Conflict of Interest Disclosures: None reported.


RESEARCH LETTER

Retrospective Review of Adverse Effects From Propranolol in Infants

Propranolol has been prescribed for decades in infants for various indications, but its effectiveness in the treatment of infantile hemangiomas (IH) was only recently described. Its perceived safety profile and efficacy is shifting the paradigm of IH treatment, which was traditionally reserved for complicated IH, to include less severe cases. The safety of systemic propranolol treatment in infants is not well studied. Reported serious adverse effects include hypoglycemia, bronchospasm, and hypotension. We reviewed a large series of infants treated with propranolol mostly for cardiac indications and aimed to identify serious adverse effects of propranolol that resulted in hospital admission.

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Methods. A retrospective medical chart review of infants who received propranolol for any indication at the Children’s Hospital of Wisconsin (CHW) was conducted after institutional review board approval. The CHW electronic database was searched to find all infants younger than 12 months who received an order for propranolol from 2004 to 2011 during any type of visit (eg, inpatient, outpatient clinic, and emergency department visits). From this group, patients who were subsequently admitted to CHW within 5 years of the initial propranolol order were reviewed to determine the reason for admission and to document serious adverse effects of propranolol, particularly bronchospasm, hypoglycemia, hypotension, and bradycardia.

Results. A total of 512 infants were identified as having received propranolol at CHW from 2004 to 2011. Of these, 132 infants were found to have an inpatient visit within 5 years of propranolol treatment initiation, and their records were reviewed in detail. Our study cohort included 63 female and 69 male infants. Age at initiation of propranolol treatment ranged from 1 day to 12 months. Most of the patients were started on propranolol therapy for cardiac abnormalities. Indications for propranolol included arrhythmias (eg, supraventricular tachycardia), congenital heart disease, esophageal varices, hypertension, and 1 case of IH. Dose at initiation ranged from 0.23 mg/kg/d to 5 mg/kg/d (average, 1-2 mg/kg/d). Frequency of administration ranged from twice daily, or every 12 hours, to 4 times daily, or every 6 hours (average, 3 times daily, or every 8 hours). Duration of therapy varied from 1 day to greater than 6 years. Eighty-seven infants continued therapy for longer than 1 month.

Of the 132 cases reviewed, no hospital admission was directly attributed to an adverse effect of propranolol. However, in 10 of 132 infants reviewed (7.6%), propranolol treatment was discontinued owing to adverse effects (Table). Bronchospasm, wheezing, or asthma exacerbation was noted in 7 infants (cases 1-7), and bradycardia was noted on monitoring in 3 infants, resulting in discontinuation of propranolol treatment (cases 8-10). No patient discontinued propranolol treatment for hypoglycemia or hypotension. However, hypoglycemia (serum glucose level, 1 mg/dL [normal, 70-126 mg/dL]) was observed in a 21-month old with a concurrent illness (1 day history of cough, fever, and fussiness, admitted for respiratory distress) who received a dose of propranolol and subsequently became lethargic and decompensated (case 11). (To convert glucose to millimoles per liter, multiply by 0.0555.) Given the complexity of the patient’s medical condition, the role of hypoglycemia in the patient’s condition is uncertain.

Table. Clinical Case Descriptions of Infants With Adverse Effects From Propranolol

<table>
<thead>
<tr>
<th>Case</th>
<th>Propranolol Indication</th>
<th>AE</th>
<th>Age at Initiation</th>
<th>Age at AE</th>
<th>Dose at AE a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tachydysrhythmia</td>
<td>Bronchospasm</td>
<td>4.5 mo</td>
<td>14 mo</td>
<td>2 mg/kg/d divided TID</td>
</tr>
<tr>
<td>2</td>
<td>Tachydysrhythmia</td>
<td>Bronchospasm</td>
<td>6 d</td>
<td>6 mo</td>
<td>3 mg/kg/d divided TID</td>
</tr>
<tr>
<td>3</td>
<td>Tachydysrhythmia</td>
<td>Bronchospasm</td>
<td>4 mo</td>
<td>11 mo</td>
<td>2 mg/kg/d divided TID</td>
</tr>
<tr>
<td>4</td>
<td>Diastolic dysfunction</td>
<td>Bronchospasm</td>
<td>3.5 mo</td>
<td>6.5 mo</td>
<td>2 mg/kg/d divided TID</td>
</tr>
<tr>
<td>5</td>
<td>Tachydysrhythmia</td>
<td>Bronchospasm</td>
<td>1 d</td>
<td>5 mo</td>
<td>2 mg/kg/d divided TID</td>
</tr>
<tr>
<td>6</td>
<td>Tachydysrhythmia</td>
<td>Bronchospasm</td>
<td>5 mo</td>
<td>10.5 mo</td>
<td>1 mg/kg/d divided TID</td>
</tr>
<tr>
<td>7</td>
<td>Tachydysrhythmia</td>
<td>Bronchospasm</td>
<td>5 d</td>
<td>18 mo</td>
<td>1.5 mg/kg/d divided TID</td>
</tr>
<tr>
<td>8</td>
<td>Tachydysrhythmia</td>
<td>Bradycardia</td>
<td>8 mo</td>
<td>10 mo</td>
<td>1 mg/kg/d divided TID</td>
</tr>
<tr>
<td>9</td>
<td>Tachydysrhythmia</td>
<td>Bradycardia</td>
<td>7 mo</td>
<td>14 mo</td>
<td>3 mg/kg/d divided TID</td>
</tr>
<tr>
<td>10</td>
<td>Tachydysrhythmia</td>
<td>Bradycardia</td>
<td>1 mo</td>
<td>1 mo</td>
<td>1 mg/kg/d divided TID</td>
</tr>
<tr>
<td>11</td>
<td>Tachydysrhythmia</td>
<td>Hypoglycemia</td>
<td>1 mo</td>
<td>21 mo</td>
<td>2 mg/kg/d divided TID</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse effect; TID, 3 times daily; Y, yes; U, unknown.
aDoses prescribed for infants in our study cohort were observed to be similar to the doses used for hemangioma treatment.
propranolol in the development of hypoglycemia is uncertain. Of note, no adverse effects related to propranolol were observed in the 1 infant treated for infantile hemangioma who was included in our study.

Comment. Limitations of the study include its retrospective nature and the reliance on the assumption that patients with significant complications would be readmitted to our hospital. The applicability of the information from our review to infants treated for the IH is also limited because most of our study patients had multiple coexisting medical conditions in contrast to the relatively healthy population with IH. While our study patients differ in this respect, the doses used in our cohort for cardiac conditions were similar to those used for IH treatment.

While this study was not designed to capture the incidence of adverse effects of propranolol, over 500 infants were identified as having received propranolol, and no serious adverse effects resulting in hospitalization were detected. Furthermore, in only 10 (7.6%) of the 132 infants who underwent full medical chart review was propranolol treatment discontinued owing to adverse effects, supporting propranolol’s relatively safe profile.2 Except for 1 patient, the adverse effect occurred 2 to 20 months after initiation of propranolol treatment, implying that serious adverse effects may be delayed and thus not detected by more intensive monitoring (ie, hospitalization) during the initiation of the drug treatment. While these findings are reassuring, only future large-scale prospective clinical trials will ensure the safety of propranolol and its position as first-line therapy for the treatment of IH.

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PRACTICE GAPS

Propranolol to Treat Hemangiomas of Infancy: Safety and Side Effect Recognition

In 2008, systemic administration of β-adrenergic blockers was found to dramatically improve hemangiomas of infancy (HOI).1 This watershed event of a new use for an established drug in the pediatric dermatologic treatment of HOI changed treatment protocols around the world.2 Concern has been raised about possible overtreatment of HOI now, compared with prior to 2008, but the change in treatment of HOI is more likely owing to the lack of low-risk interventions prior to 2008 than to current overtreatment.

Propranolol was initially used in inpatients, and as its use expanded, a variety of different inpatient and outpatient treatment protocols developed.3 Many questions remain. Is inpatient initiation necessary or can propranolol therapy be safely started in an outpatient setting? What tests should be conducted prior to starting it, and what parameters should be monitored over time? Could there be unforeseen adverse effects or complications specific to children with HOI? All of these questions need to be answered, and reports from an industry-sponsored trial are expected later this year.

In the accompanying report,4 the authors identified as many children as possible (inpatient and outpatient settings) treated with propranolol at their children’s hospital, typically for cardiovascular problems such as arrhythmias or hypertension. From this population they reviewed the records of those readmitted within 5 years of propranolol treatment initiation to examine whether those admissions were related to propranolol adverse effects. Propranolol dosing was quite varied, but the data were reassuring, similar to other reports of propranolol use in HOI.3 Of those admitted to the hospital after the initiation period, 10 of 132 discontinued propranolol treatment, typically owing to bronchospasm (7 of 10) or bradycardia (3 of 10) found on monitoring. Importantly, there were no episodes of...