Arterial Hypertension and Posterior Reversible Cerebral Edema Syndrome Induced by Risperidone

abstract

Posterior reversible cerebral edema syndrome is a generally reversible neurologic condition that is diagnosed based on distinctive clinical and radiologic findings. The condition, which is mostly associated with severe arterial hypertension, has also been reported to be induced by several medications. We made the diagnosis of hypertension with posterior reversible cerebral edema syndrome in a lean 12-year-old girl treated with the second-generation antipsychotic risperidone. We applied the Naranjo Adverse Drug Reaction Probability Scale and the World Health Organization–Uppsala Monitoring Centre system for causality assessment to the present case. Both scales indicated that a relationship to risperidone was likely. Second-generation antipsychotic agents may occasionally induce an increase in blood pressure even in the absence of overweight. Given this possibility, we recommend routine monitoring of blood pressure during therapy with these agents. Pediatrics 2014;133:e771–e774

AUTHORS: Gregorio Paolo Milani, MD, Mario Giovanni Bianchetti, MD, Marta Benedetta Maria Mazzoni, MD, Fabio Triulzi, MD, Massimo Carlo Mauri, MD, Carlo Agostoni, MD, and Emilio Filippo Fossali, MD

Pediatric Emergency Department, Neuroradiology Department, and Clinical Psychiatry, Clinical Neuropsychopharmacology, Foundation IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milan, Italy; Division of Pediatrics, Mendrisio and Bellinzona Hospitals and University of Berne, Berne, Switzerland; and Department of Clinical Sciences and Community Health, University of Milan, IRCCS Ospedale Maggiore Policlinico, Pediatric Clinic 2, Milan, Italy

KEY WORDS arterial hypertension, posterior reversible cerebral edema syndrome, risperidone, second-generation antipsychotic drugs

Dr Milani had primary responsibility for the management of the patient, wrote the first draft of the manuscript, and prepared the final version of the manuscript; Dr Bianchetti prepared the final version of the manuscript; Dr Mazzoni reviewed the literature; Dr Triulzi had primary responsibility for the management of the patient; Dr Mauri had primary responsibility for the management of the patient and reviewed the literature; Dr Agostoni wrote the first draft of the manuscript; Dr Fossali had primary responsibility for the management of the patient and wrote the first draft of the manuscript; and all authors approved the final version of the manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-1301
doi:10.1542/peds.2013-1301

Accepted for publication Aug 2, 2013

Address correspondence to Gregorio Paolo Milani, MD, Pediatric Emergency Department, Via Commenda 9, Milan, Italy, 20122.
E-mail: yoyobiancorosso@hotmail.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
Copyright © 2014 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
The second-generation antipsychotic agent risperidone is approved, along with other agents, for the treatment of children and adolescents with schizophrenia or bipolar disorders.1 It is well tolerated, with 10% of children withdrawing from treatment because of adverse events.2 Similar to other antipsychotic drugs, the adverse effects of risperidone include insomnia, agitation, anxiety, headache, somnolence, dizziness, tiredness, poor concentration, nausea, extrapyramidal symptoms (including tremor, dyskinesia, rigidity, and akathisia), weight gain, and low blood pressure.2,3 We describe here the occurrence of severe arterial hypertension with posterior reversible cerebral edema syndrome that we believe are directly attributable to long-term management with risperidone.

CASE REPORT

A previously normotensive 12-year-old Italian girl was admitted to the emergency department with a 2-day history of asthenia, lack of appetite, mild generalized headache, insomnia, and 2 episodes of visual impairment lasting ~5 minutes.

Since she was 8 years old, the girl had experienced episodes with decreases in emotion, cognition, and energy associated with sadness, isolation, poor concentration, and low activity affecting the normal psychosocial functioning. Periods of abnormally elevated and irritable mood lasting 8 to 10 days as associated with a decreased need for sleep and her attention being easily drawn to insignificant external stimuli had also been reported. Based on these data, the diagnosis of bipolar type I disorder* was made, and oral risperidone 0.75 mg twice daily was started when she was 10 years old. No adverse effects were noted, and her parents reported improved health-related quality of life, scholarly activities, and social interactions. The girl was free of any other medication, and there was no known social drug or alcohol use.

On admission, general conditions and results of visual and neurologic examinations were unremarkable; body weight was 38.9 kg (36th percentile), body height was 1.512 m (62th percentile), BMI was 17.0 (35th percentile), axillary temperature was 36.3°C, oxygen saturation was 96%, and heart rate was 66 beats per minute. Blood pressure was increased, with systolic values ranging between 140 and 155 mm Hg (stage 2 hypertension5: >135 mm Hg) and diastolic values ranging between 95 and 105 mm Hg (stage 2 hypertension5: >93 mm Hg). A few minutes later, the girl experienced 3 generalized convulsions lasting 3, 5, and 8 minutes, respectively; these were managed with intravenous diazepam. Intravenous nitroprusside (initially 0.3 mg/kg per minute, subsequently increased to 3 μg/kg per minute), later given with oral amlodipine 0.15 mg/kg daily, decreased systolic and diastolic blood pressure by ≤10 and ≤5 mm Hg, respectively.

Results of initial investigations were normal, including renal function; circulating sodium, potassium, and calcium; and arterial blood gases. Laboratory investigations were normal, including liver function tests, full blood count, and electrolytes.ตาราง 1

<table>
<thead>
<tr>
<th>Anticancer agents*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents: carboplatin, chlorambucil, cisplatin, cyclophosphamide (mostly used in combination with corticosteroids)</td>
</tr>
<tr>
<td>Antimetabolites: cytarabine, fluorouracil, gemcitabine, methotrexate</td>
</tr>
<tr>
<td>Inhibitors of angiogenesis: inhibitors of vascular endothelial growth factor (bevacizumab), thalidomide</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors: pazopanib, sorafenib, sunitinib</td>
</tr>
<tr>
<td>Inhibitors of epidermal growth factor receptor: cetuximab, pazopanib</td>
</tr>
<tr>
<td>Inhibitors of cytotoxic T-lymphocyte antigen 4: ipilimumab</td>
</tr>
<tr>
<td>Inhibitors of B-cell receptor signaling: rituximab</td>
</tr>
<tr>
<td>L-asparaginase</td>
</tr>
<tr>
<td>Topoisomerase inhibitors</td>
</tr>
<tr>
<td>Vinca alkaloids: vinblastine, vincristine, vinflunine, vinorelbine</td>
</tr>
<tr>
<td>Corticosteroids (high doses)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
</tr>
<tr>
<td>Calcineurin inhibitors: cyclosporine, tacrolimus</td>
</tr>
<tr>
<td>Rapamycin (sirolimus)</td>
</tr>
<tr>
<td>Antitumor necrosis factor agents: etanercept, infliximab</td>
</tr>
<tr>
<td>Inhibitors of interleukin-12 and interleukin-23: ustekinumab</td>
</tr>
<tr>
<td>Interferon-α</td>
</tr>
</tbody>
</table>

Miscellaneous

Levamisole

Polyclonal intravenous immunoglobulin

Toxicity: alcohol abuse, cocaine, ephedra overdose

* Many anticancer agents included in this section are also used for nononcologic conditions (eg, renal diseases, systemic lupus erythematosus).

FIGURE 1

Brain MRI of a 12-year-old Italian girl with recurrent episodes of mania and major depression. (A) Fluid-attenuated inversion recovery images document the extent of cerebral lesions with oral risperidone 0.75 mg twice daily; and (B) their complete normalization 2 weeks after discontinuing this second-generation antipsychotic agent.
urinalysis; urinary toxicology screening; abdominal ultrasound; and cerebrospinal fluid testing. A brain computed tomography scan, performed 4 hours after admission, was unremarkable. Twenty-four hours later, a brain MRI showed many infra- and supratentorial high signal intensities distributed bilaterally in the cortical and subcortical parieto-occipital regions on fluid-attenuated inversion recovery sequences (Fig 1). The subsequent diagnostic evaluation failed to reveal possible causes of hypertension, including altered thyroid function, mercury poisoning, cardiac diseases with left ventricular hypertrophy (by electrocardiography and echocardiography), renal artery stenosis (by Doppler ultrasonography), or catecholamine-secreting tumors (by both abdominal computed tomography and measurement of urinary catecholamine levels).

Risperidone was discontinued after considering the aforementioned normal results on investigations and the data suggesting that both first- and second-generation antipsychotic agents have occasionally been associated with an increase in blood pressure.\(^6\) Within 5 days, the patient’s blood pressure was \(\leq 95^{th}\) percentile\(^5\) (ie, \(\leq 123/81\) mm Hg), and the drug management with nitroprusside and amlodipine was discontinued. A repeat brain MRI, performed 2 weeks after admission, revealed a complete resolution of the abnormalities (Fig 1). One year later, the girl was doing well with family-focused cognitive behavior therapy and no drug medication. Her blood pressure was 108/56 mm Hg.

To objectively establish the casual relationship between risperidone and arterial hypertension with posterior reversible cerebral edema syndrome, we applied the Naranjo Adverse Drug Reaction Probability Scale and the probabilistic causality assessment system proposed by the World Health Organization–Uppsala Monitoring Centre.\(^7,8\) Their use has been widely advocated in clinical practice and in the literature because of their simple structure and easy reproducibility.\(^9\) Both scales indicated that a relationship between risperidone and arterial hypertension with posterior reversible cerebral edema syndrome was likely.\(^7,8\)

**DISCUSSION**

Posterior reversible cerebral edema syndrome, first described by Hinchey et al in 1996,\(^10\) is also referred to as posterior reversible encephalopathy syndrome, posterior reversible leukoencephalopathy syndrome, hyperperfusion encephalopathy, and brain capillary leak syndrome.\(^10–14\) It is a potentially reversible clinicoradiologic entity characterized by insidious onset of headache, confusion, visual disturbances, and seizures associated with brain edema, which predominates in the posterior areas and in the white matter on imaging. Most cases of this condition occur in patients with severe hypertension.\(^10–15\) It has been argued that the term posterior reversible cerebral edema syndrome is unsatisfactory because the condition is not always reversible and often not confined to the posterior regions of the brain.\(^10–14\)

We presume that in the described patient, posterior reversible cerebral edema syndrome had been caused by severe hypertension resulting from risperidone use.\(^15\) This syndrome has been associated with several other medications,\(^10–14\) as shown in Table 1.

Low blood pressure secondary to autonomic nervous system dysfunction is a common effect with second-generation antipsychotic agents.\(^4,16\) Very rarely, these agents paradoxically produce high blood pressure.\(^7,16\) Most cases of hypertension associated with these agents occur in patients who are overweight or being concurrently treated with selective serotonin reuptake inhibitors. At this stage, the mechanism by which these drugs increase blood pressure in a small minority of patients is still unclear.

**CONCLUSIONS**

Risperidone is an effective medication for children and adolescents with bipolar type I disorders. The current case report supports the notion that second-generation antipsychotic agents may occasionally induce an increase in blood pressure. Given this possibility, we recommend routine monitoring of blood pressure during therapy with these agents.

**REFERENCES**

5. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation,


Arterial Hypertension and Posterior Reversible Cerebral Edema Syndrome Induced by Risperidone

Gregorio Paolo Milani, Mario Giovanni Bianchetti, Marta Benedetta Maria Mazzoni, Fabio Triulzi, Massimo Carlo Mauri, Carlo Agostoni and Emilio Filippo Fossali

Pediatrics; originally published online February 24, 2014;
DOI: 10.1542/peds.2013-1301

Updated Information & Services
including high resolution figures, can be found at:
/content/early/2014/02/18/peds.2013-1301

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2014 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™
Arterial Hypertension and Posterior Reversible Cerebral Edema Syndrome Induced by Risperidone
Gregorio Paolo Milani, Mario Giovanni Bianchetti, Marta Benedetta Maria Mazzoni, Fabio Triulzi, Massimo Carlo Mauri, Carlo Agostoni and Emilio Filippo Fossali

*Pediatrics*; originally published online February 24, 2014;
DOI: 10.1542/peds.2013-1301

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/early/2014/02/18/peds.2013-1301