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# Peripheral sensory disturbances related to treatment with fluoroquinolones

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The symptoms and possible risk factors of peripheral sensory disturbances related to fluoroquinolones are reviewed on the basis of 37 reports submitted to the Swedish Adverse Drug Reactions Advisory Committee.

In 25 patients (68%), symptoms occurred within 1 week after start of treatment. Paraesthesia was the most common complaint and occurred in 81% of the cases. Fifty-one per cent of the reports concerned numbness/hypoaesthesia, 27% pain/hyperaesthesia and 11% muscle weakness. Seventy-one per cent of the patients recovered within 2 weeks after drug discontinuation. Possible predisposing factors were impaired renal function, diabetes, lymphatic malignancy and treatment with another drug known to cause neuropathy.

## Introduction

Fluoroquinolone antibiotics represent a new generation of quinolones with fewer adverse effects than the original quinolone nalidixic acid, introduced over 30 years ago for treatment of urinary tract infections. Among patients treated with fluoroquinolones, 0.9–1.6% experience adverse reactions relating to the central nervous system (CNS), including headache, dizziness, drowsiness, agitation, psychosis and convulsions (Stahlmann, 1990). Fluoroquinolones, like nalidixic acid and other predecessors, can be associated with peripheral sensory disturbances (PSD), although few reports have been published (Swedish Study Group, 1988; Chan *et al.*, 1990; Aoun *et al.*, 1992; Rollof & Vinge, 1993). The characteristics of such reactions based on the Swedish register for adverse drug reactions (ADRs) are surveyed in this report.

## Materials and methods

Since 1965, Sweden has had a reporting system for ADRs. Reporting to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) is obligatory for suspected new or serious ADRs. All reports are stored in the database SWEDIS (Swedish Drug Information System). Reports from SWEDIS concerning PSD associated with fluoroquinolones until end of 1993 were reviewed. Cases were identified as those describing paraesthesia, numbness, sensation loss, hyperaesthesia, pain, neuropathy

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**Table.** Details of 37 cases of peripheral sensory disturbances related to fluoroquinolones

| Cases<br>Age (years)<br>Sex | Drug, Dose (mg/day) | Time to onset | Symptom, Location | Other symptoms | Concomitant medication | Duration of symptoms after discontinuation |
|---|---|---|---|---|---|---|
| 1 36F | NOR, 200 | 1 h | PAR, NUMB; hands, feet | Spells of absences, headache, dizziness, chromatopsy | Mini-contraceptive pill | 1 day |
| 2 40F | NOR, 200 | 1 h | PAR, HYP; perioral | Itch | No | Much better after 24 h |
| 3 23F | NOR, 400 | *c.* 12 h | PAR, pain; right arm, right hand | No | No | 2–3 days |
| 4 66F | NOR, 800 | 12 h | PAR, pain; fingers | Local oedema | No | 1 day |
| 5 75F | NOR, 800 | 1–2 days | PAR, pain; legs | No | Paracetamol, terbutalin | 3–4 days |
| 6 37M | NOR, 400 | 1–2 days | PAR; right arm + leg | No | No | Few days |
| 7 45M | NOR, 400 | 2 days | PAR, NUMB; legs (burning), hands (cold) | Weakness | No | NR, months |
| 8 37F | NOR, 400 | 2 days | HYPO, pain; right leg, right cheek | Difficult control of leg | No | 1–2 weeks |
| 9 NR | NOR, 400 | 2 days | Sensation loss; fingertips | Dizziness, vomiting, diarrhoea, convulsion | No | NR |
| 10 84F | NOR, 800 | 2 days | PAR, NUMB; feet | No | No | NR |
| 11 52F | NOR, 400 | 2 days | PAR, NUMB; hands, feet | Dizziness, muscle cramps and pain | No | Months |
| 12 84M | NOR, 400 | 2 days | PAR, NUMB; hands, feet, legs | Muscle weakness, atactic gait | Digoxin, potassium, frusemide | Slow recovery, better but not recovered after 1 month |
| 13 47F | NOR, NR | 2–3 days | PAR, NUMB; arms, one leg | Dizziness, headache | No | Some hours |
| 14 33F | NOR, 800 | 2–3 days | NUMB; legs | Weakness legs, fatigue | No | 8 weeks |
| 15 27M | NOR, 400 | 2–3 days | NUMB; fingers, toes | Diarrhoea, vomiting, fever, arthralgia | No | Few days |
| 16 35M | NOR, 400 | 2–3 days | PAR, NUMB; arms, legs, whole body | Fatigue | Ibuprofen | Few days |
| 17 36F | NOR, NR | Few days | NUMB; hands, feet, one leg | Muscle cramps in jaw, neck, arm | Metronidazole (total 2.4 g) | 1–2 weeks |
| 18 68F | NOR, NR | Few days | PAR, NUMB; feet, neck, ankles, right hand's finger | Fatigue | Prednisolone | NR |
| 19 31F | NOR, 400 | Few days | PAR (burning), HYP; mainly thighs | Weakness in legs, fatigue | No | NR, <2 months |
| 20 47F | NOR, 400 | Few days | PAR; first legs, then hands and neck | Initially dizziness, then difficulty sleeping, sometime difficulty walking, standing, fatigue | Sucralfate as necessary | Somewhat more than 1 year |

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|---|---|---|---|---|---|---|
| 16 35M | NOR, 400 | 2–3 days | PAR, NUMB; arms, legs, whole body | Fatigue | Ibuprofen | Few days |
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| 18 68F | NOR, NR | Few days | PAR, NUMB; feet, neck, ankles, right hand's finger | Fatigue | Prednisolone | NR |
| 19 31F | NOR, 400 | Few days | PAR (burning), HYP; mainly thighs | Weakness in legs, fatigue | No | NR, <2 months |
| 20 47F | NOR, 400 | Few days | PAR; first legs, then hands and neck | Initially dizziness, then difficulty sleeping, sometime difficulty walking, standing, fatigue | Sucralfate as necessary | Somewhat more than 1 year |
| 21 85F | NOR, 800 | 5 days | PAR; hands, feet | Itching rash | No | NR, symptoms come and go |
| 22 28F | NOR, NR | 5 days | PAR; whole body | No | No | Few days |
| 23 63M | NOR, 200–400 | 5–6 days | PAR; pain; legs, genitals | Difficulty walking, local oedema | Sodium bicarbonate | 6 weeks |
| 24 68M | NOR, 800 | 6–7 days | PAR, pain; legs, arms | No | No | Few weeks |
| 25 72M | NOR, 800 | 7–8 days | HYPO, NUMB; left arm, body | No | No | NR |
| 26 71F | NOR, NR | 7–8 days | PAR; whole body | Warmth | Hydrochlorothiazide, paracetamol, amiloride, dextropropoxyphene, potassium, verapamil | 1–2 days |
| 27 39F | NOR, 400 | 7–8 days | PAR, pain; right thigh | No | Amiloride, frusemide, magnesium, potassium, iron injections | NR, markedly better in 3 days |
| 28 68M | NOR, 200–400 | 11 days | PAR, pain; feet | No | Digitoxin, metroprolol, insulin, frusemide, potassium | Significantly better after 4 days |
| 29 30M | NOR, 200 | 11 days | PAR, NUMB; legs, abdomen | No | Desmopressin test 24 h earlier | <1 day |
| 30 50M | NOR, 1200 | 11–12 days | PAR, NUMB; thighs | Elevated liver enzymes | No | <1 week |
| 31 89M | NOR, 400 | 19–20 days | PAR, HYP; legs | No | No | *C.* 1–2 weeks |
| 32 40M | CIPRO, 1000 | 7–8 days | PAR; right cheek, ear, neck | No | No | 4 h |
| 33 16M | CIPRO, 1000 | 1–2 weeks | PAR, pain; legs, feet | 1 month later opticus neuritis | Chloramphenicol since 1 month earlier, cyclosporin, phenytoin, rifampicin | Better 1 month after ciprofloxacin and chloramphenicol were withdrawn |
| 34 48F | CIPRO, 1000 | 7–8 weeks | PAR, NUMB; hands, feet | No | Metronidazole (total *c.* 50 g), propranolol, naproxen, terbutalin, oestradiol | NR |
| 35 62F | CIPRO, 1000 | 3–4 months | PAR, HYPO; feet, hands | 6 weeks earlier onset of dizziness | Metronidazole (total *c.* 75 g) for 2 weeks | NR |
| 36 49F | CIPRO, 1500 | 4 months | PAR, NUMB; feet | Hepatitis | Metronidazole (total *c.* 170 g), gentamicin, clindamycin, cefuroxime | NR, <10 months |
| 37 62M | TEMA, 600 | 2 days | PAR; whole body | No | Atenolol | Few days |

M, male; F, females; NOR, norfloxacin; CIPRO, ciprofloxacin; TEMA, temafloxacin; PAR, paraesthesia; NUMB, numbness; HYP, hyperaesthesia; HYPO, hypoaesthesia; NR, not reported.

and polyneuropathy judged by SADRAC to be probably or possibly related to the treatment.

The fluoroquinolones under consideration are norfloxacin (introduced 1986), ciprofloxacin (introduced 1986), ofloxacin (introduced 1990) and temafloxacin (introduced 1991, withdrawn 1992). Total sales of drugs from pharmacies have been computerised since 1972. Annual usage of drugs can be expressed in defined daily doses (DDDs) or in number of packages sold. The number of reports is related to these sales parameters on an annual basis.

## Results

There were 582 ADR reports on fluoroquinolones by 1993. The 37 reports on PSD are shown in the Table. There were 21 women and 15 men, with a mean age of 51 years (range 16–89).

Thirty-one reports concerned norfloxacin, five ciprofloxacin and one temafloxacin. Norfloxacin was prescribed for urinary tract infection ($n = 26$), genital infection ($n = 3$), and fever of unknown cause ($n = 2$). Ciprofloxacin was prescribed for osteitis ($n = 2$), abscess ($n = 2$) and prostatitis ($n = 1$) and temafloxacin for sinusitis ($n = 1$).

Paraesthesia of the feet, legs, hands and/or arms was reported in 30 cases (81%). Nineteen reports (51%) concerned numbness/hypoaesthesia and 10 (27%) pain/hyperaesthesia. Muscle weakness was reported in four cases (11%). In six cases (16%) symptoms were unilateral. Concomitant symptoms included dizziness ($n = 6$), fatigue ($n = 5$), muscle cramps or convulsions ($n = 3$), local oedema ($n = 2$), headache ($n = 2$) and gastrointestinal side effects ($n = 2$). Two patients had elevated liver enzymes. In one patient (no. 11), examination by EMG and nerve conduction velocity because of persistent symptoms after 2 months revealed no sign of neuropathy.

Possible predisposing factors for neuropathy were identified in several cases: impaired renal function (nos 23 and 28), diabetes mellitus (nos 12 and 28), lymphatic malignancy (nos 31 and 33), previous anorexia nervosa (no. 27), or inflammatory processes; polymyalgia (no. 18), chronic osteitis (no. 35), and intracerebral abscess (no. 36). Five patients concomitantly received another drug known to cause neuropathy: metronidazole (nos 17, 34, 35, 36) or chloramphenicol (no. 33). One patient on ciprofloxacin (no. 34) also took naproxen, a combination which has been associated with adverse neurological effects (Rollof & Vinge, 1993). Another 12 patients received concomitant medication not associated with PSD. Two patients (nos 7 and 18) had previously experienced similar paraesthesia during treatment with norfloxacin, and two (nos 26 and 22) during treatment with nitrofurantoin and trimethoprim respectively.

The onset of symptoms after start of treatment varied from 1 h to 4 months. In 25 patients (68%), symptoms occurred within 1 week and in 32 patients (86%) within 2 weeks. Excluding the 13 cases where a CNS effect or allergy were reported, and the seven cases lacking information on dose or time to onset, the mean time to onset was 11 days for the 200 mg dose, 6 days for a mean dose of 300 mg, 3.5 days for the 400 mg and 3.4 days for the 800 mg dose.

The duration of symptoms in the 28 cases where information was provided varied from a few hours to over a year. Seventeen patients (61%) recovered within 1 week and 20 patients (71%) within 2 weeks. There was no relation between the time to onset and the duration of the symptoms.

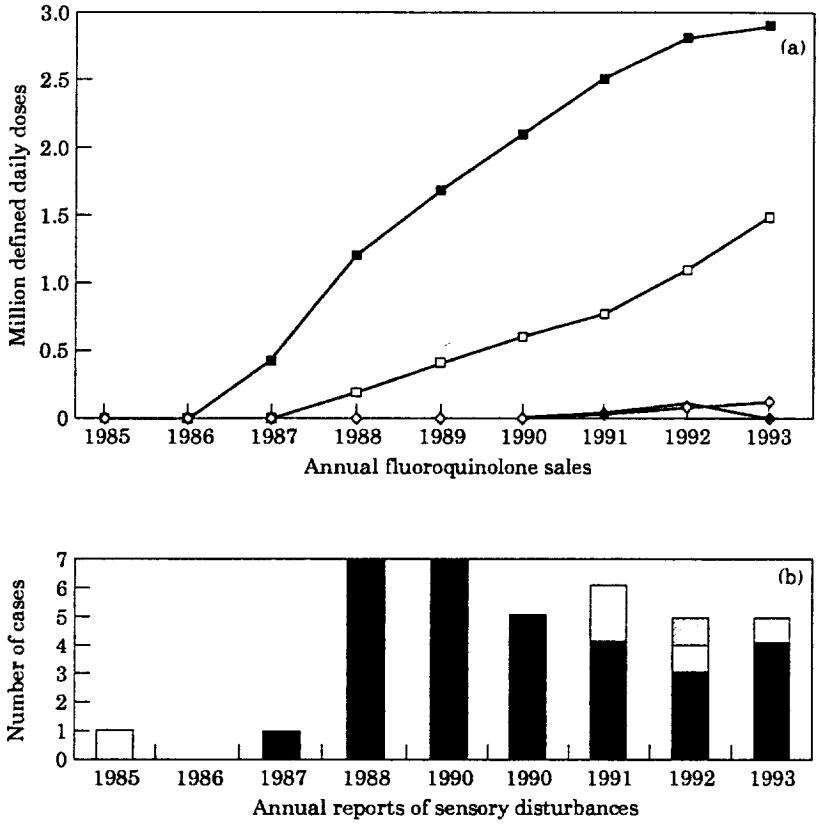


**Figure.** Annual number of reports of sensory disturbances (b) in relation to annual fluoroquinolone sales (a) in Sweden. (a) ■, Norfloxacin; □, ciprofloxacin; ◆, temafloxacin; ◇, ofloxacin. (b) ■, Norfloxacin; □, ciprofloxacin; ▨, temafloxacin.

The Figure shows the annual number of reports in relation to the annual sales of fluoroquinolones in Sweden in DDDs. For norfloxacin and temafloxacin the DDD is 800 mg, for ciprofloxacin 1000 mg. During the first years after marketing, reports increased largely in parallel with the increasing number of fluoroquinolone prescriptions. Later, reports declined despite a continuous increase in sales. This pattern is well known from registers of ADR reports, and probably reflects a decrease in the alertness of the reporting physicians after the first years (Rawlins, 1988).

## Discussion

ADR reports represent an important means of detecting infrequent reactions. The incidence can only be roughly estimated because of underreporting. In a Swedish study, only 20–80% of serious and dramatic ADRs recognised by physicians were reported (Wiholm, 1983). If the 14 reported cases for norfloxacin in 1988–89 are related to the 147, 438 and 218,357 packages sold in the same years, a risk of one case for every 1250 to 2500 treatments could be expected (if it is assumed that only 5–10% of cases are reported). This estimate must be viewed with great caution as the actual reporting rate is unknown and the denominator is approximate, but it may give some indication of

the incidence. For ciprofloxacin and temafloxacin, the number of reports are insufficient for estimations.

An important issue is whether fluoroquinolones differ in their capacity to induce PSD. Clinical reporting cannot be used to compare ADR incidences because of reporting rate differences. Comparisons are only valid in carefully designed studies with an adequate sample size in relation to the event. It is worth noting, however, that all except one patient on ciprofloxacin received treatment with metronidazole or chloramphenicol, which are both associated with neuropathy (Blain & Lane, 1991). Whether ciprofloxacin alone was responsible for the neuropathy is unknown. The drug combination might have additional or potentiating effects on peripheral nerves.

We found the highest incidence of PSD during the first weeks of treatment, while others have reported symptoms first after several months (Aoun *et al.*, 1992). One possible explanation for our findings is that most treatments are given for 7–10 days; another is that the association is more obvious, and thus more likely to be reported, shortly after the drug has been started. It is possible that the risk may be further increased in patients on long term treatment, as suggested for metronidazole (Duffy *et al.*, 1985).

PSD seems to be unrelated to age or gender, as the age and gender distribution was similar to that of all ADR reports on fluoroquinolones. We identified a few possible predisposing factors. As fluoroquinolones are excreted by the kidneys, patients with impaired renal function may have increased serum concentrations of the drug. Patients with diabetes mellitus may have a lower threshold for drug-induced peripheral neuropathy (Blain & Lane, 1991). The patients with lymphatic malignancy may have been treated with neurotoxic antineoplastic drugs, thereby increasing the risk for neuropathy (Aoun *et al.*, 1992). It should be noted, however, that these patient groups are at increased risk of bacterial infections and fluoroquinolone treatment may be more common.

The exact mechanism of PSD due to fluoroquinolones is unknown. The diversity of symptoms and difference in onset and recovery times suggest that more than one mechanism is likely. The pathological changes in drug-induced peripheral neuropathy consist of axonal degeneration with secondary breakdown of the myelin sheath, or more rarely primary segmental demyelinisation (Blain & Lane, 1991). In two patients on fluoroquinolones (Aoun *et al.*, 1992; Rollof & Vinge, 1993), EMG showed indications of toxic axonal neuropathy, but the causative role of the fluoroquinolone was not established in one of these cases (Rollof & Vinge, 1993). Similar changes may have been present in most of our patients, although patient no. 11 had normal EMG and nerve conduction velocity despite continuing symptoms.

In some cases, signs of CNS toxicity were present. There is no evidence that the association of fluoroquinolones with convulsions, attributed to the inhibition of cerebral GABA-receptors (Stahlmann, 1990), is relevant to the pathogenesis of PSD. An effect on blood vessels in the brainstem was suggested in a patient with lymphatic malignancy who developed transient acute hemiparesis after treatment with ciprofloxacin (Rosolen, Drigo & Zanesco, 1994). Also in some of our cases (nos 6, 8, 25), symptoms were unilateral and affected both the upper and lower body. Allergic skin reactions may be misinterpreted as numbness and paraesthesia. This could be suspected in the patients with additional itch or rash (nos 2 and 21). The very rapid onset of symptoms in some of the cases (nos 1–4) may be due to physiological alterations in peripheral neuronal processes.

If PSD is suspected in a patient on a fluoroquinolone, the treatment should be changed to an antibiotic not known to cause neuropathy if possible. As the number of patients treated with fluoroquinolones is growing, it can be expected that the number of patients who experience such reactions will increase.

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