CASE REPORT

Ciprofloxacin-associated choreoathetosis in a haemodialysis patient

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SUMMARY

This report describes a case of drug-associated choreoathetosis in a patient receiving ciprofloxacin. A 72-year-old haemodialysis patient presented with a 4-day history of progressive weakness, restlessness and involuntary movements of all limbs. He had been prescribed ciprofloxacin 500 mg twice daily for a lower respiratory tract infection 7 days previously. He had generalised choreoathetosis affecting both upper and lower limbs. The temporal relationship with drug exposure and a dose which was on the upper limit for his renal impairment implicated ciprofloxacin as the culprit. His symptoms completely resolved within 1 week of drug withdrawal and never recurred subsequently.

BACKGROUND

Fluoroquinolone antibiotics are commonly prescribed in medical practice owing to their broad spectrum antimicrobial coverage, good oral bioavailability and well-tolerated side effect profile. Although rare (1–7%) central nervous system (CNS) side effects of fluoroquinolones are well described, including confusion, disorientation, psychosis, hallucination and seizures. Elderly patients and those with reduced kidney function are more susceptible to these as renal excretion of the drug correlates with its half-life.[1] Thus, appropriate dose reduction based on a patient's glomerular filtration rate and severity of infection is an important consideration when initiating therapy.

CASE PRESENTATION

A 72-year-old man with end-stage kidney disease (ESKD) attended for routine haemodialysis. He complained of a 4-day history of feeling weak with 'shakiness of his arms and legs'. He was quite incapacitated with the movement disorder which had been almost continuous for 4 days. He slept very little over this period as a consequence.

Medical history included end-stage kidney failure owing to diabetic nephropathy for which he received haemodialysis three times a week over the previous 6 years, type 2 diabetes mellitus of 10 years, previous transient ischaemic attack, hypertension and hypercholesterolaemia. Chronic medications included alfacalcidol, pregabalin, aspirin, atorvastatin, folic acid, sevelamer, calcium acetate, gliclazide prolonged-release and darbepoetin alfa. He was started on ciprofloxacin 500 mg twice daily 7 days previously for a lower respiratory tract infection and esomeprazole 4 days previously for dyspepsia by his primary care physician. He had no known drug allergies.

He was oriented in time, place and person and had denied any headaches, palpitations or chest pain. He had no history of recent head trauma. On examination, he was observed to be restless and had generalised choreoathetosis affecting his upper and lower limbs, face and tongue (see video 1). His body temperature was 36.5°C, blood pressure predialysis was 140/73 mm Hg, Glasgow Coma Scale was 15/15. Cardiovascular, respiratory and abdominal examinations were all unremarkable. Cranial nerve function was normal and no focal neurological deficit in peripheral nervous system examination was detected. Laboratory results showed normal full blood count, glucose 7.4 mmol/l, urea 16.9 mmol/l and creatine of 797 μmol/l, potassium 4.0 mmol/l, corrected calcium 2.23 mmol/l and magnesium 0.98 mmol/l. Liver function tests were within normal limits. He was admitted for investigation and management of his choreoathetosis.

INVESTIGATIONS

Contrast-enhanced CT scan of the brain performed within 24 h of presentation revealed an ill-defined 1.3 cm hyperdense mass in the left lateral ventricle with a central area of calcification. This finding was unchanged when compared with a scan performed 5 years previously and was thought to represent a tuber. No mass was identified and midline structures were central.

DIFFERENTIAL DIAGNOSIS

Drug-induced choreoathetosis was the most likely diagnosis, given the temporal relationship between drug exposure and onset of symptoms. Based on documented physiological actions of fluoroquinolones on γ-aminobutyric acid A ($GABA_A$) receptors causing CNS side effects, ciprofloxacin was regarded to be the most rational drug candidate.

TREATMENT

Ciprofloxacin and esomeprazole were discontinued on admission. The patient was started on low dose risperidone 0.5 mg twice daily to control his symptoms.

OUTCOME AND FOLLOW-UP

His choreoathetosis completely resolved within 6 days of discontinuation of both medications. Esomeprazole was restarted at that point and risperidone was discontinued. There had been no recurrence of symptoms for 1 year following his discharge. The patient passed away 2 years following the discharge due to cardiogenic shock following an ST-elevation myocardial infarction.

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Video 1 Restlessness and generalised choreoathetotic movements of the limbs, with lip-smacking and tongue protruding.

He did not develop choreoathetosis or any other neurological disorder following this short-lived episode.

DISCUSSION

Ciprofloxacin has good oral bioavailability of approximately 70–85%.[1] Peak plasma concentration reached 2.5 μg/ml 1–2 h following a 500 mg oral dose. Plasma half-life ranges between 3.5 and 4.5 h, but can approach 8 h in end-stage kidney disease.[2] Plasma protein binding varies between 20% and 40%. Cerebrospinal fluid (CSF) concentration is approximately 10% of plasma concentration when meninges are not inflamed.[3] Fluoroquinolones undergo renal excretion predominantly with 40–50% of an oral dose being excreted unchanged in the urine. Urinary excretion is by active tubular secretion and virtually complete by 24 h. Only small amounts are removed by haemodialysis or peritoneal dialysis.[3] The recommended oral dose for patients with ESKD varies ranges between 250 and 500 mg every 12 h.[1]

The spectrum of side effects owing to the fluoroquinolones is wide, ranging from mild gastrointestinal disturbances (dyspepsia, diarrhoea, nausea and vomiting) to tendon rupture and CNS side effects (hallucination, confusion, psychosis, disorientation, hallucination and seizure).[4 5] Less common CNS side effects include confusion and paranoid ideation, ataxia and peripheral neuropathy.[6] Few cases have reported propriospinal myoclonus,[7] oral-facial dyskinesia[5] and Tourette-like syndrome.[8] CNS side effects account for 0.9–2.1% of quinolone side effects.[7] To our knowledge, this is the first report of ciprofloxacin-associated choreoathetosis.

It has been postulated that fluoroquinolones antagonise the $GABA_A$ receptor in the basal ganglia.[9] By inhibiting $GABA_A$ binding, a hyper-excitable neuronal state ensues which can explain the movement disorders seen rarely with this class of medication.[5 6] Although pregabalin does not bind GABA receptors, it is unclear whether the use of this medication modified the presentation in this case. One might expect that pregabalin binding of α subunits of voltage-gated calcium channels with associated inhibition of excitatory neurotransmitters might have abrogated the clinical condition. The regulation of quinolone concentration in the CSF is still poorly understood. Tamai *et al*[10] have shown that the brain distribution of quinolones is restricted by the action of multiple efflux transporters, including P-glycoprotein, MRP1 and an unknown anion-exchange transporter.

In conclusion, we report a case of ciprofloxacin-associated choreoathetosis in a chronic haemodialysis patient. This adverse effect was likely exacerbated by the large dose of ciprofloxacin prescribed and potentially genetic factors in drug CNS disposition. There was also the potential for previously undocumented drug interactions in this case.

Learning points

- It is important to consider medication side-effects in the differential diagnosis of chorea.
- Choreoathetosis is a presentation of the rare CNS side effects associated with the fluoroquinolones.
- It is important for renal and general physicians to be aware of dosage adjustments when prescribing fluoroquinolones in patients with impaired renal function.

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