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To the Editor

Ciprofloxacin Induced Acute Small Fibre Neuropathy. Case Report

Ciprofloxacin safety is similar to other antibiotic. However, it's use has been associated with various systemic adverse effects which vary from a mild form like gastroenteritis to a severe one like acute renal failure. The central nervous system (CNS) adverse effects include headache, confusion and seizure.[1] However; there are rare reports of peripheral neuropathies. These patients have experienced parathesia, hypoesthesia, dysesthesias and weakness. The CNS and peripheral nervous system (PNS) side effects of ciprofloxacin can occur even after the first dose.[2] The treatment should be stopped in order to prevent irreversible damage.

Case Report

A 49-year-old patient with a past medical history of hypertension and lumbar spondylosis was treated with regular botulinum toxin injections for detrussor muscle hyperactivity. Three weeks earlier, he had received an intravesical botulinun toxin injection and over the ensuing two weeks he developed fever, rigors and dysuria. His general practitioner prescribed him ten days cefadroxil for a presumed UTI but, as his symptoms remained, the antibiotic was changed to oral ciprofloxacin. Within 24 hours he developed a severe burning sensation in his feet, in the left more than the right, necessitating urgent admission to hospital. His treatment for UTI continued with intravenous ciprofloxacin as the urine culture grew *pseudomonas* species sensitive to the antibiotic. On examination, he was oriented and alert but pyrexial. He was unable to stand due to burning feet pain. His cranial nerves and upper limbs were normal. In the lower limbs he had normal muscle bulk and no fasciculation. Power testing was normal proximally but limited distally due to severe pain; tone and reflexes were normal and plantars were down going bilaterally. Sensory examination showed severe allodynia up to mid-calf in the left leg and in the dorsum of the right foot. Joint position and vibration sensation were normal bilaterally.

He had a white cell count (WCC) of 12.7 and a CRP 152, both attributed to the UTI. The rest of his blood tests, including blood glucose, urea and electrolytes, liver function tests, thyroid function tests, immunoglobulins, immunoglobulin electrophoresis and autoimmune and vasculitis screens, were normal.

Radiological examinations including chest, abdomen and lumbar spine X-rays and abdominal ultrasound, were all normal. Magnetic resonance imaging (MRI) of thoracic and lumbar spine showed some degenerative changes at the L4/L5 and L5/S1 levels with mild exit narrowing at L4/L5 level but no spinal cord compression, reflecting his background history of lumbar spondylosis. No surgical intervention was deemed necessary.

The standard nerve conduction study (NCS) results performed in the second week of his admission did not show evidence of large fibre neuropathy, nor any evidence of a focal left sciatic or a lumbosacral radiculopathy in his lower limbs. The responses from the sural and superficial peroneal nerves were within normal limits bilaterally. These were slightly asymmetrical, with smaller responses in the left leg probably explained by a mild degree of peripheral oedema. Tibial and peroneal motor responses were within normal limits, with no asymmetry and normal F-waves. Electromyography (EMG) examination from left tibialis anterior and left medial gastrocnemius showed no evidence of active or chronic denervation.

Small fibre assessment with thermal sensation threshold study showed evidence of small fibre impairment in both his upper and lower limbs:

- Cold sensation threshold: elevated in the upper limb 24°C and lower limbs 17.3°C [Normal values are 28.55°C and 25.39°C respectively].
- Warm sensation threshold: elevated in the upper limb 36.4 °C and lower limbs 49.8°C [Normal values 34.89°C and 43.58°C respectively].
- Cold pain threshold: mildly elevated in the upper limbs 0.6°C. [Normal value is 2.39°C]
- In the lower limbs, cold stimulus evoked paradoxical sensations with cold being felt as heat.
- Heat pain threshold: normal in the upper 49.8°C and lower limbs 50.0+°C. [Normal values are 51.53°C and 50.34°C respectively]
- Area: S1 Left Foot Dorso-lateral. (Table1)
- Area: C6 left hand Palmar Thenar. (Table 2)

His ciprofloxacin treatment for UTI was stopped five days after his admission, following neurology team review. He had symptomatic treatment for the hyperesthesia. His peripheral neuropathic pain resolved after three weeks.

Discussion and Literature Review

In 1992, a case report in the Lancet discussed a 37-year-old man who developed peripheral neuropathy whilst taking oral pefloxacin 400mg twice daily for five months. All symptoms were reported in the lower limbs, and all were sensory in nature.

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Table 1: Area: S1 Left Foot Dorso-lateral

	Temp ° C	Difference		Temp ° C	Difference
Warm Threshold	49.8	17.8	Hot Pain	50.0+	18.0
Cold Threshold	17.3	14.7	Cold Pain	0.0+	32.0+

Table 2: Area: C6 left hand Palmar Thenar

	Temp ° C	Difference		Temp °C	Difference
Warm Threshold	36.4	4.4	Hot Pain	49.8	17.8
Cold Threshold	24.2	7.8	Cold Pain	0.6	31.4

Discontinuation of pefloxacin resulted in a dramatic improvement of his peripheral neuropathic symptoms within 10 days. Peripheral neuropathic symptoms also developed when the patient was given ofloxacin and ciprofloxacin. [3]

In 1996, the Swedish Adverse Drug Reactions Advisory Committee reported 37 cases of peripheral sensory disturbance relating to the quinolones between 1985 and 1993.[4] In 68% of patients, symptoms occurred within one week after starting treatment. Paraesthesia was the most common complaint. Seventy one percent of the patients recovered within two weeks after drug discontinuation. In 2001, Cohen published 45 self-referred cases associated with peripheral nervous system side effects such as tingling, numbness, burning pain, twitching, or spasm.[5]

In our case, we were able to establish the association of ciprofloxacin treatment and the development of a small fibre neuropathy following the first dose, based on clinical and neurophysiological findings. The severe distal burning and the neuropathic examination findings came on shortly after initiating treatment; these improved upon withdrawal of treatment suggesting that, in the absence of any other precipitating cause, the ciprofloxacin contributed to the development of the neuropathy. In addition, the lack of neurophysiological evidence for large fibre neuropathy and the results of thermal sensation threshold studies support our diagnosis that ciprofloxacin treatment can cause a predominantly small fibre neuropathy.

Conclusion

To the best of our knowledge, small fibre neuropathy associated with ciprofloxacin treatment has not been reported before. In our case we were able to demonstrate this adverse effect based on clinical presentation and neurophysiological studies. The message to take home is to avoid prescribing ciprofloxacin unnecessarily, especially when other alternative treatments can be used and the treatment should be immediately discontinued if a patient experiences such a reaction.

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