Use of Cholic Acid in patients with Smith-Lemli-Opitz syndrome

Smith-Lemli-Opitz syndrome is an autosomal recessive disorder caused by variants in DHCR7, resulting in a metabolic error in cholesterol biosynthesis. More severely impacted patients have very low levels of cholesterol and high levels of the precursors 7-dehydrocholesterol (7-DHC) and 8-dehydrocholesterol (8-DHC). Patients with more severe disease present with unusual features, including multiple birth defects, and often have feeding problems with difficulty gaining weight. Levels of total body cholesterol may be so low that the child does not have enough cholesterol to use as a substrate for making bile acids, which are necessary for absorption of certain nutrients.

Cholic acid was given to patients with severe SLOS in the 1990's and was helpful in allowing patients to absorb nutrients in the diet and cholesterol supplementation. After a period of many years, cholic acid is now available for use again. It is being marketed under the name Cholbam. A small pilot study of 12 patients was performed to show that cholic acid was tolerated and could be used safely in children with SLOS. Their cholesterol levels increased with cholic acid administration. This study was recently published.

Not every child with SLOS requires Cholbam treatment. If the true cholesterol level is well above 100, there is sufficient cholesterol present to perform the normal physiologic functions in the body including making adequate bile acids. However, children with more severe disease, whose cholesterol levels are well below 100, and who are experiencing difficulty with growth, and/or impaired liver function, may benefit from Cholbam use, although this has not yet been proven scientifically.

Cholbam in and of itself, is NOT a treatment for SLOS. Its purpose is to be used in conjunction with cholesterol in the diet, or supplemented with a special cholesterol suspension, to allow the cholesterol being given to be better absorbed.

In order to determine if Cholbam is indicated, the following steps are recommended:

1. A special blood test to determine the true level of cholesterol should be performed as well as checking levels of the precursors 7-DHC and 8-DHC. This test must be done in a special lab which is able to differentiate between Cholesterol and the precursors. Checking cholesterol in a regular hospital lab or a lab not able to differentiate cholesterol from its precursors is not adequate.
2. Children who would benefit from Cholbam the most are those young children with very severe cholesterol deficiency. These severe patients may have a cholesterol level less than 30, and often manifest severe failure to thrive and feeding issues. These patients, often young infants, may also show elevations in liver transaminases which can become quite severe.

3. Patients with cholesterol levels between 30-100 may also benefit from Cholbam. The patients who tolerated Cholbam during the pilot study mentioned above demonstrated increases in Cholesterol level while on treatment and the medication was well tolerated.
4. Whether treatment with Cholbam will be helpful in patients with cholesterol levels in the range of 30-100 has not been shown in a large enough study. Questions which remain are whether it will help a child grow, protect from progressive liver disease, and whether there are other benefits in terms of metabolic improvements (for example, decreasing levels of precursors and sustained increase in cholesterol levels).
5. In order to use Cholbam safely, levels of cholesterol and precursors should be followed, as well as liver function tests. Clinical parameters such as weight, height and BMI should also be followed to help determine benefit of treatment.
6. All medications have benefits as well as side effects. Problems with Cholbam include diarrhea if used in too high a dose and elevations of liver function enzymes. These side effects should be followed closely in patients treated with Cholbam.
7. Patients whose cholesterol levels are well above 100 probably do NOT need Cholbam treatment, but whether there may be some benefit to using it in this milder group is unknown. A placebo- controlled trial could help answer this question.

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