaesthetics, proton pump inhibitors and analgesics) were collected. If a patient was exposed to a suspected drug after the reaction without an allergic reaction, this was noted as a negative DPT. DPT were performed according to the local protocols, consisted of ≥3 incremental steps and were considered positive if consistent objective symptoms were reproduced as based on the interpretation of the attending allergist.

Outcome of diagnostics evaluation was defined as:

1. Definitive immediate allergic hypersensitivity: suggestive history (typical symptoms and time interval; reaction <1 h after drug exposition or <2 h for NSAID) confirmed by detection of a culprit drug with ≥1 positive diagnostic result;
2. Probable immediate hypersensitivity: suggestive history without identification of culprit drug. (Eg other causes excluded, skin tests/specific IgE negative and DPT not feasible);
3. Non-specific mast cell degranulation: suggestive symptoms of mild cutaneous symptoms, negative diagnostics;
4. Hypersensitivity unlikely: uncharacteristic history without identification of culprit drug;
5. Idiopathic angioedema: isolated angioedema without identification of culprit drug;
6. Other diagnosis: NSAID-exacerbated disease (NERD) or transfusion-related acute lung injury (TRALI).

This study was approved by the Medical Ethics Review committee [protocol number 14-478/C]. Exemption regarding obtaining informed consent was granted according to the GDPR. Two hundred forty-six patients were included (Table 1).

A specific causal agent could be identified (definite immediate hypersensitivity) in 97 patients (39.4%) and was considered probable in another 51 (20.7%) patients. In fifty-eight (23.6%) patients, the reaction was supposedly caused by non-specific mast cell degranulation, whereas in 30 patients (12.2%) an underlying POH was

considered to be very unlikely. In ten patients, an alternative diagnosis could be made, including spontaneous angioedema (n = 7, 2.8%), NERD (n = 2, 0.8%) and TRALI (one patient, 0.4%). In five of the 97 patients with definite immediate hypersensitivity, sensitization of two potential culprits was demonstrated.

TABLE 1 Baseline characteristics of patients with suspected perioperative drug hypersensitivity reactions

	Total N = 246
Patients per centre, no. (%)	
University Medical Centre Utrecht, Utrecht	111 (45.1%)
University Medical Centre Groningen, Groningen	54 (22.0%)
Erasmus Medical Centre, Rotterdam	55 (22.4%)
Saint Antonius Hospital, Nieuwegein	26 (10.6%)
Mean age, years (SD)	47.5 (18.7)
Female sex, no. (%)	159 (64.6)
Children, no. (%)	17 (6.9)
Female, no. (%)	7 (41.2)
History of previous perioperative reactions, no. (%)	33 (13.4)
History of spontaneous urticaria and/or angioedema, no. (%)	16 (6.5)
Reported earlier drug hypersensitivity, no. (%)	33 (13.4)
Diagnostic delay, no. (%)	
<1 month	23 (9.3)
1-2 months	28 (11.4)
2-6 months	91 (37)
6-12 months	56 (22.8)
>12 months	35 (14.2)
Unknown	13 (5.3)
Cutaneous symptoms, no. (%)	
No symptoms	26 (11.3)
Local symptoms	57 (24.8)
Generalized symptoms	133 (57.8)
Only “Anaphylaxis” documented in medical chart	14 (6.1)
Respiratory symptoms, no. (%)	78 (31.7)
Circulatory symptoms, no. (%)	
No symptoms	125 (50.8)
Tachycardia	1 (0.4)
Hypotension	101 (42.2)
Circulatory arrest	7 (2.8)
Only “Anaphylaxis” documented in medical chart	12 (4.9)
Modified Ring and Messmer classification, no. (%)	
Grade I	73 (29.7)
Grade II	107 (43.5)
Grade III	52 (21.1)
Grade IV	7 (2.8)
Unknown	7 (2.8)

Abbreviation: SD, standard deviation.

Key messages

- In 39.4% of patients with a perioperative hypersensitivity reaction the culprit could be identified
- Reactions were most frequently caused by antibiotics particularly cefazoline
- Other culprits include NMBA patent blue dye and chlorhexidine comparable to current literature

Of the 102 causative agents found, antibiotics were the most frequently identified causal drugs with 28.4%, of which cefazolin was the most frequently identified antibiotic (n = 22; 75.9%) (Table 2). Second in rank were NMBAs (20.6%). Almost half of these reactions were caused by rocuronium. The third and fourth most often identified causal agents of POH were patent blue (n = 15; 14.7%) and chlorhexidine (n = 10; 9.8%), respectively.

The 102 causal drugs were most commonly identified by means of a positive skin test (n = 82), positive specific serum IgE (n = 4), or a combination of both (n = 4) (Table 2). DPT were occasionally performed and tested positive in 12 patients, mainly for diclofenac (n = 5).

Since variable diagnostic evaluation of hidden allergens NRL and chlorhexidine may affect the diagnostic yield, we studied whether its evaluation changed over time. Diagnostic tests for NRL were carried out in 65% of the patients, without a significant variation over time and positive results were found between 2002 and 2013. The incidence of chlorhexidine testing on the other hand significantly increased; while testing for chlorhexidine started in 2007 with only 11% of patients tested in 2007–2008, this proportion increased up to 69% in 2013–2014.

We describe the retrospective evaluation of a Dutch cohort of 246 patients with suspected POH. Causative agents could be identified in 97 patients, most frequently antibiotics, NMBAs, patent blue dye and chlorhexidine. These findings are generally consistent with literature, confirming that antibiotics are an important causative agent of POH.[3] It is not surprising that cefazolin and rocuronium were the most regularly identified culprit antimicrobial prophylaxis and muscle relaxant, respectively, since these drugs are also the most frequently described drugs for these indications in the Dutch perioperative setting. The fraction of antibiotics found as culprit drug (28.4%) is comparable to other countries.[4] Reactions triggered by NMBAs were less common, probably due to very limited usage of the cross-sensitizing agent pholcodine in the Netherlands. The proportion of sensitization was comparable to other studies for chlorhexidine (9.8%)[3,5] and NRL (4.9%).[8]

In 39% and 21% of the referred patients, a drug hypersensitivity was definite or probable. These proportions are relatively low compared with literature and are probably partly related to the inclusion of all POH, regardless of the severity grade in this daily practice cohort. If both mild and severe POH are included, the diagnostic yield appears to be around 50%;[4] however, the yield may increase

if inclusions are limited to severe multi-organ reactions.[3] The time period in which this study was performed may also affect the outcomes, since particularly in the earlier years, hidden allergens may have been overlooked and testing of all administered drugs was less advocated.

The strength of this study is the relatively large population, collected from four independent hospitals, and an unbiased inclusion of all patients referred for POH. Centre-specific differences can be seen as a reflection of daily practice. For ≥80% of patients, the diagnostic evaluation was initiated within one year. An estimation of the most likely diagnosis was made for patients in which no causal drug was identified. Hereby, an overview of diagnostic conclusions is given for all patients who are referred for evaluation of POH. Objective criteria for the diagnosis of drug allergy were predefined, and all data were scored by an experienced (dermato-)allergologist. Nevertheless, several limitations should be borne in mind. The

TABLE 2 Overview of detected culprit drugs and diagnostic methods

Culprit drug	Total number	Total percentage	Specific IgE, no.	Positive skin test, no.	Positive DPT, no.[a]
Total number of potential culprit drugs	**102[b]**	**100**	**9**	**86**	**12**
1. Antibiotics	29	28.4		27	2
Cefazolin	22	75.9		20	2
Amoxiciline/clavulanic acid	2	6.9		2	
Amoxicilline	2	6.9		2	
Clindamycin,penicillin, rifampicin	1 Each	Each 3.4		Peni 1 Rifamp 1	
2. NMBA	21	20.6	1	20	
Rocuronium	10	47.6	1	9	
Mivacurium	5	23.8		5	
Atracurium	3	19		3	
Vecuronium	2	9.5		2	
Cisatracurium	1	4.8		1	
3. Patent blue dye	15	14.7		15	
4. Chlorhexidine	10	9.8	6	7	
5. NSAID	5	4.9			5
6. Opioids[c]	5	4.9		5	
Sufentanil	3	60		3	
Remifentanyl	2	40		2	
7. Hypnotics (propofol)	5	4.9		5	
8. Latex	5	4.9	2	4	
9. Colloids	2	2.0		1	1
Hydroxyethylstarch	1	50		1	
Gelatine	1	50			1
10. Local anaesthetics (articaine)[d]	1	1.0			1
11. Proton pump inhibitors (pantoprazole)	1	1.0			1
12. Anti-emetics (ondansetron)	1	1.0		1	
13. Sugammadex[e]	1	1.0		1	
14. Paracetamol	1	1.0			1

All positive results of different diagnostic detection methods are listed in the Table; multiple tests (ie both skin test and specific IgE) can be positive per patient. Drug names and percentages within subgroups are marked in italic script.

Abbreviations: DPT, drug provocation test; NMBA, neuromuscular blocking agent, NSAID, non-steroidal anti-inflammatory drug.

[a]DPT was performed according to the local protocols, consisted of ≥3 incremental steps and were considered positive if consistent objective symptoms were reproduced as based on the interpretation of the attending allergist.

[b]Including five patients with two potential culprit drugs identified.

[c]One patient had two positive ICT for two different synthetic opiates, counted as one culprit.

[d]One patient had two positive ICT for two different local anaesthetics, counted as one culprit.

[e]Patient with indolent systemic mastocytosis.

inclusion time and retrospective design of the study are clear restraints with a high dependency on the information given by the referral. The diagnostic evaluation remains incomplete for hidden allergens even at the end of the inclusion time despite the current recommendation to investigate these allergens in all patients.[6] This may have led to underreporting, although the ranking of occurrence rates for these culprits in our study remains comparable to literature.

Other important limitations are the lack of tryptase measurements, which are strongly advocated and nowadays better implemented in clinical practice, and a lacking gold standard (DPT) in many cases which potentially leads to incorrect interpretation of (false) positive skin tests for certain agents such as propofol and atracurium. This restriction is not unique to our centres and affects the results of many studies. For optimal data, we rely on initiatives such as the Danish Anaesthesia Allergy Centre, where anaesthesiologists and allergists have joint forces in collaborative anaesthesiology and allergy units where these high-risk DPT can be performed.[9]

In conclusion, the evaluation of patients with POH in the Netherlands reveals similar results as other European clinical studies on this subject, showing a diagnostic yield of 39% with antibiotics, NMBAs, patent blue dye and chlorhexidine as the most commonly identified culprits of POH.

KEYWORDS

anaphylaxis, drug allergy, drug hypersensitivity reaction, general anaesthesia, perioperative

ACKNOWLEDGEMENTS

The authors thank Myrthe Purmer for her indispensable contribution to data collection, data analysis and drafting the first version of the manuscript.

CONFLICT OF INTERESTS

H.N.G. Oude Elberink's institution has received consultancy fees from ALK-Abelló. H.N.G. Oude Elberink has received fees for delivering lectures from Chiesi, ALK-Abelló and Meda, has received consultancy fees from ALK-Abello, has received research support from Novartis, MEDA Pharma, Mead Johnson, ALK-Abello, Shire and Chiesi and has received payment for developing educational presentations from ALK-Abello. H. Röckmann is a member of the national advisory board Novartis, has received research support from Novartis and Pharming. The other authors declare that they have no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors aided in the design of the study, manuscript, tables, figures and reviewed the article. HOE, VN, MvM, RT and HRH contributed to acquisition of data and design of statistical analysis. AvdV performed analyses and drafted figures and tables. AvdV and HRH drafted the article, which was then revised and given final approval of the version to be published by all authors. All authors read and approved the final manuscript.

FUNDING INFORMATION

No funding was provided for this study.

Annick A. J. M. van de Ven[1]
Joanne N. G. Oude Elberink[1]
Vera Nederhoed[2]
Maurits S. van Maaren[3]
Ron Tupker[4]
Heike Röckmann-Helmbach[2]

[1]*Department of Internal Medicine and Allergology, University Medical Centre Groningen, Groningen, the Netherlands*
[2]*Department of Dermatology and Allergology, University Medical Centre Utrecht, Utrecht, the Netherlands*
[3]*Department of Allergology, Erasmus Medical Centre Rotterdam, Rotterdam, the Netherlands*
[4]*Department of Dermatology, St Antonius Hospital, Nieuwegein, the Netherlands*

Present address

Vera Nederhoed, Geriatric medicine, Axioncontinu Utrecht, Utrecht, the Netherlands

Correspondence
Dr. Heike Röckmann-Helmbach, Department of Dermatology, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.
Email: H.Rockmann@umcutrecht.nl

ORCID

Annick A. J. M. van de Ven https://orcid.org/0000-0001-7032-9571

REFERENCES

1. Mertes PM, Ebo DG, Garcez T, et al. Comparative epidemiology of suspected perioperative hypersensitivity reactions. *Br J Anaesth*. 2019;123(1):e16-e28.
2. Tacquard C, Collange O, Gomis P, et al. Anaesthetic hypersensitivity reactions in France between 2011 and 2012: the 10th GERAP epidemiologic survey. *Acta Anaesthesiol Scand*. 2017;61(3):290-299.
3. Harper N, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th national audit project (NAP6). *Br J Anaesth*. 2018;121(1):159-171.
4. Lobera T, Audicana MT, Pozo MD, et al. Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. *J Investig Allergol Clin Immunol*. 2008;18(5):350-356.
5. Opstrup MS, Malling H-J, Krøigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy–a large single-centre evaluation. *Allergy*. 2014;69(10):1390-1396.
6. Garvey LH, Ebo DG, Mertes P-M, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. *Allergy*. 2019;74(10):1872-1884.

7. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy*. 2002;57(1):45-51.
8. Blaabjerg MS, Andersen KE, Bindslev-Jensen C, Mortz CG. Decrease in the rate of sensitization and clinical allergy to natural rubber latex. *Contact Dermatitis*. 2015;73(1):21-28.
9. Garvey LH, Ebo DG, Krøigaard M, et al. The use of drug provocation testing in the investigation of suspected immediate perioperative allergic reactions: current status. *Br J Anaesth*. 2019;123(1):e126-e134.

How to cite this article: van de Ven AAJM, Oude Elberink JNG, Nederhoed V, van Maaren MS, Tupker R, Röckmann-Helmbach H. Causes of perioperative hypersensitivity reactions in the Netherlands from 2002 to 2014. *Clin Exp Allergy*. 2021;00:1–5. https://doi.org/10.1111/cea.14042