Clozapine-Induced Urinary Incontinence: Incidence and Treatment With Ephedrine

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Background: Treatment with the atypical antipsychotic drug clozapine appears to be associated with an increased incidence of urinary incontinence (UI). We posited that the potent anti-α-adrenergic effects of clozapine were involved, and hence that an α-adrenergic agonist would reduce UI. We tested this hypothesis by using ephedrine, an approved α-adrenergic agonist.

Method: Fifty-seven inpatients with schizophrenia or schizoaffective disorder (DSM-IV) who met the Kane criteria for being treatment refractory were treated with clozapine (75–900 mg/day). Patients who developed UI were then openly treated with ephedrine in increasing doses until UI was attenuated or a dose of 150 mg/day was attained.

Results: Seventeen patients developed UI as evidenced by either urine-stained sheets/clothing or direct patient reports. In 2 cases, the UI was sufficiently severe that adult diapers had to be used. Comparison of patients who developed UI and those who did not showed that UI was associated with female gender and with concomitant treatment with typical antipsychotic drugs. One patient was treated with a behavioral program, but the remaining 16 patients were treated with ephedrine. Ephedrine treatment was very effective, with 15/16 patients showing improvement within 24 hours after reaching maximum ephedrine dosage. Twelve of 16 (including the 2 most severe) eventually had a complete remission of their UI. In the remaining 4 patients, 3 had a reduction in the frequency of UI and 1 showed no response. These benefits have been maintained over the course of 12 months of subsequent treatment for several patients. There were no side effects associated with the use of ephedrine nor were there any changes in neuropsychiatric status.

Conclusion: Ephedrine appears to be a safe and effective treatment for clozapine-associated UI. By inference, it is likely that clozapine may cause UI via its anti-α-adrenergic properties.

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The incidence of urinary incontinence in hospitalized psychiatric patients is estimated to be between 5% to 11% and may be increased in those with severe psychosis.[1] The latter group may be predisposed to urinary incontinence for several reasons. Psychosis *per se* may be associated with increased urinary incontinence.[2] Furthermore, patients with poor antipsychotic response are often treated with high doses of antipsychotic drugs; these may produce urinary incontinence as a side effect.[3,4]

There are several approaches to reducing antipsychotic drug–associated urinary incontinence. These include (1) using the minimal effective dose of antipsychotic drug, (2) selecting antipsychotic drugs with weak anticholinergic and antiadrenergic properties, (3) and adding drugs such as benztropine, oxybutynin, or amantadine.[5] The effectiveness and practicality of such maneuvers have not been extensively studied. The need for better treatment of antipsychotic drug–associated urinary incontinence has been underscored by the increasingly widespread use of clozapine, which appears to be associated with a much higher incidence of urinary incontinence (up to 42%) than other antipsychotic drugs.[1,6–8]

The mechanism by which clozapine and other antipsychotic drugs cause urinary incontinence remains to be well defined. It is known that urinary continence and micturition are controlled both by sympathetic and parasympathetic mechanisms as well as by voluntary influences. Continence is maintained by both a β-adrenergically mediated relaxation of the bladder wall smooth muscle and α-adrenergically mediated contraction of the trigone and internal sphincter.[5,9,10] Micturition depends on cholinergically mediated bladder wall contraction. Voluntary mechanisms are cortically mediated via the spinal reflex arc as well as through control of the external sphincter and perineal muscles.

A number of mechanisms have been proposed for the production of urinary incontinence by typical antipsychotic drugs. Some have suggested that dopamine blockade in the basal ganglia may contribute to urinary incontinence.[3] However, such a mechanism would not explain

why the incidence of treatment-associated urinary incontinence is higher for the relatively weak dopamine antagonist clozapine than for typical antipsychotic drugs with stronger antidopaminergic properties. On the other hand, urinary incontinence is more frequently associated with both clozapine and phenothiazines, both drugs with considerable α-adrenergic-blocking properties.[11–13] α-Adrenergic blockade could lead to urinary incontinence by decreasing internal bladder sphincter tone.[11] If the latter were true, then adjunctive use of an appropriate α-adrenergic agent would presumably attenuate clozapine-associated urinary incontinence.

This hypothesis ran contrary to clinical practice. Our urologic and gynecological consultants recommended trials of drugs such as oxybutynin and doxazosin for clozapine-associated urinary incontinence. Oxybutynin exerts a direct spasmolytic and antimuscarinic action on the detrusor muscle of the bladder. This results in increased urinary bladder capacity, diminished frequency of uninhibited contractions of the detrusor muscle, and a delay in the initial desire to void. In our clinical experience, however, oxybutynin does not reduce clozapine-induced urinary incontinence (M.A.F., P.E.K. 1994. Unpublished observations). Doxazosin, an α-adrenergic blocker, appears to relax prostatic smooth muscle and reverse outflow obstruction produced by an enlarged prostate. However, many of our patients with clozapine-associated urinary incontinence were women, or men without signs of prostatic hypertrophy. One patient had already failed a trial of doxazosin. The addition of benztropine for the treatment of clozapine-associated sialorrhea in five patients did not reduce their concomitant urinary incontinence. Accordingly, a trial of an α-adrenergic agonist in clozapine-induced urinary incontinence seemed warranted.

Ephedrine is an approved commercially available α-adrenergic agonist, which increases the action of endogenous amines and releases norepinephrine from its intraneuronal storage sites.[14] By stimulating both α- and β-adrenergic receptors in the bladder, ephedrine could facilitate contraction of the trigone and internal sphincter as well as relaxation of bladder smooth muscle, respectively. Both actions would promote urinary continence. Ephedrine-associated side effects are minimal and thought to be due to its CNS-stimulating effects. Although there are case reports of psychotic symptoms associated with overuse or abuse of ephedrine,[15–17] we judged that moderate ephedrine doses posed minimal risk of psychotic exacerbation in clozapine-treated patients. Accordingly, we undertook a trial of adjunctive ephedrine in patients with clozapine-associated urinary incontinence who had failed to respond to therapy with other agents. Based on our initial success, we expanded our use of ephedrine in patients with clozapine-associated urinary incontinence.

METHOD

Fifty-seven inpatients with schizophrenia or schizoaffective disorder (DSM-IV) who met the Kane criteria[18] for being treatment refractory and who were treated openly with clozapine (75–900 mg/day) were screened for urinary incontinence. Urinary incontinence was deemed to be clozapine-associated if either urine-stained clothing or bedding was noted or if the patient complained of urinary incontinence *after* the initiation of clozapine therapy. All patients developing urinary incontinence had at a minimum, a urinalysis. In addition, selected patients underwent gynecological or urological evaluation to rule out treatable organic etiology. Ephedrine (as a single drug entity) was started at 25 mg q.h.s. and increased in 25-mg increments up to a maximum of 150 mg/day. The final dose was administered as either a single bedtime dose or in divided doses throughout the day, depending on the pattern of urinary incontinence (nocturnal vs. diurnal) and treatment response. Patients were informed why ephedrine was prescribed and were asked to report any changes to the clinical staff. Similarly, nurses were aware of the ephedrine trial and were instructed to inquire about urinary incontinence and check clothes and bedsheets. Charts were reviewed for demographic and clinical characteristics of patients, with particular attention to preexisting conditions and concurrent medications that might contribute to urinary incontinence. Brief Psychiatric Rating Scale (BPRS) assessments were completed at baseline, Week 6, and quarterly therafter.[19] Clozapine-treated patients with urinary incontinence were compared with those without urinary incontinence by t test or chi-square test as appropriate. Patients were followed for up to 12 months.

After the addition of ephedrine, urinary incontinence was judged to be worse, unchanged, partially improved, or completely remitted. Complete response was defined as continence (no further reports from the patient/staff of incontinence and no urine stains on the patient's clothing/bedding); partial response was merely a reduction in the incidence of urinary incontinence. For purposes of analysis, patients with a partial response were considered to be nonresponders. The determination was based on chart notation of staff and patient observations, with particular emphasis on urine-stained sheets or clothing. The distribution of ephedrine responses was analyzed by the chi-square test.

RESULTS

Urinary incontinence developed in 17 of 57 patients after the initiation of clozapine therapy. One patient had an exacerbation of preexisting urinary incontinence due to obstetric complications. In the other 16, urinary incontinence developed de novo. Two female patients with urinary incontinence had previously been treated unsuccessfully with oxybutynin 5 mg four times daily for several

Table 1. Characteristics of Treatment-Refractory Patients Who Received Clozapine*

Characteristic	UI	Non–UI	χ^2 p Value
Number of patients	17	40	
Age, mean y (range)	44.9 (32–69)	43.6 (27–72)	NS
Sex			
Male	11	36	.03
Female	6	4	
Mean clozapine dose, mg (range)	441.2 (200–700)	473.8 (75–900)	NS
Receiving typical APD, N	9	9	.02
Typical APD dose in chlorpromazine equivalents, mean mg (range)	441.2 (0–1000)	137.5 (0–1000)	.004
Concomitant medications			
Benzodiazepine	6	7	NS
Anticholinergic	5	8	NS
β-Blocker	6	8	NS

*Chi-square analysis based on N = 16. Abbreviations: APD = antipsychotic drug, NS = not significant, UI = urinary incontinence.

Table 2. Ephedrine Effects on Clozapine-Induced Urinary Incontinence

Patient	Age (y)	Gender	Clozapine (mg/d)	Ephedrine (mg/d)	Response[a]
1	52	M	450	50	2
2	53	M	650	75	1
3	46	M	500	25	2
4	39	F	400	50	2
5	50	M	600	150	0
6	38	F	450	50	2
7	46	M	650	25	2
8	43	M	450	25	2
9	36	F	400	25	1
10	47	M	400	25	2
11	42	F	550	75	2
12	69	F	200	25	1
13	56	F	350	75	2
14	32	M	200	50	2
15	38	M	225	25	2
16	37	M	300	50	2
17	39	M	700	0	2
Mean	44.9		439.7	47.1	2 (mode)

[a]Response: 0 = no change, 1 = reduction in frequency of incontinence, 2 = complete cessation of incontinence.

months. Two patients, including one with preexisting urinary incontinence, required the use of adult diapers.

Clozapine-treated patients who did and did not develop urinary incontinence did not differ significantly in their mean age or mean daily dose of clozapine (Table 1). However, patients who developed urinary incontinence were significantly more likely to receive a typical antipsychotic agent in addition to clozapine ($p = .024$, χ^2) and were more likely to be receiving a higher dose of the typical agent (in chlorpromazine equivalents) than the patients who were treated with concomitant typicals but who did not develop urinary incontinence ($p = .004$, χ^2). Furthermore, the UI group included significantly more female patients than the non-UI group ($p = .03$, χ^2). The use of ancillary medications such as anticholinergics, benzodiazepines, and propranolol was not significantly different in the UI group as compared to the non-UI group.

One patient remained continent with a behavioral intervention program. Twelve of 16 patients treated with ephedrine had a complete response to treatment; 3 others had a partial response (Table 2). One patient showed no response to ephedrine. The ephedrine doses ranged from 25 to 150 mg/day. No patients had an exacerbation of their urinary incontinence. The distribution of ephedrine responses was both clinically and statistically significant ($p < .001$, χ^2). The following case vignettes illustrate the complicated clinical characteristics of patients with clozapine-induced urinary incontinence.

CASE REPORTS

Case 1

This 47-year-old man with chronic undifferentiated schizophrenia was admitted owing to poor symptom response to haloperidol 30 mg/day. Clozapine was initiated and titrated to 200 mg b.i.d. Three weeks after reaching his maximum dose, the patient experienced urinary incontinence. A 1-week course of doxazosin 2 mg orally at bedtime was ineffective. Doxazosin was discontinued, and ephedrine 25 mg orally at bedtime was started. After 2 days of ephedrine therapy, the patient had a significant reduction in urinary incontinence.

Case 2

This 32-year-old man with chronic paranoid schizophrenia and alcohol abuse was admitted to the hospital when he experienced paranoid delusions and violent behavior. He was determined to be resistant to typical antipsychotic drugs and began clozapine treatment. During the titration phase, he complained of several adverse events including excessive sedation, sialorrhea, and urinary incontinence; the latter was first reported 14 days after initiation of clozapine therapy. Ephedrine 25 mg b.i.d. was started. A rapid and complete response of the urinary incontinence was noted within the first 24 hours of ephedrine therapy.

Case 3

This 38-year-old woman with schizophrenia, posttraumatic stress disorder, and partial complex seizures was started on clozapine therapy for treatment-refractory auditory and visual hallucinations. Several months after the initiation of clozapine therapy (450 mg/day), she began to complain of urgency, urinary incontinence, and occasional nocturnal enuresis, which she treated by wearing adult diapers. Her gynecologist treated her with oxybutynin 5 mg q.i.d. for several months without success. During a readmission for a psychotic exacerbation, the urinary incontinence worsened as the dose of cloza-

pine was increased to 500 mg. Oxybutynin was discontinued, but urinary incontinence persisted. Two months later, ephedrine 25 mg orally at bedtime was started and produced a rapid improvement in her symptoms. Increasing ephedrine to 50 mg q.h.s. resulted in full resolution of urinary incontinence.

DISCUSSION

In our patient sample, clozapine-associated urinary incontinence was identified in 30% of our patients with refractory psychosis who were treated with clozapine. We found that although traditional urological agents such as oxybutynin and doxazosin were ineffective, the addition of ephedrine rapidly, dramatically, and safely reduced the urinary incontinence. Despite one report[20] of the effectiveness of anticholinergics (trihexyphenidyl 5 mg) administered at bedtime in some patients with clozapine-associated urinary incontinence, a substantial proportion of our patients were receiving benztropine 0.5 to 2 mg at bedtime for sialorrhea but continued to have nocturnal urinary incontinence. Our results must be understood within the limitations of this study.

We considered urinary incontinence to be present either if stained clothes or sheets were observed by caregivers, or if patients or caregivers complained about urinary incontinence and no evidence of infection was obtained on urinalysis. Although in most cases nurses or caregivers confirmed that patients complained of urinary incontinence, the validity of employing such reports is not known. However, because of the social stigma attached to enuresis, we believe that reporting bias would lead to underestimation of the true incidence. Such considerations may explain the wide divergence in previous reports, in which the incidence of clozapine-associated urinary incontinence has ranged from 2.4% to 42%.[1,6–8] Therefore, while our 30% incidence of urinary incontinence certainly falls within the reported range, the true incidence remains to be determined.

We treated patients in an open and naturalistic fashion. Patients were aware that attention was being paid to their urinary incontinence, and such measures could have increased the possibility of a type I error. In addition, many of our patients were on adjunctive psychotropics. Indeed, our statistical analysis suggests that adjunctive typical antipsychotic drugs contributed to the development of clozapine-associated urinary incontinence. Furthermore, in some patients, clozapine-associated urinary incontinence may be a transient phenomenon,[1] perhaps related to sedation. Thus it is conceivable that ephedrine treatment merely coincided with a spontaneous remission of the urinary incontinence. We did not discontinue ephedrine to determine whether urinary incontinence reemerged. On the other hand, all except 1 of our patients developed urinary incontinence de novo after starting clozapine. For many of our patients, urinary incontinence had been unremitting for several months or more, well beyond the period during which clozapine-associated sedative effects generally subside. Indeed, in our first 2 patients, a trial of oxybutynin had had no effect on urinary incontinence. Thus it is unlikely that the urinary incontinence we observed can be dismissed as merely a transient phenomenon. The rapid onset and sustained nature of ephedrine effects on urinary incontinence are certainly compatible with a true therapeutic drug action.

We noted no medical, psychiatric, or behavioral complications of ephedrine treatment on the basis of either clinical observations or quarterly BPRS assessments. This was true even for those patients who received a high dose (150 mg/day) and/or were receiving ephedrine for a long period of time (12 months). Given that BPRS assessments were administered quarterly, however, we cannot preclude the possibility that ephedrine caused transient psychiatric changes. We also note that most of our patients were medically healthy or medically stable. In medically unstable patients, ephedrine should be used cautiously.

There are several mechanisms by which ephedrine could potentially reduce urinary incontinence. Insofar as clozapine causes sedation, and sedation per se can contribute to urinary incontinence, perhaps nonspecific activating effects of ephedrine attenuate urinary incontinence. Several considerations suggest that the latter is unlikely. First, neither BPRS scores nor clinical notations suggested that patients were more alert during ephedrine treatment. Second, clozapine-induced sedation is typically a transient phenomenon that occurs early during the course of clozapine treatment.[21,22] In our sample, many patients developed urinary incontinence after a period of clozapine treatment (mean = 2.5 months; range, 14 days to 7 months) sufficient for tolerance to develop to sedative effects. Thus, while we cannot preclude the possibility that clozapine sedative effects contribute to urinary incontinence, sedation alone cannot account for the phenomenon.

The alternative explanation is that α-adrenergic effects have a specific influence on urinary incontinence. One level of influence may occur at the level of the bladder, as we initially posited. A second level of influence may be exerted at the level of the brain. Ambrosini[3] postulated that urinary incontinence could result in the face of reduced dopamine transmission with secondary noradrenergic hypoactivity in the basal ganglia. The latter is not inconsistent with our findings, namely that the incidence of urinary incontinence was higher in patients treated with a combination of clozapine and typical antipsychotic drug—in other words, a potent α-adrenergic antagonist in combination with a potent dopamine antagonist. On the other hand, we found that urinary incontinence also developed in patients treated only with clozapine. In this regard, we note that central dopamine systems are both

heterogeneous and interdependent[23] and that some, limited evidence, supports regional dopaminergic hypoactivity.[24,25] It may be that if treatment-resistant patients have a greater degree of dysregulation of dopamine/noradrenaline systems, they may be more vulnerable to urinary incontinence mediated via central mechanisms.

Another possible explanation for the increased urinary incontinence in patients receiving typical antipsychotic drugs with clozapine is that a pharmacokinetic interaction may have occurred between the typical antipsychotic drugs and clozapine. Clozapine may decrease the clearance of typical antipsychotic drugs, resulting in higher serum concentrations. Alternatively, the typical antipsychotic drugs may affect the clearance of clozapine.[26] We are not aware of systematic research in this area. Furthermore, since we did not measure serum concentrations in our patients, the possibility of a drug interaction resulting in elevated serum concentrations is unknown.

We found that females were more likely to develop urinary incontinence than males. While females in general are more likely to have urinary incontinence than men, this is typically associated with obstetrical trauma (stress incontinence). However, only 1 of the women in our group of patients with urinary incontinence had had children, making this explanation less likely. Whether this reflects a generally higher incidence of urinary incontinence in women due to anatomical features and obstetrical history or some gender-specific action of clozapine is unclear.

CONCLUSION

Clozapine appears to be associated with a high incidence of urinary incontinence. Combination use of a typical antipsychotic drug with clozapine may increase a patient's risk of developing urinary incontinence. Our preliminary data suggest that ephedrine may be a safe and effective treatment for clozapine-associated urinary incontinence. Its rapid mode of action and lack of psychiatric effects suggest that it may be useful for treatment of urinary incontinence associated with other psychotropic drugs. While our results are compatible with the hypothesis that clozapine-associated urinary incontinence is mediated via anti-α-adrenergic actions, the latter remains to be confirmed in larger, controlled trials.

Drug names: amantadine (Symmetrel), benztropine (Cogentin and others), clozapine (Clozaril), doxazosin (Cardura), haloperidol (Haldol and others), oxybutynin (Ditropan, Dridase), propranolol (Inderal and others), trihexyphenidyl (Artane and others).

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