# Fluoroquinolone Induced Tendinopathy: Report of 6 Cases

LAURENT ZABRANIECKI, ISABELLE NEGRIER, PASCALE VERGNE, MARIE ARNAUD, CHRISTINE BONNET, PHILIPPE BERTIN, and RICHARD TREVES

*ABSTRACT.* We describe 6 cases of fluoroquinolone induced Achilles tendinitis in 4 women and 2 men, mean age 68.6 years. Patients presented with pain and swelling of sudden onset, which was most often bilateral. Tendon rupture was frequent, accompanied by nodules and ecchymoses. The diagnosis was clinical, occasionally ultrasonography was helpful; the role of magnetic resonance imaging has yet to be defined. Certain risk factors were found, particularly association with longterm steroid therapy, and close surveillance of high risk subjects is mandatory. Although proper dosage and duration of treatment were respected, the principal fluoroquinolones were clearly incriminated. We found no correlation between treatment duration and the degree of involvement. Nevertheless, immediate discontinuation of the antibiotic and placement of both Achilles tendons at rest is essential. Early and appropriate management did not prevent prolonged recovery times and there was always a risk of functional sequelae. This side effect is class related and rare. Its physiopathologic mechanism is poorly understood. (*J Rheumatol 1996;***23:516–20**)

*Key Indexing Terms:*
FLUOROQUINOLONE TENDINOPATHY TENDINITIS TENDON RUPTURE

New generation fluoroquinolones are synthetic antibiotics that act by inhibiting bacterial DNA gyrase (topoisomerase II)[1-3]. These antibiotics have had increasingly widespread use due to their excellent gastrointestinal absorption, widespread tissue diffusion, a long half-life (allowing 2 daily doses), bactericidal action with low minimal inhibitory concentration, and wide spectrum[1,2,4,5]. Nevertheless, their indications should be limited to urinary and prostatic infections, serious intestinal infections, bronchopulmonary infections in predisposed individuals, invasive otitis externa, osteomyelitis, septic arthritis, or septicemia due to gram negative organisms.

Side effects are infrequent (usually 4 to 8%, exceptionally 16%), often minor (only 1 to 2.8% require cessation of treatment), dose dependent, and reversible[2,4-6]. Studies of the adverse effects have revealed similar results: gastrointestinal (1 to 7%), rash (0.5 to 2.5%), central and peripheral neurologic disorders (0.1 to 0.3%, even as high as 6.3% for others), gait disturbances (<1%), elevation of serum transaminases (1.8 to 2.5%), and very rare hematologic abnormalities[2,3,4,7].

Rheumatologic involvement is rare and consists of myalgia (< 0.8%), arthralgia, and arthritis (0.4%); a single study reported a frequency of 7%[7]. These joint lesions (known since the first generation quinolones[8] and described during preliminary animal studies) consist of nonerosive bilateral symmetric oligoarthropathy, mechanical in nature, that affects primarily the lower extremities. The clear yellow joint fluid reveals predominantly lymphocytes[9-13]. This condition preferentially occurs in adolescents during their pubertal growth spurt during longterm treatment (> 3 months); in these cases incidence may reach 45%[9]. Related to quinolone toxicity (direct or indirect) against chondrocytes, the lesions subside upon discontinuation of the antibiotic and recur when it is reintroduced[3,9-11,14]. For this reason this class of drugs is contraindicated during pregnancy, breast feeding, and adolescence. Finally, cases of tendinitis have been described. We report 6 cases observed in our department over one year.

## CASE REPORTS

*Patient 1.* A 68-year-old man with peripheral vascular disease was hospitalized in urology for prostatitis. He had received norfloxacin (800 mg/day) for 2 days, then pefloxacin intravenously (800 mg/day) for 4 days. On the 6th day he complained of pain in both Achilles tendons upon walking. Palpation revealed a tender swelling with no signs of tendon rupture. Fluoroquinolone was discontinued and he was placed on strict bed rest. After 6 days, the pain disappeared as well as the edema; walking was resumed without difficulty.

*Patient 2.* A 92-year-old woman with a history of hyperuricemia presented with the abrupt inability to walk. Examination revealed bilateral rupture of the Achilles tendons with edema and ecchymoses. She had been receiving ofloxacin (400 mg/day) for 48 h for an upper respiratory tract infection. Ultrasonography and magnetic resonance imaging (MRI) confirmed bilateral tendon rupture. No other causes could be implicated. The antibiotic was discontinued and below the knee casts were placed for one month. At 6 weeks, walking was exceedingly difficult despite physical therapy.

*From the Department of Rheumatology, CHRU Dupuytren, Limoges, France.*

*L. Zabraniecki, MD, Trainee in Rheumatology; I. Negrier, MD; P. Vergne, MD, Trainee in Rheumatology; M. Arnaud, MD; C. Bonnet, MD; P. Bertin, MD, PhD, Assistant Professor; R. Treves, MD, Professor of Rheumatology.*

*Address reprint requests to Dr. L. Zabraniecki, CHRU Dupuytren, Department of Rheumatology, 2 Avenue Martin Luther King, 87042 Limoges, France.*

*Submitted June 8, 1995 revision accepted September 18, 1995.*

*Patient 3.* A 75-year-old man with adenocarcinoma of the prostate with longterm steroid therapy had been receiving norfloxacin (800 mg/day) for 6 days for a urinary tract infection. Four days after beginning the antibiotic, he developed pain in both Achilles tendons, then difficulty in placing the left foot. Examination revealed a tender swelling of both Achilles tendons with ecchymoses over the left tendon and apparent weakness of the triceps surae muscle. Ultrasonography confirmed the finding of bilateral tendinitis complicated by a partial tendon rupture on the left side. With discontinuation of the fluoroquinolone, rest, and the use of a heel piece, walking with difficulty was recovered at 3 weeks.

*Patient 4.* A 75-year-old woman having longterm steroid therapy for rheumatoid arthritis (RA) had taken pefloxacin (800 mg/day) 15 days previously for a bronchopulmonary infection. Examination revealed bilateral, painful, swollen Achilles tendons with no signs of tendon rupture. Discontinuation of the antibiotic and rest (initially in bed) led to recovery in 6 weeks.

*Patient 5.* A 69-year-old woman with RA that required longterm steroid therapy had pefloxacin (800 mg/day) for 48 h for a bronchopulmonary infection. Since the previous evening she had been complaining of pain in her right Achilles tendon. The tendon was swollen, without ecchymoses, and very tender to palpation. Discontinuation of the fluoroquinolone and rest permitted recovery in 8 days.

*Patient 6.* A 34-year-old woman was treated with pefloxacin (800 mg/day) for 3 months for osteomyelitis of the left calcaneum. She had pain in the right Achilles tendon upon walking of 15 days' duration. The tendon was tender to palpation and swollen, but with no signs of infection. Ultrasonography confirmed the diagnosis of uncomplicated right Achilles tendinitis. With rest and discontinuation of the antibiotic, recovery was obtained in one month.

In these 6 cases (Table 1) fluoroquinolones were implicated, according to Bégaud[15], very probably in Patients 1, 3, 5, probably in Patient 2, and possibly in Patients 4 and 6.

Despite our small number of cases of fluoroquinolone induced tendinopathy, we compared our findings with those reported in the literature.

## DISCUSSION

In 1983, Bailey reported the initial cases of tendinitis in patients with kidney failure who had received treatment with norfloxacin[16]. MacEwan reported in 1988 a case of bilateral Achilles tendinitis caused by ciprofloxacin[17]. The first reports of tendon rupture in a patient taking pefloxacin were by Ribard[18,19], Perrot[20], and Jorgensen[14] in 1991. Thereafter, a cause and effect relationship for pefloxacin was recognized and published in *Le Vidal* (the physician's desk reference of drugs in France) in 1992. In July 1992, a drug monitoring study found about 100 cases in France[21,22]; until that time only about 15 cases had been published and 21 cases had been reported to the World Health Organization.

*Incidence (per instance of fluoroquinolone use).* Fluoroquinolone induced tendinopathy is estimated to be 15 to 20/100,000[21].

*Predisposing factors.* Our series comprised 4 women and 2 men, which does not correspond to the usual male:female ratio of 2:3. However, 5 of our 6 cases were over 68 years of age, in agreement with 2 of 3 reports, which involved subjects over 60 years of age[6,14,20–25]. Longterm steroid therapy was the principal associated risk factor we found (3 of 6 cases), an association that has often been reported[6,7,21,23,26–28] and is to be avoided. More rarely, one finds peripheral vascular disease (as with Patient 1), kidney failure, gout (Patient 2, however, had hyperuricemia without gout), and spondyloarthropathy (here, it was 2 patients with RA), which are classical causes of tendinitis[23–25,27,29].

*Table 1.* Summary of patient presentation and outcome.

| | Patients | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| | M, 68 yrs<br>Prostatitis | F, 92 yrs<br>Sinusitis | M, 75 yrs<br>Cystitis | F, 74 yrs<br>Bronchopulmonary infection | F, 69 yrs<br>Bronchopulmonary infection | F, 34 yrs<br>Left calcaneum osteomyelitis |
| Symptoms | Bilateral Achilles tendinitis | Bilateral Achilles rupture | Bilateral Achilles tendinitis with left partial rupture | Bilateral Achilles tendinitis | Right Achilles tendinitis | Right Achilles tendinitis |
| Imaging | Not done | Pathological ultrasonography and MRI | Pathological ultrasonography | ND | ND | Pathological ultrasonography |
| Fluoroquinolone: dose mg/24 h (T/d), duration of treatment, delay of onset | Norfloxacin 800 (2) 36 h, delay 5 days pefloxacin IV 800 (2) 4 days, delay 5 days | Ofloxacin, 400 (2), 48 h, 48 h | Norfloxacin, 800 (2), 6 days, tendinitis: 4 days, rupture: 6 days | Pefloxacin, 800 (2), 15 days, 10 days | Pefloxacin, 800 (2), 48 h, 24 h | Pefloxacin, 800 (2), 3 mo, 2.5 mo |
| Risk factors | Lower extremity peripheral vascular disease | Hyperuricemia | Longterm steroid prostatic neoplasia | RA with longterm steroid | RA with longterm steroid | None |
| Treatment (after stopping fluoroquinolone) | Rest | Rest and below the knee casts | Rest and heel piece | Rest | Rest | Rest |
| Outcome | Recovery in 6 days | Walking difficult at Week 6 | Walking difficult at Week 3 | Recovery in 6 weeks | Recovery in 8 days | Recovery in 4 weeks |
| Imputability* (Begaud[15]) | Very probably, 14B3 | Probably, 13B2 | Very probably, 14B2 | Possibly, 12B3 | Very probably, 14B3 | Possibly, 12B3 |

* I: intrinsic imputation (I0 to I4); B: bibliographic imputation (B1 to B3).

*Manifestations.* Fluoroquinolone induced tendinitis is distinguished from other forms of tendinitis by its abrupt onset and sharp pain that occurs spontaneously, upon walking or palpation. It may occasionally arise only hours after the initial dose of fluoroquinolone[27]. We noted substantial swelling; signs of inflammation that mimic phlebitis have been reported[19]. Involvement is frequently bilateral (2/3 of our cases)[6,19,21,24]. There is a predilection for the Achilles tendon, but other tendons have been reported: the quadriceps[6,30], extensor pollicus longus[27], peroneus brevis[14], and those of the rotator cuff[30-32]. This distribution emphasizes the role that mechanical forces play in the pathophysiology of this tendinopathy. Tendon rupture is almost always preceded by pain, and may be partial or complete, spontaneous or after an effort, at the bony insertion or 2 to 3 cm above (a poorly vascularized area)[23]. Rupture is often accompanied by a diminution of the pain. Tendon palpation reveals edema and occasionally nodules[14]; we noted associated ecchymoses (Patients 2 and 3). Difficulty or inability to perform plantar flexion of the foot points to the diagnosis (Thompson's sign). Our results were similar to others, since this complication arose in one-third of our cases[6,19,21].

*Mode of onset.* This side effect first appeared in France with pefloxacin, and most cases occurred in connection with it. This fluoroquinolone may have been too frequently used in our country, where it had been mostly marketed. But this side effect is class related[27] and can thus occur with all the fluoroquinolones (norfloxacin, ofloxacin, and pefloxacin are 3 commonly used fluoroqinolones in France) at normal dosage and duration of treatment (a mean of 20.5 days in our cases; 15 days for Borderie[19]).

The severity is usually proportional to treatment duration. Uncomplicated tendinitis is seen when treatment duration has been less than 5 days, with increased frequency of tendon rupture after the 3rd week of treatment[6,21]; however, this delay was variable (from a few hours to 2.5 months in our series, as high as 90 days in others[33]).

*Imaging techniques.* The diagnosis of tendinopathy is essentially clinical. Ultrasonography (with a high frequency probe) can occasionally confirm partial or complete tendon rupture. It appears that MRI, useful in other forms of tendinopathy[35], can be helpful in establishing an early diagnosis by providing precise information about the lesion (as in Patient 2). On T1 weighted images, intermediate signal flame shaped intratendinous foci can be visualized. An increased signal surrounding the lesion is seen on T2 weighted images. With recent ruptures, one can see edema, hemorrhage, and fiber discontinuity, since the torn ends have an increased signal on spin-echo imaging. By providing precise information concerning the degree of involvement, MRI could allow more appropriate management[30,34-36]. Nevertheless, MRI has frequently disclosed intratendinous foci during treatment with fluoroquinolones in the absence of any clinical signs[30,34]. Do these represent edema or preexisting degenerative lesions?

Diagnosing fluoroquinolone induced tendinopathy requires ruling out other causes (infectious, inflammatory, traumatic, iatrogenic, idiopathic, and the presence of microcrystals). This is problematic only when more than one cause is possible; in these instances, Bégaud's criteria are helpful[15].

*Treatment.* Treatment consists of immediate discontinuation of the fluoroquinolone with placement of the tendons at rest[28], which may prove difficult when there is bilateral involvement (as in Patients 1 and 4, who required one week of strict bed rest with its attendant risks in the elderly). Forearm crutches, heel pieces, splints in case of partial rupture (Patient 3), and even below the knee casts if the rupture is complete (Patient 2) are helpful for periods of 6 weeks to 6 months[19,20,29,37]. Early and prolonged physical therapy is often necessary in these elderly patients. Our 2nd case illustrates the possible serious consequences. Surgery is rarely performed and there is a paucity of information concerning results[14,26,27], which are sometimes good[19]. This method is apparently being abandoned in elderly subjects[6] because the local involvement[33] renders the repair unreliable. Thus, prevention is crucial, requiring close surveillance of high risk patients.

*Outcome.* In general, with early diagnosis and management, tendinitis heals slowly. Edema can persist for several weeks. Delays in healing of 1 to 3 months have been reported[17,19,24]; in our series, the mean recovery time was 3 weeks (only 6 days for Patient 1, 6 weeks to resume normal walking for Patient 4). In the drug monitoring study, 50% had recovered in 30 days[21]. However, early management does not always prevent tendon rupture, which can occur after discontinuation of the fluoroquinolone[20,23,26,27,33,37]. When tendon rupture occurs, healing time is considerably lengthened. It was 4.5 weeks in our study, 2 to 3 months for Cohen[24], 3 to 6 months for Perrot[37]. In these instances, functional sequelae are frequent: A favorable outcome was obtained in only 55% in the drug monitoring study[21] and a total temporary incapacity in 44%[6]. Our 2 cases with tendon rupture (Patients 2, 3) still had difficulty walking after one month followup. The reintroduction of fluoroquinolones must be proscribed[6].

*Pathophysiology.* The precise pathophysiological mechanism remains unknown. Few histological studies exist. Jorgensen[14] described degenerative lesions with numerous fissures, interstitial edema with no cellular infiltrate, and tendon necrosis with signs of neovascularization; the Achilles tendon was involved as well as the adjacent peroneus brevis tendon. Upon surgical intervention, Chaslerie and Franck reported that the injured tendons appeared necrotic[26,27]. These lesions lack specificity and closely resemble those found with idiopathic tendon rupture[38]. They most likely involve an ischemic process[14,23,27]. This mecha-

nism may provide at least partial explanation for cases of enthesitis with multiple tendon involvement, with rupture that occurs 2 to 3 cm above the point of tendon insertion or that occurs after discontinuation of fluoroquinolone, and the predisposing role of arteritis obliterans and its associated arthritis (osteochondrosis with punched out lesions and vesicles in the intermediate germinal zone without signs of inflammation)[3,14,33]. MRI abnormalities in asymptomatic subjects may correspond to this edema secondary to ischemia. Furthermore, the role played by mechanical stress is not negligible (involvement primarily of the Achilles tendons), nor is that of prior subclinical lesions (accounting for the sudden onset in certain cases, the occurrence in areas of pressure, the predisposing role of steroids and old age). Finally, a toxic effect on collagen may also occur during muscle, joint, and tendon involvement[26]. An autonomic nervous system disturbance or immunoallergic phenomena (as seen during rare cases of subacute synovitis) related to therapy with fluoroquinolones cannot be excluded[14]. The origin is thus probably multifactorial. Discovery of the precise mechanism will allow for more appropriate preventive measures.

A rare side effect with sometimes serious consequences, fluoroquinolone induced tendinopathy was recognized tardily after the substantial rise in the prescription of these antibiotics. The indications must be well defined to avoid new complications and increasing drug resistance (chromosomal in nature ) of these potentially mutagenic molecules[39]. They should not be employed as a first-line drug for nosocomial infections unless they are used in association with other drugs[2,4]. Numerous resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* have already appeared.

In conclusion, fluoroquinolone induced tendinopathy is manifested by the sudden onset of swelling and tenderness, which is often bilateral and complicated by tendon rupture in 1 of 3 cases (with nodules and ecchymoses). High risk patients require close surveillance, especially those under corticosteroid therapy and the elderly, in whom there is enhanced risk of functional sequelae as well as the dangers of prolonged bed rest. Management consists of immediate discontinuation of the fluoroquinolone and placement of both tendons at rest. A history of tendinitis or arthritis due to these antibiotics represents a new contraindication to their use. Patient selection for these drugs must take this potential complication into account.

## REFERENCES


1. Modai J: Péfloxacine: Bilan et perspectives cliniques *Rev Med Int 1986;*7:205–10.
2. Hooper DC, Wolfson JS: Fluoroquinolone antimicrobial agents. *N Eng J Med 1991;*324:384–94.
3. M'Bappé, Hayem G, Kahn MF: Effets indésirables des quinolones sur l'appareil locomoteur. In: De Seze S, Ryckewaert A, Kahn MF, Kuntz D, Guerin C: *Actualités Rhumatologiques 1993.* Paris: Expansion Scientifique Française, 1993:302–10.
4. Halkin H: Adverse effects of the fluoroquinolones. *Rev Infect Dis 1988;*(suppl 1)10:258–61.
5. Arcieri G, Griffith E, Gurenwaldt G, *et al:* Ciprofloxacine: An update on clinical experience. *Am J Med 1987;*82:381–6.
6. Lafon M: Tendinopathies et fluoroquinolones. *Concours Méd 1993;*115:819–25.
7. Lanoux P, Legin C, Reksa A, Heindl MC, Penalba C: Effets secondaires des fluoroquinolones. Etude rétrospective sur l'année 1992. *Sem Hôp Paris 1993;*69:1273–6.
8. Bailey R, Natale R, Linton A: Nalidixic acid arthralgia. *CMA Journal 1972;*107:604–5.
9. Pertuiset E, Lenoir G, Jehanne M, Douchain F, Guillot M, Menkès CJ: Tolérance articulaire de la péfloxacine et de l'ofloxacine chez les enfants et adolescents atteints de mucoviscidose. *Rev Rhum 1989;*56:735–40.
10. Kesseler A, Lacassie A, Hugot JP, Talon P, Thomas D, Astier L: Arthropathies consécutives à l'administration de péfloxacine chez un adolescent atteint de mucoviscidose. *Ann Pédiatr* (Paris) *1989;*36:275–8.
11. Ollier S, Laroche M, Arlet P, Montane P, Durroux R, Le Tallec Y: Arthropathie à la péfloxacine. A propos d'une observation. Etude histologique de la synoviale. *Rev Rhum 1990;*57:671.
12. Jeandel C, Manciaux MA, Bannwarth B, *et al:* Arthritis induced by norfloxacin. *J Rheumatol 1989;*16:560–1.
13. Seigneuric C, Plantavid M, Bouygues D, Cassou M, Amar J, Cascarigny F: Manifestations articulaires sous péfloxacine chez l'adolescent. *Presse Méd 1990;*19:428.
14. Jorgensen C, Anaya JM, Didri C, *et al:* Arthropathies et tendinopathie achilléenne induites par la péfloxacine. A propos d'une observation. *Rev Rhum 1991;*58:623–5.
15. Bégaud B, Evreux JC, Jouglard J, Lagier G: Imputabilité des effets inattendus ou toxiques des médicaments. *Thérapie 1985;*40:111–8.
16. Bailey RS, Kirk JA, Peddie BA: Norfloxacin induced rheumatic disease. *NZ Med J 1983;*96:590.
17. McEwan SR, Davey PG: Ciproflaxacin and tenosynovitis. *Lancet 1988;*15:900.
18. Ribard P, Kahn MF: Rheumatological side effects of quinolones. *Baillere's Clin Rheumatol 1991;*5:175–91.
19. Ribard P, Audisio F, De Bandt M, Kahn MF, Palazzo E, Meyer O: 5 cas de tendinite d'achille, dont 2 avec rupture, au cours de traitements par les fluoroquinolones. *Rev Rhum 1991;*58:728.
20. Perrot S, Ziza JM, De Bourran-Cauet G, Desplaces N, Lachand AT: Nouvelle complication liée aux quinolones: La rupture du tendon d'Achille. *Presse Méd 1991;*20:1234.
21. Royer RJ, Pierfitte C, Netter P: Features of tendon disorders with fluoroquinolones. *Therapie 1994;*49:75–6.
22. Pierfitte C, Gillet P, Royer RJ: More on fluroquinolone antibiotics and tendon rupture. *N Eng J Med 1995;*332:193.
23. Borderie P, Marcelli C, Leray H, *et al:* Ruptures spontanées du tendon d'Achille après transplantation rénale: Rôle favorisant des fluoroquinolones. *Rev Rhum 1992;*59:652.
24. Cohen de Lara A, Rosenberg F, Struz P: Trois nouveaux cas de tendinopathie achilléenne après traitement par fluoroquinolones. *Rev Rhum 1992;*59:652.
25. Leray H, Mourad G, Chong G, Marcelli C, Borderie P, Mion C: Ruptures spontanées du tendon d'Achille après transplantation rénale: Rôle des fluoroquinolones. *Presse Méd 1993;*22:1834.
26. Franck JL, Bouteiller G, Chagnaud P, Sapene M, Gautier D: Rupture des tendons d'Achille chez deux adultes traités par Péfloxacine dont un cas bilatéral. *Rev Rhum 1991;*58:904.
27. Chaslerie A, Bannwarth B, Landreau JM, Yver L, Bégaud B: Ruptures tendineuses et fluoroquinolones: Un effet indésirable de classe. *Rev Rhum 1992;*59:297–8.
28. Direction de la pharmacie et du médicament — Les fluoroquinolones. *Concours Méd 1993;*11:811.

29. Boulay I, Farge D, Haddad A, Bourrier P, Chanu B, Rouffy J: Tendinopathie à la ciprofloxacine avec possibilité de rupture partielle du tendon d'Achille. *Am Méd Int 1993;*144:493–4.
30. Koeger AC, Chaibi P, Roger B, *et al:* Apport de l'IRM dans les complications tendineuses des fluoroquinolones. *Rev Rhum 1993;*60:752.
31. Falt-Rolachon I, Pireyre C, Rolachon A, Gaudin P, Troussier B, Phelip X: Rupture bilatérale de la coiffe des rotateurs lors d'un traitement par Ofloxacine. A propos d'une observation. *Rev Rhum 1993;*60:752.
32. Borderie P, Marcelli C, Hérisson C, Simon L: Spontaneous rotator cuff tear during fluoroquinolone antibiotics treatment. A report of 2 cases (abstr). *Arthritis Rheum 1993;*(suppl 9)36:163.
33. Ribard P, Audisio F, Kahn MF, *et al:* Seven Achilles tendinitis including 3 complicated by rupture during fluoroquinolone therapy. *J Rheumatol 1992;*19:1479–81.
34. Quinn S, Murray W, Clark R, Cochran C: Achilles tendon: MR imaging at 1.5 T1. *Radiology 1987;*164:767–70.
35. Gillet P, Blum A, Pierfitte C, *et al:* Fluoroquinolone associated Achilles tendinitis: MRI findings (abstr). *Arthritis Rheum 1993;*(suppl 9)36:163.
36. McQueen C, Williams G: Effects of quinolone antibiotics in tests for genotoxicity. *Am J Med 1987;*(suppl 4A)82:94–6.
37. Perrot S, Kaplan G, Ziza JM: 3 cas de tendinite achilléenne sous Péfloxacine dont deux avec rupture. *Rev Rhum 1992;*59:162.
38. Jouglard JP: Les ruptures tendineuses. Dans: Serratrice G: *Le tendon normal et pathologique.* Séminaire de Monte Carlo, 13–14 February 1976.
39. Schlûter G: Ciprofloxacin: Review of potential toxicologic effects. *Am J Med 1987;*82:91–3.