Antimicrobial Safety and Tolerability: Differences and Dilemmas

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The adverse drug reactions associated with antimicrobials have become a topic of major importance and concern in the last few years. Antimicrobial toxicity may take many forms, varying from mild, transient phenomena to dramatic, life-threatening events such as seizures or cardiac arrhythmias. We review the toxicity of antimicrobials in general and of the fluoroquinolones in particular and attempt to explain the adverse events by use of structure–adverse event relationships where possible. There are currently 5 main mechanisms that can be invoked to explain antimicrobial toxicity: direct effects, hypersensitivity, changes in microbial flora, drug interactions, and microbial lysis. The adverse drug reactions seen with fluoroquinolones are explained on the basis of these 5 mechanisms. The various organ systems affected by the fluoroquinolones are considered; then individual members of the fluoroquinolone class are reviewed. The unexpected and dramatic problems encountered with temafloxacin and trovafloxacin are discussed as well.

Since their discovery a few decades ago, antimicrobials have proven themselves to be life-saving magic bullets; some of their discoverers have been rewarded with no fewer than 3 Nobel prizes. However, there is a dark side to these compounds in the form of adverse events. These may be mild, transient laboratory phenomena that the patient may not even be aware of, or they may be dramatic, life-threatening events in the form of seizures, cardiac arrhythmias, or anaphylaxis. We review some of the mechanisms of antimicrobial toxicity, beginning with antimicrobials in general, then focusing on the fluoroquinolone class of drugs. Our purpose is to draw clinicians’ attention to this problem, to highlight just how little is known about toxicity in general, and to highlight problems associated with many of the drugs that we prescribe on a daily basis in particular.

MECHANISMS OF ANTIMICROBIAL TOXICITY

There are 5 main mechanisms of antimicrobial toxicity: direct effects, hypersensitivity, changes in microbial flora, drug interactions, and microbial lysis. Each is discussed in more detail below.

Direct effects. Direct effects on tissues and organ systems resulting in toxicity have been described with a number of antimicrobial agents. Some of the best known examples include chloramphenicol and anemia; amphotericin B and hypokalemia; and aminoglycosides and eighth-nerve toxicity. The exact mechanism may vary, but it is thought that in each of these situations, the adverse effect was the result of a direct interaction between the drug and/or one of its metabolites and a specific tissue or organ in the body. The reversible myelosuppressive effects seen with chloramphenicol are the result of inhibition of mitochondrial protein synthesis, whereas irreversible aplastic anemia is thought to be secondary to changes in stem cell genes [1, 2].

The hypokalemia observed in some patients treated with amphotericin B is the result of a reduction in renal blood flow and a distal tubular permeability defect [3]. Some patients treated with aminoglycosides have unfortunately experienced eighth-nerve damage, resulting...
in either deafness or vertigo. These adverse events result from aminoglycoside-induced damage to either the inner hair cells of the organ of Corti or the sensory cells of the vestibular system [4, 5].

**Hypersensitivity.** The terms “drug allergy” and “hypersensitivity” are often misused, particularly in the context of antimicrobials and selected adverse reactions. Patients often describe a response as an allergy when in fact it is often clear that none of the 4 types of hypersensitivity reactions associated with allergies have been involved. The most common examples of this are gastrointestinal (GI) upset or diarrhea associated with an antimicrobial substance; these obviously do not represent hypersensitivity reactions. The reaction of primary concern for physicians is type I hypersensitivity, because there is a risk that the response may proceed to anaphylaxis. Other examples thought to be mediated by a hypersensitivity mechanism are Coombs’ positive hemolytic anemia, serum sickness, Stevens-Johnson syndrome, and erythema nodosum.

**Changes in microbial flora.** It is known from animal and human studies that a course of antimicrobial therapy, particularly of broad-spectrum agents, may diminish much of the host flora and render the subject at risk of colonization and possible infection by another pathogen. One of the most common examples is vaginal Candida infection in women who have recently completed antimicrobial therapy. More extreme examples are patients who develop fungal superinfection after a course of antimicrobial therapy for a known bacterial infection—for example, Aspergillus pneumonia in a patient who recently finished a course of treatment for bacterial peritonitis.

**Drug interactions.** The ingestion of 2 or more drugs may result in unforeseen and unexpected adverse reactions. At one end of the extreme, one drug may render another useless by interfering with its absorption, whereas in other cases, drugs may display synergistic toxicity, resulting in adverse events that neither drug alone would produce. An example of the former can be seen with ingestion of tetracyclines or fluoroquinolones and antacids. Chelation with cations will seriously impair absorption of the antimicrobial drug. Other types of toxicity are hypoglycemia seen with chloramphenicol and tolbutamide and absorption of the antimicrobial substance. These obviously do not represent hypersensitivity reactions. The reaction of primary concern for physicians is type I hypersensitivity, because there is a risk that the response may proceed to anaphylaxis. Other examples thought to be mediated by a hypersensitivity mechanism are Coombs’ positive hemolytic anemia, serum sickness, Stevens-Johnson syndrome, and erythema nodosum.

**Microbial lysis.** It is thought that the occasional worsening of a patient’s clinical condition may be secondary to the release of toxic products after microbial lysis. Two well-known reactions are the Jarisch-Herxheimer reaction, seen when patients with syphilis of the brain are treated with IV penicillin [7], and erythema nodosum leprosum, which describes the appearance of disseminated, tender, inflamed nodules that erupt over the skin that are associated with fever and, in some cases, polyneuritis, glomerulonephritis, and severe joint pain. This is seen in up to 50% of patients with lepromatous leprosy treated with dapsone [8].

**FLUOROQUINOLONES: GENERAL CONSIDERATIONS**

The fluoroquinolones are, to say the least, an interesting and at times unpredictable class of antimicrobial agents. They include a number of compounds that are used extensively in clinical practice, and these drugs have had a major impact on antimicrobial chemotherapy. The quinolones are synthetic agents that date back to the early 1960s, to the discovery of nalidixic acid, which was used primarily as a urinary tract antiseptic. Later development provided agents with broader activity, increased potency against selected pathogens, and improved pharmacokinetic and pharmacodynamic characteristics.

The structural feature that remains constant throughout the drug class is the bicyclic aromatic core consisting of 2 fused 6-membered rings. Classification of the quinolones has not been officially formalized, and in a recent book dealing with these drugs, 2 different classifications were proposed [9]. Both use the concept of first-, second-, and third-generation compounds. However, one system appears to be based primarily on an in vitro spectrum of activity, whereas the other system seems to be dependent on the structural characteristics of the various agents [10, 11]. In the former classification proposed by Ball [10], first-generation compounds provide coverage primarily for the Enterobacteriaceae. The second-generation compounds are divided into those with enhanced but predominant gram-negative activity and those with balanced broad-spectrum activity. Third-generation drugs are those with enhanced gram-positive activity [10].

In the Gootz and Brighty classification, as one moves from first- to second-generation agents, the main changes are the addition of fluorine at the 6 position and a piperazine derivative at the 7 position. As one moves to the third-generation agents, a 2,4-difluorophenyl is added at the 1 position, and the 7 position could have a piperazine, a pyrrolidine, or more complex cyclic diamine [11].

Just as there are structure-activity relationships, there are also structure-side effect relationships that have been determined (figure 1). Examination of the fluoroquinolone molecule reveals some interesting positions whose substituents are worthy of comment, notably R1, R7, and X8. The R1 substituents usually encountered in most fluoroquinolones are ethyl, cyclopropyl, and 2,4-difluorophenyl. The R1 cyclopropyl appears to increase theophylline interactions and clastogenicity. The 2,4-difluorophenyl group has not been implicated directly in any toxic reactions; however, it is worth noting that both temafloxacin and trovafloxacin have this substituent at the R1 position.

Positions 3 and 4 are linked to metal binding and chelation,
and there is some suggestion that R5 substituents may influence phototoxicity and genetic toxicity. Without question, though, the most important site for structure–side effect relationships is R7. Substituents at this site are involved with CNS toxicity, specifically convulsions, because this site has the greatest influence on \( \gamma \)-aminobutyric acid (GABA)–binding inhibition [12]. It also is important for nonsteroidal anti-inflammatory drug–potentiated CNS effects and quinolone–theophylline interactions [12]. In studies of mammalian cell cytotoxicity, the adverse changes were most dependent on the groups at R7 and X8 [13]. Three-substituted pyrrolidines at R7 and halogens at X8 provided the most cytotoxic compounds [13].

Quinolones are usually zwitterions, and any changes that increase water solubility in the physiologic pH range of urine, such as alkyl substitution of the R7 substituent, will diminish the likelihood of crystalluria [12]. X8 is the single most important site for phototoxicity and plays a role in genetic toxicity as well.

**SYSTEMS**

Adverse drug reactions can involve specific organ systems, such as the GI tract, the CNS, or the kidneys, or may represent a hypersensitivity reaction. For the fluoroquinolone class of antimicrobials, the most common adverse effects involve the GI tract, skin, CNS, and events that resemble allergic reactions [14, 15]. Here we review the individual systems and the types of adverse events that have been described, as well as their postulated mechanisms of action.

**GI tract.** The adverse events reported for fluoroquinolones involving the GI tract are usually mild and do not often require discontinuation of therapy. It is not presently clear that any structure–adverse event relationship exists, and adverse effects associated with the GI tract are thought to be due to either GI irritation, a CNS effect, or both [12, 16]. The most commonly reported events are nausea and vomiting, but other events include dyspepsia, anorexia, and diarrhea, with an overall incidence of 2%–20% [17–22]. Although pseudomembranous colitis is certainly an unusual adverse event, it has been reported with quinolone use [23, 24]. Taste perversion rates of 17% overall have been reported in patients treated with grepafloxacin [25].

The rank order of fluoroquinolone agents for GI adverse effects is as follows: fleroxacin, grepafloxacin > trovafloxacin > sparfloxacin > pefloxacin > ciprofloxacin, levofloxacin > norfloxacin > enoxacin > ofloxacin [22].

**CNS.** Adverse events involving the CNS are the second most frequently encountered form of quinolone toxicity and are usually divided into minor and serious events. The overall incidence is 1%–2% and includes a broad range of effects, such as dizziness, drowsiness, headache, sleep disorders, acute organic psychosis, delirium, and convulsions [12, 22]. CNS effects can occur as a result of either direct action of a drug on CNS receptors or as a result of interaction between a quinolone and another pharmacologic agent. Direct actions themselves can be further divided into blocking of the GABA receptor and primary excitatory effects mediated via the N-methyl-D-aspartate (NMDA) receptor mechanisms [18, 26].

If the fluoroquinolone binds to the GABA receptor, it prevents the natural ligand GABA from binding, resulting in CNS stimulation. This can be augmented by the presence of 4-phenylacetic acid, which is an active metabolite of the nonsteroidal agent fenbufen [27]. This unfortunate interaction was dramatically highlighted when 7 Japanese patients experienced seizures while on enoxacin and fenbufen therapy [28].

The R7 side chain substituent correlates best with the degree...
of GABA-binding inhibition. Unsubstituted piperazines exhibit the greatest degree of binding, with pyrrolidyl quinolones intermediate in their effect and bulky alkylated side chains showing the least amount of binding [12, 29]. Certain β-lactams, such as penicillins, cephalosporins, and carbacephams, are also capable of interfering with GABA binding, resulting in adverse effects on the CNS [30].

It has been suggested that the likelihood of convulsions occurring in animal models is more closely related to the NMDA receptor and may explain the higher incidence of CNS effects seen in trovafloxacin postmarketing surveillance data. This receptor has been postulated to play a role in seizures secondary to fluoroquinolones in animals and may be prevented with the use of NMDA antagonists [31].

We alluded to drug interactions as a possible mechanism for CNS toxicity, and the example we gave was of fenbufen and its metabolite 4-biphenylacetic acid enhancing quinolone binding to the GABA receptor. Another example is the interaction between fluoroquinolones and theophylline. Theophylline is metabolized by cytochrome P-450 enzymes that in turn may be inhibited by certain fluoroquinolones. Inhibition of theophylline metabolism would inevitably result in CNS toxicity that might include seizures [12, 32]. Other types of drug interactions will be discussed in a separate section. The rank order of fluoroquinolones associated with adverse drug reactions of the CNS is as follows: fleroxacin > trovafloxacin > grepafloxacin > norfloxacin > sparfloxacin > ciprofloxacin > enoxacin > ofloxacin > pefloxacin > levofloxacin [22].

Liver. Adverse events involving the liver vary from mild elevation of liver enzymes to cholestatic syndromes to hepatic failure resulting in liver transplantation or death. Recent events involving trovafloxacin have once again shown how potentially dangerous clinical trials involving new chemotherapeutic agents can be. The trovafloxacin issues are discussed in a separate section that deals with unexpected adverse events, as were seen with trovafloxacin and one of its predecessors, temafloxacin.

In general, elevations of liver enzymes are noted in 2%–3% of fluoroquinolone recipients. These are usually mild elevations that are not associated with any overt clinical findings, and the elevation typically reverts to normal levels when the drug is discontinued. Hepatotoxicity can occur as the result of a direct chemical effect because many drugs are concentrated in the liver; hepatotoxicity may also occur by drug allergy or hypersensitivity reactions.

Skin. The use of skin as a category is, in a sense, misleading because the skin is not directly involved by the drug in the way that the liver or CNS are. Instead, it often represents a final common pathway as a means of expression of toxicity mediated either by an allergic reaction, a histamine release phenomenon, or photosensitivity. Drug allergy can be expressed in a number of ways, and skin reactions vary from a mild rash to urticaria to a severe exfoliative dermatitis. The overall rate of adverse events involving skin with fluoroquinolone use is 0.5%–3% [21].

As part of allergic or hypersensitivity responses to foreign molecules, anaphylactic reactions may occur. Although usually thought of as more likely to occur with a β-lactam, both anaephylactoid and anaphylactic reactions have been seen in up to 1.2 cases per 100,000 patients treated with the drug [21].

The term “photosensitivity” includes both photoallergy and phototoxicity. The former is rare, requires previous exposure to the offending fluoroquinolone, and is dependent on the presence of photohaptenic substituents [33]. The clinical manifestations typically appear a day or so after exposure. This is in contrast to phototoxic reactions, which are more frequent and can appear in anyone, even with initial exposure, providing that there was sufficient exposure to ultraviolet light and that a drug known to cause it was used by the patient.

The mechanism of phototoxicity is believed to be due to the generation of singlet oxygen and toxic radicals. After exposure to ultraviolet A radiation, certain fluoroquinolones induce toxic agents that can in turn damage cell membranes, resulting in an inflammatory response [34, 35]. The greatest degree of phototoxicity occurs when the X8 substituent is a halogen, particularly fluorene, and a bulky side chain; a methyl group at R5 may contribute as well [12, 22]. The rank order for phototoxicity is as follows: lomefloxacin, fleroxacin > sparfloxacin > enoxacin > pefloxacin > ciprofloxacin, grepafloxacin > norfloxacin, ofloxacin, levofloxacin, trovafloxacin [22].

Cardiac. The main area of interest relating to cardiac toxicity is prolongation of the QT interval. This phenomenon was well described with erythromycin, and it appears that it may be an effect of fluoroquinolones as a class. The mechanism by which this occurs is not known, although it is thought that it is likely multifactorial in nature. Certainly female sex appears to be one predisposing factor [36]. During trials with sparfloxacin, it was noted that clinically significant QT prolongation to >500 ms was occurring. Later, it was found that serious cardiac events occurred in 7 patients receiving sparfloxacin, all of whom had underlying cardiac disorders [37]. Animal studies revealed that at high doses, even with ciprofloxacin (300 mg/kg), ventricular tachycardia could be induced [38].

The obvious concern is QT prolongation and the development of a form of ventricular tachycardia known as torsade de pointes. The problem is that there is no established threshold for an upper limit of QT duration beyond which arrhythmia will occur and below which one is known to be safe.

The package inserts of moxifloxacin and gatifloxacin indicate that these drugs have been associated with QT prolongation and that they should be avoided in certain patients. The patients who should avoid these drugs are people with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA or class III antiar-
### Table 1. Overall incidence (%) of adverse effects associated with fluoroquinolones on the basis of US and European data.

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Total adverse effects</th>
<th>Gastrointestinal effects</th>
<th>CNS effects</th>
<th>Skin effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin po</td>
<td>5.8</td>
<td>3.4</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>9.1</td>
<td>3.9</td>
<td>4.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Pefloxacin</td>
<td>8</td>
<td>5.6</td>
<td>0.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>4.2</td>
<td>2.6</td>
<td>0.89</td>
<td>0.53</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2–9.9 (3.3)</td>
<td>5.1</td>
<td>0.2–1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>NS</td>
<td>5.1</td>
<td>5.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Sparfloxacin (400 mg or 200 mg)</td>
<td>21</td>
<td>11</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Sparfloxacin RTI (400 mg or 200 mg)</td>
<td>Overall: 32; related: 25.3</td>
<td>10</td>
<td>0.3</td>
<td>1.9*</td>
</tr>
<tr>
<td>Grepafloxacin (600 mg)</td>
<td>Related: 47</td>
<td>15</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Trovafloxacin RTI (100 mg or 200 mg)</td>
<td>Related: 12.7</td>
<td>6.1</td>
<td>4.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Trovafloxacin (100 mg or 200 mg)</td>
<td>27</td>
<td>4–7</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Moxifloxacin (400 mg)</td>
<td>Related: 27; comparators: 24.5</td>
<td>8</td>
<td>5.4</td>
<td>2</td>
</tr>
</tbody>
</table>

**NOTE.** NS, not stated; po, oral; RTI, respiratory tract infection. Data from [14].

* Phototoxicity, 7.4.

rhythmics because of the lack of clinical experience with these drugs in such patient populations.

**Musculoskeletal.** Adverse events involving the musculoskeletal system are either arthropathy or tendonitis. Arthropathy is thought to be an effect of the drug class, and in animal models, it has been described with all fluoroquinolones, without any 1 structure predominating [12]. Although a good deal of controversy surrounds this subject, it is thought that the overall incidence is on the order of 1% [39]. Typically, it seems to involve weight-bearing joints of patients <30 years of age and disappears after discontinuation of therapy.

Tendonitis and tendon rupture are rare events associated with fluoroquinolone use, but when they occur, the Achilles tendon is typically involved, either unilaterally or bilaterally. Predisposing factors may include steroid use, renal disease, hemodialysis, and transplantation [14]. It is an effect of this class of drugs, and inflammation may persist for several months in 10% of patients who develop this problem [40].

**Renal.** Nephrotoxicity is uncommon, but when it is seen, can be a result of either direct damage or a hypersensitivity response. Renal adverse events include crystalluria, hematuria, interstitial nephritis, and acute renal failure. Usually patients are older, with most >65 years of age [22, 41]. Crystalluria is a reflection of the solubility of a fluoroquinolone in urine. Most agents in this drug class are zwitterions and are less soluble under neutral or alkaline pH conditions. Because human urine is usually acidic, crystal formation is less likely to occur.

**INDIVIDUAL DRUGS**

In this section, we consider selected quinolones individually. The drugs we consider are ciprofloxacin, levofloxacin, sparfloxacin, grepafloxacin, and moxifloxacin, which provide a representative sampling of both older and newer agents. Table 1 lists the overall incidence of the 3 most common adverse effects by system associated with fluoroquinolones from both US and European databases.

**Ciprofloxacin.** Ciprofloxacin is a second-generation fluoroquinolone that has been marketed worldwide for over a decade and that has a remarkable safety record. As shown in table 1, the overall incidence of adverse effects involving the GI tract, CNS, and skin is 5.8%, with values for each of these of 3.4%, 1.1%, and 0.7%, respectively [21]. Occasional episodes of severe CNS and liver toxicity have been reported manifesting as convulsions and serious elevations of liver function test values and liver failure, respectively [41, 42]. Renal toxicity has also been reported secondary to hypersensitivity and has included renal failure, with 12 patients requiring dialysis in 1 series [43].

As if to prove that no drug is free of adverse effects, despite its remarkable safety record, fatal hypersensitivity vasculitis has been reported with ciprofloxacin therapy [44]. Ciprofloxacin is also one of a number of agents, including norfloxacin, pefloxacin, enoxacin, and sparfloxacin, which are known to cause tendonitis [45].

**Levofoxacin.** Levofloxacin is the active l-isomer of of-
loxacin and as such is not as new an agent as some might think. Generally, the drug has been quite safe and well tolerated, and other than ciprofloxacin, it is one of the fluoroquinolones that has seen considerable postmarketing clinical use. The overall incidence of possible or probable drug-related adverse effects is 2%–9.9% [46–48]. If we look at specific side effects such as dizziness and phototoxicity, the differences between levofloxacin and some of the other fluoroquinolones are highlighted. For example, with trovafloxacin, the incidence of dizziness was reported as 12.5 per 100,000 patients receiving the drug, compared with 0.5 per 100,000 for levofloxacin (US Food and Drug Administration, data on file). For phototoxicity, rates of 0.03% for levofloxacin versus 7.9% for sparfloxacin dramatically emphasize the differences between these agents [14, 22]. Although no problems with corrected QT (QTc) prolongation were noted during the development of levofloxacin, some cases of torsade de pointes (0.3 per 100,000 patients treated) have been reported in the postmarketing phase (US Food and Drug Administration, data on file).

Sparfloxacin. This is one of the compounds with a halogen (fluorine) at the 8 position. Adverse effects of sparfloxacin and its comparators were examined in 6 phase 3 trials, and sparfloxacin did statistically worse in 3 categories (phototoxicity, pruritus, and increased QTc interval) and statistically better in 6 categories (diarrhea, nausea, insomnia, abdominal pain, taste perversion, and vomiting). We have already mentioned that serious cardiac events occurred in 7 patients receiving sparfloxacin [49]. As with all halogenated fluoroquinolones at the 8 position, phototoxicity is one of the main adverse effects.

Grepafloxacin. Grepafloxacin had been on the market for a few years and has been used primarily as a respiratory tract anti-infective agent. It generally compares well with other agents, including nonquinolone comparators, with a few notable exceptions, such as a remarkably high incidence of taste perversion. In patients receiving 600 mg/day, this side effect was reported in 26% of patients [50]. Overall, figures of 17% for taste perversion and 15% for nausea were reported for grepafloxacin in preregistration trials, and abnormal liver function tests were reported in up to 16% of patients given the drug in Japan [51, 52].

A few months ago, the drug was withdrawn from the market because of concerns about cardiac safety. In a review of the safety of the drug, it was determined that because an effect of grepafloxacin on cardiac repolarization manifested as QT interval prolongation, some patients may be at risk of torsade de pointes when treated with this agent.

Moxifloxacin. Moxifloxacin is a promising new compound that is still undergoing clinical trials; it has been released into the market in a number of countries. Obviously, far fewer patients have received moxifloxacin than have received any of the above agents, but it is still worthwhile to look at the data available so far. The incidences of GI and CNS effects reported are 7.8% and 2.9%, respectively (Bayer AG; data on file for 4296 patients) [53]. It is not associated with any significant degree of phototoxicity, and the mean prolongation of the QTc interval in studies specifically designed to monitor this phenomenon was 6 ms [53]. No associated arrhythmias or other cardiovascular events have been reported [53].

Special situations. Two fluoroquinolones, temafloxacin and trovafloxacin, are of special interest because of unexpected adverse effects. Temafloxacin was an oral fluoroquinolone with a broad spectrum of in vitro activity, and its launch was met with a great deal of enthusiasm and expectation. It was withdrawn a few months later because of a constellation of adverse events that have come to be known as the temafloxacin syndrome. This is defined as hemolytic anemia or involvement of at least 2 of the following 3 systems in the absence of hemolysis: renal, hepatic, and coagulation [54]. Hemolytic anemia is defined as decreased concentration of hemoglobin associated with an increased level of bilirubin, increased lactate dehydrogenase, decreased serum haptoglobin, and hemoglobinuria, free hemoglobin in plasma, or both. Renal dysfunction is defined as an increase in serum creatinine to at least 1.5 mg/dL. Hepatic dysfunction is defined as aspartate aminotransferase levels of >120 U/L, total bilirubin of 4 mg/dL, or both. Coagulopathy is defined as a platelet count of < 100 X 10^7 cells/L, protime increased by at least 1 s, or evidence of disseminated intravascular coagulation. The typical presentation included discolored urine, fever, jaundice, nausea, vomiting, abdominal pain, myalgia, back pain, or some combination of these, and in most patients, it resolved several days to weeks after discontinuing therapy.

Of the case patients reviewed, 95 met the criteria for hemolysis and 19 met the criteria for multisystem disease. The demographic characteristics of the patients with hemolysis did not reveal anything obvious. The mean age was 57 years, with women outnumbering men, which likely reflects increased temafloxacin use by women rather than any sex-related susceptibility. Over half the patients with hemolysis (58%) had been given doses of 600 mg b.i.d., whereas 39% received 400 mg b.i.d.

The mean time to onset of hemolysis was 6.4 days. Of those with hemolysis, 10 of 95 had received only 1 dose of temafloxacin, and 7 of these had been given a quinolone before this; 4 of 7 had been given temafloxacin a few weeks before. Of the 85 who had received >1 dose, only 11 had been given fluoroquinolone previously.

The severity of hemolysis did not correlate with the dose of drug or the indication for quinolone treatment. Of the 95 patients with hemolysis, renal dysfunction developed in 54, and
34 (63%) needed dialysis. Renal biopsy studies showed acute tubular necrosis together with "pigmented casts" and evidence of "hemoglobin plugging." Forty-eight (51%) of 95 patients had evidence of hepatic dysfunction, and 33 (35%) had evidence of coagulopathy. Four patients experienced CNS complications, including seizures secondary to cerebrovascular accidents. Two patients with hemolysis died of ischemic colitis and disseminated intravascular coagulation and of renal failure.

The mechanism by which the temafloxacin syndrome occurred is not fully understood. Three questions regarding this syndrome remain: Was hemolysis the result of direct toxicity, or was it immune mediated? Did hemolysis lead to renal, hepatic, and coagulation abnormalities, or was some common underlying process responsible for all of the manifestations? And what is it about the temafloxacin molecule that caused any or all of these problems?

In an excellent review of this subject, Blum et al. [54] postulate that temafloxacin induced an immune hemolytic anemia likely secondary to immune complex formation and that hemolysis led to the involvement of the other systems. The structural aspect of the temafloxacin molecule that has been associated with the most speculation is the difluorophenyl substituent at the N1 position. This is the same substituent that is seen with tosufloxacin and trovafloxacin.

Trovafloxacin has also been associated with unexpected adverse events. After its release, postmarketing surveillance revealed a surprisingly high incidence of hepatotoxicity. Of 2.5 million patients treated with the drug, a total of 140 cases of serious hepatic events were noted, with 14 cases of acute liver failure [55, 56]. The unpredictable toxic reactions took place 1–60 days after the start of therapy and were possibly immunological in nature. In one-third of patients, there was evidence of hypersensitivity reactions, and in a small number of patients, the toxicity followed exposure to a second course of treatment with trovafloxacin or another fluoroquinolone. Although most patients recovered completely, 5 required liver transplants, and 5 deaths (1 after liver transplant) have been associated with trovafloxacin-induced hepatotoxicity, although the relationship is not proven. A review of the cases has not revealed any factors that are predictive of hepatotoxicity and has not indicated a subgroup of patients in which such reactions are more likely to occur.

Six patients of the first 40 to experience serious toxicity had evidence of eosinophilic hepatitis on liver biopsy, and 30% of patients with toxicity had peripheral eosinophilia. To put it in its proper perspective, however, an incidence of 0.0056% (140 in 2.5 million) is certainly rare and is similar to the reported rates of liver toxicity associated with the β-lactam antibiotics fluoxacillin and amoxicillin–clavulanic acid [57, 58].

The only other adverse effect of trovafloxacin that stands out is dizziness. This occurred with an incidence of 11%, was dose related, mild, tended to disappear after the first few doses, and occurred more often in women of childbearing age [59].

It is clear that antibiotics are miraculous agents that are literally capable of saving life and limb. Their use, however, can be associated with toxicity, and the more we understand the complex arena of the structure–adverse event relationships, the more likely we will be to avoid adverse consequences as new compounds are developed. It has also become apparent that with adverse events of low frequency, postmarketing surveillance assumes more importance than ever before.

References


