Organic psychosis induced by ofloxacin and metronidazole

Introduction

Antimicrobial agents are a recognized cause of psychopathological and neurological adverse drug reactions (*Table 1*) (Farrington et al, 1995). However, relatively few of these patients are seen by psychiatrists. This article presents an unusual case in a young woman.

Discussion

A catatonic, depressive or organic stupor was initially considered in the differential diagnosis. Subsequently, a schizophreniform psychotic picture emerged and then a gradual and spontaneous reduction of all symptoms without psychotropic medication. The patient described many symptoms at different times during this episode, e.g. paranoid delusions, delusions of reference and control, third person auditory hallucinations, suicidal ideation, tearfulness, psychomotor retardation and psychomotor agitation.

There was no identifiable stressor that could have triggered a disassociative stupor

Case Report

An 18-year-old black African woman was referred to the on-call medical team by her GP with a history of confusion and stupor. Three weeks before admission she complained of abdominal pain and was treated for urinary tract infection with co-amoxiclav. After 1 week, as her pain persisted, co-amoxiclav was stopped and she was treated for presumed pelvic inflammatory disease with ofloxacin 400 mg twice daily and metronidazole 400 mg three times daily. After 2 days on this combination she started to develop confusion, so her mother stopped the ofloxacin. The next day her GP advised her to also stop the metronidazole. During the next 5 days she became increasingly confused, frightened, almost mute and at times immobile. She was referred urgently to the accident and emergency department from where she was admitted to the medical ward. On examination, apart from a slight temperature which did not persist, her vital signs were normal. The neurological examination was limited because of poor cooperation, but no gross abnormality was noted except for absent plantar reflexes. No abnormality was seen in the cardiovascular, respiratory or abdominal systems. Her initial investigations were: urinalysis showed trace blood and trace nitrates; urea and electrolytes, liver function tests, chest X-ray and computed tomography of the head were all normal, her C-reactive protein (CRP) was < 1 mg/litre (normal range (NR) $= 0.8$–2.0 mg/litre); haemoglobin was 14.1 g/dl (NR $= 11.5$–16.5 g/dl); white blood cell count was 3.6×10^9/litre (NR $= 4.0$–11.0×10^9/litre) and platelets were 131 x 10^9/litre (NR $= 130$–400×10^9/litre).

A comprehensive assessment of her mental state soon after admission revealed a completely mute woman, sitting up in bed and looking very frightened. She shed a few tears and the affect was a mixture of anxiety, sadness and confusion. She was able to turn on command towards her mother and aunt and was able to write, on command, one simple word. However, she did not cooperate with the request to nod her head as an alternative to answering questions with a yes or no. Her motor activities ranged from mostly immobile when the psychiatric assessment took place to periods of agitation later on during the admission. Objectively she appeared low in mood. There was no evidence initially to suggest that she was experiencing hallucinations in any modality. After a few days in hospital, she started improving spontaneously. She started to speak to her mother, asking things that initially made little sense. She also felt paranoid when she heard visitors speak in the room adjacent to hers. By day four she started to make significant progress. Subsequent investigations were undertaken, with the following results: magnetic resonance imaging of the brain and electroencephalogram were normal, haemoglobin electrophoresis showed that she had the sickle cell trait, syphilis serology was negative, her CD4 count was 720 cells/μl, antinuclear antibodies was negative, and anti-double-stranded DNA and CRP were normal.

Repeat neurological examination after 1 week of admission revealed moderate hyperreflexia bilaterally but flexor plantar responses. Her CRP remained normal. The neurologist felt that an acute encephalitic infection was unlikely but recommended a lumbar puncture to exclude this. However, neither the patient nor her mother consented to lumbar puncture. A viral serology was also done as viral encephalitis was considered as one of the differential diagnoses, but while the first sample had raised immunoglobulin M, a sample sent to a reference laboratory found no immunoglobulin M, suggesting an original false positive result. After 3 weeks on the medical ward she was discharged home. She had improved greatly by then and her speech and movements were more spontaneous, albeit hesitant.

When she was followed up in the psychiatric outpatient department 2 days after her discharge, she complained of feeling anxious and slowed down. She remembered her admission to the medical ward well and felt guilty for letting her family down. She explained that while on the medical ward she had been hearing voices that were terrifying her. On mental state examination she was very cooperative, initially tense but she relaxed later on and managed to smile. Speech was of normal volume but reduced in rate and quantity. There was no formal thought disorder. Her affect appeared initially to be rather flat. There was no active suicidal intent. She described delusions of reference and was convinced that people on the radio were referring to her. She also gave a vague description of persecutory ideas stating that other people were trying to harm her. There was no thought insertion, broadcast or withdrawal, but she mentioned that she was controlled by an external power. She also had been hearing voices outside her head talking about her in the third person and making threatening remarks. There were no visual hallucinations. Cognition was grossly intact and she had insight into the fact that she had been mentally unwell and appeared happy to accept medication.

She was prescribed risperidone 2 mg at night and citalopram 20 mg in the morning. She missed her next outpatient appointment in 8 weeks time and when she did finally attend 3 months after the initial episode, she said that she had been feeling 100% back to her normal self within 4 days of being discharged from the medical ward, despite not taking any of the prescribed medication. She remembered the psychotic episode quite well, but stated that she wanted to forget it. She could not think of any stress whatsoever before developing the symptoms. She remained well at the time of her next appointment 7 months after the initial episode and was subsequently discharged from psychiatric follow up.

and the negative viral serology, and normal C-reactive protein level and neurological examination made the possibility of viral encephalitis, and hence an organic stupor, unlikely. Her initial confusional state lifted soon after admission, but psychotic and affective symptoms persisted making the diagnosis of delirium less plausible. The onset of symptoms soon after initiation of antimicrobial agents, and complete recovery after their cessation, makes this more likely to be a case of organic psychosis induced by an idiosyncratic reaction to a combination of ofloxacin and metronidazole.

Both ofloxacin and metronidazole have been associated with neurological adverse drug reactions. For metronidazole adverse effects like ataxia, incoordination of movements, psychotic reactions including confusion and hallucinations have been reported very rarely. Psychiatric symptoms have been reported more often with fluoroquinolones like ofloxacin (Gleckman et al, 1979; Cohen et al, 1984; Blomer et al, 1986).

In a retrospective study of 4189 people by Hollweg et al (1997), the suspicion of psychopathological adverse drug reactions during treatment with ofloxacin or ciprofloxacin was documented in 24 patients. The findings included delirious states, paranoid, depressive and manic syndromes, agitation, sleep disturbance, sopor and stupor. In older patients delirium and paranoid symptoms are prominent whereas affective disturbances occur more often in younger patients. However, in most cases multiple morbidity, liver or kidney disease, simultaneous treatment with immunosuppressants and other medications, former psychiatric disorder or psychosocial stress factors were present. While pathophysiological mechanisms leading to adverse CNS effects are not completely understood, Hollweg et al (1997) believed that γ-aminobutyric acid (GABA)-ergic and monoaminergic mechanisms might play a major part.

Unseld et al (1990) used intravenous infusion of ofloxacin and took subsequent electroencephalographic measurements from frontal and occipital lobe placements of electrodes. The electroencephalographic readings exhibited excitatory effects after an infusion of ofloxacin, primarily in the central area. This was enhanced in a group that also received an infusion of flumazenil, a GABA antagonist. Subsequent midazolam infusions increased slow wave activity as well as beta total band interval.

Table 1. Anti-infectious drugs with potential CNS effects

Drug	Class	Symptoms
Aciclovir	Antiviral	Hallucinations, paranoia, confusion, anxiety, depression
Amantadine	Antiviral	Visual hallucinations, paranoia, nightmares, mania, delirium (intravenous, intrathecal)
Cephalosporins	Antibacterial	Confusion, disorientation, paranoia, hallucinations
Cycloserine	Antibacterial	Anxiety, depression, confusion, psychosis
Dapsone	Leprostatic	Insomnia, agitation, hallucinations, mania, depression
Fluoroquinolones (ofloxacin, ciprofloxacin, norfloxacin)	Antibacterial	Delirium, psychosis
Ganciclovir	Antiviral	Hallucinations, delirium, agitation, confusion
Gentamicin	Antibacterial	Hallucinations, confusion, disorientation
Isoniazid	Antituberculin	Depression, agitation, hallucinations, paranoia
Ketoconazole	Antifungal	Hallucinations
Metronidazole	Antibacterial, antiprotozoal	Uncontrollable crying, depression, agitation, disorientation, hallucinations
Nalidixic acid	Antibacterial	Confusion, depression, hallucinations
Procaine derivatives	Antibacterial	Confusion, anxiety, psychosis, agitation, depression, panic
Sulfonamides	Antibacterial	Depression, euphoria, confusion, disorientation, hallucinations
Tobramycin	Antibacterial	Delirium, agitation, hallucinations
Trimethoprim-sulfamethoxazole	Antibacterial	Depression, disorientation, hallucinations, delusions, psychosis
Zidovudine	Antiviral	Mania, paranoia, hallucinations

From Farrington et al (1995)

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Conclusions

This case is unusual because florid psychotic and affective symptoms occurred in a young female, who had no previous psychiatric history or any precipitating stresses, following treatment with ofloxacin and metronidazole. Her spontaneous recovery backs the hypothesis of an idiosyncratic reaction, with psychotic and affective symptomatology, to the antimicrobial agents used to treat her pelvic inflammatory disease. The precise mechanism through which antimicrobial agents induce psychotic symptoms remains unclear. BJHM

The authors are very grateful to Michelle Blythe for the excellent secretarial support.

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