REVIEW ARTICLE

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Fluoroquinolone-Induced Renal Failure

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Contents

Abstract

Fluoroquinolones are generally well tolerated, clinically useful antimicrobials. This paper highlights rare, but potentially serious, adverse effects involving the kidney. Other antimicrobials have long been known to cause various forms of nephrotoxicity occurring as allergic interstitial nephritis, granulomatous interstitial nephritis, necrotising vasculitis, allergic tubular nephritis or a tubular necrosis. A Medline search (1985 to May 1999) of ciprofloxacin, norfloxacin, levofloxacin, ofloxacin, trovafloxacin, enoxacin, sparfloxacin, grepafloxacin, gatifloxacin, clinafloxacin and moxifloxacin was conducted to ascertain the incidence and features of fluoroquinolone nephrotoxicity. Unfortunately, the data primarily consist of case reports and temporally related events. The incidence of these adverse effects is hard to estimate, and the cause may be multifactorial. While the use of ciprofloxacin appears to increase the risk, this may be due to its longer and more widespread use when compared with the newer agents.

Antimicrobials often concentrate in the kidney and can potentially damage the organ by a variety of mechanisms, including direct tubular injury, interstitial inflammation (allergic interstitial nephritis), changes in renal electrolyte levels, or damage to the glomerular apparatus.[1,2]

Acute renal failure was a rare adverse event associated with the older quinolone antibacterials, e.g. piromidic acid.[3] Cases resembled intense interstitial nephritis and were suggested to involve a hypersensitivity reaction.[3] Early review of ciprofloxacin also noted haematuria, minor transient elevations in the levels of serum creatinine or blood urea nitrogen, and hyaline and amorphous casts in the urine.[4]

1. Literature Search

A Medline search (1985 to May 1999) of cip-

rofloxacin, norfloxacin, levofloxacin, ofloxacin, trovafloxacin, enoxacin, sparfloxacin, grepafloxacin, gatifloxacin, clinafloxacin and moxifloxacin was conducted to ascertain the incidence and features of fluoroquinolone nephrotoxicity. Unfortunately, the data primarily consist of case reports and temporally related events. The incidence of these adverse effects is hard to estimate, and the cause may be multifactorial.

2. Ciprofloxacin Nephrotoxicity

Other antimicrobials have long been known to cause various forms of nephrotoxicity occurring as allergic interstitial nephritis, granulomatous interstitial nephritis, necrotising vasculitis, allergic tubular nephritis or a tubular necrosis. Nephrotoxic reactions to newer fluoroquinolones appear to be unusual but potentially serious.

2.1 Allergic Interstitial Nephritis

Allergic interstitial nephritis (AIN) is thought to be the most common cause and is attributed to a type III hypersensitivity reaction.[5] The identification of fluoroquinolone-induced AIN is usually based on the clinical presentation which includes acute arthralgia, eosinophilia, eosinophiluria, fever, skin rashes, proteinuria, haematuria, pyuria, loin pain and renal failure.[6-8] Onset of symptoms and azotaemia occur most commonly within 3 to 10 days after initiation of the fluoroquinolone (table I). A history of recent exposure to a potential nephrotoxin, and improvement after the drug is discontinued, are also typical.[8]

The clinical course and laboratory findings in AIN are unspecific, not dose related, and are often complicated by other concurrently administered agents.[21] Nonoliguric renal failure is more common than oliguric renal failure.[17] Glomerular filtration is often unaffected, as acute drug-induced AIN is a disease affecting the tubular system of the kidney more than the glomeruli.[8] Renal biopsy is almost always needed to make a definitive diagnosis of AIN. However, this may not always be practical, depending on the patient's overall condition.

Treatment of fluoroquinolone-induced AIN consists of hydration and perhaps transient dialysis. Corticosteroid use remains controversial and is still not proven to benefit clinical outcome. Although it has been reported to be successful in several cases of acute antibiotic-induced AIN, use of corticosteroids is seldom indicated provided that the offending drug is withdrawn. Corticosteroid treatment may also be dangerous and is often withheld.[26] Most cases resolve in time with normalisation or near normalisation of renal function.

2.2 Interstitial Nephritis

Table I summarises cases of interstitial nephritis following administration of fluoroquinolones. Typically, acute renal toxicity developed within hours to weeks in patients who had pre-existing underlying renal pathology.[8,9] Other than elevation of serum creatinine levels, clinical manifestations and abnormal laboratory findings are often not characteristic.[13] Urinalysis results include pyuria (white cells), granular casts, microscopic haematuria, white cells and proteinuria.[5,11] Urinalysis demonstrated yellow-orange crystals inside casts in one patient with bilateral flank pain, and fever developed within hours of the first dose.[14]

2.3 Granulomatous Interstitial Nephritis

Another possible mechanism of fluoroquinolone nephrotoxicity centres on the possibility of a cell-mediated process, implicated by the finding of granulomatous interstitial nephritis (GIN). GIN is characterised by granulomas formed by nodular infiltrates comparable in size to a glomerulus. The cellular infiltrate consists predominantly of histocytes and T lymphocytes. Giant multinucleated cells are occasionally seen.[6] Drug-induced GIN can occur with or without vasculitis or glomerulonephritis. Sulfa drugs and penicillins account for approximately 50% of reported cases of GIN, with nonsteroidal anti-inflammatory drugs and diuretics accounting for 30% and 15% of cases, respectively.[6] A renal biopsy is useful in guiding therapy because patients with GIN may benefit from a prolonged

Table I. Reports of fluoroquinolone-associated nephrotoxicity

Age (y)/gender drug (mg)	Underlying condition	Duration of therapy before ARF	Other nephrotoxic drugs	Baseline, peak, final creatinine levels (μmol/L where available)[a]	Type of ARF	Intervention other than discontinuation of fluoroquinolone therapy	Reference
55/M CIP 500 bid	UTI	12 days	Furosemide, amiloride, glibenclamide (glyburide)	81, 237, 107 at 7mo	AIN	Renal biopsy	9
71/M CIP 250 bid	Septicaemia	3 weeks		161, 883 after 3wk, 460 by 3wk	AIN	Renal biopsy, prednisolone 60 mg/day	9
41/M CIP 500 bid	Biopsy proven IgA nephropathy	3 days	Captopril	309, 619, 314	Suspected AIN	Prednisolone 60 mg/day	9
73/M CIP 500 bid	Acute bronchitis		Paracetamol (acetaminophen), prochlorperazine	NA, 1391, 265 at 2mo	AIN	Prednisolone 40 mg/day	9
59/M CIP 500 bid	UTI	1st day		133, 265, NA			5
68/F CIP 500 bid	Sinusitis	10 days		106, 398, 159			5
50/F CIP 500 bid	Bacterial enteritis			301, 389, NA			5
73/M CIP 200 IV q12h	Pneumonia	2 days		128, 292, NA			10
31/F CIP 250 bid	Respiratory tract infection			NA, 220, 125 2mo later	AIN	Renal biopsy, prednisone 40mg bid	11
73/F CIP 500 bid		6 days	Cisplatin, etoposide, fluorouracil	110, 390, NA			11
68/M CIP 500 bid			Gentamicin, amphotericin	Peak 540			11
45/F CIP NA	UTI			Peak 194		Biopsy	12
52/F CIP 500 bid	Cellulitis		Naproxen	Peak 469	GIN	Biopsy	6
67/M CIP 750 q8h	UTI	5 days	Cisplatin	87, 796, 89	Oliguric	None	13
60/F CIP 750 q8h	Neutropenic fever	3 days	Cisplatin, interferon, NSAID	62, 1485, 133	Anuric	Haemodialysis	13
73/M CIP 750 q8h	Neutropenic fever	11 days	Cisplatin	88, 186, 88	Nonoliguric	None	13
69/F CIP 750 q12h	Breast abscess	10 days	Vancomycin	53, 1193, 53	Oliguric	None	13
62/F CIP 750 q8h	Neutropenic fever	6 days	None	88, 760, 80	Nonoliguric	None	13
47/M CIP 500 q12h	Great right toe infection	2 days	Cyclosporin	106, 345, 141	Nonoliguric AIN	None	14
80/M CIP NA	Sternal wound infection	4 weeks	Digoxin, furosemide, amiodarone	106, 469, 239	AIN	Biopsy High dose prednisone and cyclophosphamide	15
81/M CIP 500 q12h	Epididymitis		None	115, 707, 265	AIN	Biopsy	15
15/F CIP 10-15 x 10^3	Overdose	1 day	Trazodone	194, 548, NA	ATN	Biopsy	16
29/F CIP 21 x 10^3	Overdose	1 day		110, 320, NA	AIN	Prednisone × 7 days	17
35/M CIP 750 q8h	Cellulitis	4 days	Cyclosporin	Normal, 1246, back to baseline over 2wk			18

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Table I. Cont

Age (y)/gender drug (mg)	Underlying condition	Duration of therapy before ARF	Other nephrotoxic drugs	Baseline, peak, final creatinine levels (μmol/L where available)[a]	Type of ARF	Intervention other than discontinuation of fluoroquinolone therapy	Reference
11/M CIP 150 bid	Typhoid fever	14 days		74, 1183, 79	AIN	Renal biopsy Prednisolone 70 mg/day × 3 days, taper over 1wk	19
64/F CIP 750 bid	Pneumonia	11 days		Normal?, 725, 186 19 days later	AIN	Renal biopsy, prednisone 40 mg/day tapered to 20 mg/day because of psychosis, then tapered further to 5mg qod for an indefinite period	20
75/F NOR 400 bid	UTI			Normal, 451 on day 6	AIN	Renal biopsy	21
31/F CIP NA	Respiratory tract infection	3 days	None	Peak 700	AIN	Prednisone	22
73/F CIP NA	UTI	6 days	Cisplatin, etoposide, fluorouracil	NA	Oliguric	None	22
68/M CIP NA	UTI	2 days	Amphotericin B	NA	NA	None	22
53/M CIP 750 bid	Febrile neutropenia	1 day	High dose chemotherapy	133, 530, normal on 3rd day	possible AIN	Methylprednisolone sodium succinate 120 mg/day	23
56/F CIP 750 bid	Febrile neutropenia	1 day	High dose chemotherapy	53, 398, normal on 4th day	possible AIN, oliguric	Methylprednisolone sodium succinate 60 mg/day	23
78/M CIP 500 bid	Wound	7 days	Ranitidine, phenytoin	80, 274, 62	AIN	Prednisone 60mg 10-day taper course	24
69/F CIP 500 bid	MAI	10 days		NA, 1.1 × normal, 6.8 × normal			25
74/F CIP 500 od	Pyelonephritis	10 days		1.3 × normal, 2 × normal, 1.3 × normal			25
77/M CIP 500 od	Pulmonary tuberculosis	8 days		NA, 1.1 × normal, 1.5 × normal, normal			25
47/M CIP 500 bid	Toe infection	1 day	Cyclosporin	212, 345, 141			14
68/F NOR 400 bid	Pyelonephritis	7 days	Bendroflumethiazide	238, 685, 637	AIN	Renal biopsy	26
70/F CIP 750 bid	Fever with angiitis	9 days	Carboplatin	77, 429, 110	AIN	Renal biopsy	26
NA CIP	NA				AIN		27
21/F CIP 500 bid	UTI		Amphotericin, tobramycin	NA, 354, 97			7
84/F CIP 500 bid	Pneumonia	6 days	Metronidazole	61.88, 1211, NA	AIN		8
25/F CIP 250-500 bid	Pneumonia	7 days		NA, 213, 144	AIN	Renal biopsy	28
73/F CIP 500 PO bid	Bronchitis			NA, 805, 97		Prednisone 60 mg/day, renal biopsy	29

a The 3 levels are given where available however, the baseline value was not always provided with the peak and final values.

AIN = allergic interstitial nephritis; **ARF** = acute renal failure; **ATN** = acute tubular necrosis; **bid** = twice daily; **CIP** = ciprofloxacin; **F** = female; **GIN** = granulomatous interstitial nephritis; **IV** = intravenously; **M** = male; **MAI** = *Mycobacterium avium* infection; **mo** = months; **NA** = not available; **NOR** = norfloxacin; **NSAID** = nonsteroidal anti-inflammatory drug; **od** = once daily; **PO** = orally; **qod** = every other day; **qxh** = every *x* hours; **UTI** = urinary tract infection; **wk** = weeks.

course of corticosteroid therapy.[6] The prognosis of GIN is generally good.

In instances of fluoroquinolone-induced renal failure, blood urea nitrogen (BUN) is often only moderately elevated.[5] The increased creatinine to BUN ratio suggests increased creatinine production, decreased creatinine elimination, or methodological artifact.[5] One possibility is decreased tubular secretion. Ciprofloxacin undergoes active tubular secretion in addition to glomerular filtration and could interfere with the secretion of creatinine and result in diminished creatinine elimination.[5]

2.4 Acute Renal Failure

Acute renal failure is probably not dose related and has occurred with doses of ciprofloxacin as low as 200 to 250mg twice daily. Resolution of the acute renal failure has usually occurred within 1 to 8 weeks of discontinuation, with or without the administration of a short course of corticosteroid therapy.[15] Treatment with corticosteroids is controversial. Although reported to be successful in several cases of acute antibacterial-induced interstitial nephritis, corticosteroids are seldom necessary if the offending drug is withdrawn.[26] Treatment of fluoroquinolone-induced AIN has also included hydration and (rarely) transient dialysis. Most cases resolve in time with normalisation or near normalisation of renal function, further supporting the diagnosis of drug-induced disease.[13]

2.5 Acute Tubular Necrosis

Acute tubular necrosis has also been reported with ciprofloxacin.[16] In this case, a 15-year-old girl ingested 7.5 to 10.0g of ciprofloxacin with 100mg trazodone 24 hours before admission. Laboratory data on admission included a creatinine level of 2.2 mg/dl and BUN of 10 mg/dl. Over the next 4 days, her BUN and creatinine rose to 21 and 5.2 mg/dl, respectively. The creatinine reached a maximum of 6.2 mg/dl on day 6, when the patient became anuric. One week after ingestion, her creatinine level began to decrease with a concomitant rise in urine output. The distal nephron can also be involved in acute renal failure, and electron microscopy or plastic-embedded sections may be necessary to define its involvement.[16]

2.6 Crystalluria

Another postulated mechanism of fluoroquinolone nephrotoxicity is renal damage due to a foreign body reaction caused by crystallisation of the antimicrobial.[5,9] In mild forms of renal disease, tubular acidification defects are associated at an early stage. This may lead to precipitation of fluoroquinolones, which is more likely in a neutral to alkaline environment.[9] Animal studies suggested the relative insolubility of ciprofloxacin at alkaline pH leading to crystalluria and resultant tubular damage due to a foreign body reaction.[4] Five of 6 healthy volunteers given single doses of 500 and 1000mg of ciprofloxacin presented crystals in 22 of 36 urine samples when their diet was supplemented with sodium bicarbonate. Crystalluric urine samples showed a pH >7.3.[30] Crystalluria occurred in only 1 volunteer on a regular diet, after a 1000mg dose.[30] Ciprofloxacin is associated with crystalluria mainly when the urine pH is >7.0.[6] Crystalluria with a urine pH of 5.0 suggests that the crystals sometimes seen in these cases were probably oxalate rather than ciprofloxacin.[6] However, adequate hydration appears to prevent acute renal failure induced by ciprofloxacin in neutropenic patients given ciprofloxacin 750mg every 8 hours (based on data indicating reduced oral absorption).[13] A reduction to 500mg every 8 hours and adequate hydration resulted in no cases of nephrotoxicity in 61 low risk febrile neutropenic patients randomised to receive oral ciprofloxacin plus amoxicillin/clavulanic acid.[19]

2.7 Drug Interactions

Very often, other agents have been coadministered in the cases presented, possibly resulting in drug-drug interactions not previously reported. In several patients, other potentially nephrotoxic agents had been recently administered.[13] Although other drugs have been coadministered, the cases suggest a temporal relationship for fluoroquinolone administration and renal failure. Cip-

rofloxacin coadministration with cyclosporin has resulted in acute renal failure, which appears not to be related to inhibition of P450 enzyme metabolism of cyclosporin.[18,24] In other cases, patients had underlying medical diseases such as carcinoma or diabetes mellitus, which may have predisposed to toxicity.

3. Nephrotoxicity with Other Fluoroquinolones

Two cases of norfloxacin-associated AIN have been reported to date.[21,26] A Medline search did not reveal reports or cases of nephrotoxicity to other marketed fluoroquinolones or the investigational agents moxifloxacin, gatifloxacin or clinafloxacin. However, it must be noted that the use of most other fluoroquinolones has not been as extensive as that of ciprofloxacin to date. In a rabbit model, levofloxacin 30 or 120 mg/kg daily for 10 days was not associated with nephrotoxicity.[31] Cases have included rechallenges with recurrence of symptoms and nephrotoxicity.[5,11] Patients experiencing ciprofloxacin nephrotoxicity have successfully been switched without adverse effect to ofloxacin, a fluoroquinolone with even more extensive renal elimination.[25] These data imply that fluoroquinolones are not equal in nephrotoxic risk, and that the risk is not entirely dependent on the degree of renal elimination, as levofloxacin is almost totally eliminated through the kidney.

A multisystem syndrome consisting of haemolysis and often combined with renal failure, coagulopathy and hepatic dysfunction known as the 'temafloxacin syndrome' has been estimated to occur in 1 per 3500 patients treated with temafloxacin, 1 per 17 000 treated with ciprofloxacin, 1 per 25 000 treated with norfloxacin, and 1 per 33 000 treated with ofloxacin.[32] Blum et al.[33] recently reviewed 114 cases[33] of this syndrome and found new onset renal toxicity in 54 cases (haemolysis), with dialysis required in 34 cases. Renal dysfunction was associated with the onset of haemolysis on the first day of temafloxacin use ($p < 0.05$) and with the presence of disseminated intravascular coagulation ($p < 0.05$), but was not associated with age, gender, dose, indication of treatment, hepatic dysfunction, or degree of haemolysis. Patients typically presented with discoloured urine, fever, jaundice, chills, nausea, vomiting, abdominal pain, myalgia, and/or back pain. In most cases, the 'temafloxacin syndrome' resolved without sequelae within days to weeks of drug discontinuation. Renal toxicity was described as an elevation of creatinine level to at least 132 μmol/L. Unfortunately, there is limited opportunity to predict (before widespread use) whether new fluoroquinolones will produce syndromes which occur as infrequently as this.

4. Conclusion

Fluoroquinolones are usually well tolerated with a minimum of serious adverse effects. Renal toxicity is uncommon. Lipsky and Baker[34] have summarised the nephrotoxic potential of fluoroquinolones as follows: nearly all reported cases of acute renal failure associated with fluoroquinolones have involved patients over the age of 50 years. They also noted that renal failure may be due to a hypersensitivity reaction, or a direct toxic effect. These authors estimated the incidence of elevated serum creatinine levels related to therapy with ciprofloxacin, norfloxacin, ofloxacin or pefloxacin to range from 0.2 to 1.3%. Furthermore, the incidences of azotaemia with ciprofloxacin, ofloxacin and pefloxacin have been estimated to range from 1.8 to 13.1 per 1000 patients treated. Crystalluria, interstitial nephritis and acute renal failure have not been causally associated with levofloxacin, sparfloxacin, grepafloxacin or trovafloxacin.[34]

The absence of any distinguishing clinical features of nephrotoxicity other than elevation of serum creatinine levels following administration of a fluoroquinolone necessitates that a high index of suspicion be maintained.[13] AIN due to quinolone therapy may possibly go undiagnosed in several cases because of the gradual onset of symptoms, lack of oliguria and absence of any effect on the circulatory system. The possibility of 'silent' acute renal failure makes routine and close follow-up of renal function parameters and clinical course in pa-

tients prescribed fluoroquinolones mandatory, especially in transplant patients or others who may be on nephrotoxic immunosuppressive or chemotherapeutic agents.[35] In general, treatment will primarily involve immediate discontinuation of the offending agent.

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