New treatment strategy for Smith-Lemli-Opitz syndrome

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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, 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 signaling 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.\(^{4,5} \)

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 simultaneously to remove precursors while supplying extra cholesterol from the donor 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/h 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

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Jankovic and Marsden 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 \( \text{BZ} \), which is part of the GABA\(_A\)-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. 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.