

Case Report

Anaphylaxis to ethylene oxide – a rare and overlooked phenomenon?

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Spina bifida patients have been reported to be at increased risk of anaphylactic reactions during general anaesthesia. Following a reaction, latex is often incriminated as spina bifida patients are known to have an increased incidence of latex allergy. Ethylene oxide (EO) has recently been suggested to be an alternative cause, but in many cases reported in the literature, it seems that EO has not been considered as a cause. EO is a highly reactive gas widely used to sterilise heat-sensitive medical devices, and traces of EO can be found in many of the same products as latex.

We present the case of a spina bifida patient with a known latex allergy, where EO was found to be the cause of an anaphylactic reaction during general anaesthesia. In addition, we describe measures taken during preparation

of a subsequent general anaesthesia to minimise exposure to EO.

Spina bifida patients seem to be at increased risk of sensitisation against EO due to repeated exposure, but only limited literature is available. To ensure that EO is considered as a cause in these cases, we recommend that testing for latex and EO go hand in hand following an anaphylactic reaction in this high-risk population.

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ETHYLENE oxide (EO) is a highly reactive gas, widely used for sterilising heat-sensitive medical devices.¹ A few cases of anaphylaxis to EO are reported in surveys concerning allergic reactions during anaesthesia.^{2,3} Poothullil was the first to report sensitisation, defined as presence of IgE antibodies against EO, in patients undergoing chronic haemodialysis.⁴ This discovery led to a change from using EO in the filters and tubing used in haemodialysis.⁵ Later, allergic reactions to EO have been reported in patients with spina bifida.^{6–8} This population frequently has extensive exposure to EO during repeated surgical procedures, often starting shortly after birth.

Case report

In 2009, a 21-year-old male, born with spina bifida cystica with meningocele and hydrocephalus, was referred for investigation at the Danish Anaesthesia Allergy Centre following suspected

anaphylaxis during anaesthesia. He had a ventriculoperitoneal shunt inserted at birth and had undergone multiple orthopaedic, urologic, and gastric operations, all in uneventful general anaesthetics. His latest uneventful operation was replacement of the ventriculoperitoneal shunt 3 months prior to referral to the Danish Anaesthesia Allergy Centre. He was non-atopic but diagnosed with latex allergy at the age of 15 years. As a result of neurogenic bladder, he practices daily self-catheterisation with latex-free catheters.

Due to formation of a subdural hygroma following shunt replacement, he was scheduled for an evacuation during general anaesthesia in a latex-free environment. General anaesthesia was induced and maintained with propofol and remifentanyl. Rocuronium was used for neuromuscular blockade. Chlorhexidine was used as a disinfectant, and local infiltration with bupivacaine was applied. Infusions of dicloxacillin and hydroxyethyl starch were started, and the surgical staff had begun sterile

draping, when a sudden severe hypotension (44/23 mmHg) combined with tachycardia (125 beats per minute) was observed. Ephedrine and phenylephrine had no effect. Due to flushing, an anaphylactic reaction was suspected, and only after volume resuscitation and three intravenous injections of adrenaline 0.02 mg, the circulation was stabilised. Antihistamines and steroids were administered and after an observation period, surgery was completed uneventfully. Initially, the reaction was thought to be caused by exposure to a cushion under the patient's legs, which possibly contained latex. A blood sample taken 80 min after the event showed elevated serum tryptase at 57.2 µg/l (baseline value 6 weeks later 16.9 µg/l), highly suggestive of anaphylaxis.

Investigations at the Danish Anaesthesia Allergy Centre using skin testing, IgE antibody testing, histamine release test, and provocation tests, as appropriate for the individual allergens, were negative for propofol, remifentanyl, rocuronium, chlorhexidine, bupivacaine, dicloxacillin, and hydroxyethyl starch. As expected, skin prick test and histamine release test were positive for latex. IgE antibodies against latex was only slightly elevated at 0.63 kU_A/l (<0.35 kU_A/l), and unexpectedly, IgE antibodies against EO was highly elevated at 35.8 kU_A/l (<0.35 kU_A/l – ImmunoCAP, Phadia AB, Uppsala, Sweden). A histamine release test (Reflab, Copenhagen, Denmark), performed as previously described,⁹ was positive for EO.

Subsequent surgery and anaesthesia to re-insert a ventriculoperitoneal shunt was carried out in a latex-free environment, but reducing exposure to EO proved a time-consuming challenge. We procured syringes, surgical drapes, surgical equipment, and intravenous catheters sterilised without EO. Some of the medical devices, such as the intra-arterial catheter and infusion lines, could not be

procured non-EO sterilised. For the latter, we used almost expired medical devices, opened them 24 h prior to the operation, irrigated them with warm sterile saline, and left them in a well-ventilated room, covered with a steam-sterilised drape, until use. Most importantly, a gamma-sterilised gravity-assisted valve shunt (Christoph Miethke GmbH & Co, Potsdam, Germany) was implanted to avoid prolonged EO exposure. With regard to the endotracheal tube, we chose a clean one which was not sterilised. The patient was pre-medicated with antihistamines and steroids, and no reaction occurred during, or after, the procedure.

Discussion

It has been reported that patients with spina bifida have a risk of anaphylaxis in the operating room of 7% per procedure, which is significantly higher when compared to a population of non-spina bifida patients.¹⁰ Therefore, the spina bifida population represents a challenge to the anaesthesiologist both pre-operatively and in the case of an anaphylactic reaction.

In the present case, a patient with spina bifida, and known latex allergy, had an anaphylactic reaction during surgery despite a latex-free environment. Subsequent investigations showed highly elevated levels of IgE antibodies against EO and negligible change in IgE antibodies against latex.¹¹ This increases the suspicion that the reaction was caused by EO. A literature review reveals very few other cases where EO has been suspected to be the cause of anaphylaxis during surgery in spina bifida patients and the problem is likely to be rare (Table 1).

In a controlled retrospective study of a spina bifida population, Pittman et al. found a prevalence of IgE antibodies against EO of 17/75 (23%) and

Table 1

Reports of anaphylactic reactions in patients with spina bifida due to ethylene oxide.

Authors	VP shunt	EO tests			Latex tests			EO as the cause (AC)
		SPT	IgE	HR	SPT	IgE	HR	
Moneret-Vautrin ⁶	?	+	+	N/A	+	–	N/A	Yes
Moneret-Vautrin ⁶	?	+	–	N/A	+	+	N/A	Possible
Moneret-Vautrin ⁶	?	+	+	N/A	+	+	N/A	Yes
Demontoux ⁸	?	Prior allergy known to EO, other causes excluded, no testing described						Yes
Goeters ⁷	Yes	N/A	+	N/A	+	+	N/A	Yes
Present case	Yes	N/A	+	+	+	+	N/A	Yes

VP, ventriculoperitoneal; EO, ethylene oxide; SPT, skin prick test; IgE, IgE antibody test; HR, histamine release test; AC, author conclusion; N/A, not available; ?, not reported.

against latex of 44/75 (59%). Interestingly, 15 of the 17 (89%) with IgE antibodies against EO also had IgE antibodies against latex. Based on these data, it could be speculated that one-third (15/44) of spina bifida patients with latex allergy are sensitised against EO. Sensitisation against EO increases the risk of a clinical reaction on exposure to EO, but the relative few cases reported suggest that in most cases, surgery and anaesthesia are uneventful despite exposure to EO in sensitised patients.¹¹

In the literature, however, we found several reports where authors, without describing exclusion of EO as the cause, conclude latex to be the cause of anaphylaxis during anaesthesia in patients with spina bifida.^{12–15} Some patients even had surgery in latex-free environment, but, still, the conclusion was that accidental latex exposure might have occurred.^{14,15} Some of these cases could potentially have been due to EO, and thus, the scale of the problem is likely to be underestimated.

While ensuring a latex-free environment during anaesthesia has become easier, as many companies now produce latex-free utensils, avoiding EO represents a real challenge. EO sterilisation is the preferred method when it comes to medical devices such as infusion sets, syringes, intubation equipment, surgical drapes, gowns and gloves, and many implantable utensils such as ventriculoperitoneal shunts, dialysis catheters, and stents.

Thus, it is important, at an early stage, to identify patients where avoidance of EO during surgery is necessary to avoid a clinical reaction. Unfortunately, limited knowledge is available in this area, and thus, recommendations are based on a few retrospective studies and case reports.

In the few patients who have had clinical reactions attributed to EO, avoidance of EO-sterilised equipment should be attempted, if at all possible, or at least kept to a minimum. Our efforts to reduce EO content in the EO-sterilised medical devices were based on the findings that removal of EO from a plastic material is increased with increasing temperature.¹⁶ Furthermore, diffusion of EO from the device is increased by irrigation with saline and aeration of the device by removing plastic wrapping.^{16,17} However, the benefit of reducing EO concentrations through these rinsing procedures should be balanced against the increased risk of microbiological contamination. As an EO-free environment is virtually impossible to achieve, we recommend that the patient be pre-treated with antihistamines and steroids. Possible symptoms and signs of anaphylaxis should be anticipated during the procedure, as

prompt treatment with adrenaline will improve the chance of a good outcome.¹⁸

In patients with IgE antibodies against EO but no clinical reactions, care should probably be taken to minimise EO exposure especially during large procedures, which lead to extensive cumulated exposure from many utensils at the same time. A higher incidence of IgE antibodies against EO has been found in spina bifida patients¹¹ and dialysis patients,⁵ and advice should probably be limited to these categories of patients for the time being. Some studies suggest that prolonged and/or repeated exposure may increase the risk of reactions.^{10,11} Lastly, it may be that implantation of EO-sterilised utensils increases the risk of sensitisation in exposed patients, and of clinical reactions in already sensitised patients.¹⁹ However, this remains speculative and will have to be the subject of future studies.

Isolating the allergen causing an anaphylactic reaction in the operating room is a major challenge. In some cases of anaphylaxis, the attending personnel, on speculative grounds, incriminate the most obvious allergen, thereby missing less obvious, but important, allergens such as latex, chlorhexidine, and EO. This should be discouraged, as wrong guesses on potential allergens increases the subsequent risk to the patient.²⁰ In this context, the widespread use of EO, but relatively limited knowledge about its allergenic potential, means that reactions to this compound can go unnoticed. This may increase the risk of further reactions on future exposure during surgery and anaesthesia. Therefore, we suggest that patients with suspected anaphylaxis during anaesthesia should always be referred for investigation in specialist centers, and that investigation of patients with spina bifida should always include EO as well as latex.

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