

Case Report

Perioperative anaphylaxis from locally applied rifamycin SV and latex

D. G. Ebo¹, G. Verheecke², C. H. Bridts¹, C. H. Mertens¹ and W. J. Stevens^{1*}

¹Department of Immunology, Allergology and Rheumatology, University Antwerp (UA), Belgium.

²Department of Anaesthesiology, AZ Klina Brasschaat, Belgium

*Corresponding author: Immunologie, Allergologie, Reumatologie, Universiteit Antwerpen, Campus Drie Eiken (T4.01), Universiteitsplein 1, 2610 Antwerpen (Wilrijk), Belgium. E-mail: immuno@ua.ac.be

A patient developed severe anaphylaxis during irrigation of a wound with rifamycin SV. The temporal relationship between application of rifamycin SV, the positive skin test and basophil activation test for rifamycin SV strongly supported diagnosis of anaphylaxis from the locally applied antibiotic. However, after operation the patient had two anaphylactic reactions with pruritus, urticaria and angio-oedema after routine care by a nurse, and these were probably caused by natural rubber latex. This case report has several messages. First, it is not widely appreciated that topically applied drugs and related compounds can elicit life-threatening anaphylaxis. Second, it illustrates patients can present with more than one allergy. Finally, it provides an opportunity to summarize the applications of flow cytometry-assisted quantification of *in vitro* activated basophils in diagnosing the cause of anaphylaxis during anaesthesia.

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'The diagnosis of anaphylaxis during anaesthesia is not straightforward. Identification of the cause is difficult and, too often, not done', is one of the major conclusions of the Editorial 'Anaphylaxis and anaesthesia—all clear now?' published in this Journal.¹ Moreover, it has also been clearly demonstrated an informed guess is not a reliable way of determining the cause of a presumed allergic reaction during anaesthesia and may put a significant number of patients at unnecessary risk.²

Apart from prompt recognition and adequate treatment of the acute episode it is important to determine the agent(s) responsible to avoid subsequent administration. Unfortunately, correct identification of the causative agent(s) can be difficult. First, multiple drugs need to be administered, as no single agent supplies all pharmacological needs. Second, a broad spectrum of different drugs or metabolites can elicit immune and non-immune-mediated pathologies with distinct and sometimes unclear mechanisms. Third, the causative structure (epitope) is frequently unknown. Finally, the result of an *in vitro* or *in vivo* test might not be predictive for the clinical outcome, and challenge tests are hampered by several practical and ethical issues. Consequently, the availability of a safe, quick and reliable assay allowing simultaneous testing of different compounds

would be more than welcome. Ideally, such a test should provide the physician with an instrument that, apart from identification of the responsible compound(s), might also allow assessment of cross-reactivity and tailoring of safe alternatives.

Flow cytometry assisted analysis of *in vitro* activated basophils (basophil activation test: BAT) is based upon quantification of changes in expression of basophilic activation markers after challenge with a specific allergen. These changes can be detected on a single cell basis by multicolour flow cytometric analysis using specific monoclonal antibodies. Since its introduction, the BAT has proven to be a rapid and reliable tool for the diagnosis of different IgE-mediated allergies.³ Ideally, testing should be carried out between 6 weeks and 12 months after the acute event and blood should be handled within 3 h of sampling.

Case report

A 30-yr-old man was referred to our clinic as an outpatient after a severe anaphylactic reaction with profound hypotension, bronchospasm, tachycardia and angio-oedema during general anaesthesia for an arthrodesis. His previous history

revealed postoperative 'urticaria' after surgery 1 year before the current episode. However, confirmation of diagnosis at that time was not attempted. Review of his current anaesthetic report disclosed that the reaction had started 90 min after induction of anaesthesia with cisatracurium, propofol and sufentanil, but almost immediately after irrigation and disinfection of the surgical wound with rifamycin SV. In addition, the postoperative report revealed that at 2 and 6 h after surgery, the patient had a brief episode of pruritus, urticaria and angio-oedema both after care by a nurse wearing natural rubber latex (NRL) gloves.

Laboratory analysis, carried out 6 weeks after the current acute event, showed a normal peripheral blood count, complement profile and normal concentrations of protease inhibitors. Total immunoglobulin E (IgE) was 536 kUa litre⁻¹ and IgE for *Hevea latex* 3.12 kUa litre⁻¹. Specific IgE for succinylcholine, chlorhexidine and ethylene oxide was negative (<0.35 kUa litre⁻¹, Immuno-CAP, FEIA method, Phadia AB, Brussels, Belgium). Skin tests included latex (Stallergenes, Genval, Belgium), chlorhexidine-digluconate 2% in alcohol 70% (prick test, serial dilution 10⁻³ up to 10⁻¹), a serial dilution of 5 neuromuscular blocking agents (NMBAs): succinylcholine (Myoplegine®, 50 mg ml⁻¹), cisatracurium (Nimbex®, 2 mg ml⁻¹), atracurium (Tracrium®, 10 mg ml⁻¹), rocuronium (Esmeron®, 10 mg ml⁻¹) and vecuronium (Norcuron®, 4 mg ml⁻¹), the analgesic sufentanil (Sufenta®, 0.005 mg ml⁻¹) and anaesthetic propofol (Diprivan®, 10 mg ml⁻¹) as well as rifamycin sodium (Rifocine®). Skin prick and intradermal testing was performed according to the recommendations from the Société Française d'Anesthésie et de Réanimation (SFAR).⁴ Briefly, with the exceptions of atracurium (dilution 1/10) and succinylcholine (dilution 1/5), all prick tests were carried out with a non-diluted stock solution. All intradermal tests, except succinylcholine (dilution 1/500) and atracurium (dilution 1/1000) were performed at a 1/10 dilution. All skin tests were negative other than Rifocine® (wheal/flare 10/30 mm, diluted 1/100) and latex (wheal/flare: 3/6 mm).

Flow cytometric quantification of activated basophils was performed with a triple labelling technique using a mixture of anti-CD123-phycoerythrin, anti-human leukocyte antigen (HLA) DR-peridinin chlorophyll protein and anti-CD63-fluorescein isothiocyanate (FITC) antibodies (kindly provided by BD Biosciences, Erembodegem, Belgium). In this technique, basophils are identified as CD123+/HLA DR- cells. Subsequently, within these cells the percentage of activated basophils, that is co-expressing CD63, is quantified (Fig. 1). Results are expressed as the percentage of CD63+ basophils. Apart from negative and positive control stimulation, basophil activation included all NMBA mentioned earlier and NRL, both with known active concentrations and a serial dilution of the antibiotic rifamycin SV in the patient and rifamycin SV in two control individuals that demonstrated a negative skin prick test for this antibiotic (undiluted).

Basophil activation with NMBA induced almost no increased CD63 expression relative to spontaneous expression (<2%). Results of BATs with rifamycin SV are shown in Figure 2. Basophil activation with NRL was 75% (no. <17%⁵).

The timescale of the initial reaction and the application of Rifocine®, and the positive skin test and BAT strongly suggest that the locally applied antibiotic was the causative agent. Rifocine® (active component: rifamycin sodium, CAS 14897-39-3) is a semi-synthetic macrocyclic antibiotic derived from natural rifamycin B that is produced by *Amycolatopsis rifamycinica* sp. Because of its broad spectrum of activity against Gram-positive and Gram-negative bacteria it is used for wound cleaning before closure. Despite this widespread use, anaphylaxis from rifamycin SV is not well recognized.⁶⁻⁹ Nevertheless, in these case reports it is clearly stressed that potentially life-threatening perioperative anaphylaxis does not *per se* need parenteral administration of the drug but might result from topical application.

It is not widely appreciated that patients with perioperative anaphylaxis might present more than one allergy (double or multiple sensitization).⁴ Our patient, also demonstrated an IgE-mediated allergy to NRL which probably accounted for the postoperative reactions. From these data it is apparent that one should always take care to identify all causative agents.

Applications of flow-assisted analysis of in vitro activated basophils in anaesthesia

Neuromuscular blocking agents

Generally, the diagnostic approach of NMBA-induced hypersensitivity reactions starts with appropriate skin tests, currently considered as the 'reference test'. However, the specificity of skin tests, particularly intradermal tests, and the occurrence of false positives may be a concern and false negative results still occur.¹

Evidence has accumulated that flow cytometry can contribute to the diagnosis of anaphylactic and anaphylactoid reactions from NMBA. In a series of 21 patients with definite anaphylaxis from these drugs, the sensitivity and specificity of a CD63 based assay was 64 and 93%, respectively.¹⁰ More recently, comparable sensitivity and specificity data have been achieved in other studies.¹¹⁻¹³ The low sensitivity of BAT in these studies probably results from the heterogeneous populations studied and that thresholds between patients and control individuals were set arbitrary. In our own comparison of 14 patients with skin test proven anaphylaxis from rocuronium and 8 individuals that tolerated administration of rocuronium and demonstrated a negative skin test, sensitivity of the test was 91.7% and specificity 100% (*Allergy*, in press). However, in two patients, the test could not be interpreted because of non-responsiveness of the cells to drug and

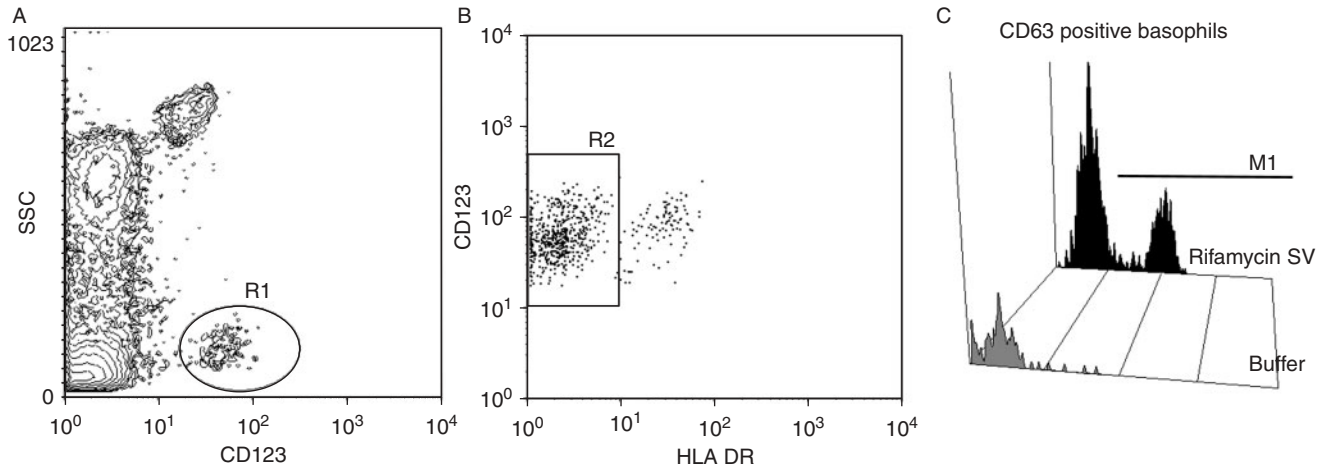


Fig 1 Flow cytometric analysis of basophils selected on a CD123+/SSC gate (R1) (A) and CD123/HLA DR– gate (R2) (B). (C) CD63 expression after challenge with buffer and rifamycin SV. Marker M1 denotes CD63 positive basophils and was set on FITC-conjugated irrelevant isotype control antibody.

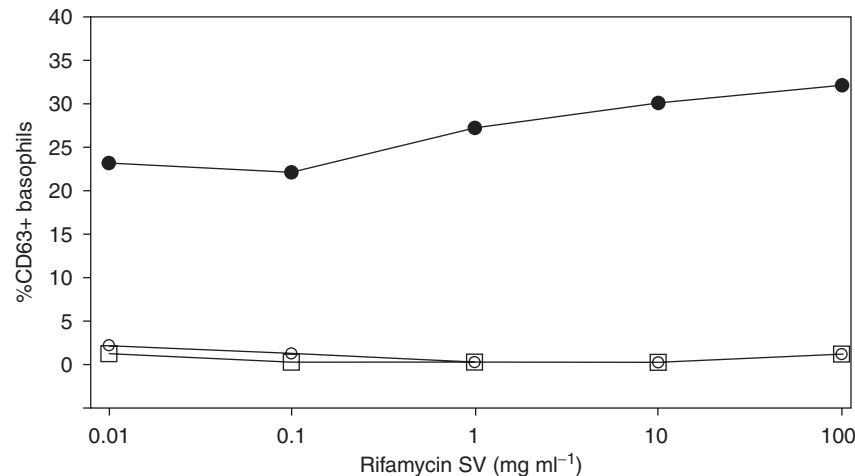


Fig. 2 Percentage CD63 positive basophils in the patient (closed circles) and two controls (open circles and squares) for stimulation with rifamycin SV.

positive control stimulation with anti-IgE. In this study, in accordance with others, flow cytometry proved also very helpful to identify extensive cross-reactivity between rocuronium and vecuronium and to identify cisatracurium as a potential safe alternative. Most importantly, skin tests and the BAT appear clearly complementary in identifying potential clinically relevant cross-reactivity.

Natural rubber latex

In most patients suspicion of allergy from NRL can readily be confirmed by quantification of specific IgE, a positive skin test, or both.¹⁴ However, some patients may need additional testing to establish correct diagnosis. Application of flow cytometry in the diagnosis of NRL allergy was first described by our group.⁵ From this study, it was concluded that the technique is highly sensitive (93.1%) and specific (91.7%).

β-Lactam antibiotics

A third important cause of anaphylaxis during general anaesthesia is antibiotics, particularly penicillin and other β -lactams. In a comparative analysis between quantification of specific IgE and basophilic expression of CD63, in 58 patients with skin test proven β lactam allergy and 30 healthy control individuals, sensitivity and specificity of the assays were 38 and 87%, for IgE, and 50 and 94%, for the flow cytometric test, respectively.¹⁵ Similar results were found by Torres and colleagues,¹⁶ indicating a positive BAT result for β -lactams to be highly supportive of a diagnosis.

Miscellaneous

Anaphylaxis during general anaesthesia can be triggered by a wide range of compounds given perioperatively. Currently, in the absence of appropriate *in vitro* tests, diagnosis

for most of these agents is based upon history, skin tests and particularly exclusion of other possible causes.¹⁷ Flow-assisted analysis of *in vitro* activated basophils has been shown to offer a confirmatory test in anaphylaxis from hydroxyethyl starch, low molecular weight heparins, patent blue, hyaluronidase (review in press, *Allergy* 2006).

Conclusion

Although currently a research tool, flow cytometry assisted quantification of *in vitro* activated basophils can provide the anaesthetist and allergist with a novel diagnostic instrument. The technique allows a safe, quick and simultaneous investigation of different drugs and related compounds. However, comprehensive studies with well-characterized patient and control groups are required to further validate the technique and allow its introduction in mainstream diagnostic application.

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