

Immediate Allergic Hypersensitivity to Quinolones Associates with Neuromuscular Blocking Agent Sensitization

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What is already known about this topic? Most patients who experience an immediate hypersensitivity reaction to neuromuscular blocking agents (because of quaternary ammonium sensitization) have never previously been exposed to the drug.

What does this article add to our knowledge? A high prevalence of quaternary ammonium sensitization has been found in patients with quinolone immediate allergic hypersensitivity.

How does this study impact current management guidelines? Pending more information, neuromuscular blocking agent sensitization should be evaluated in patients in whom quinolone immediate allergic hypersensitivity is diagnosed.

BACKGROUND: We identified a case of quinolone allergic hypersensitivity associated with quaternary ammonium (QA) sensitization, the allergic determinant of neuromuscular blocking agents (NMBAs). Concomitant sensitization to several chemically different drugs is rarely reported and raises the question of a nonfortuitous association.

OBJECTIVE: We evaluated a potential association between quinolone immediate allergic hypersensitivity and NMBA sensitization.

METHODS: QA-specific IgE detection was prospectively performed in 26 patients who presented an immediate hypersensitivity reaction to quinolones: 17 with a confirmed allergic hypersensitivity and 9 with allergic hypersensitivity not confirmed. We also included a control population of 88 outpatients without a history of quinolone or NMBA hypersensitivity. Patients with positive QA-specific IgE benefited from a NMBA allergologic workup.

RESULTS: The prevalence of positive QA-specific IgE was significantly higher in patients with quinolone allergic hypersensitivity (9/17, 53%) compared with patients with allergic hypersensitivity not confirmed (1/9, 11%) than in controls (3/88, 3.4%). In the quinolone allergic population, ofloxacin elicited inhibition of the 4 positive QA-specific IgE sera tested, in a dose-response manner. Among the 9 patients with positive QA-specific IgE, the QA sensitization (positivity of specific IgE) was confirmed by positive skin tests and/or basophil activation tests to at least 1 NMBA in 5 of the 7 tested patients.

CONCLUSION: We report here the first documentation of a high prevalence of QA sensitization in patients with quinolone allergic hypersensitivity. These results suggest a new way for NMBA sensitization. It thus seems appropriate to investigate NMBA sensitization when quinolone allergic hypersensitivity is diagnosed. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:273-9)

Key words: Quinolones; Neuromuscular blocking agent; Quaternary ammonium ions; Drug immediate hypersensitivity; Drug allergy; Sensitization; Cross-reactivity

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Abbreviations used

BAT- basophil activation test
 NMBA- neuromuscular blocking agent
 QA- quaternary ammonium
 sIgE- specific Immunoglobulin E
 ST- skin test

However, some immediate-type hypersensitivity reactions have been reported. These reactions are due either to immune allergic mechanisms (IgE mediated) or to nonallergic mechanisms.^{2,3} The distinction between these reactions is mandatory because the diagnosis of allergic hypersensitivity reactions leads to the exclusion of this family of antibiotics, to prevent future accidents. This differential diagnosis is mainly based on a documented clinical history, skin tests (STs), and biological assays.^{3,4} These investigations are known to be not fully reliable. Thus, the provocation test remains the “gold standard” for a definitive diagnosis of allergy, despite the underlying risks.⁵

In our daily practice, we have identified neuromuscular blocking agent (NMBA) sensitization in a patient allergic to quinolone. Concomitant allergic immediate hypersensitivities to different drug families are exceptionally reported in the literature.⁶ This index case led us to hypothesize a potential association between immediate allergic hypersensitivity to quinolones and NMBA sensitization. The clinical and practical consequences of this observation justified evaluation of the prevalence of NMBA sensitization in a prospective cohort of patients who were referred to our department for the investigation of immediate reactions induced by quinolones.

METHODS**Index case**

A 63-year-old woman was referred to our department for the investigation of anaphylactic shock that occurred 5 minutes after the ingestion of ofloxacin to treat pyelonephritis. She presented with laryngeal edema, dyspnea, hypotension, tachycardia, and a skin rash, which were treated with epinephrine and high-volume fluid infusion. She had undergone kidney surgery under general anesthesia 15 years before, without any other medical history except recurrent urinary infections treated with quinolones. An immediate allergic hypersensitivity to quinolones was diagnosed on the basis of clinical history and the positivity of STs and basophil activation tests (BATs). Specific IgE (sIgE) to quaternary ammonium (QA), the antigenic determinant of NMBAs,⁷ was tested coincidentally during the emergency management of this patient and was found to be positive. In this context, we decided to perform STs and BATs to NMBAs, which were positive for suxamethonium, vecuronium, pancuronium, and rocuronium, and thus confirmed the positivity of QA sIgE.

Patients

Twenty-six patients who presented with immediate adverse reactions to quinolones were included in this prospective study. They all developed symptoms suggestive of immediate hypersensitivity⁸ less than 1 hour after quinolone intake. The severity of the immediate allergic hypersensitivity reactions ranged from grade I to grade III, according to the Ring and Messmer classification.⁹ Among these patients, 17 had an allergy to quinolones

by the positivity of STs and/or BATs and/or challenge tests. The demography and the clinical data of these patients are presented in Table I. None of them had ever experienced any previous hypersensitivity reaction to NMBAs. The 9 other patients constituted a first control group with allergic hypersensitivity not confirmed. All these 9 patients, for whom the combination of STs and basophil activation did not support an allergic reaction, underwent a challenge test with the culprit drug. These tests were well tolerated by all of them, thus confirming the lack of allergic hypersensitivity; the characteristics of these patients are summarized in Table II. No previous hypersensitivity reaction to NMBAs was reported for these patients. The second control population comprised 88 outpatients, consecutively consulting for other inflammatory diseases, such as atopic dermatitis, food allergy, chronic urticarial, or psoriasis management, without any history of quinolone or NMBA hypersensitivity.

Skin tests

For quinolones, prick-tests were done as a first step, with drug concentrations ranging from 5 to 40 mg/mL (levofloxacin, 5 mg/mL; lomefloxacin, 40 mg/mL; moxifloxacin, 40 mg/mL; norfloxacin, 40 mg/mL; ofloxacin, 5 mg/mL; piperidic acid, 40 mg/mL) as described elsewhere.⁵ If negative, intradermal tests at low concentrations (1/1000, 1/100 dilutions of the prick solutions) were performed. For NMBAs, STs were performed according to the latest guidelines of the French Society of Allergy (Société Française d'Allergologie) and the French Society of Anesthesia and Intensive Care (Société Française d'Anesthésie et de Réanimation).¹⁰

Provocation tests

When a provocation test was undertaken, a single-blind placebo-controlled oral provocation was performed with the culprit quinolone. The procedure included 3 steps: a placebo oral administration (1 mL of saline serum), then (30 minutes later) the intake of 1/100 dilution (in 1 mL of saline serum) of the total dose, followed (60 minutes later) by the total dose. The total dose corresponded to the lower concentrations of commercialized tablets for adults (levofloxacin, 500 mg; lomefloxacin, 400 mg; moxifloxacin, 400 mg; norfloxacin, 400 mg; ofloxacin, 200 mg; piperidic acid, 400 mg). It was conducted in an intensive care unit if the initial reaction was severe (grade II or III) or under strict medical monitoring in the other cases (during 24 hours).

Total and sIgE measurement

Total IgE and morphine sIgE (c260) were determined with the ImmunoCAP fluorescence enzyme immunoassay technique (Thermo Fisher, Uppsala, Sweden). For sIgE, results >0.10 kU/L was considered positive. All assays were performed according to the manufacturer's recommendations.

Inhibition assays

Inhibition tests of QA-specific IgE by ofloxacin were performed; vecuronium and amoxicillin were used as positive and negative controls, respectively. Briefly, sera were diluted 1:1 in 4 tubes that contained 4 consecutive logarithmic dilutions of the drug (ranging from 0.005 mg/mL to 5 mg/mL) or buffer alone as a control for 1 hour under shaking. Results were expressed as a percentage of inhibition.

TABLE I. Demography and results of quinolone allergologic workup of patients with quinolone immediate allergic hypersensitivity

Patient	Sex	Age (y)	Culprit quinolone	Time to onset of reaction (min)	Severity of reaction	Delay between reaction and tests (mo)	Previous exposure to NMBAs	STs (wheal/flare in mm)	BAT	Provocation test
1	F	38	Ofloxacin	5	II	8	Yes	Neg	Neg	Not tolerated
2	M	56	Ofloxacin	10	I	2	Yes	IDT 1/10 (17/17)	Pos	NA
3	F	80	Moxifloxacin	<5	III	4	Yes	PT (8/28)	Pos	NA
4	F	44	Norfloxacin	15	III	3	Yes	Neg	Pos	NA
5	F	74	Ofloxacin	<5	I	2	Yes	Neg	Pos	NA
6	F	74	Levofloxacin	30	III	2	No	IDT 1/100 (10/42)	Pos	NA
7	F	68	Levofloxacin	45	II	4	Yes	PT (10/22)	Pos	NA
8	F	52	Lomefloxacin	5	III	3	No	Neg	Pos	NA
9	M	64	Levofloxacin	15	II	2	Yes	IDT 1/100 (8/23)	Pos	Not tolerated
10	F	43	Levofloxacin	<5	III	15	No	PT (10/31)	Pos	NA
11	F	60	Pipemidic acid	45	III	10	No	PT (14/32)	Neg	NA
12	F	18	Ofloxacin	<5	III	2	No	IDT 1/100 (14/49)	Neg	NA
13	F	88	Ofloxacin	5	III	3	Yes	IDT 1/1000 (19/55)	Pos	NA
14	F	64	Ofloxacin	5	III	1	Yes	IDT 1/1000 (11/31)	Pos	NA
15	F	73	Ofloxacin	30	I	3	Yes	IDT 1/100 (12/42)	Uninterpretable	NA
16	F	31	Lomefloxacin	30	II	4	Yes	Neg	Pos	NA
17	F	22	Ofloxacin	45	III	2	No	PT (22/95)	Pos	NA

Neg, Negative; Pos, positive; IDT, intradermal test; PT, prick-test; NA, not attempted.

TABLE II. Demography and results of quinolone allergologic workup of patients with quinolone allergic sensitivity not confirmed

Patient	Sex	Age (y)	Culprit quinolone	Time to onset of reaction (min)	Severity of reaction	Delay between reaction and tests (mo)	Previous exposure to NMBAs	STs (wheal/flare in mm)	BAT	Provocation test
18	F	50	Levofloxacin	10	II	9	Yes	Neg	Uninterpretable	Tolerated
19	F	48	Moxifloxacin	10	I	4	No	Neg	Neg	Tolerated
20	F	44	Levofloxacin	10	II	5	Yes	Neg	Neg	Tolerated
21	M	29	Levofloxacin	60	I	2	No	IDT 1/100 (8/17)	Neg	Tolerated
22	F	55	Ofloxacin	60	I	3	Yes	Neg	Neg	Tolerated
23	F	42	Ofloxacin	30	I	35	Yes	Neg	Neg	Tolerated
24	F	26	Lomefloxacin	60	I	25	Yes	Neg	Doubtful	Tolerated
25	F	35	Moxifloxacin	30	II	15	No	Neg	Neg	Tolerated
26	F	35	Moxifloxacin	15	II	13	Yes	Neg	NR	Tolerated

Neg, Negative; Pos, positive; IDT, intradermal test; PT, prick-test; NA, not attempted.

Basophil activation tests

BATs against culprit drugs were performed to measure CD203c expression in the basophil population, as described elsewhere.⁵ Basophils were defined as cells that express CRTH2 with low side scatter, among the CD3⁺ cells. The positivity threshold was defined with the negative control without any drug. Anti-IgE (from Beckman Coulter, Fullerton, Calif) was used as a positive control. All the results are expressed as the percentage of CD203c⁺ basophils among the total basophil population. Three drug dilutions were tested: 1, 0.5, and 0.1 mg/mL for the quinolones and 1/1000, 1/100, and 1/10 dilutions of the prick solutions for the NMBAs. Results were considered positive when at least 2 sequential drug dilutions induced >10% CD203c⁺ basophils above the negative control value.

Flow cytometric analysis

Samples were stained with the following antibodies: fluorescein isothiocyanate anti-CRTH2, phycoerythrin anti-CD203c,

and phycoerythrin-cyanine 5 anti-CD3 (all from Beckman Coulter). Samples were run on an Epics XL flow cytometer (Beckman Coulter) and analysed with expo32 software.

Statistical analysis

Statistical significances were assessed with either the Student test or χ^2 test. Levels of significance are expressed as *P* values ($*P < .05$, $**P < .01$, and $***P < .001$).

RESULTS

Immediate allergic hypersensitivity to quinolones associates with a high prevalence of QA-specific IgE

NMBA sensitization is commonly evaluated with the detection of QA-specific IgE. Several studies have reported that morphine is an excellent provider of QA structure^{7,11} and is thus commonly used in laboratories to detect QA sIgE. Morphine sIgE was measured in the 3 populations of the study: patients with quinolone immediate allergic hypersensitivity, patients with

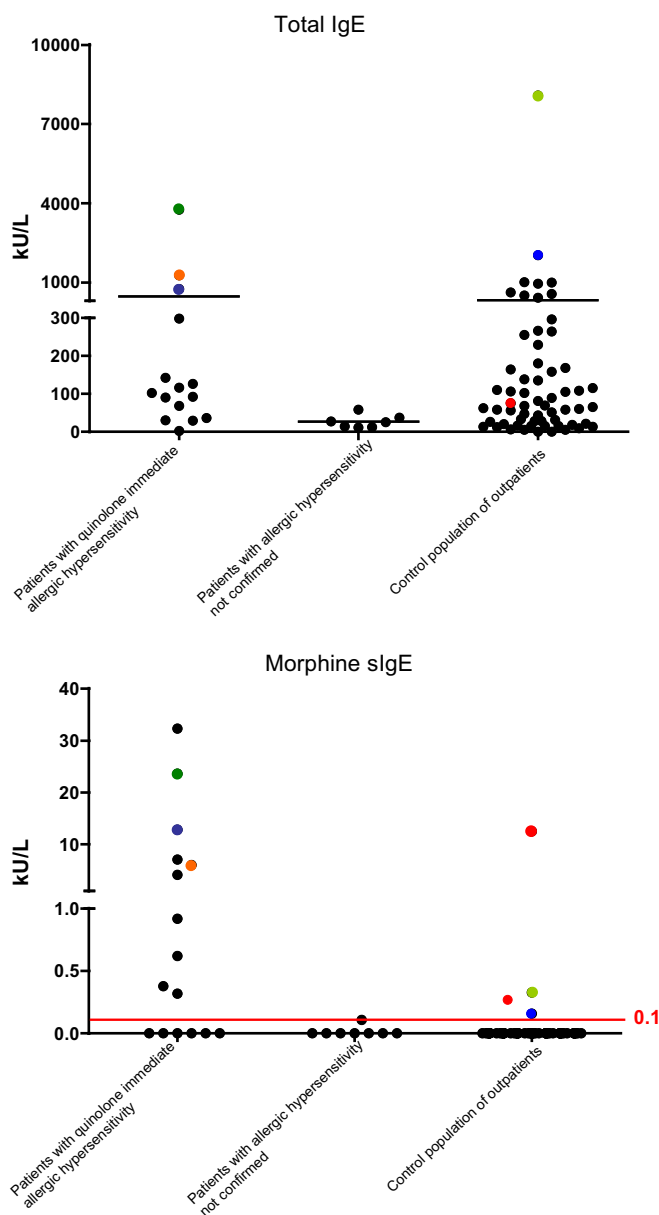


FIGURE 1. Total and morphine sIgE in the patients with quinolone immediate allergic hypersensitivity, in the patients with allergic sensitivity not confirmed and in the control population of outpatients. Results are expressed as kU/L. The positivity threshold is represented by a red line. The 3 control patients with positive morphine sIgE are represented with the same colors in the 2 graphs.

allergic hypersensitivity not confirmed, and in the control population of outpatients. The prevalence of positive morphine sIgE was significantly higher in patients with quinolone immediate allergic hypersensitivity (9/17, 53%) than in patients with allergy not confirmed (1/9, 11%) and in control outpatients (3/88, 3.4%; $P < .05$ and $P < .0001$, respectively; Figure 1). The presence of sIgE was confirmed with another QA structure provider (p-aminophenylphosphoryl-choline) in 6 of 13 patients with immediate allergic hypersensitivity (46%) and 0 of 5

patients with allergic hypersensitivity not confirmed (Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Because high levels of total IgE have been shown to lead to false-positive results of drug-specific IgE,¹² we thus evaluated total IgE levels in all populations. No significant difference was observed between patients with quinolone immediate allergic hypersensitivity and patients with allergy not confirmed ($P = .26$), patients with quinolone immediate allergic hypersensitivity and outpatients ($P = .63$), and patients with allergy not confirmed and control outpatients ($P = .48$).

Three patients of the control population displayed positive morphine-specific IgE. Two of them exhibited morphine-specific IgE at 0.16 and 0.33 kU/L, respectively, associated with high levels of total IgE (2031 and 8083 kU/L, respectively), suggesting a nonspecific positivity of morphine IgE. The third patient had 12.5 kU/L of morphine IgE and normal total IgE (81 kU/L). The 3 patients had no previous history of allergy to morphine or NMBAs, and all NMBA STs and BATs were negative, which did not confirm the allergy to NMBAs.

Similarly, 3 patients (patients 2, 14, and 15) of the immediate allergic hypersensitivity group displayed elevated total IgE (3759, 746, and 1277 kU/L, respectively). These 3 patients had high levels of morphine sIgE (23.6, 12.8, and 6.0 kU/L, respectively). Compared with the low levels of nonspecific positivity described in the control population, these high levels did not seem to correspond to a nonspecific detection. Furthermore, patients 14 and 15 had positive NMBA STs, confirming the true positivity of morphine sIgE.

QA-specific IgE of patients allergic to quinolone are inhibited by quinolone molecules

The high prevalence of QA sIgE in patients allergic to quinolone raised the question of a potential cross-reactivity between NMBAs and quinolones. To investigate this hypothesis we performed inhibition assays. We selected sera from 4 patients who all experienced immediate allergic hypersensitivity reactions to the same quinolone: ofloxacin (Figure 2, A). Inhibition curves clearly showed that the preincubation of these sera with increasing doses of ofloxacin inhibited the QA sIgE. As a positive control of inhibition, we used an NMBA, vecuronium (Figure 2, B), which leads to an even less pronounced inhibition than that observed with ofloxacin. Amoxicillin, used as a control of inhibition specificity, did not inhibit the QA sIgE (Figure 2, C).

Biological QA sensitization is confirmed by NMBA STs

STs are the most important tool in the diagnosis of NMBA immediate allergic hypersensitivity, because challenge tests are not ethically feasible,¹³ and their sensitivity is widely recognized today. After the evaluation of biological QA sensitization, patients with positive QA sIgE were then recalled for further investigations to confirm this sensitization. Seven patients underwent STs for all the commercially available NMBAs in France: suxamethonium, vecuronium, pancuronium, rocuronium, mivacurium, cisatracurium, and atracurium. According to the latest guidelines of the French Society of Allergy (Société Française d'Allergologie) and the French Society of Anesthesia and Intensive Care (Société Française d'Anesthésie et de Réanimation),¹⁰ BATs were performed as a complementary diagnosis tool, with the same NMBAs. Five patients among the 7 presented at least 1 positive ST and/or BAT to NMBAs (Table III).

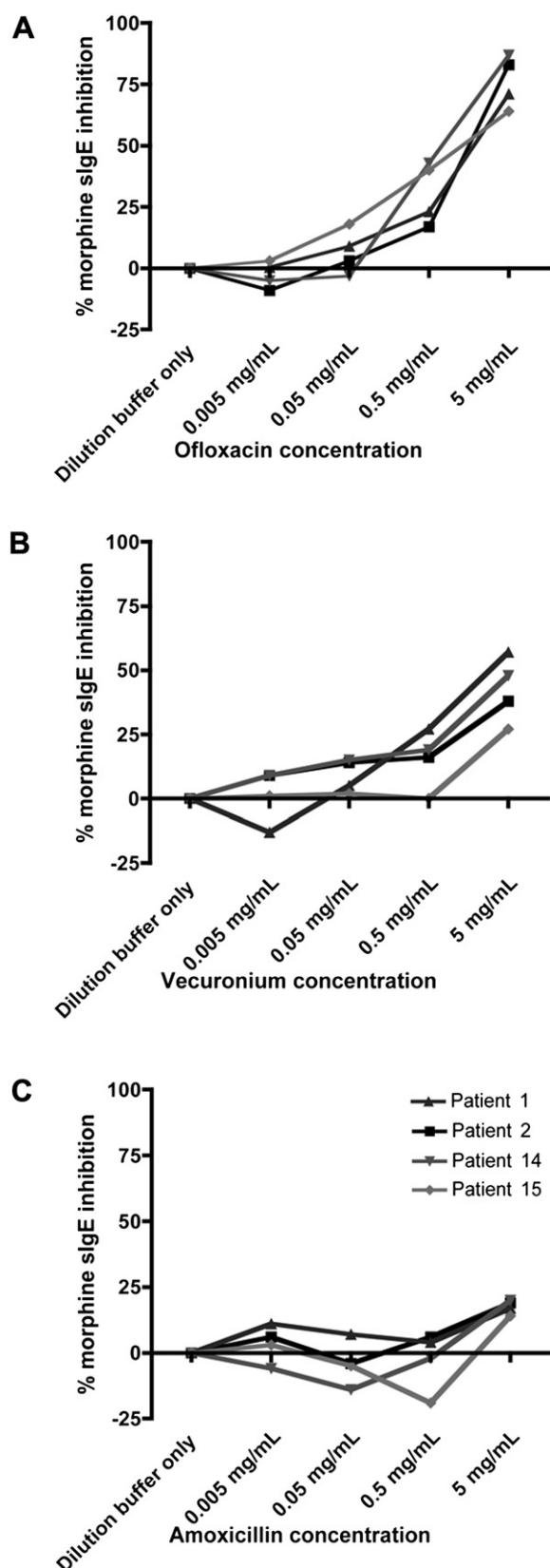


FIGURE 2. Inhibition assays of morphine sIgE. Inhibition assays of morphine sIgE of 4 patients by ofloxacin (A), vecuronium (B), and amoxicillin (C). Results are expressed as a percentage of inhibition.

Interestingly, among the 4 former patients with positive QA sIgE inhibition assays to vecuronium, 3 also showed positive STs and/or BATs to vecuronium and only the fourth remained negative for vecuronium, together with the other 6 NMBAAs tested.

DISCUSSION

The fortuitous and unexpected detection of QA sIgE in a patient who developed an immediate allergic hypersensitivity reaction to quinolones allowed us to demonstrate the higher prevalence of QA sIgE in patients allergic to quinolone than in patients not allergic to quinolone. Furthermore, we showed that these sIgEs cross-react with both quinolones and NMBAAs and are associated with positive STs and BATs to NMBAAs. We can thus assume that immediate allergic hypersensitivity to quinolones is associated with NMBA sensitization, although its clinical relevance remains undefined.

For many years, it has been reported that the majority of patients (85%) who experience an immediate hypersensitivity reaction to NMBAAs during surgery have never previously been exposed to the drug.¹⁴ Baldo and Fisher⁷ showed in 1983 that the antigenic determinants of NMBAAs recognized by IgE are quaternary and tertiary ammonium ions. These structures are widely present in our everyday environment (foods, cosmetics, disinfectants, etc), which can thus explain the prior sensitization through exposure to NMBA-related structures. Nevertheless, Baldo et al¹⁵ emphasized that not all patients react with all NMBAAs, even if multiple sensitization appears in most patients. Indeed, according to the QA hypothesis, sIgEs are directed not only against QA ions but also toward neighboring structures. These findings have already had practical consequences: the detection of sensitization to NMBAAs should be done via the detection of QA or tertiary ammonium ion sIgE. Numerous studies have evaluated different providers of such structures in IgE detection assays, and, because morphine appears to be one of the best of them,¹⁵ morphine-based assays are currently used in the biological diagnosis of NMBA immediate allergic hypersensitivity.¹¹

More recently, Florvaag et al¹⁶ showed that the prevalence of morphine sIgE is closely related to the consumption of cough syrups that contain a morphine derivative: pholcodine. Indeed, morphine sIgEs were much more frequently detected in Norway than in Sweden, where the use of these cough mixtures is restricted. Interestingly, this IgE sensitization directly correlated to the incidence of NMBA anaphylaxis in these 2 countries. After this pilot study, pholcodine-containing drugs were removed from Norway in March 2007. After a 3-year withdrawal, significant decreases of morphine sensitization and anaphylactic reactions to NMBAAs were observed in that country.¹⁷

The contribution of pholcodine to NMBA sensitization was then confirmed in an international study, showing a significant association between pholcodine consumption and morphine and NMBA sensitization in the 9 countries included. However, the results in the United States do not support the pholcodine hypothesis: a prevalence of 5% of morphine sIgE was detected, although no drug that contains pholcodine is available in this country. These former data suggest that other substances, as yet unknown, may lead to IgE sensitization to NMBAAs.¹⁸

Similarly to NMBAAs, quinolones can induce immediate allergic hypersensitivity after the first-ever use. Sachs et al¹⁹ reported that 43% of patients developed anaphylaxis after the

TABLE III. Results of the NMBA allergologic workup of the patients allergic to quinolone

Patient	Suxamethonium (10 mg/mL)	Vecuronium (4 mg/mL)	Pancuronium (2 mg/mL)	Rocuronium (10 mg/mL)	Mivacurium (2 mg/mL)	Cisatracurium (2 mg/mL)	Tracrium (10 mg/mL)
1							
ST	Neg	Pos (IDT 1/10)	Neg	Neg	Neg	Neg	Neg
BAT	Pos	Neg	Neg	Neg	Neg	Neg	Neg
2							
ST	Neg	Neg	Neg	Neg	Neg	Neg	Neg
BAT	Neg	Neg	Neg	Neg	Neg	Neg	Neg
5							
ST	Pos (IDT 1/10)	Pos (IDT 1/10)	Neg	Neg	Neg	Neg	Neg
BAT	Pos	Neg	Neg	Neg	Neg	Neg	Neg
7							
ST	Neg	Neg	Neg	Neg	Neg	Neg	Neg
BAT	Neg	Neg	Neg	Neg	Neg	Neg	Neg
9							
ST	Pos (PT)	Pos (PT)	Pos (PT)	Pos (IDT 1/100)	Pos (PT)	Neg	Neg
BAT	Pos	Pos	Pos	Pos	Pos	Neg	Neg
14							
ST	Pos (PT)	Pos (IDR 1/1000)	Pos (PT)	Pos (PT)	Neg	Neg	Neg
BAT	Pos	Pos	Pos	Pos	NR	NR	NR
15							
ST	Pos (PT)	Pos (IDT 1/10)	Neg	Neg	Pos (IDT 1/1000)	Pos (IDT 1/100)	Pos (IDT 1/1000)
BAT	Neg	Neg	Neg	Neg	Neg	Neg	Neg

Neg, Negative; Pos, positive; IDT, intradermal test; PT, prick-test; NR, not realized.

first dose or within the first 3 days of their quinolone treatment, suggesting that IgEs able to recognize quinolones were already present in these patients and that this sensitization was induced by another component that shares a common antigenic determinant.¹⁹ We have shown that quinolone immediate allergic hypersensitivity is frequently linked to NMBA sensitization, and we detected sIgE that cross-reacts with quinolones and NMBA structures. After the pholcodine story, we thus hypothesized that exposure to quinolone could represent a new way of sensitization to NMBAs. Furthermore, exposure to QA structures could explain the generation of IgE reacting to quinolones and the occurrence of immediate allergic hypersensitivity after the first use of these drugs.

To understand the chemical basis of the cross-reactivity between quinolones and NMBAs, we analyzed the structures of these 2 drug families. Compared with NMBA structures, quinolones do not harbor QA determinants. However, most of them have a piperazine cycle which, on protonation, could mimic substituted ammonium and thus explain the cross-reactivity of sIgE between quinolones and NMBAs by sharing a potential common epitope. On the basis of this observation, we conducted molecular modelizations between these 2 drug families, according to the method developed by Baeck et al.²⁰ We were not able to demonstrate the presence of any common area of immune recognition between quinolones and NMBAs. To date, the cross-reactivity between these 2 families of drugs is not understood. As to the possible involvement of quinolone metabolites, further investigations are required for a better understanding of the biochemical mechanisms involved.

A quandary encountered in numerous studies on allergy is the lack of a "gold standard" to define the allergic nature (or not) of hypersensitivity reactions. Thus, a weakness of our study is the heterogeneity of the tests used to determine whether a patient

presented with allergic hypersensitivity or nonconfirmed sensitivity to quinolones. Patients with a nonconfirmed allergy were defined as tolerating an oral challenge, independently of the ST or BAT results. Assessing allergic hypersensitivity is trickier because of the ethical problem of performing oral challenges in patients with a high probability of allergy and thus a high probability of developing potentially life-threatening symptoms. With these considerations, only 2 subjects (11.8%) with allergic hypersensitivity underwent all 3 diagnostic tests. Four patients (23.5%) were defined as allergic on the basis of positive BAT (with completely negative quinolone ST results and no confirmatory quinolone oral challenge), and 2 patients (11.8%) on the basis of positive intradermal ST results to high concentrations of ofloxacin (0.5 mg/mL and 0.05 mg/mL) without confirmatory quinolone oral challenge.

In conclusion, this study represents the first description of an important clinical/biological observation: patients with quinolone immediate allergic hypersensitivity display a significantly higher prevalence of QA sensitization than patients with quinolone immediate nonallergic hypersensitivity reactions and the general population. Thus, it seems appropriate to investigate NMBA sensitization when quinolone immediate allergic hypersensitivity is diagnosed. These results suggest a new way for NMBA sensitization to occur, in addition to the well-described pholcodine involvement. Benefiting from the experience of the pholcodine story, multicenter studies have to be conducted to verify the strong association between immediate allergic hypersensitivity to quinolones and NMBAs.

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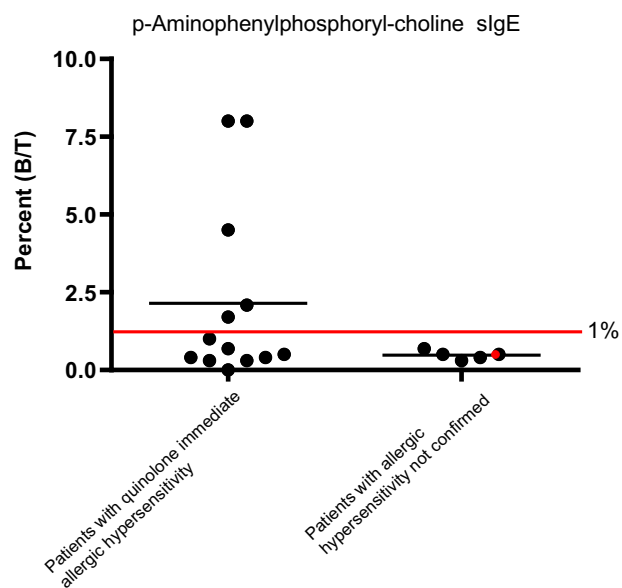


FIGURE E1. p-Aminophenylphosphoryl-choline sIgE in the patients with quinolone immediate allergic hypersensitivity and in patients with allergic sensitivity not confirmed. Results are expressed as bound fraction/total fraction (B/T). The positivity threshold is represented by a *red line*.