

Quinolone hypersensitivity

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Purpose of review

Quinolones are potent antibacterial agents that can cause drug hypersensitivity reactions affecting different organs. A better understanding of the underlying mechanism and the level of crossreactivity within different quinolones is needed to handle and prevent these diseases.

Recent findings

The adverse side-effects caused by quinolones are the result of different immunological mechanisms and cause quite different diseases. The development of an assay detecting quinolone-specific IgE revealed specific antibodies in more than 50% of patients with immediate-type reactions, and the majority of sera also reacted with related compounds. In maculopapular drug exanthemas caused by ciprofloxacin, specific T cells could be detected and cloned. They reacted with ciprofloxacin directly, and crossreactivity to related compounds was detected in approximately 50% of the clones.

Summary

Quinolones can cause drug hypersensitivity reactions by different immunological mechanisms. In-vitro analysis suggests that crossreactivity is common.

Keywords

adverse effects, hypersensitivity, quinolones, specific IgE

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Introduction

Quinolones are synthetic antibiotics with a potent antibacterial efficacy. Some infectious diseases, previously needing intravenous therapy, are now treated orally, such as acute pyelonephritis, prostatitis and Gram-negative osteomyelitis; some new fluoroquinolones have an excellent activity against *Streptococcus pneumoniae*. As a result of these features, they are becoming more widely used, and new fluoroquinolones are still in development.

Their primary target is the bacterial enzyme DNA gyrase or topoisomerase II, which renders the DNA molecule compact and biologically active. Their basic structure is shown in Fig. 1. They are nitrogen-containing, eight-membered heterocyclic aromatic compounds with a ketone group at position 4 and a carboxylic group at position 3. The main ring contains one nitrogen atom at position 1 (quinolones), and analogues have additional nitrogens at position 2 (cinnolines) or position 8 (naphthyridines) or positions 6 and 8 (pyridopyrimidines).

The structure of quinolones is directly related to their activity but also to their side-effect profiles.

In general, the quinolones have a good safety profile, but severe, sometimes fatal, adverse reactions have been described. These kinds of adverse effects, often suggestive of an immune mechanism, are very rare, usually less than one case among 50 000 treatments. They have thus not been picked up during phases I–III of clinical trials, but only in post-marketing surveillance (Table 1). Newer fluoroquinolones are extremely successful compounds with a broader antibacterial activity and an enhanced potency but also a wider spectrum of unpredictable, sometimes life-threatening adverse reactions.

Some configurations of the molecules are related to particular side-effects [1]: (1) fluorine or chlorine at position 8 is related to enhanced Gram-positive potency but severe phototoxicity, see sparfloxacin, fleroxacin, lomefloxacin, sitafloxacin; Bay 3118 has been withdrawn in phase III; the development of clinafloxacin has been discontinued; (2) difluorophenyl substitution at position 1 is common to temafloxacin, trovafloxacin and tosu-floxacin, all causing severe, presumably immune-mediated side-effects in selected organs; (3) fluoronaphthyridone core nuclear structure with a nitrogen at position 8 is common to tosu-floxacin and trovafloxacin,

which caused hepatitis, nephritis and thrombocytopenia (Table 1).

Adverse reactions with probable or demonstrated immune pathogenesis

A medline review of the literature since 1966 revealed 384 case reports, by 166 authors, of unpredictable adverse reactions to quinolones, suggesting an immune mechanism. Ciprofloxacin was the compound most frequently implicated, because of its high consumption all over the world, with 152 cases; other quinolones follow with decreasing frequency, with 50–10 cases described: ofloxacin, cinoxacin, nalidixic acid, pefloxacin, norfloxacin, lomefloxacin and pipemidic acid; less than 10 cases have been reported for the other quinolones.

Immediate adverse reactions such as urticaria, angioedema and anaphylactic shock were most frequently described. Other reactions with a presumable immune mechanism are more rare: haemolytic-uraemic syndrome, haemolytic anaemia, thrombocytopenia, leukopenia or pancytopenia, acute interstitial nephritis, photosensitization, acute hepatitis and acute cholestatic jaundice, Stevens–Johnson and Lyell syndromes, fixed drug eruption, cutaneous vasculitis, macular-papular

exanthema, acute pancreatitis, serum sickness-like disease, angioimmunoblastic lymphadenopathy, acute generalized exanthematous pustulosis and eosinophilic meningitis (Fig. 2).

Fatal reactions

Fatal reactions have been reported with: trovafloxacin: acute hepatitis [2]; ciprofloxacin: Lyell syndrome [3–5], hepatitis [6,7], acute interstitial nephritis [8,9], pancytopenia [10], angioimmunoblastic lymphadenopathy evolving to malignant T-cell lymphoma [11], Schönlein–Henoch syndrome [12], fatal shock in an AIDS patient [13]; temafloxacin: haemolytic anaemia with kidney deficiency in one patient and haemolytic anaemia with ischaemic colitis and disseminated intravascular coagulation in another [14]; ofloxacin: hepatitis [15], systemic haemorrhagic vasculitis [16]; nalidixic acid: haemolytic anaemia [17]; gatifloxacin: hepatitis [18]; levofloxacin: hepatitis [19]; pipemidic acid: Lyell syndrome [20].

Figure 1. General structure of quinolones

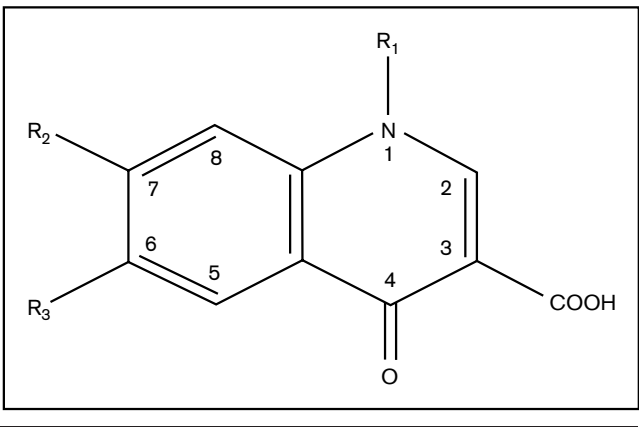
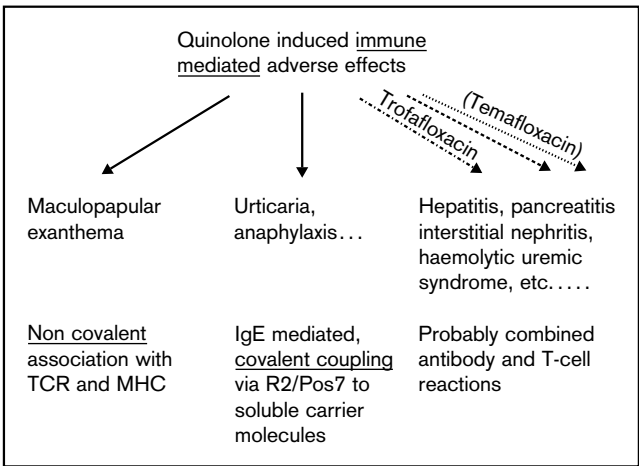


Figure 2. Schematic overview of some immune mechanisms leading to distinct clinical manifestations: IgE and exclusive T-cell-mediated reactions seem to differ in the way the drug is presented and recognized



The pathomechanism of other severe side-effects is not well understood. MHC, Major histocompatibility complex; TCR, T-cell receptor.

Table 1. Serious quinolone adverse effects

Enoxacin	1985	Severe interactions	Substituted by later quinolones
Pefloxacin	1985	Photoreactions (France)	Substituted by later quinolones
Fleroxacin	1990	Phototoxicity/CNS toxicity	Withdrawn
Lomefloxacin	1993	Convulsions	Substituted by later quinolones
Temafloxacin	1992	Haemolytic-uraemic syndrome	Withdrawn post launch
Bay 3118	1993	Severe phototoxicity	Withdrawn phase III
Sparfloxacin	1994	Phototoxicity/Arrhythmias	Warnings (France, Japan)
Tosufloxacin	1996	Thrombocytopenia/nephritis	Warnings (Japan)
Trovafloxacin	1999	Hepatic necrosis/failure	Restricted/suspended
Grepafloxacin	1999	Arrhythmias/torsade de pointes	Withdrawn
Clinafloxacin	1999	Phototoxicity/hypoglycaemia	Withdrawn

CNS, Central nervous system. Reproduced from Ball [1], with permission.

Immediate-type anaphylactic reactions

Anaphylactic reactions occurring within 1 h from the intake of quinolones, suggesting a type I (IgE-mediated) allergic mechanism, have been described by 16 authors [21–44] in 167 individuals; among them 39 patients also experienced anaphylactic shock. Numerous cases have been described with ciprofloxacin in AIDS patients [13,27,29,39,44].

Skin tests producing an immediate response (prick and intradermal) were performed by numerous authors; the results are considered to be unreliable, because they were also positive in healthy controls [24,25,43]. These false-positive results were probably triggered by a direct histamine release. Indeed, the administration of very high oral doses of balofloxacin and ofloxacin in the dog (40–100 times the therapeutic dose) led to an increase in plasma histamine and generalized rash [45].

As a result of the unreliable skin tests and the lack of an in-vitro test to detect specific IgE, the diagnosis of quinolone-induced immediate hypersensitivity is based solely on provocation test. A challenge test with a drug suspected of an immediate reaction may be very risky, and one must consider the risk–benefit ratio carefully. Challenges were performed by various authors, with positive results, even when skin test was negative [21,24,25,28,37,46,47].

A valuable contribution to the demonstration of the IgE-mediated nature of these reactions has been the work of Manfredi *et al.* [31]. The authors studied 55 patients reporting 69 immediate reactions, such as generalized itching, urticaria and angioedema. Anaphylactic shock occurred in nine instances. Most patients in the study were taking only the quinolone antibacterial agent at the appearance of the symptoms. The majority (80%) reported the intake of the same or another quinolone in the past, without any reaction, suggesting a true sensitization.

Specific serum IgE was demonstrated in 30 cases, using epoxy-activated sepharose 6B with a spacer arm, according to the method of Baldo and Harle [48]. This solid phase is particularly suitable for identifying specific IgE towards drugs with a low molecular weight. The specificity of the binding has been established by means of inhibition methods [49], using quinolone molecules and other non-related drugs. A high degree of crossreactivity among quinolones emerged not only from the clinical history, but also by the in-vitro test; 80% of patients showed specific serum IgE to more than one quinolone.

Delayed maculopapular exanthemas

Quinolones can also elicit immune reactions in which T cells are directly involved. These may account for more

severe reactions such as hepatitis or bullous skin disease, and also for the rather frequent maculopapular drug eruption. Recently, Schmid *et al.* (unpublished data) analysed four patients with delayed reactions (maculopapular drug eruption) to ciprofloxacin or norfloxacin treatment, and generated T-cell clones specific to these quinolones. Three different patterns of crossreactivity could be found; some T-cell clones reacted exclusively with ciprofloxacin, some recognized two quinolones only and some T-cell clones showed a broad crossreactivity, recognizing up to five different compounds. Interestingly, the T-cell clones recognized ciprofloxacin without the need for covalent binding to a protein, suggesting that IgE and T cells react with different structures, namely a quinolone covalently bound to a peptide for IgE and the quinolone structure itself for T cells.

Photosensitivity

Photosensitivity is one of the major side-effects of quinolones; photo-onycholysis has also rarely been reported [50]. Many authors described photosensitive reactions [51–63] as early as nalidixic acid was extensively used, but fluoroquinolones have also been responsible for these cases, leading sometimes to the withdrawal of the molecule, for example feroxacin. Quinolones can elicit both phototoxic and photoallergic reactions.

An immune mechanism has been demonstrated in patients with photosensitivity and positive oral photo-challenge with lomefloxacin, feroxacin and enoxacin [64]. Peripheral blood mononuclear cells from these patients have been photomodified with quinolones by means of exposure to ultraviolet A light *in vitro*; they were able to stimulate a weak but definite proliferation of homologous peripheral blood mononuclear cells.

Haematological and coagulation disorders

Temafloxacin is a trifluorinated quinolone antibiotic approved in the United States in 1992 and voluntarily withdrawn from the world markets by the manufacturer 4 months later because of the high frequency of severe, even fatal adverse reactions. The Food and Drug Administration (USA) described 95 cases, considered to be severe, of 'temafloxacin syndrome', characterized by severe haemolysis, sometimes accompanied by the involvement of other organs, resulting in a multiorgan syndrome with acute renal failure, occasional eosinophilia, thrombocytopenia, disseminated intravascular coagulation and abnormalities of liver function. On the basis of available data, the authors indicated that the haemolytic anaemia was presumably caused by circulating immune complexes [14]. In some patients, this diagnosis was confirmed *in vitro* [65]. It is noteworthy that the spectrum of reactions reported with the use of temafloxacin seems qualitatively similar to that reported with

ciprofloxacin, but the frequency of severe adverse reactions was very different. This was estimated at one per 3500 patients for temafloxacin as opposed to one per 17 000 for ciprofloxacin, one per 25 000 for norfloxacin and one per 33 000 for ofloxacin [66].

Occasional cases of thrombocytopenia and acute haemolytic anaemia have been described since the appearance of nalidixic acid [17,67–70], and after with fluoroquinolones, by various authors [71–76]; one reporting 19 cases in which pefloxacin was suspected [77].

Ciprofloxacin has been suspected to provoke leukopenia [78], fatal pancytopenia [10], acquired transitory von Willebrand syndrome [79] caused by the elicitation of a factor VIII inhibitor [80], Schönlein–Henoch purpura [81], and fatal thrombotic thrombocytopenic purpura [12].

Acute interstitial nephritis

Quinolone-induced renal toxicity is very uncommon; but cases of acute interstitial nephritis caused by an immune mechanism have been described by 28 authors [8,9,82–107] in 46 cases. The clinical presentation includes acute arthralgias, eosinophilia, eosinophiluria, fever, skin rashes, proteinuria, haematuria, pyuria, loin pain and renal failure [108]. The majority was elicited by the use of ciprofloxacin (37) but also norfloxacin (five), piromidic acid (three) and ofloxacin (one). Unfortunately, only case reports and temporally related events were described and no in-depth analysis was attempted. The diagnosis of interstitial nephritis has been confirmed by a biopsy in 14 instances. Autoantibodies against a 65 000 kD protein expressed in human normal kidney and liver microsomes have been found in four cases, and in two cases of acute quinolone-induced hepatitis [90]. A lymphocyte transformation test has been performed in seven individuals with negative results [84,87,91,93,100,105], and a macrophage migration inhibition was performed in one [105].

Acute hepatitis and acute cholestatic jaundice

Various fluoroquinolones have been implicated in cases of acute hepatitis and acute cholestatic jaundice [2,7,15,18,19,90,109–126]: ciprofloxacin, ofloxacin, norfloxacin, pefloxacin, levofloxacin, gatifloxacin, enoxacin and moxifloxacin. An exceeding rate of hepatotoxicity emerged for trovafloxacin, a third-generation, highly potent compound. Since its use was authorized in the United States in December 1997, 152 cases of serious hepatic events have been reported to the Food and Drug Administration (140 in the United States and 12 in Europe). Liver transplants were needed in six patients and death occurred in five. It was then suspended in Europe and restricted in the United States in June 1999, although hepatotoxicity had occurred very rarely (0.006% of treated patients). The association with

hypersensitive manifestations such as skin rashes, and the presence of eosinophils both in the liver biopsy and in the peripheral blood suggested an immune mechanism [2].

Crossreactivity

Crossreactivity is becoming an increasing problem, as these compounds tend to be used more widely. The structural similarity of quinolones, the clinical data of crossreactions and some in-vitro analysis suggest a frequent crossreactivity [21,25,36,46,55,59,60,127–129].

The clinical data and the available in-vitro data suggest that a patient with a severe reaction to one quinolone should not be treated again with another quinolone. If, however, the reaction was mild, an attempt at a renewed treatment can be undertaken. Indeed, in a recent safety study with gemifloxacin, only 10% of patients who had previously developed a mild exanthema to gemifloxacin reacted to ciprofloxacin (unpublished data). Therefore, as outlined in the accompanying review on cross-reactivity [130] the structural relationship and the strengths of immune reaction appear to decide whether crossreactivity has become clinically manifest.

Conclusion

Quinolones, like other antibacterial agents, can cause immune-mediated adverse side-effects. Whereas the risk–benefit profile is considered to be low for most reagents, others have been withdrawn from the market because of severe and sometimes fatal side-effects. Some side-effects have recently been systematically analysed. Anaphylactic reactions are associated with the production of IgE antibodies to the quinolone, which are crossreactive with different other quinolones *in vitro*. No general pattern can be delineated, suggesting that in a patient with such reactions all other quinolones are contraindicated, because clinical crossreactivity is well documented. Similarly, in some cases of maculopapular exanthema, ciprofloxacin-specific T cells have been shown, which crossreact with related compounds. Further studies are needed to understand the relationship of the more severe, immune-mediated reactions and the sometimes preferential manifestation of hypersensitivity in certain organs.

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