An exploratory study for bladder dysfunction in atypical antipsychotic-emergent urinary incontinence

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ABSTRACT

Introduction: This is an exploratory study, which aimed to analyze urodynamic findings in patients who are on atypical antipsychotics and present with urinary incontinence (UI) in order to understand the mechanisms of antipsychotic-emergent UI.

Patients and Methods: Eight patients (34 ± 7.6 years; five males and three females) diagnosed with schizophrenia or other psychotic disorders, who were on risperidone, olanzapine, or clozapine monotherapy and having UI were recruited. Urodynamic study was performed in all patients.

Results: Six out of eight (75%) patients had abnormal urodynamic findings. Three of them had detrusor overactivity (DO) without detrusor-sphincter dyssynergia (DSD); two had DO with DSD; and one had hypoactive detrusor with nonrelaxing sphincter during void phase. The common urinary symptoms were urgency, enuresis, and straining to void urine. Significant postvoid residual urine was found in two patients.

Conclusion: The evidence of bladder dysfunction in atypical antipsychotic-emergent UI is similar to that present in patients with neurological disorders. Urinary complaints in patients on antipsychotics thus need to be evaluated and managed systematically using the protocol followed for neurological conditions.

Key words: Adverse effects, atypical antipsychotics, bladder dysfunction, urinary incontinence, urodynamic study

INTRODUCTION

Urinary incontinence (UI) is a known adverse effect of antipsychotics with reported incidence figures varying from 0.23% to 30%.[1] The mechanism leading to this adverse effect is unclear. Primary alpha-adrenergic blockade[2] and hypodopaminergic state, with also secondary reduced adrenergic activity in the basal ganglia and other parts of the brain,[3] are the two commonly held postulates. They are countered by the lack of systemic alpha-adrenergic blockade symptoms, like hypotension in such patients,[4] and the higher UI rates with clozapine,[5] respectively. The other hypotheses are serotonergic antagonism (5HT-1A), overflow incontinence secondary to antimuscarinic effect, and induced diabetes insipidus.[1,6,7]

These hypotheses have been derived indirectly from the various treatments used to treat UI in this situation; treatments which had limited success only. An alternative approach would be needed to directly study the voiding

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process in these patients to derive a more convincing hypothesis and then develop treatments accordingly.

Urodynamic study (UDS) may offer a means to examine the same. A study that performed urodynamic test on rats found that effects of clozapine on voiding urine were mostly centrally mediated. It led to a significant decrease in micturition volume, contraction time, expulsion time, and amplitude and high-frequency oscillations of detrusor. There was an associated increase in postvoid residual volume, pressure threshold, and bladder capacity. The definition of these terms and those used later in the study are stated in Box 1. Overall, clozapine reduced the voiding efficiency of the bladder in the rats. Here, only contraction time and bladder capacity were affected by peripheral anticholinergic effects. Risperidone and olanzapine have effects similar to clozapine on voiding process of rats when examined through urodynamic test.

UDS performed in 12 patients with antipsychotic-emergent UI had findings different from that of animal model. Here, nearly half of the patients had low bladder compliance; this contributed to increased urgency. One-third of the patients had clear detrusor overactivity (DO) during voiding. A normal urodynamic pattern was present in only one-fourth of the patients. The study indicated the possibility of different sets of action of antipsychotic on patients with associated UI, which may be independent of anticholinergic properties of the antipsychotics.

**Aim of the study**

Keeping this possibility in mind, the present study was done to analyze the urodynamic findings in patients on atypical antipsychotics developing UI. This study was an exploratory study given limited and variable findings in literature.

**PATIENTS AND METHODS**

Eight patients (mean age: 34 ± 7.6 years, range: 23–45 years) diagnosed with psychotic disorder under the group of F-20 to F-29 according to the International Classification of Diseases, Tenth Edition presenting with UI while on monotherapy with atypical antipsychotics were recruited for the study. They received treatment from the Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India. The study was approved by the Institutional Ethics Committee (No. NIMHANS/90th IEC/2014 dated March 27, 2014). All patients gave written informed consent before taking part in the study. The details about demography, clinical features, and treatment are presented in Table 1.

Two patients were on trihexyphenidyl along with risperidone. Those patients, who were prescribed additional psychotropic medications, were excluded from the study. Other exclusion criteria were the presence of any substance use (other than nicotine), any neurological disorder, brain trauma, primary urogenital disease, or urological illness. Patients reporting UI/nocturnal enuresis even before the commencement of antipsychotics were also excluded from the study. The confirmation of psychotic illness and exclusion of other disorders were done clinically, both by history and detailed physical, neurological, and mental status examination.

The urinary complaints were reported either by patient directly or confirmed from him/her after initial reporting by the family member. A detailed history was taken to ascertain the nature of urinary problems and confirming the absence of any urinary symptom before the commencement of antipsychotics. The routine and microscopic examination of urine and urine culture were performed for all patients. None of them had any abnormality in these two tests. After these results only, urodynamic assessment was conducted. They were also advised bowel program on the previous day and enema for bowel evacuation in the morning on the day of procedure. UDS (filling and voiding cystometry) was performed in all patients using multi-channel urodynamic equipment - Primus (LifetechBiomedica, USA), as per the International Continence Society guidelines. It consisted of filling and voiding cystometry and measurement of residual urine. Cystometry was performed with normal saline (0.9%) at a medium filling rate (10–100 ml/min). Detrusor pressure during the filling and voiding phase, intravesical and abdominal pressure, and cystometric capacity of the bladder and compliance were recorded. Sphincter electromyography was performed in all patients to observe sphincter activity. Voiding phase consisted of recording detrusor pressure, abdominal pressure, and volume voided by the
patients. Sphincter activity including detrusor-sphincter dyssynergia (DSD), if present, was recorded. Postvoid residual volume was also recorded in all the patients.

RESULTS

The details of urinary problems of eight patients and findings from their UDS are shown in Table 2. None of the patients had low bladder compliance. Urgency was the most common symptom (six patients, 75%) followed by nocturnal enuresis, which was present in four patients (50%). Difficulty to pass urine was reported by four patients. Overactive detrusor with or without DSD was observed in five patients (62.5%).

DISCUSSION

This study highlights the utility of UDS in antipsychotic-emergent UI. With 75% of patients (six out of eight) having abnormal UDS findings, it validates their complaints and the difficulty related to micturition. There is a substantial chance of lower urinary tract dysfunction, particularly bladder in patients having antipsychotic-related UI, and this should not be ignored. UDS can help manage urinary complaints more precisely.[23]

We found DO in 62.5% of patients (five out of eight). This also matched with their primary complaints of increased frequency, urgency, and nocturnal enuresis along with UI.[16] The earlier study on the similar population observed that 33% of the patients had DO according to the UDS.[11] Compared to that study, the present study found DO as the predominant pathophysiology behind antipsychotic-emergent UI.

DO has been found in many patients with neurological illnesses such as multiple sclerosis, spinal cord injury, myelopathies, stroke, and Parkinson’s disease, wherein the neurological impairment is central or suprasacral.[15,17] DO with synergic sphincters is more likely due to the defects in central inhibitory control over pontine micturition center and motor efferent to bladder.[18] The inhibitory control is primarily managed by prefrontal cortex and anterior cingulate cortex through peri-aqueductal gray.[19] However, infarcts in basal ganglia and thalamus might also give rise to DO with synergic sphincter.[20] Antipsychotics act on these regions.[21] There is a possibility that clozapine’s heightened neuronal activity through serotonin 1A receptors in prefrontal cortex[22] might antagonize the peripheral antimuscarinic effect on bladder.[11] Clozapine reduced prefrontal cortex activation while other antipsychotics were found to increase it.[23] This might be the reason for clozapine-associated higher prevalence of UI compared to other antipsychotics.[24] The amplified sensation of bladder fullness due to increased activation of insula or parasympathetic system[19] might be the other possible mechanism for DO in antipsychotic-emergent UI.

Two patients (25%) had DSD along with DO; both had complaints of straining to void urine along with incontinence. One of them also had significant postvoid residual urine. DSD has been associated with impaired voiding, elevated residual urine, and incontinence, and found in patients with suprasacral cord lesions.[16] The premorbid presence of undetected suprasacral abnormalities which exaggerated the differential effect of antipsychotics on autonomic system is one of the possibilities for the findings. This needs exploration in future studies. In an earlier study, no patient on antipsychotics with UI was found with DSD.[11]

One patient had underactive bladder with nonrelaxing sphincter and led to urine retention. The anticholinergic properties of atypical antipsychotics can lead to urine retention. However, similar findings were found in UDSs on rats administered with atypical antipsychotics, where effects were shown to be more centrally mediated rather than due to peripheral anticholinergic effects.[8] Concurrently, it needs to be considered that animal models are not so effective to translate accurately the findings for these human urinary conditions.[18]

In neurology patients, the lower urinary tract dysfunction, if untreated, has been found to cause urinary tract infection, vesico-ureteral reflux, and various upper urinary tract complications such as hydronephrosis and renal impairment.[24] Hence, such patients are evaluated thoroughly with urine diary, urine analysis, ultrasonography, and UDS. The urinary complaints are then managed with conservative, pharmacological and neuromodulation treatment.[24-26] As discussed above, the bladder dysfunction with the possible causes of central and suprasacral defects has a high likelihood to occur in patients on antipsychotics presenting with UI. This study thus questions the current

| Variable | Description |
|----------|-------------|
| Total patients | 8 |
| Age (years) | 34±7.6 (23-45) |
| Gender, n (%) | Male 5 (62.5), Female 3 (37.5) |
| Duration of illness (years) | 4.1±1.9 (1.5-6.4) |
| Diagnosis, n (%) | Schizophrenia 5 (62.5), Persistent delusional disorder 1 (12.5), Psychosis unspecified 2 (25) |
| Number of patients on risperidone (average dose at mg/day) | 4 (6) |
| Number of patients on clozapine (average dose at mg/day) | 2 (250) |
| Number of patients on olanzapine (average dose at mg/day) | 2 (12.5) |

SD – Standard deviation

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CONCLUSIONS

This study indicated DO with or without DSD to be responsible in majority of the cases of urinary complaints and UI associated with atypical antipsychotics. We recommend UDS evaluation for such patients, particularly who has long-standing urinary problem due to antipsychotics for better management and to avoid complications. There is a possibility of more than one mechanism for UI associated with antipsychotics and might be centrally mediated; the role of antidopaminergic or anticholinergic as the mechanisms is very unlikely, particularly in atypical antipsychotics. We need to go a long way to decipher these mechanisms.

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Conflicts of interest
There are no conflicts of interest.

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