RESEARCH LETTER

Safety of Propranolol Therapy for Severe Infantile Hemangioma

Infantile hemangioma is a vascular tumor characterized by rapid growth during the first weeks of life and spontaneous involution over a few years.1 Severe forms require systemic therapy. Propranolol induces regression, but safety data are lacking in children.2,3

Methods | The French Health Products Agency (ANSM) allows compassionate use of promising off-label drugs without available therapeutic alternatives. Children throughout France with proliferative infantile hemangioma requiring systemic therapy for life-threatening (ie, potential airway obstruction) or functional risks (ie, amblyopia) or severe ulceration were referred to specialist centers for compassionate use of pediatric oral propranolol.4 Analyses involved data collected between April 2010 and April 2013 of consecutive children enrolled during this period after ANSM institutional board approval and parents’ verbal consent.

Demographic and clinical data were collected at inclusion. Adverse drug reactions (ADRs) were collected by questioning parents and reviewing the child health record at each monthly visit for up to 2 years. Causality was established by the pharmaceutical company providing propranolol using the standard method in France, confirmed by ANSM and the first author, and based on chronological, clinical, and pharmacological criteria on a scale from 0 (unlikely) to 5 (very likely) with 2 or greater considered possibly related to propranolol.5

Results | Of 922 patients referred, 906 were treated with propranolol and had a median age of 114 days (interquartile range [IQR], 1-2282 days; mean, 185 days). Indications for treatment included functional impairment in 72.4%, severe ulceration in 40.0%, and life-threatening conditions in 16.2% (Table 1). Before inclusion, 43 patients had received systemic therapies, mainly corticosteroids (n = 34). Propranolol was administered at a median dose of 2.0 mg/kg/d (IQR, 0.4-4.0 mg/kg/d) for a median duration of 198 days (IQR, 3-929 days). Median duration of follow-up was 396 days (IQR, 18-730 days). Of 313 children who stopped propranolol by April 2013, 83.7% stopped for satisfactory efficacy and 5.8% for ADRs.

Of 922 patients, 81 (8.8%) had 133 ADRs, including 24 (2.6%) with 36 serious ADRs (Table 2). The most commonly reported ADRs were respiratory disorders (mostly infections), which were reported in 31 patients (serious ADRs related to propranolol in 6 patients). The most serious ADRs were cardiac and metabolic disorders.

Four patients had cardiac ADRs, 2 of which were serious ADRs related to propranolol. One death occurred in a 5-month-old child with biliary atresia and portal hypertension, with satisfactory cardiac monitoring, after 14 days of propranolol treatment (dose: 2 mg/kg/d) for hemangioma. Fatal atrioventricular block occurred 15 minutes after sclerotherapy with lauromacrogol for esophageal varices. Causality with propranolol was considered doubtful. In the second case, bradycardia was detected on cardiac monitoring 9 days after initiation of propranolol in a 4-month-old child with metabolic disease; the holter electrocardiogram improved after discontinuation.

Four patients experienced serious hypoglycemia, including 2 children aged 8 and 9 months with hypoglycemic seizures 5.5 and 7 months after propranolol introduction, respectively. One hypoglycemic seizure occurred due to viral gastroenteritis (after fasting and vomiting) and 1 after poor food intake; both recovered after glucose perfusion.

Table 1. Demographic and Clinical Data at Inclusion of 906 Children Followed up in the French Compassionate Use Program for Propranolol

<table>
<thead>
<tr>
<th>No./Total (%) of Children</th>
<th>Sex</th>
<th>Age at Inclusion, median (range), d</th>
<th>Weight, median (range), kg</th>
<th>Height, median (range), cm</th>
<th>Medical history</th>
<th>Hemangioma localization</th>
<th>Hemangioma gravity factor</th>
<th>Functional impairment</th>
<th>Life-threatening conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>226/902 (25.1)</td>
<td>5.8 (2.0-23.8)</td>
<td>59.2 (34-121)</td>
<td>Prematurity</td>
<td>Facial</td>
<td>Severe ulceration</td>
<td>347/867 (40.0)</td>
<td>138/854 (16.2)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>676/902 (74.9)</td>
<td></td>
<td></td>
<td>Bronchiolitis or bronchitis</td>
<td>Internal</td>
<td>Functional impairment</td>
<td>634/876 (72.4)</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>Asthma</td>
<td></td>
<td>Life-threatening conditions</td>
<td>138/854 (16.2)</td>
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<td></td>
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<td></td>
<td></td>
<td>Familial or personal history of atopy</td>
<td></td>
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</table>

* Unless otherwise indicated.

* There were 905 children with data available.

* There were 900 children with data available.

* There were 777 children with data available.
Table 2. Description of Adverse Drug Reactions (ADRs) and Serious ADRs (SADRs) Related to Propranolol Classified by Organ System Disorder

<table>
<thead>
<tr>
<th>Type of Organ System Disorder</th>
<th>No. (%) of Patients With an ADR (n = 81)†</th>
<th>No. (%) of Patients With an SADR (n = 24)§</th>
<th>Median (Range) No./Total (%)</th>
<th>Propranolol Withdrew Median (Range) No./Total (%)</th>
<th>Successfully Restarted</th>
<th>Resolution of ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>31 (38.3)</td>
<td>10 (41.7)</td>
<td>6 (25.0)</td>
<td>8 (4-11)</td>
<td>90 (7-222)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Sleep</td>
<td>20 (24.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (5-16)</td>
<td>49 (0-305)</td>
<td>2 (2-3)</td>
</tr>
<tr>
<td>Vascular</td>
<td>9 (11.1)</td>
<td>2 (8.3)</td>
<td>8 (3.3)</td>
<td>7 (2-12)</td>
<td>5 (1-97)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Digestive</td>
<td>9 (11.1)</td>
<td>1 (4.2)</td>
<td>6 (2.5)</td>
<td>4 (3-6)</td>
<td>71 (2-73)</td>
<td>2 (2-2)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>4 (4.9)†</td>
<td>4 (4.9)§</td>
<td>4 (16.7)†</td>
<td>9 (5-15)</td>
<td>87 (0-218)</td>
<td>1.5 (1-3)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4 (4.9)†</td>
<td>2 (2.5)</td>
<td>3 (12.5)†</td>
<td>4 (1-5)</td>
<td>9 (1-19)</td>
<td>2 (2-2)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (13.6)</td>
<td>4 (16.7)†</td>
<td>0 (0)</td>
<td>6 (1-14)</td>
<td>71 (4-187)</td>
<td>2 (1-2)</td>
</tr>
</tbody>
</table>

† An ADR was defined as any undesirable experience associated with the use of a medical product in a patient. Patients could have more than 1 ADR.
§ An SADR was defined as any ADR leading to death, life-threatening injury, hospitalization (initial or prolonged), disability or permanent damage, or other important medical events as judged by the investigator.

Causality with propranolol was determined by the relationships of time to drug intake, effect of dechallenge or rechallenge of propranolol, absence of other disease or drugs explaining the ADR, and whether the ADR was a known adverse effect of propranolol. These relationships were assessed on a scale from 0 (unlikely causality) to 5 (very likely causality). Patients with a score of 2 or greater were considered to have an ADR possibly related to propranolol.

All 4 patients had hypoglycemia and 2 of the 4 experienced hypoglycemic seizures.

There was 1 death.

There was 1 purpuric eruption, 1 breath-holding spell, 1 febrile urinary tract infection, and 1 fall after hitting a door (classified as an SADR due to hospitalization).

Prescribers must counsel parents at each follow-up visit to discontinuate propranolol during fasting and intercurrent diseases. Limitations include the lack of placebo-controlled trials and small sample size. Even though propranolol could be missed, and there was control group attribution of causality may not be accurate, but the criteria used are well established.
Physical Activity vs Health Education for Cognition in Sedentary Older Adults

To the Editor Dr Sink and colleagues1 reported that a 24-month moderate-intensity physical activity program did not improve global or domain-specific cognitive function compared with a health education program in sedentary adults. We have concerns about their working definition of moderate-intensity physical activity, the implementation and monitoring of the intervention, and the intensity of the physical activity intervention.

The latest guidelines for older adults from the American College of Sports Medicine2 define moderate-intensity aerobic exercise training as 60% or greater maximal oxygen uptake (V\textsubscript{O}\textsubscript{2max}). Because V\textsubscript{O}\textsubscript{2max} or exercise intensity was not measured in this study, it is unknown whether the intervention met these latest guidelines.

Cardiorespiratory stress testing would have allowed the authors to determine V\textsubscript{O}\textsubscript{2max} and therefore to set appropriate aerobic exercise training intensity. Stress testing provides important baseline information and is the criterion standard for assessing changes in cardiorespiratory fitness.

Studies, such as the one by Tyndall et al,3 provide the necessary control measurements to determine whether improvements in cardiorespiratory fitness confer benefits on cognitive performance in older, healthy, sedentary adults. Such testing is normally conducted in exercise studies in which cognition is a main outcome and is essential to provide new insights on dose intensity and exercise duration for brain health.4

In the study by Sink and colleagues,1 exercise sessions were unsupervised and adherence to the exercise program was measured by self-report along with 1 week of accelerometry data every 6 months. The authors claimed that the physical activity levels were maintained or increased during the 24-month period, but only difference scores were presented, making it unclear if the weekly dose of exercise recorded by the physical activity group actually met the study’s goal of 150 minutes/week.

The dose intensity was low and training sessions (30 minutes) were short. The fact that those older than 80 years and those with the lowest physical activity levels benefited suggests that exercise dose was important. Physiological studies suggest that dose intensity much higher than that achieved is required to produce benefit.3,5 Exercise studies should address dose intensity.

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In Reply The purpose of the Lifestyle Interventions and Independence for Elders (LIFE) study was to test whether a...