New treatment strategy for Smith-Lemli-Opitz syndrome

Petra Jank, Ron Wevers, Jan de Jong, Estela Rubio-CozaBo, Jan Smeitink

Smith-Lemli-Opitz syndrome is caused by deficient activity of \(\Delta^7\)-dehydrocholesterol reductase, the final enzyme of the cholesterol biosynthesis pathway, resulting in low cholesterol and high concentrations of its precursors, \(\Delta^7\)-dehydrocholesterol (7DHC) and 8DHC in blood and tissues.\(^1,2\) Cholesterol fulfills an essential role during embryogenesis where it functions as a transporter-molecule for hedgehog signalling proteins required for normal morphogenesis.\(^3\) Without cholesterol their transport is impaired.\(^1\) These findings may explain the phenotypic consequences of \(\Delta^7\)-reductase deficiency as observed in Smith-Lemli-Opitz syndrome: microcephaly, distinctive facies, organ malformations, syndactyly/polydactyly, and genital abnormalities. Once morphogenesis is complete, it is not known whether the low cholesterol or the increased concentration of precursors is more harmful. In abetalipoproteinaemia, cholesterol concentrations are similar to those in Smith-Lemli-Opitz syndrome without clinical side-effects; we thus postulated that 7DHC, 8DHC, or both may be the toxic substances. Therapeutic trials of dietary supplementation of cholesterol with or without bile acids have shown that plasma cholesterol concentration can be increased in some patients. Concentrations of the precursors 7DHC and 8DHC, however, were only marginally altered and clinical results so far have been disappointing.\(^1,2\)

We performed repeated exchange transfusions in combination with inhibition of de-novo cholesterol synthesis with a HMG CoA-reductase-inhibitor in a 3-month old girl with this disorder, after having obtained informed parental consent. This strategy aimed simply to remove precursors while supplying extra cholesterol from the donor

### Table

<table>
<thead>
<tr>
<th>Day</th>
<th>Plasma Cholesterol</th>
<th>7DHC</th>
<th>7DHC/CH ratio</th>
<th>7DHC</th>
<th>7DHC/CH ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0th</td>
<td>1338 (100)</td>
<td>362 (100)</td>
<td>0.27</td>
<td>1273 (100)</td>
<td>1087 (100)</td>
</tr>
<tr>
<td>38th</td>
<td>1106 (99)</td>
<td>272 (75)</td>
<td>0.23</td>
<td>1454 (114)</td>
<td>830 (76)</td>
</tr>
<tr>
<td>93rd</td>
<td>1608 (120)</td>
<td>149 (41)</td>
<td>0.09</td>
<td>1762 (138)</td>
<td>388 (36)</td>
</tr>
<tr>
<td>147th</td>
<td>2312 (173)</td>
<td>191 (58)</td>
<td>0.08</td>
<td>2621 (207)</td>
<td>470 (43)</td>
</tr>
<tr>
<td>190th</td>
<td>2584 (234)</td>
<td>160 (44)</td>
<td>0.06</td>
<td>2700 (212)</td>
<td>400 (37)</td>
</tr>
</tbody>
</table>

Exchanging transfusions were on days 1, 4, 11, 39, 60, 148, 150, and 152. Simvastatin was begun on day 20, daily doses of 2 mg/kg increasing to 4 mg/kg at day 30, and 6 mg/kg from day 40. Immediately before exchange transfusions, C1b-cholesterol, concentrations shown in parentheses.

Gas chromatograph analysis of steroids in plasma (\(\mu\)mol/L) and erythrocyte membrane (\(\mu\)mol/L) isolated erythrocytes during therapy and percentage of initial concentration

blood and inhibit renewed de-novo production of precursors at a higher level in the cholesterol pathway. The girl underwent eight whole-blood exchange transfusions during a period of 5 months. Total exchanged volume accounted approximately for eight times her circulating blood volume. Oral simvastatin treatment was begun on day 20. No complications or drug-related adverse effects were documented. Sterol plasma and erythrocyte-membrane concentrations during the treatment period of 190 days showed a substantial decrease of 7DHC (and 8DHC), as well as an increase in and finally a normal cholesterol (table). After the first three exchange transfusions, plasma 7DHC increased from 151 to 332 \(\mu\)mol/l over 5 days. After exchange transfusions four and five (days 39 and 40), plasma 7DHC concentrations remained stable. Mental, motor, and social development improved. At age 8 months, the child’s neuromotor development corresponded to a child of 5 months on the Bayley scales of infant development. Measurements of head circumference, height, and weight followed the same percentages as before the start of treatment.

Repeated exchange transfusions in combination with a HMG CoA-inhibitor reduced plasma and erythrocyte membrane precursor concentrations and improved the plasma 7DHC/cholesterol ratio greatly in this child. We are encouraged to explore the long-term effects of this treatment strategy as a potentially useful therapeutic option in the treatment of young patients with Smith-Lemli-Opitz syndrome.


### Zolpidem in Parkinson’s disease

Antonio Daniele, Alberto Albanese, Guido Guinot, Bruno Gogoni, Paolo Bartolomeo

Jankovic and Marsden\(^1\) suggest that drugs that enhance neurotransmission of \(\gamma\)-aminobutyric acid (GABA) could be helpful in Parkinson’s disease, but there is little evidence to support this claim. Zolpidem, an imidazopyridine short-acting hypnotic drug used to treat insomnia, shows high selectivity for the benzodiazepine subtype receptor BZ\(_2\), which is part of the GABA\(_B\)-receptor complex. The highest density of zolpidem-binding sites is in the output structures of the basal ganglia: the ventral globus pallidus and the substantia nigra pars reticulata.\(^2\) We observed a 61-year-old woman with a 25-year history of Parkinson’s disease who received zolpidem for insomnia. After the first 10 mg dose, she showed no drowsiness, but a substantial improvement in akinesia and rigidity. Such antiparkinsonian effects were similar to those of levodopa. Other hypnotics (triazolam, zopiclone) were ineffective. This patient received zolpidem (10 mg four times daily) without dopaminergic drugs for 5 years, with relief from Parkinsonian symptoms and no side-effects. We therefore conducted a double-blind, placebo-controlled crossover study of zolpidem in ten patients with clinically diagnosed Parkinson’s disease.\(^3\)
Parkinson’s Disease Rating Scale to assess motor function; their mean disease duration was 9·2 years (6·9), and their mean Hoehn and Yahr score in “off” conditions was 2·9 (1·2).

Zolpidem was administered in one 10 mg oral dose. All patients responded to zolpidem’s hypnotic effect, latency of antiparkinsonian effects being slightly longer, whereas their duration was shorter. Zolpidem did not induce dyskinesias, even in the three patients who had had levodopa-induced dyskinesias. The only adverse effect associated with zolpidem was drowsiness, which occurred in four patients (mild in one, moderate in another, and severe in two patients). No drowsiness was observed in three of the four most severely affected patients.

These preliminary findings suggest that zolpidem therapy could be helpful in a subpopulation of Parkinsonian patients, possibly with severe Parkinson’s disease. There is increasing evidence that in Parkinson’s disease, nigrostriatal dopamine deficiency leads to overactivity of inhibitory neurons in the internal globus pallidus, with subsequent overinhibition of the thalamus and the cerebral cortex. Zolpidem might induce selective inhibition of GABAergic inhibitory neurons in the internal globus pallidus and the substantia nigra pars reticulata. This mechanism should activate both the thalamus, with the supplementary motor area, and the pedunculopontine nucleus, with the reticulospinal and vestibulospinal pathways. If so, zolpidem could provide a pharmacological equivalent of posteroventral pallidotomy. Selective GABAergic agonists, such as zolpidem, that act within the basal ganglia may represent a new therapeutic approach in Parkinson’s disease and could be beneficial in patients who have complications associated with long-term levodopa treatment.

The mean age of the patients was 69·9 years (SD 11·9), their mean disease duration was 9·2 years (6·9), and their mean H oehn and Yahr score in “off” conditions was 2·9 (1·2). Zolpidem produced significant motor improvement (table). Six patients (three of the four most severely affected and three of the six less severely affected) showed motor improvement of between 21% and 59%, mostly in facial expression, rigidity, akinesia, bradykinesia, posture, and gait. In zolpidem responders, clinical effects on Parkinsonian symptoms appeared about 45–60 min after administration of the drug and lasted for about 2–4 h. Thus, compared with the latency and duration of zolpidem’s hypnotic effect, latency of antiparkinsonian effects was slightly longer, whereas their duration was shorter. Zolpidem did not induce dyskinesias, even in the three patients who had levodopa-induced dyskinesias. The only adverse effect associated with zolpidem was drowsiness, which occurred in four patients (mild in one, moderate in another, and severe in two patients). No drowsiness was observed in three of the four most severely affected patients.

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Spinal meningeal diverticula in autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease (ADPKD) is a common heritable connective-tissue disorder associated with mitral-valve prolapse, arterial dissection, and intracranial aneurysms. There are no known spinal manifestations of ADPKD. Among 178 patients with ADPKD who we screened for intracranial aneurysms, three had spinal meningeal diverticula.

A 43-year-old woman was found to have an incidental thoracic paraspinal mass. At age 49, she presented with a 3-week history of headache and visual blurring. The headache was aggravated by the upright position. Neurological examination was normal. Magnetic resonance imaging (MRI) scans revealed a “sagging” brain with low-lying cerebellar tonsils and obliteration of the suprasellar cistern suggestive of intracranial hypotension, and multiple thoracic meningeal diverticula (figure). The headaches resolved spontaneously over 1 month.

A 54-year-old woman presented with a 3-month history of low back and left leg pain. Neurological examination was normal. MRI revealed meningeal diverticula of the right L2 and both S1 nerve roots. These findings were interpreted as incidental.

A 28-year-old woman had a 2-month history of postural headaches. Physical examination was normal. A chest radiograph revealed an 8 cm mass in the left upper thorax. Lumbar puncture could only be performed with the patient in the sitting position; the opening pressure was “very low”. Cerebrospinal fluid (CSF) examination showed 6 nucleated cells per µL and a total protein of 65 mg/dL. At thoracotomy, a cyst was found in the vertebral gutter at the T4 level; it was covered with parietal pleura, communicated with the spinal canal, and was filled with CSF. The back wall of the cyst was sewn down over the hole connecting it to the spinal canal. Examination of the cyst wall revealed fibrous connective tissue. The headaches resolved.

Spinal meningeal diverticula are abnormal outpouchings of the common dural sac, the spinal arachnoid, or the nerve root sheath. Meningeal diverticula are occasionally found as incidental lumbosacral nerve roots, but they are very rare in the remainder of the spine. Although the aetiology of spinal meningeal diverticula is unknown, it is likely that an underlying weakness of the meninges is involved. Spinal meningeal diverticula have been described in patients with Marfan syndrome, neurofibromatosis, and generalised connective tissue disorders of uncertain type. The association of spinal meningeal diverticula with ADPKD suggests that ADPKD is a more generalised connective tissue disorder than previously appreciated.

Two of our patients had typical complaints of intracranial hypotension and laboratory or radiographic studies supported this diagnosis. Spontaneous intracranial hypotension is usually caused by CSF leaks from spinal meningeal diverticula or dural rents. The term “spontaneous” is used to distinguish it from...