

ANAPHYLACTIC SHOCK INDUCED BY GADOTERATE MEGLUMINE (DOTAREM®)

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SUMMARY : The use of contrast agent for magnetic resonance imaging improves the effectiveness of this diagnostic examination. Complexes of gadolinium, which appear to be well tolerated, are used for this purpose. A few cases of anaphylactic shock have been attributed to these agents. We report a case of anaphylactic shock due to gadoterate meglumine (DOTAREM®). While undergoing a magnetic resonance imaging examination, a 33-year-old nonatopic female patient became severely hypotensive, lost consciousness, and had generalized erythema immediately after the intravenous injection of this product. She recovered rapidly after she was given injection of epinephrine and her blood volume was restored with intravenous fluids. That DOTAREM® had caused this immediate hypersensitivity reaction was proven by the positivity of prick-test and intradermal test at 10⁻³ (0,37 mg/ml) and in vitro leukocyte histamine release test. The results of these tests indicated that it was the gadoteric acid rather than the meglumine component of DOTAREM® that was responsible: positivity of IDR at 10 mg/ml. Skin tests and leukocyte histamine release test to gadopentetate dimeglumine (MAGNEVIST®) were negative. In addition of the exceptional character, this observation provides evidence for an immediate hypersensitivity without cross reactivity with gadopentetate dimeglumine.

Key-words: Anaphylaxis - Leukocyte histamine release - Gadoterate meglumine - Drug adverse reaction - Drug allergy - Gadolinium-based magnetic resonance contrast agent.

INTRODUCTION

The use of contrast media for magnetic resonance imaging improves the effectiveness of this diagnostic examination. This has led to the use of gadolinium (Gd) complexes which are well tolerated (1). The occurrence of allergic events including anaphylactic shock is exceptional (2-9). We now report a case of anaphylactic shock to gadoterate meglumine (DOTAREM®) where for the first time a mechanism of immediate hypersensitivity to gadoteric acid could be established by skin tests and leukocyte histamine release.

CASE REPORT

A 33 year old woman, houseworker, underwent a cranial magnetic resonance imaging examination to explore difficulty marching that had been progressing over a period of several months. She had no history of

previous allergies. Immediately after the intravenous injection of 100 ml of DOTAREM® (37,69 g of gadoterate meglumine), the patient lost consciousness briefly, had seizures and developed generalized erythema with the complete loss of detectable blood pressure. She was given repeated intravenous bolus of epinephrine conjugated with a large intravascular volume expansion. She recovered completely in one hour. There were no subsequent complications or sequelae.

The investigations were performed one year later. She underwent a series of skin prick-tests (SPT) with a battery of inhalant allergenic extracts including *Dermatophagoïdes Pteronyssinus*, *Dermatophagoïdes Farinae*, *Alternaria*, *Aspergillus*, *Penicillium*, cat epithelia, dog epithelia, as well as timothy, Bermuda grass, birch, mugwort, plantain, cypress, olive and parietaire pollens. None gave a positive response. The prick-test to positive control (codeine phosphate 9%) was positive (wheal of 3mm diameter), the prick-test to diluent control was negative.

SPT with DOTAREM®, gadoterate de meglumine (370 mg/ml) was positive with a wheal of 3-mm diameter surrounded by a slight erythema. SPT were negative in ten controls.

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Intradermal tests (IDT) were performed with a volume of 0.05 ml with 10 fold increasing dilution from 1/1000 of drug to pure. SPT to 10 controls were negatives. An intradermal test (IDT) with DOTAREM® at 0,37 mg/ml (1/1000 dilution) resulted in a wheal 6mm in diameter and erythema 25 mm in diameter. The SPT with gadoteric acid (DOTA-Gd, Guerbet, Roissy, France) was negative while IDT to undiluted DOTA-Gd (10 mg/ml), was positive (wheal 6 mm, erythema 30 mm). SPT and IDT with meglumine (1 mg/ml) and also with MAGNEVIST® (gadopentetate dimeglumine 4 690 mg/ml) were negative.

Leukocyte histamine release was carried out by incubating the patient's blood with each of the above four products separately, using previously described method (10). A positive response was obtained with DOTAREM®, maximum histamine release being 42% at a concentration of 1588 mg/ml, while none of the other products (gadoteric acid, meglumine and gadopentetate dimeglumine) resulted in significant histamine release (less than 5%) (figure 1).

DISCUSSION

The case we report denotes an immediate hypersensitivity mechanism, with DOTAREM®. According to the results of the skin tests, the gadoteric acid but not the meglumine component is responsible. This demonstrates for the first time that IgE mediated anaphylaxis might be caused by DOTAREM®. It is interesting to note that our patient does not present cross-sensitization to gadopentetate dimeglumine, another contrast agent used in magnetic resonance imaging (RMI). The absence of cross-reactivity between DOTAREM® and MAGNEVIST® might be explained by difference in the chemical structures of these two drugs (figures 2 and 3).

In RMI, the image is constructed from a signal emitted by hydrogen atoms spinning in their equilibrium state after having been excited by a given radiofrequency wave. The use of contrast agents improves the signal and consequently the diagnostic power of the examination. These agents are paramagnetic substances, especially gadolinium (Gd), a metallic ion in the lanthanide, or rare earth family (11). In its free form, however, Gd is a strong cell poison. In the first place, at that level it interferes with the calcium exchange involved in myocardial contraction, mitochondrial respiration, coagulation and neurotransmission. Second, it accumulates and can precipitate in the reticuloendothelial system. In order to neutralize these toxic effects and at the same time to retain its desired properties of contrast media for RMI, the GD ion has to be com-

plexed with organic ligand. Four drugs are available. Gadopentetate dimeglumine (MAGNEVIST®) includes diethylene-triamino-penta-acetic acid (DTPA) which linear complexes with GD (Gd - DTPA). Two meglumine molecules neutralize the two free carboxylic groups remaining in Gd-DTPA, thereby forming dimeglumine gadopentetate (figure 2). Gadodiamide (OMNISCAN®) is a second contrast product with a structure similar to that MAGNEVIST, except that it is a derivative of DTPA (the carboxylic groups are replaced by two methylamide groups). More recently, it has been proposed to use macrocyclic complexes such as tetraazacyclododecane tetracetic acid (DOTA) with GD

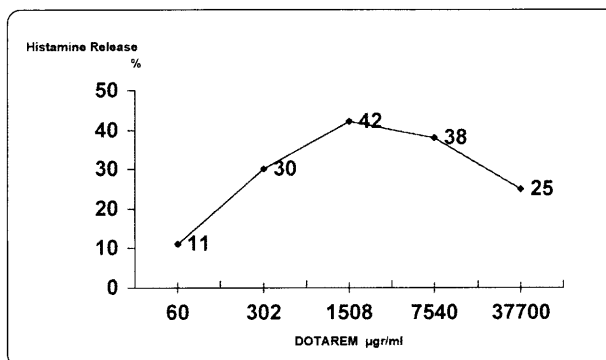


Figure 1 : Leukocyte histamine release test to Dotarem®.

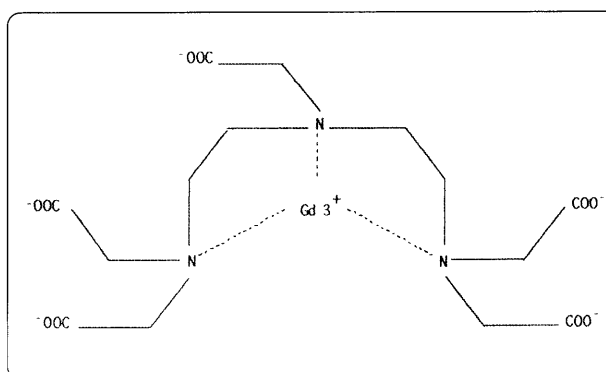


Figure 2 : Structural formula of Gd-DTPA (MAGNEVIST®) (3).

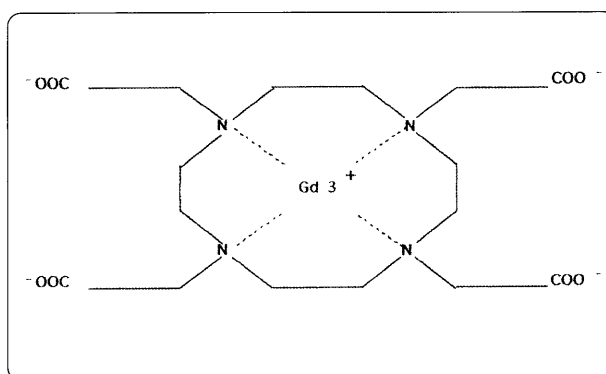


Figure 3 : Structural formula of Gd-DOTA (DOTAREM®) (3).

(DOTAREM®). The shape is a cavity that can contain the Gd ion. The addition of a molecule of meglumine results in the neutralization of the free carboxylic group of DOTA-Gd, forming gadoterate meglumine (figure 3). The fourth molecule, Le Gadoteridol (PRO-HANCE®) has a structure that is similar to DOTAREM®, a carboxylic group of DOTA being replaced by an amide group.

These commonly used contrast media are well-tolerated (12-14). Gadopentetate dimeglumine has been marketed since 1988 and has been the subject of many studies carried out on large series of patients. Whichever contrast agent was used, the secondary effects have almost always been rather minor or moderate (headache, vertigo, local signs at the injection site, bad taste in the mouth, nausea and/or vomiting) and did not interfere with the procedure. In some cases with an underlying neurologic condition, convulsions occurred. Cutaneous reactions (pruritus, urticaria) as well as angioedema and/or bronchospasm have been observed, suggesting either an allergic mechanism (15-17). The incidence of allergic like reaction has been estimated from 0.016% to 0.138% and the frequency of anaphylactoid shock from 0.01% to 0.001% (17, 18). The risk of inducing anaphylactic shock has been estimated at 1 per 200.000 to 450.000 injections (5, 11). A case of death due to gadopentetate dimeglumine is reported (19). According to a multicentric European study that included 4.196 patients, less than 1% had an adverse effect caused by DOTAREM® (20). The role of contrast agents in the induction of symptoms was not always established with certainty (13, 14). A case of life threatening anaphylactoid reaction to gadoterate meglumine has been described (21).

The possibility of inducing IgE antibodies specific for DTPA in animals has been reported (22). Gadopentetate dimeglumine can induce histamine release *in vitro*, as demonstrated with mastocytoma cells (23). It is not very likely, however, that this effect occurs *in vivo* in humans because the concentration in the extracellular fluid, after intravenous injection is 300 less than the experimentally determined histamine-releasing dose. The implication that gadopentetate is the cause of adverse effects *in vivo* is supported by the occurrence of events (cutaneous eruptions, bronchospasm and hypotension) that have been reported to occur after the use in scintigraphy of technetium linked to DTPA (24). A few case of allergic reactions due to DOTAREM® giving an incidence of 0.12% have been reported (20).

The mechanism, by which this patient became sensitized to DOTAREM®, when she had never received it, remains unknown. This was certainly the first time that the patient

had received this drug, which leaves us in the dark about the origin of sensitization. The absence of prior contact with the drug, required for sensitization, occurs more frequently than is realized (25). It is well known for muscle relaxants : 30% of patients who have an anaphylactic reaction to muscle relaxants are undergoing general anesthesia for the first time in their life (26).

These cases document the usefulness of allergological check-up, particularly skin testing in the diagnosis of allergic reactions to gadolinium-based magnetic contrast material. Radiologists must be aware of the possibility of IgE mediated reaction to these agents. Strategies for management of the patients presenting an allergic adverse reaction to gadolinium-based magnetic contrast material have to be developed (18), even if the frequency of these reactions is much lower than that of reactions to iodinated contrast media (27). Planned emergency medical backup is advisable to ensure resuscitation in the event of an anaphylactoid reaction to the use of gadolinium-based magnetic contrast material in-hospital setting.

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PRESS RELEASE

ALLERGY AND ASTHMA NEWS TIPS*

HORMONES IMPROVE ASTHMA AND PULMONARY FUNCTION

■ Positive effects of hormones on lung function and asthma have been observed across the life span in women. Estrogen and progesterone may play a role in strengthening respiratory muscle and increasing relaxation of bronchial smooth muscle, reducing the contractile response - and they exhibit anti-inflammatory properties. (See ACAAI News Release below)

GET KIDS WITH ASTHMA BACK TO SCHOOL, CAREGIVERS BACK TO WORK

■ New study demonstrates the effectiveness of a large-scale asthma management program on pediatric asthma patients and their caregivers. Asthma is the most common medical condition causing absence from school, with 10 days lost per child per year. Lost time from work and decreased productivity of caregivers of asthmatic children primarily accounts for an estimated \$1.2 billion in associated indirect costs. Findings demonstrate that a large-scale intervention program can produce measurable clinical and economic benefits, thereby lessening the burden of asthma on the family.

DUST MITE CONTROL FOR ASTHMA FOUND LAX

■ Johns Hopkins study shows that the parents of dust mite-sensitive, asthmatic children who saw an allergist

demonstrated significantly greater awareness of dust mite allergen control recommendations than those who had not. However, awareness did not translate into action -- no difference was noted in adherence to the practice of dust mite control recommendations between the two groups. Dust mite control behaviors included the use of allergen-proof mattress encasements, pillow encasements, and absence of wall-to-wall carpeting and stuffed animals.

BUCKWHEAT PILLOWS : NEW SOURCE OF ALLERGY ?

■ First known reported case in the United States of a person who developed asthma and worsening allergic rhinitis after exposure to a buckwheat pillow. Buckwheat (*Fagopyrum esculentum*) is a fruit related to the rhubarb plant, sometimes used as a substitute for wheat in foods like noodles, dumplings, cakes, cereals and pancakes. Buckwheat pillows, filled with buckwheat hulls, are marketed as useful treatments for a variety of ailments including headaches, snoring and lower back pain. Manufacturers frequently describe them as being nonallergenic, chemical- and pesticide-free, all natural and longer-lasting than synthetic or feather/down-stuffed pillows. Likely to gain in popularity as an alternative to synthetic pillows, their increased use could increase the risk of sensitization to buckwheat.

* From the American Academy of Allergy, Asthma and Immunology.