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Life-threatening Anaphylactoid Reactions to Propofol (Diprivan®)

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Fourteen patients who had had a life-threatening reaction within a few minutes after receiving propofol (Diprivan®) were investigated for anaphylaxis 4–6 weeks after the incident. Three kinds of immunologic tests were carried out: skin tests (prick tests and intradermal tests with the drugs used and Intralipid®, the solvent for propofol), a leukocyte histamine release test, and a radioimmunoassay (RIA) of immunoglobulin E (IgE) against propofol and muscle relaxants, when they had been given with propofol. It had been previously shown that these were always negative in patients anesthetized with propofol without any complications. Thirteen of the 14 patients had at least one positive test supporting hypersensitivity to propofol; 2 patients had three tests positive; 4 had two tests positive; and 7 had one test positive. The skin tests with Intralipid® were negative in 4 patients whose tests with propofol were positive. Two patients who had been given muscle relaxants at the same time as the propofol had positive IgE-RIA to both drugs. In one patient, results of all the tests remained negative, and the mechanism involved in the reaction remained unidentified. It is noteworthy that 9 patients of 14 had allergic histories that were known before the anesthetic (atopy; allergy to antibiotics, muscle relaxants, lidocaine, colloids) and that none of the patients had ever received propofol or Intralipid® before. It is possible that the IgE that linked abnormally with the propofol had specific binding sites for the phenyl nucleus and the isopropyl groups, which are present in propofol and many other drugs. The hypothesis that these IgEs were anomalous, and, as a result, able to have hydrophobic interactions, is also suggested. These data suggest that anaphylaxis to propofol may occur during its first use, especially in patients with a history of drug allergy. It may therefore be justified to avoid the use of propofol in those rare patients in whom an anaphylaxis to muscle relaxants has occurred. (Key words: Allergy: anaphylaxis. Anesthetics, intravenous: propofol. Immune response: anaphylactoid reaction. Immunology: IgE antibodies. Measurement techniques: radioimmunoassay.)

DURING THE INITIAL animal and clinical studies, propofol in lipid solution (Diprivan®) was thought to be a poor releaser of histamine,[1,2] and not to induce any allergy.[3] It was therefore considered to be a safe drug and had even been suggested for use in atopic and allergic patients.[2,4] In fact, soon after it became available in France, in 1987, we published two cases of severe anaphylactoid accidents involving propofol, one of which was a true anaphylaxis to the drug.[5] Other cases of localized or general erythema occurring in atopic or allergic patients have been published.[6–9] Cases of bronchospasm associated with this erythema have also been reported.[10,¶] Because several drugs, including muscle relaxants,[10,11,¶] are used simultaneously during induction of anesthesia, it is impossible to establish with certainty which drug and mechanism were involved without performing immunologic investigations. We therefore investigated 14 cases of severe life-threatening anaphylactoid reactions that occurred between 1987 and June 1991 and that were thought to involve propofol exclusively. Patients were studied with postoperative tests performed with the commercial emulsion of propofol (Diprivan®) and never with propofol alone. The term "propofol" used throughout this paper will refer to the commercial emulsion, Diprivan®.

Materials and Methods

Fourteen patients, six men and eight women (mean age 41.8 yr, range 12–70 yr), were investigated. They had a life-threatening anaphylactoid reaction in the few minutes following the intravenous injection of propofol alone (6 patients), of propofol and an opioid (2 cases), or of propofol, an opioid, and a muscle relaxant (6 patients).

The search for an immunoglobulin E (IgE)-dependent sensitization to propofol and other associated drugs was carried out 4–6 weeks after the incident. This immunologic assessment consisted in skin tests, the search for specific serum IgE, and, if possible, a leukocyte histamine release test.

SKIN TESTS

These included the prick and intradermal tests. They were carried out in patients who were not taking any drug that might alter skin reactivity, such as antihistamines or

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psychotropic and sympathomimetic drugs. The prick tests were carried out on the anterior aspect of the forearm. They were performed with a drop of undiluted commercial emulsion of propofol and its solvent, Intralipid®. The intradermal tests were performed on the patient's back with propofol and Intralipid®, both diluted to 10^{-3} (1 $\mu g \cdot ml^{-1}$ propofol), 10^{-2} (10 $\mu g \cdot ml^{-1}$ propofol), and 10^{-1} (100 $\mu g \cdot ml^{-1}$ propofol). If a muscle relaxant had been used at the same time as the propofol, it was tested in the same way with the same dilutions. Edematous and erythematous skin reactions were evaluated 15 min later and compared with a positive (codeine) and a negative (normal or phenol saline) control. A prick test was considered positive when the diameter of the edema was at least 50% that of the positive control. An intradermal reaction was said to be positive when the diameter of the edema was $\geq$ 10 mm.

These skin tests had been previously validated in 100 patients anesthetized without incident with propofol: the prick-tests with undiluted propofol were always negative, as well as the intradermal tests carried out with a 1 in 10 dilution of propofol (100 $\mu g \cdot ml^{-1}$ propofol). We therefore felt justified to conclude that these concentrations of propofol did not lead to any nonspecific histamine release. The skin tests are so specific that positive tests can be interpreted as revealing a local IgE-dependent histamine release.

Immunoglobulin E Radioimmunoassay

Specific Immunoglobulin E Radioimmunoassay for Muscle Relaxants

A quaternary ammonium group, which is the common epitope involved in muscle relaxant allergy, was coupled to sepharose as previously described.[12] The quaternary ammonium–sepharose (QAS) was prepared by an ether linkage of choline hydrochloride to galactose units of sepharose. The first steps of the QAS radioimmunoassay (RIA) were similar to those previously described for alcuronium–sepharose and choline–sepharose. Fifty microliters of gel suspension was incubated with 50 μl of serum in duplicate, while shaking, at room temperature for 3 h. The gel was then washed three times with 3.0 ml of 0.15 M sodium chloride and 0.02% of bovine albumin (wt/vol). The gel was incubated with 50 μl of ^{125}I-anti-IgE (Pharmacia) for 18 h and washed again three times with the phosphate buffer described above. The results were expressed as the percentage of total γ-radioactivity that was bound onto the gel. The upper limit of normal results of QAS-RIA was estimated at 2.5%.

Specific Immunoglobulin E Radioimmunoassay for Propofol

Propofol was bound by hydrophobic interaction to phenylsepharose by incubating one volume of propofol with one volume of phenylsepharose suspension and one volume of 0.02 $ml \cdot l^{-1}$ tris/HCl (pH 8.0) containing 1 M sodium chloride for 1 h while shaking. The gel was washed extensively (in 100-fold its volume) with the tris/HCl/sodium chloride buffer and stored in suspension in the same buffer containing 0.02% sodium azide. It was washed again before use. The IgE-RIA was then performed as follows. Fifty microliters of serum was incubated with 50 μl of propofol–sepharose gel for 3 h at room temperature. The gel was washed three times with 2.0 ml 0.02 M tris/HCl buffer containing 1.0 M sodium chloride. Anti-IgE labeled with ^{125}I-iodide (Pharmacia), 40,000 cpm, was added to each tube. The tubes were incubated overnight at room temperature and the gels were washed again three times before γ counting. The detection of specific IgE corresponded to the percentage of uptake of labeled anti-IgE onto the solid phase. In each series, control tubes were prepared in the same way, except that 50 μl of sepharose was used instead of the drug solid phase. None of the controls had more than 0.6% uptake. Inhibition of the propofol-RIA test could not be performed because the solid drug phase was prepared by hydrophobic adsorption of propofol to phenylsepharose.

The results obtained with propofol–sepharose IgE-RIA in 20 controls were 4.4 $\pm$ 1.3%. The upper limit of a normal result was therefore estimated to be 7%. The propofol–sepharose IgE-RIA was also performed in 20 patients before and after anesthesia with propofol. None of these patients had manifested any adverse reaction to the drug. The percentage uptake of labeled anti-IgE on propofol–sepharose incubated with patient sera was estimated at 5.1 $\pm$ 1.5% and 5.4 $\pm$ 1.0% 15 and 60 days, respectively, after the anesthetic. The difference was not statistically significant.

Leukocyte Histamine Release

Patients were fasted and were not taking any drugs. *In vitro* histamine release tests were carried out with whole blood anticoagulated with heparin and immediately assayed in the presence of various dilutions of propofol. Eight dilutions were prepared from the commercial solutions using histamine release buffer supplied by Immunotech® (Luminy, France): 0.5, 0.25, 10^{-1}, 0.5×10^{-1}, 10^{-2}, 10^{-3}, 10^{-5}. One-hundred-microliter aliquots of these dilutions were incubated with 200 μl blood for 30 min at 37° C. The reaction was stopped by placing the tubes in an ice bath. After centrifugation at 4° C, the supernatant was recovered and assayed for histamine using a RIA (Immunotech®) based on the competitive binding of acylated and ^{125}I-acylated histamine to tubes coated with monoclonal antibodies. The detection limit of this RIA has been estimated to be 0.2 nM.[12] Total blood histamine was quantified by freezing 50 μl heparinized blood

diluted in 1 ml distilled water. After thawing, the disrupted cell suspension was assayed for histamine by the usual procedure. Results were expressed as a percentage of total histamine; they were considered as positive when more than 10% of total histamine had been released. Two types of positive results were obtained: dose-dependent or -independent release, the latter giving a bell-shaped curve (IgE-dependent release).

Intralipid Infusion Test

After informed consent of the patients, 15 ml Intralipid was infused for 5 min. Pulse and blood pressure were recorded every minute. A dosage of blood histamine (RIA, Immunotech®) was performed before and after the infusion.

Results

Results are shown in table 1.

Patients

There was clinical skin and mucous membrane involvement in all cases, with various degrees of hypotension and tachycardia (ten cases), cardiac arrest (one case), and

Table 1. Clinical Features and Immunologic Results of the Patients Tested for Reaction Against Propofol

Patient Number	Sex	Age (yr)	Past History	Symptoms	Anesthetics	Cutaneous Tests (Prick − IDT)	IgE-RIA Propofol N ≤ 7.0%	LHR Propofol	IgE-QAS RIA N ≤ 2.5%
1*	M	66	Atopy	Erythema, facial edema, hypotension	Propofol	Prick + Propofol − Intralip. IDT + Propofol 10^{-2} − Intralip.	32%	+	
2	M	22	No	Widespread urticaria, bronchospasm	Propofol	IDT + Propofol 10^{-2} − Intralip.	9.3%		
3	F	33	Anaphylaxis to suxam., (crossed with gallam.)	Erythema, hypotension	Propofol	IDT − Propofol 10^{-1}	13.2%	−	18.5%
4	F	30	No	Erythema, bronchospasm	Propofol	Not done	13.3%		0.4%
5	F	40	Anaphylaxis to suxam. (crossed with pancur., alcur. gallam., vecur.)	Facial edema, bronchospasm	Propofol	IDT − Propofol 10^{-1}	24.2%		48%
6	M	12	No	Urticaria, collapse	Propofol	IDT + Propofol 10^{-2}	2.5%		
7	F	60	Antibiotic allergy, treatment by β-blockers	Erythema, bronchospasm, hypotension	Propofol Dextrom.	IDT − Propofol 10^{-1}	6.9%	−	2.3%
8	F	39	Antibiotic allergy, aspirin sensitivity, atopy	Urticaria, bronchospasm, hypotension	Propofol Alfentanil MLidazolam	Pricks ± Propofol − Intralip. IDT + Propofol 10^{-3} − Intralip.	4.4%		
9	M	64	Anaphylaxis to colloid (gelatin)	Erythema, bronchospasm, hypotension, cardiac arrest	Propofol Suxameth. Pancuronium	IDT + Propofol 10^{-2} − Intralip. −Pancur.	30%	+	
10	F	19	No	Erythema, bronchospasm, hypotension	Propofol Vecuronium	IDT + Propofol 10^{-3} + Vecur. 10^{-2}	10.3%		0.7%
11	F	70	Anaphylaxis to lidocaine, eczema to washing products	Erythema, collapse	Propofol Suxameth.	IDT + Propofol 10^{-2} + Suxam. 10^{-3}	8.8%		18%
12	M	54	Atopy	Erythema, bronchospasm, collapse	Propofol Vecuronium Fentanyl Midazolam	Pricks − Propofol IDT + Propofol 10^{-3} − Vecur. 10^{-1}	4.25%	+	1.4%
13	M	43	No	Erythema, edema, bronchospasm, hypotension	Propofol Vecuronium Alfentanil	IDT − Propofol 10^{-1} + Vecur. 10^{-3}	28.2%		23.5%
14	F	33	Atopy	Erythema, recurrence after reinjection of propofol	Propofol Vecuronium Midazolam Phenoperidine	IDT − Propofol 10^{-1} − Vecur. 10^{-1}	11.6%		

IDT = intradermal test; RIA = radioimmunoassay; LHR = leukocyte histamine release; QAS = quaternary ammonium sepharose; Intralip. = Intralipid; suxam. = suxamethonium; gallam. = gallamine; pancur. = pancuronium; alcur. = alcuronium; vecur. = vecuronium.

− = negative; + = positive; ± = uncertain.
* Previously published (ref. 5).

bronchospasm (nine cases). The reaction was serious enough to justify interrupting the anesthetic in 12 patients. In all cases, this evolved favorably without any after-effects after treatment with epinephrine and fluid replacement. None of the patients had ever received propofol before. Five had no history of any systemic disease. Among the other nine patients, two had crossed anaphylaxis to muscle relaxants (cases 3 and 5); two were allergic to antibiotics (cases 7 and 8); one had anaphylaxis following synthetic gelatins (case 9) and another to lidocaine (case 11); case 8 had aspirin sensitivity; and case 11 had cutaneous reactions to household washing products. Four were atopic, this being confirmed by their having specific IgE against the usual airborne allergens (cases 1, 8, 12, and 14).

The Investigations

Skin Tests

Intradermal tests were carried out in 13 patients (patient 4 refused to come to Nancy). The tests were positive to propofol in 8 patients (cases 1, 2, 6, and 8–12). The intradermal reaction to Intralipid® was performed only in 4 of these 8 patients and was negative. When the prick tests were carried out, they were positive once (case 1), uncertain once (case 8), and negative once (case 12), although the intradermal reactions were positive in all three cases. Of the six patients who had been given a muscle relaxant with propofol (cases 9–14), two had positive intradermal reactions to both drugs (cases 10 and 11), and one (case 13) had positive intradermal tests to the muscle relaxant only.

Radioimmunoassay

The specific IgE-RIA for propofol was assayed in all 14 patients. The degree of uptake was abnormally high in 10 cases (cases 1–5, 9–11, 13, and 14). Five cases had both a positive intradermal reaction and a positive RIA. The RIA alone was positive three times. The intradermal reaction alone was positive twice. The QAS-RIA was assayed eight times. Four patients had high levels; two were already known to be allergic to muscle relaxants (cases 3 and 5), and two had been given a muscle relaxant at the same time as the propofol (cases 11 and 13). In the last two cases, these matched the positive intradermal tests to the muscle relaxants.

Leukocyte Histamine Release Test

This was only carried out five times (cases 1, 3, 7, 9, and 12). A bell-shaped curve, which characterizes the release of histamine by an immune mechanism, was found in three cases (cases 1, 9, and 12).

Intralipid Infusion Test

This was carried out in four patients (cases 1, 2, 8, and 9). It was asymptomatic in every case, and blood histamine level was unchanged.

Discussion

The mechanism underlying the reaction to propofol cannot be deduced from the clinical picture. In other words, IgE-dependent anaphylaxis, immunoglobulin G–dependent immune complex anaphylaxis, or nonimmune histamine release due to complement activation or to release of other mediators such as prostaglandins[11] all may produce signs similar to those seen in our patients. Moreover, since the patients had never before received propofol, it cannot be said that an immunologic mechanism is not involved. It is well known that 20–30% of reactions involving a muscle relaxant occur during the first exposure to the drug.[13–17]

The group of tests for identifying IgE-dependent anaphylaxis has been well defined by those who study the cause of anesthetic anaphylactoid incidents.[14,16–23] These tests have been well validated with the muscle relaxants that are responsible for most cases of anaphylactic shock occurring during anesthesia, and, as a result, thousands of patients have already been tested. For muscle relaxants, the sensitivity of skin tests is 95%, that of the RIA for anti-quaternary ammonium IgE with a trial of inhibition 85%, and that of leukocyte release 70%.[12,24] The specificity of the first two tests is virtually 100%. These drugs are divalent molecules, so the linking to proteins is not necessary to bridge two molecules of specific IgE on mast cell and basophil membrane.

In our study concerning propofol, the degree of uptake found with the control sera was unusually high (upper limit of normal: 7%), especially when compared with that obtained with other drugs (muscle relaxants, thiopental, amoxicillin), where this is no greater than 2.5%.[12] This uptake of IgE from the control sera was probably nonspecific and due to the hydrophobicity of the medium and the propofol. This hydrophobicity is due to the phenylsepharose used for the noncovalent absorption of propofol and due to the propofol itself, with its phenyl nucleus and its two isopropyl groups. On the other hand, we have shown in the control study (see Materials and Methods) that the amount of uptake obtained with the sera of 20 patients anesthetized with propofol without any mishaps was within the normal range and did not change significantly after 1, 14, and 60 days (5.1 ± 1.5%, 5.4 ± 1.7%, 5.1 ± 1.4%, and 4.4 ± 1%, respectively). The high degree of uptake during the RIA with the sera of 10 in 14 patients being investigated was indeed much greater than that seen with control sera (≥7.0%). It can be surmised that either the IgE really were antibodies with specific binding sites

for propofol or that they had such a structure that they were particularly suited to hydrophobic reactions. The first postulate could be checked by an inhibition test using the positive sera. However, this could not be carried out because propofol is insoluble in a aqueous medium.

We have previously checked, in 100 controls, that intradermal tests with propofol at 100 $\mu g \cdot ml^{-1}$ concentration were always negative. Therefore, positive skin tests at lesser concentration (10 and 1 $\mu g \cdot ml^{-1}$) may be considered as indicating specific IgE, raising the possibility that propofol could bridge specific IgE on mast cells. This was confirmed by the positive leukocyte histamine release in cases 1, 9, and 12, which showed a bell-shaped curve typical of IgE involvement in the histamine release due to the basophils.[5]

The isopropyl group is a very common structure found in endogenous amino acids and lipids. Because propofol contains two of them, it may act as a divalent molecule in which isopropyl groups act as the epitopes, like quaternary ammonium ions in muscle relaxant molecules. The hypothesis that the emulsion generates micelles expressing multiple reactive groups, so that a multivalent compound is created, may be raised. Indeed, Diprivan®, and not propofol, was used for the immunologic tests (skin tests, RIA, leukocyte histamine release).

Six patients had two tests positive, thus confirming the diagnosis of anaphylaxis due to propofol (cases 1, 2, and 9–12). In cases 1 and 9, three tests were positive. The skin tests and RIA were positive in cases 2, 10, and 11, and the skin tests and leukocyte histamine release were positive in case 12. When there is disagreement among these three tests, anaphylaxis remains nevertheless very likely: we know that some cases of anaphylaxis to muscle relaxants show a similar discrepancy. In fact, there is no absolute correlation between the degree of skin sensitivity due to specific IgE being present on skin mast cells and the degree of systemic sensitization, *i.e.*, the serum titers of specific IgE. Besides, skin tests could fail, because of a lack of sensitivity, whereas a poor specificity of borderline results of RIA has to be expected. As a result, we think an IgE-dependent mechanism was involved in the reactions to propofol in those patients who had at least one test positive, *i.e.*, in 13 of the 14 patients studied. The drug implicated in producing anaphylaxis in these patients seems to be propofol. Its lipid solvent gave negative results when tested (cases 1, 2, 8, and 9), whereas the emulsion of propofol (Diprivan®) had given positive ones in the same cases. None of the patients had ever been given any Intralipid®; reactions to this are also known to be extremely rare.[25–27] Moreover, infusion tests, in four cases, were well-tolerated.

In patient 7, all of the tests were negative, such that the mechanism involved in the anaphylactoid reaction remains unidentified. But, concentrations of propofol that are close to those obtained during anesthetic induction have, *in vitro*, a nonspecific histamine-releasing effect, as we showed in atopic patients.[28] It would therefore seem likely that some of the reactions occurring with propofol may be due to this mechanism, probably potentiated by the patient's previous treatment with β blockers (case 7).[29] The possibility of inducing an anaphylactoid reaction by combining a histamine-releasing substance, such as atracurium, with propofol has already been reported.[11]

The incidence of a previous history of drug anaphylaxis in the 14 patients was high, compared to the incidence of true anaphylaxis to lidocaine (only a few reports in all of the medical literature) or to the frequency of anaphylaxis to muscle relaxants (about 1 in 7,500 anesthetics) or to that of allergy to antibiotics, which does not affect more than 3% of the population. A similar history has already been reported in patients having had adverse reactions to propofol.[6–9] That three patients (cases 10, 11, and 13) were sensitized to both propofol and a muscle relaxant is also of interest. Anaphylaxis to two drugs is a rare phenomenon. A literature survey carried out at the time of reporting two personal cases of anaphylaxis to both thiopental and a muscle relaxant did not reveal any other reports.[30] In addition, four cases of atopy in 14 patients is noteworthy; a larger series of patients will be required to interpret this. Attributing these concomitant drug allergies to chance does not seem possible. This, together with the results of the RIA to propofol, lead us to suspect a possible anomaly in these patients' IgEs. It can be noted that the phenyl nucleus and the isopropyl groups are present in numerous drugs; this could explain why there was such a high incidence of previous allergies to drugs having the same epitopes. This hypothesis is being investigated at the moment.

It may be justified to advise against using propofol for those rare patients in whom an anaphylaxis to muscle relaxants has been diagnosed or who have several proven drug allergies. Including propofol in an anesthetic protocol that includes histamine-releasing drugs, such as atracurium, should be avoided for patients who are at risk for releasing excessive amounts of histamine.

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