ACUTE URINARY RETENTION ASSOCIATED WITH SSRI (SELECTIVE SEROTONIN REUPTAKE-INHIBITORS) AND ZIPRASIDONE.

*Chung K.K., MBBS, and Chua SE, MRCPsych.

Department of Psychiatry, Queen Mary Hospital, The University of Hong Kong, 102 Pokfulam Road, Hong Kong, S.A.R. China.

*Correspondence.

Tel: +852 2855 4488

Facsimile: +852 2855 1345

Email: albertchung0@netvigator.com

Conflict of interest: None.

Case report

We present a case of Depressive Episode and Schizophrenia, in which acute retention of urine (ARU) in an adult male was associated with selective serotonin reuptake-inhibitors (SSRIs) and the atypical antipsychotic, Ziprasidone.

Mr L. was a 54 year old man with a one month history of depression, suicidal ideation and deterioration in self-care. A childhood febrile illness resulted in minor dysarthria, otherwise development was normal. Catatonic Schizophrenia diagnosed in 1977 was treated with electroconvulsive therapy (ECT) and a Depressive episode in 1997 with Fluoxetine 50mg qd. He had been well for years on Fluoxetine 30 mg om, Trifluoperazine 5mg nocte, and Trihexyphenidyl 2mg om. No past history of urinary dysfunction. On admission in September 2004, he was depressed with psychomotor retardation, but was not psychotic. Examination revealed that he was alert and orientated, afebrile, had resting hand tremor and cogwheel rigidity, dysarthria, but no focal neurology. Complete blood count; liver, renal and thyroid function tests; electrocardiogram, chest X-ray, urine culture were normal. Depressive episode, severe, without psychosis (ICD F32.2) was diagnosed, with Extra-pyramidal syndrome. Fluoxetine was gradually increased to 70mg om owing to treatment refractoriness (1). Soon after, ARU developed and Foley catheter was inserted. Urine culture was negative. Fluoxetine and Trihexyphenidyl were stopped. Citalopram was titrated up to 60mg daily, and Trifluoperazine 5mg nocte was switched to Olanzapine 5mg nocte. Micturition returned, and his mood improved. He was later discharged and continued with the above maintenance regimen. He remained well till January 2005 when mutism, negativism and waxy flexibility were

noted. Catatonic Schizophrenia, relapse (ICD F20.2) was diagnosed. He was treated with oral Lorazepam 1mg tds and catatonic signs resolved. He grew fearful and preoccupied, declining oral intake, but could still micturate normally. A stat dose of intramuscular Ziprasidone10mg replaced oral Olanzapine and he stabilized in the daytime, although he occasionally complained of "seeing and hearing ghosts and lions' at night. Oral Ziprasidone was cautiously added to 60 mg a day but after four days on Ziprasidone, he developed ARU. Catheterization released 600ml of urine, urology consultation suggested only minimal prostatic hypertrophy, urine culture and PSA were normal. Ziprasidone was switched to Amisulpride 100mg a day but micturition remained unsuccessful in the following two days and he declined oral intake again. Amisulpride and Citalopram were stopped and he received a total of eight sessions of ECT with marked improvement. Since residual psychotic symptoms persisted, Risperidone 3.5 mg a day was prescribed, and all psychotic symptoms resolved. As a precautionary measure, we also substituted Citalopram for Venlafaxine up to 75mg a day and he remained well at 6 months post-discharge.

Discussion

We report the first case of ARU associated with SSRI and the atypical antipsychotic Ziprasidone. Urinary retention is a recognised adverse effect of SSRIs (2). However, it is less common in atypical antipsychotics (except for Clozapine) (2) and infrequent with Ziprasidone (3)). Urinary voiding is principally mediated by central serotonin, dopamine, opioid, GABA, and nor-adrenaline mechanisms (4,5), while peripheral control of the bladder and urethra is principally cholinergic. The rhabdosphincter of the external urethral sphincter activates the somatic storage reflex. It is innervated by Onuf's nucleus in the sacral spinal cord, rich in 5-HT and

nor-adrenaline receptors (6). Thus, Duloxetine, a potent 5-HT/noradrenaline inhibitor, facilitates 5-HT and NA transmission to engage the sacral storage reflex and thus is an effective treatment for stress incontinence (5,6,19). On the other hand, Duloxetine also demonstrates moderate 5-HT blockade which is pertinent to the central control of voiding since supraspinal 5-HT receptor blockade inhibits bladder contractions and so reduces voiding (18). In our patient, Fluoxetine, Citalopram and Ziprasidone (all potent inhibitors of 5HT-2 and 5-HT transporter reuptake) (7, 8, 9) were associated with ARU (Please see Table). All have weak muscarinic affinity too (7, 8, 9). We also believe that noradrenaline reuptake inhibition was a less likely mechanism for ARU since the dose of Ziprasidone used was very low and sub-therapeutic compared to manufacturer's recommended range (3). The patient failed to micturate when Amisulpride (potent D3 blockade, no 5 HT-2 affinity nor 5 HT-NA reuptake blockade) (8) was substituted for Ziprasidone for two days. We believe that the explanation for this is unlikely to be drug-drug interactions since Ziprasidone has little inhibitory effect on key liver microsomal enzymes (3,9). Instead, it is possible that Ziprasidone had not been completely eliminated because following multiple oral dosing, Ziprasidone had undergone extensive hepatic metabolism and has a mean half-life of 5 hours (3). Due to the rapid deterioration in patient's mental including refusal of food, the clinical team decision was that further observation to confirm a temporal relationship (between stopping Ziprasidone and resumption of normal micturition) would have been difficult to justify since it would have led to delay in essential treatment. Our patient voided normally on Olanzapine 5mg or Risperidone 3.5mg (both have lower 5-HT-2 /D2 ratio, weaker 5-HT transporter reuptake inhibition than Ziprasidone and lack 5 HT-NA reuptake inhibition)(9), but Olanzapine was discontinued after re-emergence of psychotic

symptoms. It is noteworthy that Risperidone and Olanzapine inhibit external urethral sphincter activity, increase detrusor contraction and can even cause urinary incontinence (10). We avoided Haloperidol (despite its weak affinity for the 5-HT2 receptor and 5-HT reuptake transporter and hence lesser propensity to precipitate ARU) due to this patient's susceptibility to extra-pyramidal side-effects resulting in concomitant anti-cholinergic medication. ARU has been reported with Fluoxetine combined with Haloperidol (11) or Risperidone (12). ARU is only rarely associated with severity of schizophrenic symptoms (13) and in contrast to this patient, the ARU developed when catatonic and psychotic phenomena had mostly receded. Finally, we decided to switch to Venlafaxine for depression prophylaxis as it has weaker 5-HT affinity than Fluoxetine (7), and with a weaker 5-HT transporter reuptake than both Fluoxetine and Citalopram. Therefore, we conclude that potent blockade of 5-HT2 receptor together with 5-HT reuptake transporter in the course of treatment with SSRI with Ziprasidone may be associated with centrally-mediated voiding difficulty. We suggest that it is useful to monitor this problem when prescribing an SSRI with Ziprasidone.

Table: Potency (Ki inhibition constant in nmol/L) of some antidepressants, and anti-psychotics for 5-HT transporter reuptake[7, 14] and 5 HT-2 receptor[15, 16, 17,18].

DRUGS		*POTENCY, Ki* (in nmol/L)	
		5-HT 2 receptor	5-HT transporter reuptake
Anti-depressants	Fluoxetine	72	0.80
	Duloxetine	916	0.80
	Citalopram	2051	1.16
	Venlafaxine	2004	9.10
Anti-psychotics	Ziprasidone	0.72	1.24
	Clozapine	17	132
	Risperidone	10	292
	Olanzapine	10	1637
	Haloperidol	4700	1910

Reference List

1. Beasley CM, Jr., Sayler ME, Bosomworth JC, Wernicke JF. High-dose fluoxetine: efficacy and activating-sedating effects in agitated and retarded depression. J Clin Psychopharmacol 1991; 11(3):166-174

2. British National Formulary. Selective serotonin reuptake-inhibitors. British Medical Association and Royal Pharmaceutical Society. 2005, March Chp 4.3.3 URL : http://www.bnf.org/bnf/bnf/current/openat/index.htm

3. Pfizer Inc. Geodon (Ziprasidone HCl) Manufacturer's information. 2005, May. URL : http://www.pfizer.com/pfizer/download/uspi_geodon.pdf

4. Seki S, Igawa Y, Kaidoh K, et al. Role of dopamine D1 and D2 receptors in the micturition reflex in conscious rats. Neurourol Urodyn 2001;20: 105-113

5. Thor KB. Serotonin and norepinephrine involvement in efferent pathways to the urethral rhabdosphincter: implications for treating stress urinary incontinence. Urology 2003;62 (Suppl 4a): 3-9

6. Thor KB, Donatucci C. Central nervous system control of the lower urinary tract: new pharmacological approaches to stress urinary incontinence in women. J Uro. 2004, 172(1): 27-33

7. Sanz EJ, De-las-Cuevas C, Kiuru A, et al. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. Lancet 2005;365: 482-487

8. Tyson PJ, Roberts KH, Mortimer AM. Are the cognitive effects of atypical antipsychotics influenced by their affinity to 5HT-2A receptors? Int J Neurosci 2004;114: 593-611

9. Stahl SM, Shayegan DK. The Psychopharmacology of Ziprasidone: Receptor-binding Properties and Real-world Psychiatric Practice. J Clin Psychiatry 2003; 64 (Suppl 19): 6-12

10. Vera PL, Miranda-Sousa A, Nadelhaft I. Effects of 2 atypical neuroleptics, olanzapine and risperidone, on the function of the urinary bladder and the external urethral sphincter in anesthetized rats. BMC Pharmacol. 2001, 1:4

11. Benazzi F. Urinary retention with fluoxetine-haloperidol combination in a young patient. Can J Psychiatry 1996;41: 606-607

12. Bozikas V, Petrikis P, Karavatos A. Urinary retention caused after fluoxetine-risperidone combination. J Psychopharmacol 2001; 15: 142-143

13. Shiloh R, Weizman A, Dorfman-Etrog P, et al. Association between severity of schizophrenic symptoms and urinary retention. Eur Psychiatry 2001;16: 497-500.

14. Newman-Tancredi A, Gavaudan S, Conte C, Chaput C, Touzard M, Verriele L et al. Agonist and antagonist actions of antipsychotic agents at 5-HT1A receptors:

a [35S] GTPgammaS binding study. Eur J Pharmacol 1998 August 21;355(2-3):245-56.

15. Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. Biol Psychiatry 2001; 50: 345-50.

16. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L etal. Comparative affinity of Duloxetine and Venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neruopsychopharmacol 2001; 25 (6): 871-80.

17. Schmidt AW, Lebel LA, Howard HR, Zorn SH. Ziprasidone: a novel anti-psychotic agent with a unique human receptor binding profile. Eur J Pharmacol 2001; 425: 197-201.

18. Burgard EC, Fraser MO, Thor KB. Serotonergic modulation of bladder afferent pathways. Urology 2003 62 (Suppl 4A) : 10- 15.

19. Cymbalta (Duloxetine) package insert. Eli Lilly and Company. Indianapolis, IN.