Adverse drug reaction of the month

Acute psychosis in a trauma patient due to ciprofloxacin

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Ciprofloxacin and other fluoroquinolone antibiotics are increasingly used in surgical patients. We present a case of a trauma patient whose recovery was complicated by an episode of acute psychosis initially ascribed to post-operative sepsis, but which was most probably due to ciprofloxacin.

Case report

A 31-year-old man was admitted to hospital following a gunshot wound to the abdomen. He underwent emergency laparotomy at which a laceration to the right lobe of the liver, and perforations to the duodenum, jejunum and colon were found and repaired. He was admitted to the intensive care unit post-operatively, electively ventilated, and commenced on piperacillin, gentamicin and metronidazole because of peritoneal soiling. He was weaned from artificial ventilation without difficulty but remained persistently febrile while on antibiotic therapy. He was transferred to the main ward on the sixth day after admission where he was reviewed by the duty psychiatrist on the seventh day because of the possibility of post-traumatic stress disorder. He was found to be behaving appropriately with no evidence of psychiatric disorder, and it was recorded at this time that the patient had no history of prior psychiatric illness.

The patient developed a swinging pyrexia and an ultrasound scan of the abdomen revealed multiple loculated abscesses. On day 13 he was commenced on vancomycin 1g bid, ciprofloxacin 400mg bid and metronidazole 500 mg tid, following which his condition improved, but a low-grade pyrexia persisted. Fluconazole was prescribed because culture of fluid discharged from the wound produced a growth of *Candida albicans*. By day 15 he was noted to be extremely anxious by nursing and medical staff, and on psychiatric review on day 20 appeared more agitated, expressing fears about further attacks, describing nightmares and removing intravenous lines. On day 23 he developed aggressive behaviour towards members of his family and nursing staff. He removed his intravenous lines and absconded from the ward. He was found running about the hospital exhibiting visual hallucinations and paranoid delusions. An acute psychotic episode was diagnosed. Blood biochemistry and haematological results were sodium 135 mmol/l, creatinine 92 µmol/l, haemoglobin 10.4 g/dl, and white cell count $11.8 \times 10^9/l$.

Ciprofloxacin was stopped, and antibiotic therapy continued with gentamicin and metronidazole. His psychosis gradually settled over the next nine days and he was discharged on day 33. The episode was reported to the Committee on Safety of Medicines (CSM) on a yellow card as an adverse drug reaction.

Discussion

Adverse effects of ciprofloxacin involving the central nervous system (CNS) listed in the product data sheet include headache, restlessness, depression, confusion, and convulsions. The risk of convulsions is possibly increased by the concurrent administration of nonsteroidal anti-inflammatory drugs (NSAIDs). Psychosis has been reported as an adverse effect of ciprofloxacin use in several case reports in patients treated for prostatitis, gastroenteritis and urinary tract infection.¹⁻⁴ The timing of onset of the psychotic state ranged from the second dose to the eighth day of therapy. Possible predisposing factors reported include organic brain disease, pre-existing psychiatric symptoms and concurrent medication with indomethacin. The symptoms resolved between 12 hours and four days after stopping ciprofloxacin. The CSM received 17 reports of paranoia, paranoid psychosis or other psychoses associated with ciprofloxacin to 16 June 1997. In the 15 reports for which details were available the median time to onset of symptoms was five days (range 1-157). All the patients reported had recovered or were thought to be recovering when the reports were made (CSM, personal communication).

The case reported here, therefore, has a similar timescale with regard to the onset of the disorder and recovery after drug withdrawal. No reports of psychiatric disorders associated with vancomycin (which was discontinued in this patient at the same time as ciprofloxacin) could be found on a Medline search. However, two reports have been made to the CSM concerning episodes of aggression and disorientation.

The mechanism of CNS adverse effects of ciprofloxacin remain uncertain. Positron emission tomographic studies failed to show an effect on cerebral glucose or oxygen uptake, or on cerebral blood flow from ciprofloxacin administered orally.⁵

An antagonist effect at the benzodiazepine-gamma aminobutyric acid receptor has been demonstrated which can be potentiated by

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Learning points

- ciprofloxacin is occasionally associated with adverse effects in the CNS, including acute psychoses
- attention should be paid to the drug history when assessing patients who develop acute psychoses during the course of another illness

NSAIDs.^{6,7} The CNS effects of quinolones may, therefore, be related in part to interaction with CNS inhibitory pathways.

In this patient there were several factors that may have contributed to the development of the psychosis – sepsis, psychological trauma related to his injury, and concurrent medication. Not surprisingly, sepsis was initially thought to be the cause of the psychosis,

however the patient was never documented as being bacteraemic and parameters such as white cell count and fever were improving at the time the symptoms developed.

Ciprofloxacin is now a widely used antibiotic in the community and in hospitals. It is particularly useful because of its broad Gram-negative activity, good tissue penetration and the existence of an oral formulation. It is often used in abdominal sepsis, sometimes following treatment with a penicillin or cephalosporin, and in these difficult cases the occurrence of a new clinical event may not be associated with the antibiotic therapy. Continued vigilance is therefore necessary as increasing use of this drug and others of the same class in surgical patients brings an increased likelihood of little known adverse effects.

Keywords: ciprofloxacin; psychosis; adverse drug reaction

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