Iodine and chlorhexidine allergy in daily anesthetic practice:

Case report and literature review

Case Report

A 52 year, male patient is referred for removal of total knee artroplasty under general anesthesia. Removal is indicated because of low grade infection. The patient has a history of contact dermatitis on povidone iodine (Coombs and Gell classification type IV, antibody independent). At the preoperative consultation the man refers to this as being "iodine allergic". He has no history of atopy or anaphylactic reactions (Cooms and Gell classification type I). The initial total knee replacement occurred under combined spinal epidural anesthesia, postoperative insertion of a urinary catheter using chlorhexidine containing lumbrificant was uneventfull.

Premedication consisted of 1mg oral midazolam. General anaesthesia was induced with sufentanyl 15µg, propofol 180mg and rocuronium 50mg and was maintained with sevoflurane 2% in 40% oxygen. No antibiotics were given. An endotracheal tube was placed. After placing the patient in Trendelenburg position and disinfection of the skin with chlorhexidine 0.5% in alcohol 70%, a central venous line was placed. At the same time a urinary catheter was inserted after application of 11mL of intraurethral Instillagel® (CliniMed, High Wycombe, UK). Its active ingredients include 0.25% chlorhexidine. After urinary and central venous catheterization the patient was placed back into neutral position. At that point the anesthesiologist observed a hemodynamic collapse with an arterial pressure of 52/23 mmHg, tachycardia to 180 beats min^{-1} and oxygen saturation dropped to 85%. A generalized erythematous rash without urticaria was observed. There was immediate administration of 100% oxygen, 100µg epinephrine (titrated per 10µg), ranitidine 50mg, promethazine 10mg and 100mg hydrocortisone. Al medications were given IV.

Ten minutes later his arterial pressure had returned to preoperative levels (140/79 mmHg) with a heart rate of 103 beats min^{-1}. Following stabilization, the patient was transferred to the recovery room and surgery was cancelled. The rash disappeared over a few hours. The patient remained hemodynamically stable during recovery. He was extubated two hours after surgery was stopped without any respiratory compromise. No sequelae were observed or mentioned by the patient during the next anesthesia consultation, two months later.

Serum mast cell tryptase levels where measured 10 minutes after the start of the hemodynamic collapse and the next day. The first sample showed a level of 33.8 µg/L (normal under 11.4µg/L). The sample taken on the next day showed a normal value of 5.1 µg/L. On the day of surgery total IgE was normal, but serum specific IgE to chlorhexidine revealed a positive result (0.65Ua/mL, normal <0.10Ua/mL). Serum specific IgE to the other drugs administered intra-operatively, supplemented with latex, ethyleenoxide and pholcodine were negative. Skin prick tests and intradermal tests were performed 4 days after this anaphylactic event. Both were positive for chlorhexidine and negative for the administered drugs. Because povidone –iodine was used during surgery, there was no determination of specific IgE to povidone and this substance was not included in the skin prick tests.

After three months surgery was repeated. Induction of anesthesia occurred again with 15µg sufentanil, 180mg propofol and 50mg rocuronium. The antiseptic that was used for skin disinfection was a chloramine (sodiumhypochlorate) containing solution (Dakin Cooper ®, Cooperation Pharmaceutique Francaise, Cedex, France). Urinary catheterization was not performed. Anesthesia and surgery were performed uneventfully.

Discussion

Hypersensitivity

Hypersensitivity is a very general term, which includes all objective reproducible reactions, triggered by exposure to a defined stimulus that does not cause response in normal subjects. Drug allergies can be divided into allergic hypersensitivity, when there is an immunological release of histamine. Humoral immunity is responsible for the direct release of histamine via IgE and causes immediate reactions, where lymphocytic activation causes late-onset reactions. Allergic reactions have to be distinguished from non-allergic reactions in which histamine is released by direct activation of the mast cells and basophiles. Anaphylaxis is an immediate hypersensitivity reaction (allergic or non-allergic) that is potentially life-threatening for the patient. Because of the major importance of immediate reactions in anesthesiology, in the next sections these anaphylactic reactions will be discussed more extensively than the late-onset reactions.

"Iodine allergy"

"Iodine allergy" is a terminology used daily in medical practice, although there is no clear corresponding definition in the literature. The absence consensus on this issue sometimes leads to confusions and misconception about a patient's allergy. In anesthesiological practice the so-called "iodine allergy" is frequently mentioned in the context of povidone-iodine, contrast media and seafood.

Contrast media

The iodinated contrast media consist of one or multiple 2,4,6-tri-iodobenzene cycles. Pathophysiological mechanisms of immediate hypersensitivity reactions remain unclear. Complement activation by iodinated contrast media is observed in vivo and in vitro, direct and immunological histamine release have been proposed.

Furthermore, the allergenic epitope remains unknown[1]. A lot of potential epitopes are proposed, including formation of iodinated serum proteins during irradiation. One of the risk factors of sensitization could be the repeated injections of iodinated contrast media. In fact, the epitope is still not identified for iodine contrast products but does not correspond to the iodine atom[1]. If this were the case, there would be probably cross-reactivity among the different iodinated contrast media, which is very unusual despite their closely related molecular structures. Patients with a previous documented IgE-mediated hypersensitivity to an iodinated contrast medium have been safely injected during subsequent radiological procedures with another iodinated contrast medium that was negative by skin testing.[2,3] In addition, there is no role to contraindicate the use of povidone iodine in patients allergic to iodinated contrast media.

The largest prospective study on the impact of immediate reactions after injection of iodinated contrast media was published in 1990[4]. This multicenter study gathered data of more than 330 000 patients that received an iodinated contrast medium. All the observed clinical signs were collected. The minor clinical signs (no treatment indicated) occurred in 7.9%. They included: nausea, vomiting, heat sensations, flushing, pruritus, hives, coughing, sneezing, chills, palpitations, pain at the injection site, abdominal pain, chest pain etc… These minor signs were distinguished from more severe side effects that were divided into serious, very serious and death. A serious adverse effect corresponded to any symptoms or combination of symptoms requiring treatment: dyspnea, loss of consciousness, cardiovascular collapse. A very serious side effect (0,15%) corresponded to a serious adverse event that required intervention of an anesthetist or hospitalization. There were 2 deaths observed. (2/330000 = 0.0006%). An important

physicochemical feature that determines the risk of an immediate hypersensitivity seems to be the osmolality of the contrast medium.

Delayed allergy-like reactions to contrast media have been reported to occur in 2-4% after nonionic monomers and three to four times more frequently in nonionic dimers.[5] The observed reactions are mainly mild to moderate skin reactions of the maculopapular exanthtematous an urticarial/angioedematous types. Most of the reactions become apparent after a latency of 3 hours to 2 days and disappear within 1 week.[6] The incidence of more severe late-onset reactions is extremely low. There are a few cases reported of fixed drug eruption[7], life threatening late-onset angioedema[8] and fatal Stevens-Johnson syndrome[9]. It should be pointed out that a significant fraction of the cutaneous reactions occurring after contrast medium exposure, are not contrast medium-induced but rather due to other causes such as underlying disease or concomitant use of other drugs.

Povidone-iodine

Povidone-iodine was discovered in 1949 by Shelanski[10] as an agent that resembled plasma proteins but was able to form complexes with iodide en conserves its bactericide effect. He called these substance an "iodophore", literally 'transporter of iodide'. The iodophores are preparations with the following properties:[1]

- They increase the solubility of iodine;
- They are a reserve of iodine;
- They increase the dispersion and penetration of iodine;
- They reduce the equilibrium concentration of molecular unbound iodine

Thus, polyvinylpyrrolidone iodine or povidone- iodine is a complex of polyvinylpyrrolidone and iodine molecules. (Fig 1)

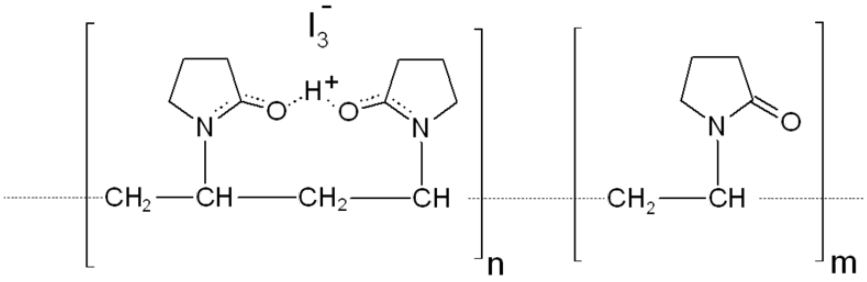

Figure 1: Chemical structure of povidone - iodine

Polyvinylpyrrolidone is the polymer of the vinylpyrrolidone also known as povidone. This is the iodophor or chemical compound in which the active iodine is retained. The majority of iodine molecules are bound to povidone (99.96%) and only a small amount of iodines is present in free form (0.04%). The free iodine is in continuous equilibrium with the complex povidone-iodine. The carrier has no intrinsic antibacterial activity. The epitope responsible for the immediate reactions with povidone iodine seems to be povidone, and not the iodine (free nor bound) as evidenced by the positive skin tests, detection of specific serum IgE by ELISA, but also the positive cellular antigen stimulation test (CAST) with povidone.[11,12,13] The incidence of hypersensitivity reactions with povidone-iodine is not known but appears to be rare in contrast to anaphylactic reactions reported with chlorhexidine or iodinated contrast media. Immediate immunological reactions to povidone-iodine (either urticarialor anaphylactic) are considered exceptional.[14] Since the 1980's only 8 cases have been published with anaphylactic reactions to povidone-iodine. According to the Ring and Messmer four-step grading[15] scale two cases involved a grade IV reaction[16], including one case in a child[17] , 3 cases described a grade III reaction[18,19,20]. The low allergic potential of povidone-iodine is known since the 1960's. Povidone –iodine was used extensively in intravenous or subcutaneous injections, either as a plasma substitute or as a support of some drugs. It never involved an immunological process.[14,21] Allergic contact dermatitis is described as a late-onset reaction to povidone-iodine. It is an uncommon entity and often misdiagnosed by practitioners, who confuse allergy with irritation.[14] Prevalence data of this entity are not published. Clinical features of immediate and late-onset reactions are observed following topical, vaginal or rectal applications.

There are no data to support cross-reactivity between shellfish, iodinated contrast agents and povidone-iodine. Therefore, the only contraindication to povidone-iodine is a previous documented hypersensitivity reaction to this antiseptic. Mind that people who have an iodine allergy will react on povidone-iodine because here (in contrast to contrast media) iodine is in an unbound equilibrium with povidone. But this allergy is extremely rare, if it exists at all. There are no reports of anaphylactic reactions to iodine solutions that have iodine as the only possible epitope (for example iodine tincture)[1].

Seafood

Fish allergens belong to the family of parvalbumins, which are muscle proteins. For cod, the major allergen is Gad c1 (Gadus callarias) also called M protein[22]. This major allergen is common to other fish species allergens. Other

major allergens were identified as Sal s1 (Salmo salar) for salmon, Solea solea for sole etc.[23] The major allergen of crustaceans is tropomyosin, which is also a muscle protein.[24] This allergen seems to be a common allergen in crustaceans and molluscs.[25] There is no cross-sensitization between crustaceans or molluscs and fish. An allergy to seafood does not contraindicate taking an iodinated drug.

Chlorhexidine

Chlorhexidine is a synthetic cationic bis-biguanide antiseptic and disinfectant (Fig 2)[26]

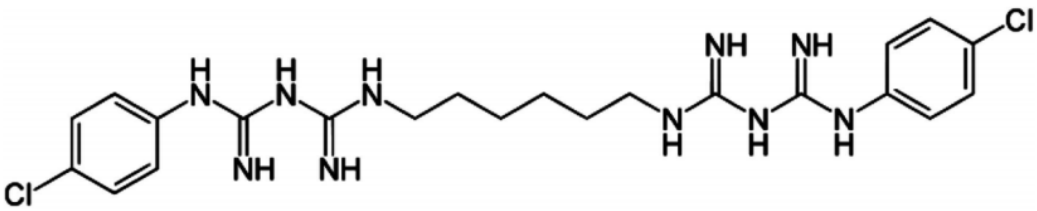

Figure 2: Chemical structure of chlorhexidine

The structure of chlorhexidine has two identical and symmetrical epitopes (figure 2). This double epitope structure of chlorhexidine is thought to bind directly to two IgE's.[26] Chlorhexidine has eliminating effects on gram-positive bacteria and gram-negative bacteria, some mycobacteria ,Candida albicans and some viruses[26]. Introduced in 1954, it has become one of the most widely used disinfectants in medical and non-medical environments. Instillagel® contains chlorhexidine 0.25%, lidocaine 2%, methyl hydroxybenzoate 0.06%, and propylhydroxybenzoate 0.025% formulated as a gel; it is a commonly used antiseptic and anaesthetic lubricant. Chlorhexidine use appears to be increasing. One of the main reasons for this increase is the good evidence that shows that chlorhexidine is more effective in preventing infection as compared with more traditional povidone-iodine solutions. Evidence has been provided for central venous catheterization[27] and clean contaminated surgery[28]. There are an increasing number of reports of anaphylaxis due to chlorhexidine. Chlorhexidine may cause anaphylaxis through the mucosal route at much lower concentration than elsewhere, generally as low as 0.05%. As in our case report reactions are most commonly seen in urological procedures or central line insertion. Exact data are missing, but there can be no doubt that chlorhexidine related anaphylaxis is far more frequent than anaphylaxis with povidone. Patients with severe anaphylactic reactions present with cardio vascular collapse and nearly all patients developed flushing or urticaria at the time of the reaction, while respiratory compromise is almost never reported, patients rarely have a history of

atopic disease, in contrast to patients with latex allergy[26]. Pathophysiological mechanisms that can explain these findings remain unclear.

As most important delayed reaction chlorhexidine elicits allergic contact dermatitis, generally after prolonged and repeated application.[29] People at particular risk of contact allergy are, apart from medical staff, patients with leg ulcers and leg eczema. The increasing use of chlorhexidine may result in rising sensitization rates to this product. Studies have shown considerable geographical variation in sensitization rates. A Swiss study showed that up to 2% of their population are sensitized to chlorhexidine.[30,31] Patients with prior sensitization to chlorhexidine and with relatively mild contact dermatitis have the potential for severe immediate type reactions[14]. Minor allergic reactions (immediate or delayed) may be overlooked or erroneously ascribed to other agents. Subsequent exposure may then lead to severe, immediate and life-threatening anaphylaxis. Furthermore chlorhexidine is liable to a number of rare side effects, such as photosensitivity, fixed drug eruption and occupational asthma, desquamative gingivitis, discoloration of teeth and tongue or distorted taste. Contact with conjunctiva can cause permanent damage, and accidental contact with the tympanum can cause ototoxicity.

Anesthetic policy in a case of suspected allergy to antiseptics

The initial diagnose of anaphylaxis is clinical. It is essential that anesthesiologists are aware of early symptoms because anaphylaxis may progress within minutes to become life- threatening. These symptoms are described according to the Ring and Messmer four-step grading scale (Fig3)[15,32]

Grades	Clinical signs
I	**Cutaneous-mucous signs:** erythema, urticaria with or without angiooedema
II	**Moderate multivisceral signs**: cutaneous-mucous signs +- hypotension +- tachycardia +- dyspnea +- gastrointestinal disturbances
III	**Life-threatening mono-or multivisceral signs:** cardiovascular collapse, tachycardia, or bradycardia +- cardiac dysrythmia +- bronchospasm +- cutaneous-mucous signs +- gastrointestinal disturbances
IV	**Cardiac arrest**

Figure 3: Clinical severity scale of immediate hypersensitivity reactions adapted from Ring and Messmer [15,32]

From the moment anaphylaxis is clinically suspected, one should immediately apply the following measures: (1) withdraw the suspected culprit drug; (2) maintain the airway with 100% oxygen; (3) provide early administration of epinephrine in case of grade III or IV reactions; (4) start fluid therapy (4) call for help, especially for grade III and IV reactions; (5) place the patient in Trendelenburg position; (7) stop or abbreviate the surgical procedure. Corticosteroids and/or H_1 receptor antagonists are often recommended in the management of anaphylaxis,[32,33,34,35] but their effects have never been evaluated in placebo controlled trials[36]. In retrospective studies analyzing recurrent episodes of anaphylaxis, corticosteroids and antihistamines did not prevent biphasic anaphylaxis, indicating that patients should be followed up carefully after apparent remission of anaphylaxis. However, corticoids are useful for angioedema. [32,33] Serum mast cell tryptase levels should be checked within 1 hour of the event and then 2-4 hours and 24 hours or more after the event[26,37]. Checking at three time points increases the sensitivity of the test. Serum specific IgE to povidone and chlorhexidine can also be checked immediately after the reaction. The investigation of drug allergy is complex and all patients with a history of suspected allergy to povidone or chlorhexidine should be referred to an allergist.[26] Skin prick testing to chlorhexidine and povidone is possible to confirm the diagnosis and exclude allergy to other products. Routine testing with chlorhexidine or povidone is not recommended as a negative skin test does not guarantee not having an allergic reaction in the future and the clinical significance of a positive test in the absence of a clear history is uncertain.[26,37] As with all drug allergies, the size of the skin test does not equate to the severity of the reaction.[26,37] A 4- to 6-week delay after the event is required before performing the skin tests to avoid a false-negative test result because of mast cell depletion. [32,33,35]

Conclusion

Although an infrequent topic in anesthesiology, the practical use and adverse effects of iodine and chlorhexidine are of great importance in daily anesthesiological practice. We present a case report of a man facing a severe anaphylactic reaction to chlorhexidine. The man mentioned an “iodine allergy”, an expression that is part of the daily semantic medical vocabulary but does not match any clinical entity. Iodine is not the responsible epitope for allergic reactions in iodinated contrast media nor in antiseptical povidone –iodine solutions, in which povidone is the responsible epitope. Anaphylactic reactions due to povidone-iodine are extremely rare, and most of them are mild. It is uncertain that iodine allergy even exists. It is theoretically possible using povidone-iodine solutions because iodine is there partially unbound. Fish allergens are identified as proteins, the so called M-proteins, so they also have

nothing to do with iodine. Allergic reactions seen with chlorhexidine are far more frequent and severe than those with povidone-iodine. There are many reports of severe chlorhexidine related anaphylaxis. Due to the antiseptic superiority of chlorhexidine there is a surge in health care use of this product. It seems reasonable to question whether this surge causes an increase in sensitization rates to chlorhexidine resulting in a rising number of cases of severe anaphylaxis to chlorhexidine. Diagnosis of peri-operative anaphylaxis to antiseptics can only be made after assembling clinical, laboratory – and skin prick tests. Diagnosis of anaphylaxis is suspected in al clinical way and severity estimated according to the scale of Ring and Messmer. Key points in treatment of anaphylaxis are appropriate administration of epinephrine and fluids. Biologic assessment can contribute to the diagnosis by determing the mast cell triptase and IgE level. Skin prick tests can be performed starting from 2 to 4 weeks after the event. Routine performance of skin prick tests has no clinical relevance.

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