PRACTICAL METHODS FOR THE RETROSPECTIVE DIAGNOSIS OF A MULTIPLE DRUG INDUCED HYPERSENSITIVITY SYNDROME

- critical review-

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Abstract:
Background: The multiple drug allergy syndrome, in absence of any past allergic history can be explained by the drug hypersensitivity syndrome or drug intolerance. The last is defined as having greater than 3 or more unrelated drug intolerant reactions or drug allergies. Beneath this syndrome usually stands a thyroid or liver dysfunction. Importance of the problem: To clarify the etiology and pathogenity of the multiple and simultaneous allergic and/or non allergic manifestations and find therapeutic alternatives, especially for patients under great surgical anesthetic risk. The diagnostic tests include for immediate allergic reactions, prick tests, intradermic drug tests and speciphic IgE, while for non allergic or for pseudo allergies(food additives), tests of histamin release and basophil activation and degranulating test.

Key words: *multiple drug allergy, perioperative anaphylaxis, sensitivity and specificity, basophil activation test, indolent mastocytosis*

Introduction:

Multiple drug intolerance syndrome is defined as having greater than 3 or more unrelated drug intolerances or allergies. It is more likely to occur with increasing age, as the number of life-time drug exposures increases and can appear in patients with true allergies as have been reported in patients allergic to penicillin and quinolones antibiotics.[1,2]

Drug hypersensitivity reactions (DHR' s) are objectively reproducible symptoms or manifestations caused by exposure to a drug at a dose tolerated by normal persons, immunologically mediated. DHR' s are adverse effects of pharmaceutical formulations(including active drugs and excipients), that clinically resemble allergy.[3]

Multiple drug allergy is a consistent health problem, with serios consequences if diagnosis is misconduct; when drug induced anaphylaxis is added, then the event may be potential lethal.[17]

Patients who have experienced documented anaphylactic reactions from previous operations or patients who have had reactions suggestive of perianesthetic anaphylaxis are the group in whom allergological investigations are mandatory. These patients have the highest risk of developing an allergic reaction, if exposed to specific anesthetic medication. *Of the perianesthetic anaphylactic reactions, 60% are IgE mediated. The guide of the French Society of Anesthesia and Resuscitation (SFAR) recommends the systematic identification of the factors that favor the materialization of a perianesthetic anaphylactic reaction.* An important risk factor is the existence during anesthesia and the preceding clinical signs suggestive of an allergic reaction. *Patients who have experienced allergic reactions to latex in various circumstances or children with multiple surgeries for spina bifida or myelo meningocel have a latex sensitization failure and, implicitly, a higher risk of latex anaphylaxis during surgery. Patients*

diagnosed with an exotic fruit allergy (kiwi, avocado, banana) and chestnuts may have a latex allergy due to the antigenic cross-reaction. A severe peri anesthetic allergic episode in the patient's history is a major risk factor.[14] *An unexplained reaction during anesthesia is also considered a risk factor for peri anesthetic anaphylaxis. Penicillin allergy is a risk factor for penicillin and cephalosporins, and barbiturate allergy is a risk factor for thiopental. Gelatin allergy may promote anaphylactic reactions to gelatin-containing plasma substitutes, and sensitization to metabisulphites (wine preservative) may trigger reactions to preparations containing these substances as excipients, such as vasoconstrictors in local anesthetics. It is claimed that an allergy to eggs and soy may promote the reaction of propofol, which contains lecithins in egg and soy in its vehicle.*[15]

The allergological evaluation for the retrospective diagnosis of drug induced immediate-type hypersensitivity reactions involves a detailed clinical history, prick skin or oral challenge tests, along with speciphic IgE measurements. Still, when anaphylaxis was present, we cannot take the risk and even the patient refuses to take the provocation drug test.The alternative of the last two decades is the functional cellular provocation tests, the basofil activation and degranulation test(BAT). The principle of BAT is to quantify, after the basophils come in contact with the allergen, in this case a drug, the up regulation of certain activation markers on the cellular surface by staining with specific fluorescent monoclonal antibodies. CD63 is a marker relased after provocation, while CD203c is an internal marker of all basophils. The use of BAT allows the rapid confirmation of the previous reaction to the culprit drug (the results can be obtained in less than 3 h) and the avoidance of a second exposure during testing.[16,17] An important aspect is to evaluate corectly the performance of the test BAT, expressed in terms of sensitivity, by dividing the number of patients with positive BAT to the total number of investigated patients, and the specificity, which is calculated by the ratio between the number of controls with negative BAT divided by the total number of healthy controls.

Methods:

The history is sometimes unreliable, when we consider the intra anesthetic hypersensitivity reactions, for several drugs are simultaneously administered*:* neuromuscular blocking agents (NMBA), antibiotics, disinfectants, hypnotics and opioids, local anesthetics or plasma substitutes, and latex products.[16] The most used method to diagnose sensitisation is skin drug testing.[10,11] They still need to be performed in an optimal time frame after the reaction.Testing within 4-6 weeks may give false negative results, asa weel as testing after several years[10], as in our case. The optimal time frame is between 6 weeks to 6 months, and the patient adressed after 5 years postevent, and also, there is the risk of re exposure to the culprit drug, either by skin test or challenge test, thus, the risk of repeating the anaphylaxis, maybe a letal risk.

Since all patient severe reactions involved histamine's discharge, and some of his clinical reactions appeared clustered, we have two possibilities: to suggest mastocytosis as a ground on which the patient strated to develop multiple drug allergies, so we have to check its major and minor criterias, or, to suggest that a sum of immediate-type and/or non immediate-type of hypersensitivity reaction were involved simultaneoulsy, on a ground of neuroimmune syndrome. *To confirm the anaphylaxis, the serum tryptase concentration were the solution, but it has to be measured only on a few hours after the cklinical reaction. There is no agreement on the cutoff value and there can be false negative results in mastocytosis, or sudden cardiac arrest, both conditions that could have been present on the patient's history during his surgery.*

Regarding the dosing of speciphic IgE, they are used to confirm drug hypersensitivity retrospectively, but there are limitations for betalactams, because the tests are altered by

the value of the total serum Ig E[18], *while for NMBA's, speciphic IgE's antibodies were identified in the serum of normal healthy controls, with no clinical reaction upon exposure.*[18, 19, 20]

The patient's first anaphylactic schock was declared to Ceftriaxone, a beta lactam derived cephalosporine class 2, and since we know that after several years after a clinical reaction, the results of skin tests may be negative, and the patient cannot undergo the challenge test, and also the speciphic IgE are not available for Ceftriaxone, we have reccomended to take the BAT test. Most of the studies used for betalactam antibiotics and cephalosporins an optimal SI> 2 and Ba%> 5%, as positive cutoffs. BAT sensitivioty is close to speciphic IgE antibodies, and the use of both tests, when possible, improves sensitivity of drug allergy diagnosis.[17] For other antibiotics, such as quinolones (Tabel 1), the patient described a type I hypersensitivity reaction, with abdominal pain and fainthess, Quincke oedema, so BAT was performed for the retrospective confirmation of his clinical reaction, using the cutoffs identified for beta lactams.[21, 22]

The second patient's anaphylactic schock was to Thiopenthal, an NMBA used in pre and intraoperative surgery. Muscle relaxants are the main cause of anaphylaxis during anesthesia.[17, 23, 24]

For NMBA it is reccomended an optimal SI> 1,76 as the cutoff for positivity, and a SI> 1,85 for Atracurium. There is still among all NMBA' s, the highest degree of variability regarding the positive thresholds. Because anaphylaxis to NMBAs is a real threat, it is wise to establish a sensitive cutoff and also a time frame for testing between 6 weeks and 3,5 years after the clinical reaction tok place, for a higher sensitivity.[17, 25]

The patient experienced possibly a non immediate hypersensitivity-type recation to Ethoricoxib, a COX 2 inhibitor NSAIDs. It is known[17, 26, 27] that NSAIDs are the second group of drugs responsible for anaphylaxis. This class of drugs behaves differently though, because there are several types of hypersensitivities described: an immediate-type is related to COX-1 inhibition, induced by multiple NSAIDs and can display cross reactivity in the same patient for several drugs from this class. And there can also exist a single drug induced immediate-type hypersensitivity, mediated by IgE. Since this is not the mechanism in multiple drug allergy syndrome, there are no speciphic IgE , only the challenge tests, considered the gold standard. But, since the patient developed dyspnoea to Etoricoxib, and he alerady had two anaphylactic schocks, we are not going to do the challenge test. Since BAT sensitivity is low and varies widely, and since up to date, there is no in vitro test to aplly and diagnose all types of NSAIDs hypersensitivity, we can only mention metamizole, that has to be used for BAT in very low concentrations, so the sensitivity is improved.[17, 28]

Taking into consideration all these above, we have reccomended and noted the following results of the patient, mentioning only the pathological.

Lab tests performed: CBC count: anemia, leukocytosis and eosinophilia(14%); hyperthyroidism, investigated immunological and by imaging, with a TSH of 0.5 mg/l (lower limit men 0,35) and paternal antecedents of thyroid dysfunction; H.Pylori present antibodies in 3,38 UI/ml titer, with histological result of the analysis of micro fragments from digestive endoscopic biopsy- hypergastrinemia; intestinal flora analysis indicates a huge E. Coli infestation, suggesting a pro inflammatory intestinal status; total IgE 235,8 UI/l, and high Ig E specific to several drugs(Table nr 2), food and outdoor allergens. A preliminary conclusion of the clinical history, brief investigations and lab results, showed sometimes discordance between BAT, clinical syndromes and specific IgE. Ex: specific Ig E for Ciprofloxacin 0,5 m UI/ml, but immediate-type reaction was present, and Clarithromycine , with Speciphic Ig-E antibodies 0,7UI/ml and BAT >2000. But, for some drugs, there was a real concordance between the high specific IgE antibodies for Thiopenthal, Ceftriaxone and Vitamin group B (>100 mUI/ml), with the BAT results and clinical reactions.

Histamine's serum level 18 times > normal [2,3], a status that needs to be explored with diaminooxidase (DAO) level ; basophil activation test (BAT) was positive for > 54 items(tabel nr 2) ; serum tryptase, which was supposed to be harvest in the first 6 hours after anaphylaxis, is 12 ng/ml. If greater than 20 ng/ml, could have suggested systemic mastocytosis, but for accomplishing the major and minor criteria, we have to proove the detection of a C - Kit point mutation on codon 816 in bone marrow or blood, a annalysis difficult to perform. Since the patient experienced a fix pustular eruption onto the face to Etoricoxib, a delayed- type of hypersensitivity reacvtion, we have performed a lymphocyte transformation test(LTT), which had a positive result, for Famotidine and Etoricoxib(with dyspnea, without wheezing). As a preliminary lab conclusion, the patient developed several types of hypersentivity reactions, immediate and delayed, thus for establishing the risk profile to a future anesthesia, we have proposed the BAT test, with a stimulation index different on class drug and a minimum percentage of activated basophils of 5%.

Table 2 – Basophil Activation Test(BAT) Stimulation Index(SI) and Raw Values for different drugs.

BAT values *(*)SI values*	**BAT values**	**Basophil Activation Test (BAT)** **Max 200**	**BAT values**	**BAT values**
Drugs allowed	Drugs allowed	Drugs allowed	**Forbidden Drugs**	**Forbidden Drugs**
Tramadol 107 *SI> 1,76	Ubistesine 85	Fentanyl 54 SI> 1,76		
Ketoprofen 50	Urografin 106	Dormicum 50	Amplicilline 247 *SI> 2	Celebrex 1852 *SI> 1,5
Augmentin 131 *SI> 2	Fortral 130 *SI> 1,76	Miostin 50	Amoxicilline 271 *SI> 2	Neuromultivit (B_1,B_6,B_{12}) 352
Ofloxacin 150 *SI> 2	Aulin 170	Lystenon 50	Bromazepam 247	Thiopenthal 1725 *SI> 1,76
Zinnat 96 *SI> 2	Flamexin 120	Tracrium 83 *SI> 1,85	Ibuprofen 314	Propofol 272 *SI> 1,76
Arcoxia 50 *SI> 1,5	Indometacin 110	Scopantyl 180	Nexium 1080	Nitroglycerine 235
Tador 93	Cefort 50 *SI> 2	Famotidina 189	Ospen 199 *SI> 2	Captopril 1273
Mydocalm 153	Ceftamil 151 *SI> 2	Alprazolam< 50	Piafen 197	
Xilina 79	Meronem 57	Digoxin 76		
Piroxicam 53 *SI> 2	Gentamicina 50			
Lorazepam<50	Pavulon 50 *SI> 1,76			
Mialgin 50 *SI> 1.85	Calypsol 55			
BAT does not indicate type I reaction	BAT does not indicate type I reaction	BAT does not indicate type I reaction	BAT Indicates a type I reaction or a degranulation of mast cells non IgE	BAT Indicates a type I reaction or a degranulation of mast cells non IgE

BAT: Basophil Activation Test; (*) SI: Stimulation Index

Lab tests and investigations reccomended:

- Skin biopsy, for eliminating the diagnosis of mastocytosis, if present in the dermis and perivascular, in the deeper derm
- Provocation tests for the drugs that have a high BAT value without ever being used by the patient
- Progressive administration for the drugs that have a high BAT and/or have had clinical expression, but cannot be replaced, in order to create a tolerance (eg. Nitrates, Famotidine, Pantoprazole).

Positive Diagnosis:

1. Multiple drug hypersensitivity syndrome
2. Anaphylaxis to Thiopental and Ceftriaxone
3. Chronic Urticaria pigmentosa
4. Hyperthyroidism
5. Hypergastrinemia, H. Pilori(+) in low titer 3,38UI/ml
6. Observation: Indolent minor mastocytosis

Differential diagnosis – Pro's and Con's:
Mastocytosis is sustained by the *PRO's*, 1. generalised urticaria pigmentosa, systemic involvment, headache, tachycardia, hypotenssion, moderate hepatomegaly, persistent rash, Darier sign; 2. Histamine>18 times to normal values;[8] 3. BAT positive score for 54 items. But, after the WHO major and minor criterias, the *CON's* are 1. The lack of skin biopsy, pointing the presence of > 15 masts cells intradermic/perivascullar (Major); 2. There is *no evaluatio*n of the mutation of 816 codon c-kit(mutation related to mastocytosis) in bone marrow/ CD2 or CD25 expression, or of the dismorphism of the mast cells. The fact that we neither do not have the negative or positive minor criterias confirmed, puts the diagnosis of mastocytosis on hold, as "Indolent minor mastocytosis".[8]
The patient's simptoms can suggest also a tumor secreting hormones, such as carcinoid tumor or feocromocitoma; the tests infirmed both and pointed to hyperthyroidism, a heredo -enharited disease from his father. The IgE mediated severe reactions, such as anaphylaxis, can induce high levels of triptase, that decreases within 4-6 hours, also histamine levels, which were 18 times > normal.[6] Same histamine discharges can occur in hypereosinofilic syndromes , mielodisplasic syndrome, mieloid leukemia. All they have been infirmed due to eosinophil's level and blood tests results, hemoleucogramme and C reactive protein, both within normal limits.

Discussions and prognostic:
The general impression of the case and we can extend to other cases in our practice, is the observation that there is quite a disparity for some drugs(eg. Clarithromycine) between the speciphic IgE antibodies, raw values of BAT and clinical reactions. An explanation could be the reaction induced by the culprit drug, nonallaergic but through direct histamin release, or the technical challenges of BAT can be involved, for we acknowledge a wide interindividual variability regarding the density of IgE receptors on the surface of the cells; also, the minimum number of gated basophils is 200, and the population can present variable responses to stimulation. The most reliable supposition for this disparity stands in the fact that using the anti-IgE antibodies during stage two of BAT test, it can stain other cells such as monocytes, eosinophils and dendritic cells, which present IgE receptors on their surface, as well as the fact that anti- IgE and IL-3, both used for priming, can activate basophils in high doses.

Speciphic observation on the case prognostic: For future surgery procedures: the patient has a BAT score for thiopental of 1725, which excludes it's further usage. In this case, a desensitization cannot be done, because of the risk of anaphylaxis to the re-exposure after his first anaphylactic schock to this drug. Reccomandation: volatile aneastetics / opioides, replacement with by Pentazocine or Phentanyl, which have a lower effect on mast cells; premedication.[8] Being

allergic with evident clinical sensitisation to intravenous or inhalatory general anaestetics (Thiopental 1725), but also to inductors of sleep and analgetics (Bromazepam 247, Propofol 272, Piafen 197), this is his major challenge in surgery. The BAT score > 200 for three beta lactam antibiotics, like Ospen (Penicillin V), Ampicillin and Amoxicillin, requires an alternative, of a 3rd or 4th generation of cephalosporines, like Ceftibuten, Cefotaxime, Cephoperazone, Cefetamet, Ceftazidime, Ceftizoxime, Ceftriaxone, Cefixime (gen.III) and Cefepime (gen. IV), or macrolides (in theory).[5] But, for macrolides, even though the patient had never taken this antibiotic, since Clarithromycine has BAT score > 2000, they are forbidden. We are dealing with the hyperreactivity of a patient who had in his past an intoxication with tetracycline. Even if different group of drugs, at the age of 4, it can induce a Multiple Antibiotic Hypersensitivity Syndrome, to other antibiotics having a different chemical structure.[1,2] Tetracicline is a very toxic drug, when taken in a large dose. It accumulates in bones and teeth, gives hepatic and renal failure, even "pseudotumor cerebri", an intracranian hypertenssion syndrome.[3] It is forbidden for children less than 8 years old, therefore we can assume that the accidental intoxication at the age of 3 had a great impact on the imunallergic reactivity of our patient.[4,5] This patient has few therapeutical alternatives for ischemic cardiomyopathy therapy or hypertension, since the BAT score for nitrates being > 250, and the ACE inhibitors will be excluded as a class effect, because the BAT score for Captopril is 1273. Therefore, we have the responsibility to fond alternative or to perform the progressive administration test for nitrates at least. Quinolones are forbidden. Several nonsteroidal antiinflammatories have high BAT values, COX-2 inhibitors, profens, Indomethacin, Nimesulide (Aulin), as well as oxicam derivatives (Piroxicam > 50, Flamexin > 120). Though, even to a 50 BAT score in case of Arcoxia (Etoricoxib), the patient developed acute urticaria and angioedema. The explanation could consist in the fact that the score for another representative of the same class, Celebrex (celecoxib) is 1852, which explains the crossed reactivity to rofecoxib.[4] The local anesthetics, stomatological are also at risk, due to BAT > 85 for xilline; as an alternative is Scandonest III, used with premedication of Prednison and Bilastine/ Levocetirizine.[9] For 31 items, the BAT is between 50-199, an interval considered to be protective for the safe usage and readminsitration of these items.

Conclusions:

The main focus for this patient is to establish a list of "secure" drugs, from each main category of drugs and for surgical procedures, to identify a therapeutic alternative for the irreplaceable drugs, that cannot be readministrated and the compulsory need of testing every each *new* drug on a progressive oral administration.

As a further research plan for future patients experiencing a multiple drug intolerance syndrome, we should take notice that the BAT had no predictive value for every drug tested and that there was a wide variability in the methodology of BAT for drugs, which leads to the conclusion that it has a good specificity, but only moderate sensitivity.

The benefits of combining in vitro tests with the rapid cellular tests, in patients with past severe reactions to multiple classes of drugs is major.

There is an incremental need for building a consensus guideline for BAT standardization.

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Supplemental material: *There are is always a very subtile distinction between conditions that can mime, due to the histamine release, diseases like mastocytosis or an severe allergic status, predisposed to anaphylaxis, while the nonallergic reactions, combined with a dysfunction of internal organs can also be responsable.*