Clozapine-induced nocturnal enuresis: diagnostic and treatment issues

AIMS AND METHOD
To report the management of three cases of clozapine-induced enuresis, by description of these cases and literature review.

RESULTS
Heavy sedation, generalised epilepsy and diabetes mellitus induced by clozapine are some of the mechanisms that underlie the emergence of this side-effect.

CLINICAL IMPLICATIONS
These cases illustrate several different pathophysiological mechanisms necessitating further diagnostic investigations before adequate treatment can be started. Clozapine-induced enuresis is probably under-reported owing to the embarrassing nature of this side-effect.

Case reports
Patient A, a female suffering from schizophrenia, complained of being unable to wake up during sleep to empty her bladder because of a very deep and long sleep. She had no complaints other than frequent bedwetting. There were no signs or symptoms of epilepsy. The patient was on 200 mg clozapine twice daily with a plasma level of 0.48 mg/l, which is well above the minimal recommended therapeutic level of 0.35 mg/l (Kronig et al, 1995) and clorazepate 10 mg three times a day. After clozapine was replaced by olanzapine, the nocturnal enuresis remitted. She experienced no relapse after the switch of the medication.

Patient B, a 27-year-old male suffering from schizophrenia, was seen for complaints of bedwetting. He was also known to have lost consciousness twice in the day time, without tongue biting or incontinence. The patient was on clozapine 400 mg once daily and lactulose 30 ml once daily. The electroencephalogram recording showed signs of a generalised epilepsy. After clozapine was replaced by olanzapine the patient experienced a relapse of his psychosis. Because his psychosis was known to be resistant to classic neuroleptic medication, clozapine 400 mg once daily was restarted, with a plasma level of 0.59 mg/l, and the olanzapine stopped. Valproic acid 500 mg three times a day was added to prevent a recurrence of seizures. His psychosis remitted and he had no further episodes of enuresis or seizures.

Patient C, a 29-year-old male suffering from schizophrenia, was seen for nocturnal enuresis. At previous investigations serum glucose levels were within the normal range. He was on clozapine 200 mg twice daily (unknown plasma level), fluvoxamine 50 mg twice daily...
and oxazepam 25 mg twice daily. When he was seen for his nocturnal enuresis the urine sample taken was positive for glucose, with serum glucose levels of 23.4 and 23.8 mmol/l and a glycosylated haemoglobin of 8.4%. After insulin therapy was started the nocturnal enuresis remitted. High doses of insulin were necessary to control the diabetes. Two years later clozapine was stopped owing to high fever and an infiltration in the left middle lung. Zuclopenthixol was initiated. After the switch of the antipsychotic medication the dose of insulin was decreased and after a few months it was stopped as the diabetes remitted.

**Discussion**

These case reports show the need for further investigations before treatment for clozapine-induced enuresis can be started. The occurrence of enuresis can be explained by several pathophysiological mechanisms.

Patients can have a recurrence of enuresis with a history of prior enuresis (Berrios, 1986). Enuresis occurring after initiation of clozapine can be attributed to the medication. Reducing sedative co-medication as well as clozapine prevents the patient from sleeping through his or her urge to void the bladder in his or her sleep, as seen in case A.

A spontaneous remission of this side-effect is possible (Warner et al, 1994). Epileptic seizures can present as nocturnal enuresis as shown in case B. During the first 6 months after marketing, 71 out of 5629 patients (1.3%) using clozapine were shown to have had generalised tonic-clonic seizures (Pacia & Devinsky, 1994). Patients with a history of seizures or epilepsy were more likely to have seizures soon after initiation of therapy. Seizures tended to occur at low doses (300 mg/day) during the titration phase and at high doses (600 mg/day) during the maintenance phase. The majority of patients who had seizures were able to continue the medication with dose reduction and more gradual dose titrating, or with the addition of anticonvulsant medication.

Recently, clozapine has been associated with the occurrence of diabetes mellitus (Wirshing et al, 1998). Fifteen cases have so far been described (Brugman et al, 2000). A positive family history of diabetes and a personal history of impaired glucose tolerance may increase the risk of developing this side-effect. Treatment of the diabetes can alleviate this indirectly caused clozapine-induced enuresis, as shown in case C.

Treatment with desmopressin (a synthetic analogue of the antidiuretic hormone vasopressin), 10 μg in each nostril at bedtime, has been suggested (Steingard, 1994; Aronowitz et al, 1995; Frankenbur et al, 1996). It decreases the formation of urine by increasing water reabsorption by the renal collecting ducts. Others have suggested the use of oxybutynin (Frankenburg et al, 1996) and trihexyphenidyl (Poyurovsky et al, 1996) to treat clozapine-induced enuresis.

**Conclusion**

Enuresis is a side-effect of clozapine that is probably underreported if not specifically asked about. The underlying pathophysiological mechanisms are varied, which necessitates further investigations prior to commencing treatment of this side-effect.

**References**


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