Acta Neuropsychiatrica
An International Journal of Translational Neuropsychiatry

Acta Neuropsychiatrica 2013
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DOI: 10.1111/acn.12008

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ACTA NEUROPSYCHIATRICA

Case Report

Urinary incontinence and diarrhoea associated with the switch from oral to injectable risperidone

Di Rosa E, Caldirola D, Motta A, Perna G. Urinary incontinence and diarrhoea associated with the switch from oral to injectable risperidone.

Objective: Urgency, urinary incontinence and bowel disturbances are distressing side effects that have been observed during treatment with risperidone and other antipsychotics probably due to the receptor affinity profile. This occurrence can lead to poor compliance and therefore impair clinical outcome.
Method: We report the case of a 50 year-old lady, who experienced urinary incontinence and diarrhoea, when switching from oral to injectable risperidone, which ceased when discontinuing the drug.
Results and conclusions: It should be taken into account that some side effects can be revealed when switching from oral to depot formulations due to non-compliance to orals; nevertheless dose-dependent mechanisms and individual metabolic variability must be considered when observing idiosyncratic reactions to drugs.

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Keywords: atypical antipsychotics; injectable resperidone; neuroleptic side effects; psychopharmacology; urinary incontinence

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Accepted for publication August 13, 2012
First published online 21 February, 2013

Our patient, a 50-year-old female, had a long history of schizoaffective disorder, treated with oral risperidone up to 4 mg/day for 1 year, at the time of admission to our psychiatric rehabilitation ward. Oral risperidone had successfully controlled this patient's thought and behavioural symptoms, including auditory hallucinations (threatening and insulting voices), reference delusions, disorganised thought and speech and frequent dysphoria, as well as mood swings and elation. However, her family reported her reluctance in complying to oral medications unless prompted. At the same time, she had complained of occasional urinary urgency and leaking, although manageable and self-limiting, which was only disclosed later on further inquiry. During the admission, long acting depot injection was offered in order to tackle the likelihood of non-compliance, as reported in her clinical records and family's statements.

Medical history included congenital cataract successfully treated at 2 years of age, polyposis vaginalis, peripheral venous insufficiency and chronic obstructive pulmonary disease. At the time of assessment she was completing a course on clarithromycin 500 mg po bd and cefodizime 1 g im od for mild infective complication of her respiratory condition due to heavy smoking (40 cigarettes a day). No known urinary dysfunction was reported nor was she suffering from urinary tract infection (UTI) or gastrointestinal conditions at the time of admission.

Long-acting injectable (LAI) risperidone 37.5 mg im biweekly was administered. Her medication also included diazepam 5 mg/day, initially maintaining the oral risperidone 4 mg/day until the third injection,

https://doi.org/10.1111/acn.12008 Published online by Cambridge University Press

according to the approved guidelines, in order to avoid psychotic relapses.

Three days following the first depot injection, the patient complained of urgency and urinary incontinence, during night and day time, and diarrhoea. UTI and other conditions were excluded. The patient was offered sanitary pads and kept on observation for the following couple of weeks. The diarrhoea gradually subsided but, as the urinary incontinence continued, we decided to stop the LAI risperidone administration. Throughout the following couple of weeks the patient reported recovered bladder-control with fewer episodes of incontinence. Her antipsychotic medication was switched to oral quetiapine, 400 mg/day.

Complete bladder control was gradually achieved and her mental state controlled.

Discussion

Literature describes urinary incontinence during treatment with typical antipsychotics and takes on board extrapyramidal involvement or else catecholamine imbalance (1–6). Atypical antipsychotics have partly reduced this problem probably thanks to their different receptor affinity.

Antipsychotic-induced urinary incontinence has been described as depending on dopamine, α_1 adrenergic and 5HT-2 and 3 receptors blockade (7,2). Faecal incontinence can be induced by α_1 adrenergic blockade in the anal sphincter (8).

Bladder voiding and continence are regulated by descendant spinal pathways involving cholinergic, serotonergic and noradrenergic systems, regulating bladder capacity and compliance and glutamatergic excitatory and γ-aminobutyric acid (GABAergic)/glycinergic inhibitory systems regulating the tone of the external urethral sphincter (9).

Risperidone exerts its activity mainly on serotonin 5-HT_2, dopamine D_2 as well as on α_1- α_2-adrenergic and histamine H_1 receptors through a receptor blockade mechanism and low to moderate affinity for 5-$HT_{1A,1C,1D}$ receptors (10). Receptor blockade, especially adrenergic, can plausibly affect bladder and bowel voiding regulating systems therefore causing enuresis and incontinence (11).

In a case report, switching to aripiprazole proved effective in resolving antipsychotic-induced urinary incontinence and retention by several compounds, both typical and atypical, including haloperidol, olanzapine and risperidone. It was argued that aripiprazole, showing partial antagonistic effect on D2 receptors and minimal effect on α_1 adrenergic receptors, had not affected bladder continence/voiding regulating systems (1).

As well as urinary and faecal double incontinence during treatment with risperidone, literature reports genitourinary disturbances, such as priapism, during the switch from oral to injectable risperidone, related to α_1 adrenergic receptor blockade (8,12). To our knowledge, this is the first report of bladder and bowel disturbances following adjunct of intramuscular long-acting risperidone to the oral treatment.

Long-acting risperidone gives a first small release, as little as 1% of the dose, from the surface of the microspheres, delivery system of the active drug, on the first day, then reaching low serum level until the third im injection when therapeutic level is finally achieved. It is therefore recommended by the official guidelines that oral risperidone be maintained for the first weeks of im treatment and then gradually tapered off. Risperidone receptor occupancy must be about 65% to provide therapeutic effect, whereas occupancy rates higher than 80% are likely to cause side effects, especially extrapyramidal. Following the first three administrations and only when long-acting risperidone medication is stabilised, 71–74% of receptors will be occupied on the first few days from the injection whilst 54–65% will be the occupancy rates towards the end of the 2 weeks from the administration of 25 and 50 mg im, respectively (10). Being the initial release of the active drug minimal, it would be be reasonable to think that the level of the drug reached via parenteral route should not outweigh the one attained through the oral route.

Risperidone's metabolism is regulated by the P450 cytocrome system. The role of the Cytochrome P450 2D6 (*CYP2D6*) gene as for both oral and injectable formulations of risperidone has been assessed in pharmacokinetic studies. People carrying the poor metabolising form of the *CYP2D6* genotype can be more prone to side effects and toxicity from the drug. It is reported in the literature that increased levels of risperidone and its active metabolite, 9-hydroxyrisperidone, are detected in poor metabolisers when administered either oral or im form of the drug possibly suggesting the need of dose adaptation for some patients. Different risperidone-9 hydroxyrisperidone ratios between risperidone forms, higher with the LAI compared to oral, are described in the literature, possibly because of the higher first-pass effect for orals. This shows regardless the individual metabolic pattern. However, results are controversial as for their relevance to clinical effects (13,14).

P450 cytocrome system can be sensibly influenced by several antibiotic medications, including ciprofloxacin, gemfibrozil, erythromycin and clarithromycin, described in the literature as playing a role as inhibitors or inducers of psychotropic drug metabolic systems, hence rising or decreasing their plasma levels (15). Clarithromycin has been assessed with regard to its potential effect on the

https://doi.org/10.1111/acn.12008 Published online by Cambridge University Press

P450 metabolic system, though not revealing any direct interaction on the *CYP2D6*. Conversely, significant inhibition *in vitro* has been described as for the Cytochrome P3A (CYP3A)-mediated metabolism of pimozide with raised plasma concentration *in vivo* and increased risk of QTc prolongation in the electrocardiogram. Our patient was medicated with clarithromycin and cefodizime on admission to the ward. Reports of possible interactions of these two drugs on metabolic patterns of other drugs are controversial (16–18). In addition, since the effect described here continued far beyond the completion of the antibiotic course, one cannot assume that any drug interaction contributed to it. However clinical practice is bound to consider possible drug interactions in order to minimise unwanted side effects possibly leading to patients' poor compliance to medications (19).

Conclusion

We considered that compliance issues might have previously hidden potential adverse effects during the oral treatment of this patient, following difficulties in managing her care at home. Nevertheless, this patient had spent some days in hospital prior to starting on the depot, when no bladder incontinence had occurred.

Our patient had fairly tolerated oral risperidone and showed urinary and gastrointestinal side effects when starting on the long-acting injection. We acknowledge that risperidone-induced faecal and urinary incontinence, in the oral form of the drug, has been long known in the literature. From our observation, being the first, even though small, drug release in the 24 h following the injection, one might speculate on some dose-dependent effect. We did not perform any metabolic study on this patient regarding her cytochrome system as this was not possible and beyond our clinical aims but could venture possible genetic susceptibility to side effects because of fault in the metabolic system of this patient.

This case description can draw attention to long-acting drugs management and the need of patient's accurate assessment of possibly undisclosed uneasy side -effects. Attention must be drawn to the impact of drugs on peripheral receptors as well as the central specific effect. We deem it useful that different genetic and metabolic patterns be considered when recording individual responses to medications bearing in mind that unexpected idiosyncratic reactions might motivate the need of caution in drug choice and management.

Acknowledgements

This work was entirely done in the Villa San Benedetto clinic. No conflict of interest to declare. This article is an original paper not currently submitted to any other journal for publication.

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