

Extrapyramidal symptoms as a side effect of Risperidone Use in children, a case-series

Charlotte Verbist^a, Katrien Jansen^{a,b}

^a Department of Paediatrics, University Hospitals, KU Leuven

^b Department of Development and Regeneration, University Hospitals, KU Leuven

charlotte.verbist@uzleuven.be

Keywords

Atypical antipsychotic drugs; risperidone; extrapyramidal symptoms.

Abstract

Atypical antipsychotics are increasingly prescribed to treat behavioural problems in children, including in children with autism. Although exhibiting fewer side effects than typical antipsychotics, paediatricians should remain aware of side effects such as extrapyramidal symptoms. These can be very severe and even irreversible if not timely detected. Therefore continued vigilance and monitoring of side effects remains extremely important.

Introduction

Risperidone, an atypical antipsychotic drug, is increasingly prescribed in children for various indications (1, 2). The European Medicines Agency approved risperidone for treatment of aggression in children with conduct disorder aged 5 years or older and aggressive behaviour in adolescents with mental retardation for a short treatment period up to six weeks (3). Even though adverse effects in atypical antipsychotics are claimed to be low, a higher rate is observed in children than in adults, including extrapyramidal symptoms such as dystonia, akathisia and parkinsonism (2, 4). In Belgium, over the past fifteen years, prescriptions for antipsychotics in minors have increased by 75.5% (5). In 2014, the prevalence of antipsychotic use in children reached 0.6% (5). With this article, we present two cases of children treated with risperidone who experienced severe side effects requiring hospitalisation. We want to raise awareness among paediatricians and emphasise that children treated with atypical antipsychotics are still at risk of these potential serious side effects.

Case

The first patient is a 14-year-old girl known with GLUT-1 (glucose transporter type 1) deficiency and juvenile absence epilepsy; she was diagnosed with autism spectrum disorder at the age of 10 years. Since the age of ten, she has been taking risperidone for psychotic symptoms and at the moment of presentation she was taking 1 mg in the morning and 1.5 mg in the evening (=0.05 mg/kg/d). Other medications included lamotrigine 100 mg twice a day. She consulted because of an already longstanding torticollis causing increasing discomfort and pain. She was diagnosed with dystonia as a side effect of risperidone which was treated with biperiden (0.1 mg/kg/dose) intravenously. Immediate beneficial effect was seen but repeated administration was required. Biperiden was continued as maintenance therapy while risperidone was slowly tapered to stop. There was a favourable evolution over time with decrease in dystonia.

The second patient is a 16-year-old boy who consulted because of neurological deterioration with complaints of torticollis, a resting tremor, bradykinesia, and rigidity. His past medical history included a diagnosis of autism spectrum disorder, and he was also followed up with a paediatric

rheumatologist in the context of suspected juvenile idiopathic arthritis (JIA) and associated guttate psoriasis. He was treated with methotrexate 20 mg, omeprazole 40 mg, vitamin D supplements, folic acid 1 mg daily, prednisolone 5 mg daily and topical calcipotriol/betamethasone and ketoconazole. For several years he has been treated with risperidone 0.8 mg in the morning and 0.9 mg in the evening for treatment of psychotic symptoms (=0.02 mg/kg/day).

Despite treatment for JIA, a painful torticollis remained present as well as regression in motor functioning that could not be explained by arthritis. Clinically, in addition to torticollis, there was also pronounced rigidity, bradykinesia, and a tremor. Biochemically, no inflammation was present. Additional imaging of the cervical spine showed no inflammatory abnormalities. To rule out an underlying neuroinflammatory disorder, central imaging was performed as well as additional blood sampling and lumbar puncture. In this patient, we noted two presentations of possible side effects of antipsychotics: dystonia and parkinsonism. Risperidone was slowly tapered to stop. At the outpatient clinic, we observed significant improvement in symptoms towards normalisation.

Discussion

First-generation antipsychotics (FGA) exert their therapeutic effect mainly through dopamine D2-receptor blockade (6). Despite beneficial effects on aggressive behaviour and psychotic symptoms, the side effects associated with the use of FGA also result from dopamine receptor blockade (6-8). These primarily include extrapyramidal symptoms and are one of the main reasons for the development of second-generation antipsychotics (SGA) (2). SGA have a broader mechanism of action and block numerous other receptors in addition to dopamine receptors, including cholinergic, noradrenergic, and histaminergic receptors (2, 6). Risperidone acts as a strong potent 5-hydroxytryptamine (5-HT) antagonist and to a lesser extent also as a dopamine D2-receptor antagonist (7). In addition to antiserotonergic and antidopaminergic activity, it also binds alpha-1-adrenergic, alpha-2 adrenergic and histamine-H1 receptors (7). Unfortunately, side effects such as extrapyramidal symptoms also result from D2-receptor blockade (7). Since atypical antipsychotics also antagonise dopamine receptors to a lesser extent, the use of atypical antipsychotics may also be associated with extrapyramidal symptoms (2, 7).

Extrapyramidal symptoms can be divided into four categories: (acute) dystonia, akathisia and parkinsonism and tardive dyskinesia (9). Acute dystonia generally occurs in the early phase after initiation of an antipsychotic drug or when the dose is increased and is defined by an abnormal contraction of muscles of the head, eyes, neck, limbs and trunk that persists for a prolonged period of time (9, 10). These spasms can give rise to torticollis and oculogyric crises, for example, and can be severely painful (10). In children treated with atypical antipsychotics, acute dystonia is seen in 2.2% (11). Akathisia is characterised by restlessness (9, 10). This includes constant movements, not being able to sit still, pacing and many other and generally occur in the early phase, several weeks after starting therapy (9, 10). Side effects such as resting tremor, bradykinesia and rigidity can occur with the use of atypical antipsychotics, which is referred to as medication-induced parkinsonism (9, 10). Onset of these side effects tends to occur early after initiation of the antipsychotic drug (9, 10). Unlike acute dystonia, akathisia and parkinsonism, tardive dyskinesia comprises a group of side effects that occur in a later phase of treatment, sometimes only after months to years of therapy (9, 10). Movements of the face, tongue, jaw, and extremities are most common, and these are involuntary and choreatic (9, 10). A systematic review reports a low one-year incidence rate of tardive dyskinesia for children treated with risperidone of 0.3% (12). Considering tardive dyskinesia has a tendency to present after several months, it is possible that these data are an underestimate due to the short duration of various studies (12).

Discontinuing the causative antipsychotic is the most critical step in treatment (8, 9). If this is not feasible, an attempt should be made to move to the lowest therapeutic dosage and if possible switch to an alternative therapy (8). Extrapyramidal symptoms are generally reversible on cessation of the causative neuroleptic drug although tardive dyskinesia may be persistent and irreversible even after cessation of the eliciting drug (8). Regarding pharmacological treatment of extrapyramidal symptoms induced by antipsychotics, limited data can be found on treatment in children (9). For acute dystonia, diphenhydramine or an anticholinergic (biperiden) may be considered and intravenous administration of benzodiazepines can be used in severe cases (9). Evidence and recommendations for treatment are primarily obtained from studies with adults implying generalisation to paediatric population remains difficult (9).

Therapeutic drug monitoring might be of interest for monitoring serum concentrations in children treated with risperidone, especially given side effects are linked with serum concentrations (13, 14). A recent prospective study shows that higher levels of active moiety, the sum of risperidone concentration and its active metabolite, 9-hydroxyrisperidone, are associated with weight gain, which in turn is related to long-term metabolic and cardiovascular risks (13). Higher serum levels in children are also associated with sedation, and higher prolactin levels (2, 13). In adults, there is a well-established correlation between higher serum concentrations and extrapyramidal symptoms (14). A therapeutic range of 20-60 µg/L for the treatment of schizophrenia is suggested in adults (13, 14). Physicians prescribing risperidone to children should be aware that pharmacokinetics and pharmacodynamics in children differ from those of adults, which reflect variations in side-effect profiles (2, 13). Children are more susceptible to weight gain and sedation than adults and paediatricians and general practitioners are probably most aware of these side effects (2, 13). While in adults, neuromotor symptoms are well-recognised side effects (2). With this article, we want to emphasise that children are also susceptible to extrapyramidal symptoms. Lastly, risperidone is primarily metabolised by CYP2D6 thereby caution is required when using comedication which include CYP2D6 inhibitors (14). In general, determining serum concentrations is rarely used in practice and more controlled specific studies are needed to determine a therapeutic range of risperidone for different indications in children.

Conclusion

Neuroleptic drugs are increasingly used in children and adolescents with behavioural disorders and are associated with serious acute and long-term adverse effects. Children are more sensitive to side effects in comparison to adults due to differences in pharmacokinetic and pharmacodynamic characteristics. In addition, it is best to aim for the lowest possible therapeutic dose. Close monitoring of side effects and, if they occur, adjustment of therapy with tapering to stop or switching to an alternative drug is crucial.

Acknowledgements

Informed consent was obtained from both patients.

Conflicts of interest

The authors have no conflict of interest to declare.

REFERENCES:

- Cooper WO, Arbogast PG, Ding H, Hickson GB, Fuchs DC, Ray WA. Trends in prescribing of antipsychotic medications for US children. *Ambul Pediatr*. 2006;6(2):79-83.
- Correll CU, Penzner JB, Parikh UH, Mughal T, Javed T, Carbon M, et al. Recognizing and monitoring adverse events of second-generation antipsychotics in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2006;15(1):177-206.
- European Medicines Agency. Opinion/decision on a Paediatric investigation plan (PIP): Risperidone 2011 [Internet]. London: EMA; 2011 [Cited 2023 January 15]. Available from: https://www.ema.europa.eu/en/documents/pip-decision/p/167/2011-ema-decision-6-july-2011-agreement-paediatric-investigation-plan-granting-waiver-risperidone_en.pdf.
- Solmi M, Fornaro M, Ostinelli EG, Zangani C, Croatto G, Monaco F, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. *World Psychiatry*. 2020;19(2):214-32.
- Deboosere E, Steyaert J, Danckaerts M. [Trends in antipsychotics use by Belgian children and adolescents between 2005 and 2014]. *Tijdschr Psychiatr*. 2017;59(6):329-38.
- Correll CU. Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents. *J Clin Psychiatry*. 2008;69 Suppl 4:26-36.
- Leysen JE, Gommeren W, Eens A, de Chaffoy de Courcelles D, Stoof JC, Janssen PA. Biochemical profile of risperidone, a new antipsychotic. *J Pharmacol Exp Ther*. 1988;247(2):661-70.
- Artukoglu BB, Li F, Szejko N, Bloch MH. Pharmacologic Treatment of Tardive Dyskinesia: A Meta-Analysis and Systematic Review. *J Clin Psychiatry*. 2020;81(4).
- Pringsheim T, Doja A, Belanger S, Patten S, group CAfMEaSoAiCCg. Treatment recommendations for extrapyramidal side effects associated with second-generation antipsychotic use in children and youth. *Paediatr Child Health*. 2011;16(9):590-8.
- Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtatabi R, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *Focus (Am Psychiatr Publ)*. 2020;18(4):493-7.
- Tural Hesapcioglu S, Ceylan MF, Kandemir G, Kasak M, Sen CP, Correll CU. Frequency and Correlates of Acute Dystonic Reactions After Antipsychotic Initiation in 441 Children and Adolescents. *J Child Adolesc Psychopharmacol*. 2020;30(6):366-75.
- Correll CU, Kane JM. One-year incidence rates of tardive dyskinesia in children and adolescents treated with second-generation antipsychotics: a systematic review. *J Child Adolesc Psychopharmacol*. 2007;17(5):647-56.
- Kloosterboer SM, de Winter BCM, Reichart CG, Kouijzer MEJ, de Kroon MMJ, van Daalen E, et al. Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *Br J Clin Pharmacol*. 2021;87(3):1069-81.
- Taurines R, Fekete S, Preuss-Wiedenhoff A, Warnke A, Wewetzer C, Plener P, et al. Therapeutic drug monitoring in children and adolescents with schizophrenia and other psychotic disorders using risperidone. *J Neural Transm (Vienna)*. 2022;129(5-6):689-701.