drug information quarterly

Psychiatric Bulletin (2001), **25**, 232–233

KING HAN KHO AND OLAF NIELSEN

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 underreported owing to the embarrassing nature of this side-effect.

Clozapine has been shown to be a superior antipsychotic (Kane *et al*, 1988). Owing to its potential for causing severe side-effects, it is usually reserved for the management of treatment-refractory psychiatric illnesses. Apart from the risk of agranulocytosis in 0.8% of the patients within a year of initiation (Alvir *et al*, 1993), clozapine has been known to cause seizures, hypotension, tachycardia, weight gain and sialorrhoea. Nocturnal enuresis is a less known side-effect; reports estimate that it occurs in 0.23% (Aronowitz *et al*, 1995) to 27% (Centorrino *et al*, 1994) of patients using clozapine. Patients are sometimes embarrassed to report this side-effect, leading to an underestimation of its incidence (Warner *et al*, 1994). It is possible that the occurrence of enuresis contributes to non-compliance of taking medication.

The pathophysiological mechanism of clozapine-induced enuresis remains unclear. It is suggested that sedation prevents the patients from waking up during sleep to empty the bladder, especially if combined with other sedative medication (Steingard, 1994). Others suggest that clozapine is a potent anticholinergic antagonist, which can lead to urinary retention and subsequent overflow incontinence (Aronowitz *et al*, 1995).

Warner *et al* (1994) report the occurrence of clozapine-induced enuresis in five out of 12 patients in the first 3 months of treatment resolving spontaneously in all cases. Centorrino *et al* (1994), however, report enuresis as a late side-effect, which is not correlated to the plasma level of the drug.

In these case reports we suggest a systematic treatment approach, as the pathophysiology of this side-effect appears to be diverse.

Case reports

Patient A, a female suffering from schizophrenia, complained of being unable to wake up 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

https://doi.org/10.1192/pb.25.6.232 Published online by Cambridge University Press

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 glycosolated 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 anticonvulsive 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 (Poyurovski *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

ALVIR, J. M., LIEBERMAN, J. A., SAFFERMAN, A. Z., *et al* (1993) Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *New England Journal of Medicine*, **329**, 162–167.

ARONOWITZ, J. S., SAFFERMAN, A. Z. & LIEBERMAN, J. A. (1995) Management of clozapine-induced enuresis. *American Journal of Psychiatry*, **152**, 472–473.

BERRIOS, G. E. (1986) Temporary urinary incontinence in the acute psychiatric patient without delirium or dementia. *British Journal of Psychiatry*, **149**, 224–227.

BRUGMAN, N. J., COHEN, D. & DE VRIES, R. H. (2000) Diabetes mellitus after treatment with clozapine. *Nederlands Tijdschrift voor Geneeskunde*, **144**, 437–439.

CENTORRINO, F., BALDESSARINI, R. J., KANDO, J. C., *et al* (1994) Clozapine and metabolites: concentration in serum and clinical findings during treatment of chronically psychotic patients. *Journal of Clinical Psychopharmacology*, **14**, 119–125.

FRANKENBURG, F. R., KANDO, J. C., CENTORRINO, F., *et al* (1996) Bladder dysfunction associated with clozapine therapy. *Journal of Clinical Psychiatry*, **57**, 39–40.

KANE, J., HONIGFELD, G., SINGER, J., *et al* (1988) Clozaril collaborative group: clozapine for treatment-resistant schizophrenia: a double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, **45**, 789–796.

KRONIG, M. H., MUNNE, R. A., SZYMANSKI, S., *et al* (1995) Plasma clozapine levels and therapeutic response for treatment-refractory in schizophrenic patients. *American Journal of Psychiatry*, **152**, 179–182.

PACIA, S. V. & DEVINSKY, O. (1994) Clozapine-related seizures: experience with 5629 patients. *Neurology*, **44**, 2247–2249.

POYUROVSKI, M., MODAI, I. & WEIZMAN, A. (1996) Trihexyphenidyl as a possible therapeutic option in clozapine-induced nocturnal enuresis. *International Clinical Psychopharmacology*, **11**, 61–63.

STEINGARD, S. (1994) Use of desmopressin to treat clozapine-induced nocturnal enuresis. *Journal of Clinical Psychiatry*, **55**, 315–316.

WARNER, J. P., HARVEY, C. A. & BARNES, T. R. E. (1994) Clozapine and urinary incontinence. *International Clinical Psychopharmacology*, **9**, 207–209.

WIRSHING, D. A., SPELLBERG, B. J., ERHART, S. M., *et al* (1998) Novel antipsychotics and new onset diabetes. *Biological Psychiatry*, **44**, 778–783.

*__King Han Kho__ Psychiatrist, __Olaf Nielsen__ General Practitioner, GGZ Delfland locatie St Jorisweg 2, 2612 GA, Delft, The Netherlands

https://doi.org/10.1192/pb.25.6.232 Published online by Cambridge University Press