

Correspondence and Replies

On the question of the association between immediate hypersensitivity to quinolones and neuromuscular blocking drug sensitization

TO THE EDITOR:

The recent study by Rouzaire et al,¹ in which the researchers concluded that immediate hypersensitivity to quinolones is “frequently linked to NMBA (neuromuscular blocking agent)

sensitization” needs to be viewed in a wider research context than that presented. The authors may be unaware of the extent and likely significance of previous work that identified tertiary and quaternary ammonium ions as IgE-binding determinants. Results of early studies²⁻⁴ showed that, apart from the presence of a tertiary or quaternary, but not primary or secondary, amino groups, a variety of chemical structures and a diverse range of pharmacologic activities may be recognized by neuromuscular blocking drug (NMBD)-reactive IgE antibodies from subjects who experienced anaphylaxis to an NMBD. Cross-reactive drugs

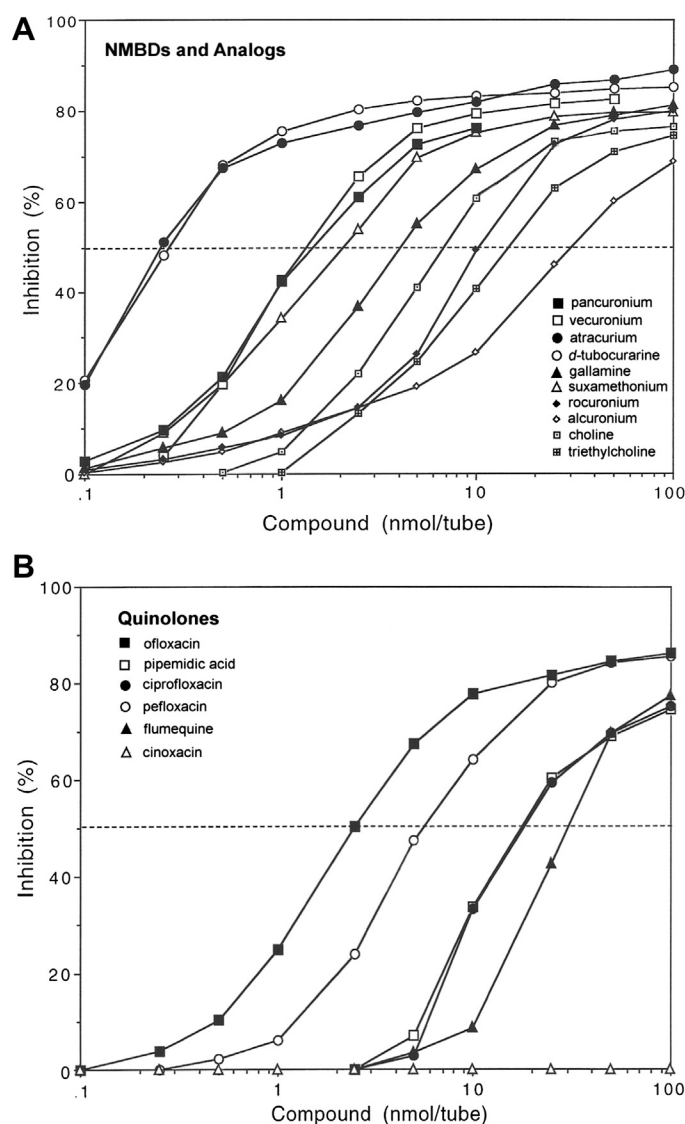


FIGURE 1. Inhibition of binding of IgE antibodies specific for tertiary and quaternary amino groups by (A) NMBDs and analogs and by (B) quinolones. Fifty percent inhibitory amounts (nmol/tube) were the following: NMBDs (atracurium 0.25, *d*-tubocurarine 0.25, vecuronium 1.4, pancuronium 1.5, succinylcholine 2, gallamine 4, choline 10, triethylcholine 15, alcuronium 30); quinolones (ofloxacin 2.5, pefloxacin 6, pipemidic acid 18, ciprofloxacin 18, flumequine 25); cinoxacin (no inhibition). Serum was from a patient with an immediate type I allergy to doxycycline. The reactive antigen used in the immunoassay was *N*-dimethyl acylurea-human serum albumin-solid phase complex. The figure was adapted from reference 7.

identified included a neuroleptic drug, an opioid analgesic, a ganglionic blocking agent, an antihistamine, an acetylcholine receptor antagonist, and an anticholinesterase inhibitor. Subsequently, sera from patients with a drug allergy, some with unknown and others with confirmed immediate hypersensitivity to an NMBD(s), were found to have ammonium group-reactive IgE antibodies to a range of different drugs, including some local anesthetics, opioids, doxycycline, and quinolones.^{3,4} For example, experiments undertaken in 1999 revealed clear IgE antibody recognition of NMBDs and the quinolones, ofloxacin, pefloxacin pipemidic acid, ciprofloxacin, and flumequine but not cinoxacin. Quantitative inhibition potencies with the NMBDs and quinolones were in the same range, namely, <1 nmol/tube to approximately 100 nmol/tube for 50% inhibition. Results with one such serum are shown in Figure 1. Findings in our laboratory over many years revealed that serum IgE antibodies reactive with tertiary and quaternary ammonium ions are not uncommon in patients with drug hypersensitivities and that this, together with the demonstration of a 9.3% prevalence of either a positive skin test to NMBDs or specific IgE antibodies in the general population,⁵ indicates that, rather than a single drug or a group of drugs (such as pholcodine or the quinolones), many other widely used sensitizing drugs with suitable ammonium ion determinants might also be candidates. All such drugs and environmental chemicals may constitute a sensitizing antigenic and/or allergenic pool but a genetic explanation in the form of so-called natural antibodies, that is, antibodies formed without exposure to foreign antigens, should also be considered, especially because allergic reactions to NMBDs, quinolones, and a number of other drugs often occur on the first exposure.⁴ One possible candidate antibody already suggested is a “natural” IgE with specificity for phosphorylcholine.^{4,6} Two other comments are in order. The description “QA-specific IgE” should be dispensed with because tertiary ammonium groups may be equally recognized by NMBD-reactive IgE antibodies. “Substituted ammonium” is preferable to “quaternary ammonium,” remembering that “substituted” here refers only to tertiary and quaternary ammonium determinants. It should also be appreciated that some antibodies are complementary to additional (near-neighbor) structures together with the ammonium group.^{4,6} Lastly, presentation of inhibition findings as evidence for specificity are of little value if results are given as weight/mL (ng or mg/mL). For inhibitory potencies to be readily assessed and compared, drug inhibition data expressed as mol (nmol or millimol) per tube or per unit volume are essential.

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REPLY:

We thank Drs Baldo and Pham¹ for their comments on our article recently published in the *Journal of Allergy and Clinical Immunology: In Practice*.² We are honored to see the interest of these famous specialists of neuromuscular blocking drugs (NMBD) sensitization for our work. These authors give to the reader a wider view on our results by emphasizing that a variety of chemical structures, presenting tertiary or quaternary ammonium, may be recognized by NMBDs-reactive IgE. In this context, Baldo and Pham are obviously very aware of the existing cross-reactivity between quinolones and NMBDs. However, this is not largely known from the scientific and medical community. It is probably due to the fact that the quinolone inhibition assays reported in Baldo and Pham's letter¹ have only been published in a thesis.³ We are pleased to see that these researchers demonstrated many years ago that quinolones (especially ofloxacin) and NMBDs are both able to inhibit substituted ammonium reactive IgE, which thus confirms our inhibition data. Indeed, these molecules contain a piperazine cycle that, upon protonation, could mimic such substituted ammonium groups.

The authors insist on the “not uncommon” presence of tertiary and quaternary ammonium reactive IgE, with a prevalence of 9.3% in the general population documented by Porri et al.⁴ We report a prevalence of 3.4% in our outpatient population, and it has been demonstrated by Johansson et al⁵ that the prevalence of such specific IgE is highly country-dependent (for example: 0.5% in Sweden and 5.5% in Norway for morphine specific IgE in 2010). As suggested by Baldo and Pham,¹ this demonstrates that NMBDs sensitization is frequent and thus seems due to “widely used sensitizing drugs that contain ammonium ion determinants,” “rather than a single drug or a group of drugs (such as pholcodine or the quinolones).” However, during the recent years, the “pholcodine story” has demonstrated that this single molecule displays, alone, a significant role in sensitization, because its withdrawal led to a dramatic decrease in substituted ammonium specific IgE prevalence and in NMBDs allergic reactions in Norway.⁶

Accordingly, the major aim of our article thus was to alert clinicians about the strong association, not widely known, that we

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