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Anaphylactoid and anaphylactic reactions to iodinated contrast material

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Some adverse reactions to iodinated contrast material (ICM) are considered allergy-like, with cutaneous, cardiovascular, respiratory, and digestive symptoms. Allergy-like reactions are usually unpredictable. Reactions are more frequent with ionic than with nonionic material, but the frequency of deaths is almost identical. In a recent study, 20 severe unexpected reactions to ICM, including 10 life-threatening reactions and one death, were investigated by measuring mediators in blood, within the first minutes or hours of reaction. The responsible ICMs were mostly ionic materials. Histamine and tryptase release correlated with the severity of the reaction. Specific IgE against the responsible ICM was significantly higher in reactors than in controls. A few patients had positive skin tests to the administered ICM, suggesting type-I allergic reaction. Only 2.4% and 3.1% of the cases yielded a positive IgE-RIA, in a second retrospective study which included 165 patients recruited during a 4-year period. In conclusion, IgE-mediated anaphylaxis is rare, but it may be one of the possible mechanisms of severe adverse reactions to ICM.

Some adverse reactions to iodinated contrast material (ICM) are delayed reactions and others are considered anaphylactoid when they are immediate and sufficiently severe to resemble anaphylaxis. In this short review, we shall discuss only immediate allergy-like reactions. The usual signs which suggest allergy are cutaneous: erythema, urticaria, swelling; cardiovascular: hypotension associated with tachycardia, cardiac arrest; respiratory: dyspnea, bronchoconstriction; and digestive: vomiting, abdominal pain, diarrhea (1). The signs may or may not be associated. Allergy-like reactions are usually unpredictable, and their

consequences may be dramatically more serious than the disease which had led to ICM administration.

In IgE-mediated reactions (2), preformed mediators are immediately released, the major one being histamine. Tryptase is released exclusively from the mast cell, and its measurement allows one to distinguish mast-cell activation from basophil (3). The clinical signs may be explained by the direct effects of liberated histamine through its receptors H_1 or H_2 , and are amplified and prolonged by the effects of newly synthesized mediators. Histamine may be released through pathways other than IgE triggering, such as complement activation and direct pharmacologic release (2).

Anaphylactoid and anaphylactic reactions are immediate reactions occurring within minutes of injection. Non-immediate reactions occur usually 6–24 h after injection and have appeared recently with the development of nonionic, dimeric contrast media (4). Their pathogenic mechanism is not yet clearly understood. It may be a cell-mediated mechanism or it may involve a type-III hypersensitivity reaction through immune complexes (5).

The literature usually covers all the immediate reactions, and especially the minor ones, such as pain at injection site, heat sensation, and nausea. These signs appeared with a high frequency when high osmolality, ionic ICM were widely used (6). In the study of Katayama et al. (7), minor reactions were reported during 7.9% of procedures, half of them being heat sensation or nausea, whereas reactions requiring treatment were observed in 0.15% of procedures. Thus, the frequency of anaphylactoid and anaphylactic reactions depends upon the definition of typical signs, and is probably better evaluated from Health Authority surveys (8–10) than from careful examination of successive patients (6). These reactions are more frequent with ionic than with nonionic material (11), but the frequency of deaths is almost identical (7). They appear more frequently in patients who have experienced a previous reaction, and in patients severely allergic to environmental antigens (12). Patients with a previous reaction to ionic contrast material react less frequently when they are administered a nonionic ICM thereafter (13).

To understand the underlying mechanisms of anaphylactoid reactions, two questions have to be answered:

- 1) is histamine responsible for the signs?
- 2) through which pathway and from which cells has histamine been liberated?

Attempts to answer the first question during the 1970s and 1980s led to measurements of histamine *in vivo* after ICM injection, and *in vitro* after cellular challenge with ICM. For

the second question, complement proteins were investigated *in vivo* and *in vitro*, and IgEs were searched for.

Cohorts of successive patients receiving ICM had systematic measurements of plasma histamine and complement fractions. These studies showed increases of histamine and activation of the complement system, in patients experiencing reactions and in patients without reactions, without any significant differences between the two groups (14, 15). However, only minor reactions were observed and very few moderate ones. *In vitro* histamine release was studied with blood from normal volunteers, and was shown to occur in a dose-dependent manner, with contrast media of high or low osmolalities, ionic or nonionic (16). When blood from patients with previous reactions was used, the release was more evident than from nonreactors (17). A study of isolated mast cells from nonreactors confirmed the release of histamine, and demonstrated the release of tryptase, but not release of the newly synthesized mediators, leukotriene C_4 and prostaglandin D_2 (18). Complement activation was shown to take place *in vitro* in controls as well as in reactors (19). These *in vitro* studies suggested a release of mediators, from basophils or mast cells exposed to ICM, probably through the complement pathway, and it was hypothesized that reactions occurred in patients who were particularly sensitive to such mechanisms or particularly reactive to the released mediators.

On the other hand, very few severe reactions were studied. Only one patient with clinical signs requiring treatment showed clearly increased plasma histamine (6). A relationship was suggested between the peak histamine level and moderate reactions (skin and/or digestive signs) (20). A study of total blood histamine concentrations in patients experiencing urticaria or asthma provided indirect evidence of histamine release (21). Urinary methylhistamine was increased in some reacting patients (22). Results of complement fraction measurements were discrepant in different patients (21, 23, 24), indicating that complement activation was not the initiating mechanism in all patients. Some authors found evidence of specific antibodies against ICM in reactors (25), whereas others did not (26). A few patients with severe reactions had positive skin tests to the responsible ICM (27, 28).

In a recent study, 20 severe unexpected reactions to ICM, including 10 life-threatening reactions and one death, were investigated by means of mediator measurements within the first minutes or hours of reaction (29). The responsible ICMs were ionic materials in 18 of the 30 cases. The increase of plasma histamine level correlated significantly with the severity of the adverse reactions. In fact, this study

demonstrated for the first time that mast cells may be involved in the mediator release provoked by ICM, *in vivo*. Mast-cell activation was evidenced by the significant correlation found between the increase of tryptase concentrations and the severity of symptoms. Complement fractions C3 and C4 were not depressed, whereas two patients exhibited anaphylatoxins C3a and C4a increases, suggesting an immune mechanism. Furthermore, specific IgE against the responsible ICM was significantly higher in 18 reactors, compared to controls, and a few patients had positive skin tests to the administered ICM, suggesting type-I allergic reaction (29).

The difference between the results of the latter study and the former ones can be explained by the mode of recruitment of the patients. Formerly, large cohorts of successive patients were investigated, but the frequency of life-threatening reactions was too low to provide an opportunity to observe severe events. Thus, only minor events or a few moderate reactions were studied. As the extent of the liberation of mediators is related to the severity of the reaction (29), it was not possible to detect any significant increases in moderate reaction.

Furthermore, it is likely that minor events proceed through a different mechanism. They appear in a great number of patients, and are preventable by premedication (30). They could be due to nonspecific, pharmacologic, low-level histamine release and correspond to the dose-dependent release found *in vitro* in nonreactors. On the contrary, an IgE-mediated pathogenic mechanism may be responsible for the most severe reactions, such as anaphylaxis, which are very rare and require emergency treatment to avoid sequelae and death. The IgE mechanism could explain the high risk of recurrence of reaction, and the ineffectiveness of premedication in some patients (27, 31). The detection of IgE by *in vivo* and *in vitro* tests should be advised when a severe anaphylactoid-type reaction to ICM has occurred. We have determined the IgE serum level to ioxithalamic acid (Télébrix) and to ioxaglic acid (Hexabrix) in 165 patients recruited during a 4-year period (Table 1) (Jean-Louis Guéant, Farès Namour, Isabelle Aimone-Gastin, unpublished data). These patients exhibited an adverse reaction to ICM. Of them, 130 and 165 were tested for ioxaglic acid and ioxithalamic acid, respectively, and only 2.4% and 3.1% of the patients had a positive IgE-RIA and exhibited severe reaction. Among the seven

Table 1. Seric IgE to ioxaglic acid and ioxithalamic acid by Sepharose-drug IgE-RIA in seven of 165 patients who had immediate allergy-like reaction

Patient no.	Drug	% uptake*	P/C**
1	ioxithalamic acid	16.1	29.3
2	ioxithalamic acid	4.1	4.4
3	ioxithalamic acid	8.1	10.2
4	ioxithalamic acid	2.9	3.3
	plus		
	ioxaglic acid	2.9	3.1
5	ioxaglic acid	10.7	11.4
6	ioxaglic acid	4.1	4.2
	plus		
	ioxithalamic acid	1.4	1.6
7	ioxaglic acid	16.3	10.0
	plus		
	ioxithalamic acid	2.3	1.7

*Percent uptake corresponds to ^{125}I -labeled anti-IgE bound to solid reactive phase incubated with patient sera, as described under methods.

** IgE-RIA was considered positive when percent uptake of tracer was at least twofold higher with patient sera than with control sera.

patients with positive IgE-RIA, three were tested simultaneously for ioxaglic acid and ioxithalamic acid (patients 4, 6, and 7, Table 1). Patient 4 had the same level of IgE detected with the two corresponding solid phases, whereas serum from patients 6 and 7 reacted mainly with the ioxaglic acid solid phase, suggesting specific recognition. This retrospective survey confirmed that IgE-mediated anaphylaxis is rare, but that it may be one of the possible mechanisms of adverse reaction to ICM, as previously reported by Mita et al. (32). A definite answer to the question of the specificity of IgE binding to ICM cannot be given, as systematic complete inhibition could not be reached when performing hapten inhibition of the Sepharose drug IgE-RIA with the soluble drug.

In conclusion, patients with severe reactions to ICM should be investigated by the allergologist, who should proceed to *in vivo* and *in vitro* tests with the responsible ICM and other ICMs, and should always investigate also other drugs possibly administered with the contrast material (33), and look for latex allergy, as latex from stoppers, gloves, and other materials may be responsible for signs as well (34).

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