Diagnosis of Perioperative Adverse Drug Reactions with Cutaneous Provocation Tests

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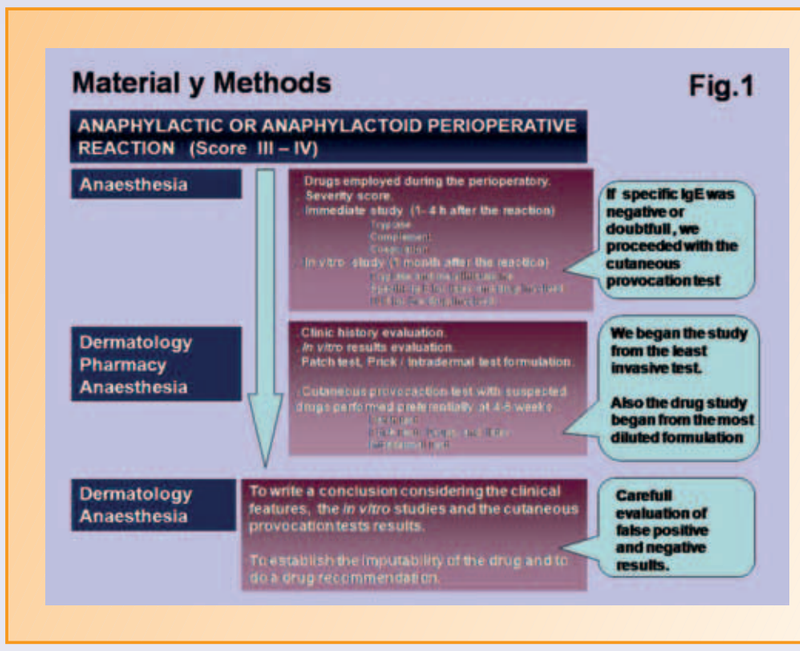
Introduction and objective

The incidence of anaphylaxis and anaphylactoid reactions during anaesthesia has been calculate to range from 1 / 3,500-5.000 to 1 / 13,000-15,000 cases.(1) A 60% of these severe reactions are considered immunologic and a 25% occurs through a direct nonimmune-mediated release of mediators from mast cells and/or basophils or result from direct complement activation. In a prospective work including 20 hospital from Catalonia (Spain) since 1996 to 1997, Escolano et al. registered 1 reaction per 10,263 anaesthetic procedures or 1 reaction per 6,973 general anaesthesias.(2) The identification of the exact drug responsible can be difficult. Many drugs capable to induce anaphylaxia are employed during the anaesthesia induction i.e. muscle relaxants, but also natural rubber latex has emerged as common cause of anaphylaxis during the perioperative act. The etiological diagnosis is time consuming. It requires a huge knowledge of each sensitization drug capacity and an accurate prococation test methodology trying to avoid false positive and negative results.

To show our experience using cutaneous provocation tests in the etiological diagnosis of perioperative adverse drug reactions.

Material and methods

A prospective epidemiological cohort risk study is going on at the "Hospitales del Mar –Esperanza, IMAS". Any severe anaphylactic or anaphylactoid perioperative reaction (score III-IV) started on a multidisciplinary diagnostic protocol. (Fig.1) The Anaesthesia Department registered the demographic data from the patient and the adverse reaction clinical characteristics. Immediately after the perioperative anaphylaxis or anaphylactoid episode, serum determinations and a careful evaluation of drugs probably involved were done. A multidisciplinar team designed an individual "patient per patient" multistep study protocol. Following the experience published previously in the literature cutaneous delayed and immediate provocation test were performed always with the surveillance of the Anaesthesia Department. (3-5).



Results

From 47 patients registered because of a perioperative drug adverse reaction (2004-2007) we could study 20 cases (18 general and 1 local anaesthesia) with cutaneous provocation tests. (Table 1,2) The responsible drug was identified in 17 cases with prick or intradermal testing. Open and occluded patch test was always negative. Drugs involved in the anaphylactic reaction through an immunologic mechanism were metamizole (n=7), diclofenac (n=2), ranitidine (n=1), cisatracurium (n=4), rocuronium (n=3), propofol (n=1), penicilline G (n=1) amoxicillin-clavulanic acid (n=2), ampicillin (n=2), midazolam (n=2), gentamicine (n=1), ondansentron (n=2) and morphine (n=1).

Patient	Clinical Score	Drug involved	In vitro study	Positive CPTest	Comments
AB,J 725...	Urticaria Breathlessness	NSAIs	Not done	ID Metamizol 1:100 ID Diclofenac 1:100	
BB,S 112...	Bronchospasm Angioedema	Local anaesthetic Muscle relaxants	Tryptase 5,7 N Complement : N	ID Bupivacaine 1:100 ID Cisatracurium 1:100000 ID Rocuronium 1:100000 ID Propofol 1:100	Latex negative
CP,L 128	Laringospasm Angioedema	NSAIs	Tryptase: Neg Methylhistamine:Pos RAST:Neg	PT ID Metamizol 1:100	Penicillin allegy Salicylic acid urticaria
DM,J 428...	Anaphylaxia	Antibiotics Local anaesthetic	Tryptase: pos12,5 Methylhistamine: Pos TTL Pos amoxicyline	Negative	Latex : negative Anaphylactoid Reaction
DH, M 204...	Anaphylaxia	NSAIs	Not done	ID Diclofenac 1:100	
F,F 102...	Anaphylaxia	Antibiotics	Tryptase: pos 17,8	PT Penicillin 1:100	Total IgE: 776
FF,F 459...	Anaphylaxia	Antibiotics	Tryptase: pos 40,1 C3 decreased Active Coagulation	PT Amoxicyline 1:100 PT Ampicyline 1:100	
JS ,I801...	Anaphylaxia	Acetaminophen Tramadol Ranetidine	Tryptase : pos	PT Ranetidine 1:100	Fig.2 (6-7)
LL,J 101...	Anaphylaxia	Antibiotics Muscle relaxants	Tryptase: pos	PT Cisatracurium 1:10 PT ID Amoxiciline 1:10	
LM,J 131...	Anaphylaxia	Antibiotics Muscle relaxants Morphine	Tryptase : 6,5 N	ID Atracurium 1:1000 ID Gentamycin 1:1000 PT Morphine 1:100	

Patient	Clinical Score	Drug involved	In vitro study	Positive CPTest	Comments
MB,A 289...	Anaphylaxis	NSAIs	All negative	PT Metamizol 1:10	Total IgE 160
OCh,G 136...	Anaphylaxis	Muscle relaxants Ondasentrom	Tryptase: 3,6 N Rocuronium TLH: positive , > 60%	ID Ondasentrom 1:10⁵ PT Rocuronium 1:10² 1:10⁵ PT Cisatracurium 1:10² 1:10⁵ PT Atracurium 1:10² 1:10⁵	Total IgE: 1759 Latex IgE : 86,7 positive class 5 Fig.2b (8)
PR,I 298...	Anaphylaxis	NSAIs Local anaesthetic Protamine	Not done	ID Metamizol 1:10 ID Protamine 1:10	Protamine immunologic reaction? Fig. 3
SG,J 109...	Anaphylaxis	Antibiotics Local anaesthetic Benzodiacepine	Tryptase : Neg Methylhistamine: Neg	ID Midazolam 5:1000 ID Ampicyline 25:100	Ampicyline was also tested at 1:1000 and 1:10
SS,L 508...	Anaphylaxis	Antibiotics Local anaesthetic Acetyl cisteine	Tryptase 36,9 Methylhistamine :Neg TLH: pos acetylcisteine pos bupivacaine	Negative	Anaphylactoid Reaction
DS,M 315...	Anaphylaxis	NSAIs	Tryptase : Pos	ID Metamizol 1/100.000	TLH interpretation of succinylcholine ?
TF,R 422...	Anaphylaxis	NSAIs	Not done	PT Metamizol 1:10	
TG, M 589...	Skin eruption Bronchospasm	Muscle relaxants Benzodiacepine Ondasentrom	Not done	PT Midazolam 1:1000 ID Rocuronium 1:1000 ID Cisatracurium 1:1000	
VR, P 143...	Anaphylaxis	NSAIs Muscle relaxants Acetaminophen Succinylcholine	Tryptase; 8,8 (N)	PT Rocuronium 1:100.000	

Table 1 and 2. Patients features
PT = Prick Test; ID = Intradermal test; Pos = Positive; Neg = Negative; N = Normal; Normal tryptase values < 13,5 mcg/l; Normal total IgE < 100 KU/L; NSAIs = non steroideal antinflammatory drugs.

Discussion and conclusion

Drug hypersensitivity can be a life threading problem during the perioperatory although the drugs are directly administered by medical specialists following well known protocols. The detailed history is of paramount importance to identify the causing responsible for each reaction. Available in vivo and in vitro test procedures to detect drug hypersensitivity reactions have limitations concerning the technique and the interpretation.

In vitro studies and cutaneous provocation tests (prick and intradermal test) are useful tools for the etiological study of perioperative adverse drug reactions helping to search an alternative drug. A successful etiologic study needs an accurate patient selection, a careful drug registration, a correct timing drug evaluation and a personalized cutaneous provocation test protocol with individualized preparation of the tested drugs at appropriate concentrations.

During this study we found some difficulties with the in vitro test asssessment and the interpretation of some positive intradermal tests. High muscle relaxant dilutions avoided false positive interpretations. For example we found in the same patient, a positive intradermal protamine test that showed just dermal oedema and a positive intradermal reaction to metamizol that showed pathologic changes of hypersensitivity disorders. The mechanism involved in such reactions are obviously different. Because there is not any protamine substitute it was difficult to made a definitive recommendation. (Fig.3).

The first consequence was the elimination of metamizole from the hospital anaesthesia protocols. Anaphylaxia and the anaphylactoid reactions needs further investigation by multidisciplinary and multicentric teams.

Fig. 2. a Positive Prick Test to ranitidine 1:100. (6-7), b Positive Prick test to ondansetron used as antiemetic in a patient with acute urticaria. (8).

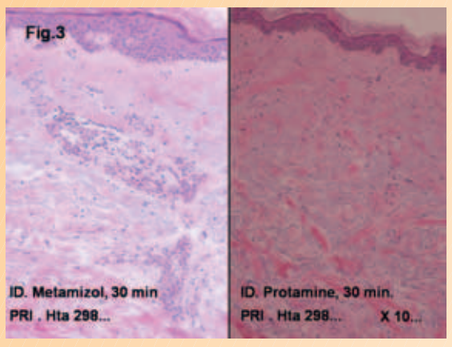


Fig. 3 Intradermal pathology. Lymphocitic perivascular dermal infiltrate with eosinophils induced by metamizol suggesting an hypersensitivity reaction. Nevertheles protamine intradermal test induced a dermal oedema with any inflamatory infiltrate.

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