Paediatric and Perinatal Drug Therapy, 2008; 8 (4)

Delayed respiratory depression after accidental risperidone overdose

H P Satish[1], H Payne[2], F Potter[2], A J Nunn[2], K Brodbelt[2]

[1]*Leighton Hospital, Mid Cheshire Hospital NHS Trust, Crewe, UK*

[2]*Royal Liverpool Children's NHS Trust, Liverpool, UK*

Corresponding author

Dr H P Satish, Mersey Deanery, Leighton Hospital, Mid Cheshire Hospital NHS Trust, Crewe CW1 4QJ, UK.
Email: drsatishhp@yahoo.com

Risperidone is an atypical anti-psychotic drug with dopaminergic and serotonergic antagonist properties. It may be beneficial in children with autistic disorder who have serious behavioural disturbances and in children with disruptive behavioural disorder.

We report a case of a 10 year old child who had delayed respiratory depression following accidental overdose, which illustrates a further problem of using 'off label' medicines in paediatrics.

Paed Perinat Drug Ther 2007; 8: 154–156

Keywords: Risperidone – overdose – respiratory depression – pipette

Case Report

A 10 year old child with mild developmental delay was brought to the Children's Emergency department with decreased responsiveness, arching and stiffness of his back. On arrival, he had a poor respiratory drive and subsequently had a respiratory arrest. He was intubated, mechanically ventilated and was transferred to the paediatric intensive care unit for further management. After 6 hours of mechanical ventilation, the child was successfully extubated. He made a complete physical recovery and was discharged from paediatric intensive care unit the following day.

On taking further history, his mother stated that in recent weeks he had developed odd behaviour including visual hallucinations. He had been assessed at a community psychiatric clinic two days prior to the incident and had been prescribed risperidone (Risperdal Liquid, 1 mg/ml; Janssen-Cilag) 0.25 mg to be taken twice a day.

His parents had collected this prescribed medication from the local community pharmacy and they had given him two doses of this medicine. His parents had brought the medicine bottle and its accompanying pipette to the hospital with them. The container had a dispensing label stating the correct amount to be administered in mg rather than the amount to be measured in ml. Communication with the dispensing pharmacist confirmed that the parent had been counselled on dose measurement.

On asking the child's mother to demonstrate how much risperidone she had given to the child using the pipette, it became apparent that she had inadvertently given a 10-fold overdose of this medication i.e. 2.5 mg on each occasion.

Discussion

Toxicity from antipsychotic drugs may result from accidental or intentional overdose or following therapeutic administration. When used therapeutically, it is reported that risperidone has

fewer extra pyramidal symptoms compared with conventional antipsychotic drugs such as haloperidol[1]. Risperidone was developed in 1988 and the FDA approved the drug for marketing in adults in 1994. The manufacturer states that the safety of adult doses higher than 16 mg/day has not been evaluated in clinical trials.

Over the past few years, risperidone has come to be used 'off label' in children for treatment of autism[2,3] and other conditions associated with serious behavioural problems[4] with starting doses about one tenth those used in adults. Literature review has identified paediatric case fatalities following risperidone overdose[5]. A systematic review by the Cochrane collaboration[6] to determine the efficacy and safety of risperidone for autism spectrum disorder concluded that risperidone can be beneficial in some features of autism. In the United Kingdom, risperidone is not licensed for use in children under 15 years[7]. In the United States[8] it is licensed for use in autistic children over 5 years and in Italy it is licensed for pervasive developmental disorders for children above 5 years.

Metabolism of risperidone occurs mainly in the liver, where it undergoes oxidation (CYP2D6) to an active metabolite, 9-hydroxyrisperidone. The half-lives of risperidone and its metabolite are 3 and 7 hours respectively. Genetic polymorphism is seen in 6–8% of white patients who are considered poor metabolisers. In poor metabolisers the half-life extends to 20–30 hours.

Reported side effects of risperidone include lethargy, dystonia, hypotension, tachycardia, dysrhythmia, and impaired concentration. Delayed respiratory failure is an unusual yet potentially life-threatening complication. Physicians should therefore be aware of this risk and appropriately monitor patients who are being treated for risperidone overdose.

In this case, the accidental overdose occurred because of an error in drawing up the prescribed dose. The pipette dispenser (Figure 1) provided with the medication is designed to be appropriate for the common range of adult dosages and is graduated in 0.25 ml (0.25 mg) amounts with alternate graduations labelled in both ml and mg. There is a graduation corresponding to 0.25 mg (0.25 ml) but it is not labelled. The graduation at 2.5 ml (2.5 mg) is labelled.

The Drug Tariff (which controls reimbursement for NHS dispensed medicines) designates risperidone liquid as a 'special container', which has been interpreted as meaning that the complete container (100 ml) and its associated pipette should be supplied together. When used 'off label' in paediatrics, the doses required are approximately 10 times smaller, so that the pipette is considered inadequate for this purpose. To provide doses as small as 0.25 ml from a pipette designed for adults may be inaccurate and the pipette should be clearly marked with graduations appropriate to paediatric doses. Oral syringes of suitable size may be more appropriate. An identical dispensing error was reported in United States in 2001 by the

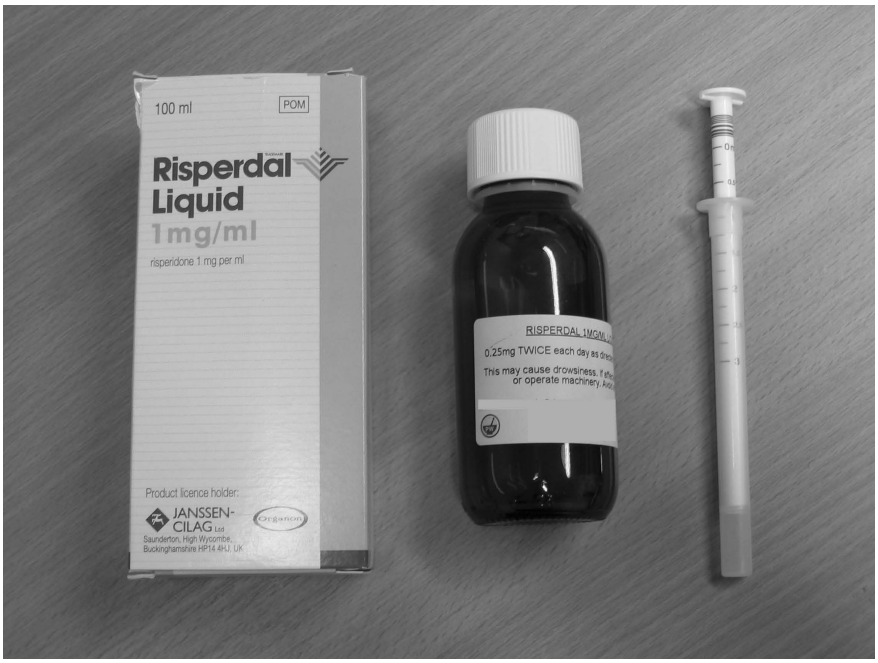

Figure 1 Packaging, container and pipette dispenser for risperidone. The pipette dispenser has labelled graduations for each 0.5 mg (0.5 ml). The graduations in between corresponding to 0.25 mg (0.25 ml) are visible but are not labelled.

National Center for Patient Safety (NCPS) of the Veteran Health Administration[9].

It was confirmed that both the pharmacist and dispensing technician were involved in counselling the parents and demonstrating the graduation on the pipette. A patient information leaflet (for adult patients) was also supplied with the medicine. Pharmacists appear to be reimbursed for risperidone medicine and pipette together such that there is no incentive to use a measuring device more appropriate to paediatric patients. The National Patient Safety Agency in the UK has been contacted and informed of the incident.

Acknowledgements

We would like to thank the parents who have consented for publishing this article.

Competing interests

None declared

Funding

None

References

1. Schillevoort I, de Boer A, Herings RM et al. Risk of extrapyramidal syndromes with haloperidol, risperidone, or olanzapine. Ann Pharmacother 2001;35:1517-1522.
2. McCracken J T, McGough J, Shah B et al. Risperidone in children with autism and serious behavioral problems. New Engl J Med 2002;347:314-321.
3. Chavez B. Role of risperidone in children with autism spectrum disorder. Ann Pharmacother 2006;40:909-916.
4. Reyes M, Olah R, Csaba K, Augustyns I, Eerdekens M. Long- term safety and efficacy of risperidone in children with disruptive behaviour disorders. Results of a 2-year extension study. Eur Child Adolesc Psychiatry 2006;15:97-104.
5. Antia SX, Sholevar EH, Baron DA. Overdoses and ingestions of second-generation antipsychotics in children and adolescents. J Child Adolesc Psychopharmacol 2005;15:970-985.
6. Jesner OS, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. Cochrane Database Syst Rev 2007: CD005040.
7. Morgan S, Taylor E. Antipsychotic drugs in children with autism. BMJ 2007;334:1069-1070.
8. Food and Drug Administration. Risperidone labelling.www.fda.gov/cder/foi/label/2006/021444s008s015,020588s024s028s029,020272s036s041lbl.pdf
9. http://www.va.gov/NCPS/alerts/Pipette.doc

CrossRefs are available in the online published version of this paper:
http://www.librapharm.com
Paper PPDT-0207_2, *Accepted for publication:* 27 February 2008
Published Online: 22 March 2008
doi:10.1185/146300908X254224