

Caveat: The following synopsis of normal liver physiology and the pathophysiology of primary biliary cirrhosis was written by a biostatistician. You get what you pay for. The author would be most grateful for corrections to any inaccurate statements: Scott Emerson, scott@emersonstatistics.com.

LIVER PHYSIOLOGY

The liver has many important functions in maintaining the physiologic balance of the human body. The most important of these functions include:

- *Digestion:* The liver excretes bile salts into the intestines. Bile aids the digestion of fats by emulsifying the fat molecules to facilitate their suspension in water, as well as by promoting the absorption of fats from the intestinal lumen into the cells lining the intestine and eventually the blood.
- *Excretion of bilirubin:* Red blood cells last for about 120 days at which time they are destroyed by the spleen. Hemoglobin (the protein which is the primary carrier of oxygen in the red blood cells) is broken down by the liver into bilirubin, and then excreted by the liver into the intestines with the bile, where it is eventually eliminated from the body.
- *Detoxification and/or excretion of drugs and hormones:* The kidneys generally have difficulty removing certain types of chemicals from the blood. There are many substances which are first modified by the liver before being excreted by the kidney. Other substances are modified by the liver and then excreted by the liver into the bile. Included among the substances excreted by the liver are various hormones, such as the steroids. The liver is also a major organ in the excretion of calcium.
- *Carbohydrate metabolism:* All blood from the intestines flows from the intestines through the liver. The liver performs many functions related to maintaining an appropriate glucose level, including the conversion of other simple sugars from the diet into glucose, the production of glycogen, and the conversion of some amino acids into glucose. The liver also uses some of the byproducts of carbohydrate metabolism to form various chemical compounds necessary for other physiologic functions.
- *Fat metabolism:* The liver is a major organ in the processing of dietary fat and the conversion of stored fat into products more readily used for energy. In particular, the liver is responsible for removing the triglycerides and fatty acids circulating in our blood after a meal and converting them to fats for storage. Also a large amount of the cholesterol used by our body is formed in the liver, and the liver is also the major site for production of fats from carbohydrates and proteins.
- *Protein metabolism:* The liver's role in protein metabolism is probably the most important of its metabolic functions. The liver functions to remove the nitrogen groups from amino acids, form urea from the excess ammonia produced in that process (the urea is excreted by the kidneys), form various proteins (especially albumin which helps regulate the amount of fluid in the blood vessels, and some of the proteins that are essential to blood coagulation) that circulate in the blood, and form some amino acids for protein production.

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis is a serious disease of the liver in which the intrahepatic bile ducts become scarred and blocked. This impairs the ability of the liver to excrete bile into the gastrointestinal tract. There follows a buildup of bilirubin in the tissues resulting in the clinical condition known as jaundice. With this decreased excretion of the bile, there tends to be a buildup of copper in the body, but the exact mechanism for this finding is unknown.

Though the initial disease affects the excretory function of the liver, the blockage of the bile ducts can eventually cause damage to the liver cells, thereby impairing the other functions of the liver relating to synthesis of proteins, metabolism of glucose and fats, and detoxification of chemicals. This advanced stage of disease is known as cirrhosis and is characterized by

- *Derangements in excretory function:* Bilirubin levels in the blood increase; estrogen levels increase (often causing proliferation of small blood vessels in the skin to form spider angiomas); an accumulation of copper in the liver and other organs, though the exact mechanism for this is unknown.

- *Breakdown of liver cells:* Certain enzymes normally found in the liver cells are released into the blood including alkaline phosphatase, AST (also known as SGOT), and ALT (also known as SGPT). The presence of high quantities of these enzymes in the blood is then used to diagnose liver damage.
- *Derangements in protein formation:* Albumin levels in the blood are decreased; the decrease in albumin allows more fluid to leave the blood and enter the tissues causing edema (swelling); proteins necessary for blood coagulation are not formed causing it to take longer for blood to clot (as measured by prothrombin time); proteins necessary for the production of platelets are decreased.
- *Portal hypertension:* The scarring of the liver affects the flow of fluids from the portal vein through the liver sinusoids. The liver becomes enlarged (hepatomegaly) and pressure builds up in the portal vein (portal hypertension). The resulting higher than normal blood pressure in the portal vein can cause fluid to move from the blood vessels into the peritoneum (ascites). In addition to this hydraulic pressure, there is some evidence that oncotic pressure (osmotic pressure due to protein gradients across tissues) can also contribute to build up of ascites. Although the liver may continue to produce albumin, the congested liver tissue can prevent the albumin from appearing at normal levels in the blood and to instead leak through the surface of the liver into the peritoneum. The combination of lower than normal oncotic pressure in the blood and higher than normal oncotic pressure in the peritoneum will also tend to move fluid from the blood into the peritoneum.
- *Derangements in fat metabolism:* Cholesterol and triglyceride levels in the blood are affected as the liver does not remove the fats absorbed into the blood from the intestines.

There is some suggestion that an auto-immune component may be responsible for the disease in patients: The patient's own immune system might be attacking his/her liver. The disease seems to affect women more than men, and is most often first diagnosed between the ages of 35 and 60. In some patients, the disease is asymptomatic, however in those patients developing signs and symptoms of liver disease, death usually occurs within 5-10 years of first diagnosis.

A randomized, double blind, placebo controlled clinical trial was conducted to test whether methotrexate might prolong the survival or progression free survival of patients exhibiting the auto-immune pattern of cirrhosis. Selected data from this clinical trial are given in the file f05proj.txt according to the format described below.

Data is available on multiple covariates which can be used to assess the severity of the disease for the trial participants at the time they entered the study (i.e., at randomization or baseline). Also available is data on the length of time patients took the study drug/placebo, the length of time the patients were observed without death, and the length of time patients were observed without serious progression of disease (as defined by death, liver transplantation, bleeding varices, hepatic encephalopathy, or development of ascites)..

Demographic:

age = subject's age at randomization
sex = indicator that subject is female
weight = subject's weight at randomization
height = subject's height at randomization

History of disease:

durdis = duration of disease (time from diagnosis to randomization)

Hepatocellular damage (measured by enzymes released by damaged liver cells):

alkphos = serum level of alkaline phosphatase
alt = serum level of ALT

Liver inflammation and cirrhosis:

splen = indicator of splenomegaly (enlarged spleen)
plt = count of platelets circulating in blood (portal hypertension)
stage = pathologic staging of disease

Lack of liver function:

bili = level of bilirubin in blood
ptsec = time to clot blood (malabsorbed vit K and no clotting factor)
alb = level of albumin (a protein) in blood

chol = serum cholesterol level (decreased fat metabolism)

The following variables measure the treatment assignment and treatment outcome. Note that some patients discontinued therapy prior to the planned end of the study due to death, liver transplantation, adverse events, other medical conditions, or personal preference.

Treatment:

tx = indicator of treatment group
stopdrug = number of days each patient remained taking study drug

Outcome:

obsprog = time until earlier of progression of disease or last follow-up
progress = indicator that progression of disease was observed
obsdeath = time until earlier of death or last follow-up
death = indicator that a death was observed

Methotrexate is also used to treat some cancers and diseases such as psoriasis and rheumatoid arthritis. Hence, there is some experience with toxicities that appear at higher doses than were used in this study. In order to assess whether one of the more serious of those toxicities, impairment of lung function, might occur in these patients, data was also collected on the ability of gases to diffuse into the blood from the lungs. DLCO is a measure of how well carbon monoxide can diffuse from inhaled air into the blood, with low values of DLCO suggesting some degree of interstitial lung disease.

Potential toxicities:

dlcoBsln = DLCO measured at the time of randomization
dlcoFnl = DLCO measured at the time the patient discontinued study drug or placebo
dlcoMin = minimum DLCO observed for the patient while taking study drug or placebo

The questions to be addressed with this data include

1. Does treatment with the study drug impart improved survival or progression free survival relative to placebo?
2. Does treatment with the study drug lead to impaired lung function as measured by DLCO?

THE DATA FILE

The ASCII file f05proj.txt contains the data for 265 patients with primary biliary cirrhosis randomized to receive either methotrexate or placebo in the clinical trial. Each row of the file corresponds to a single patient. (The first row of the file contains the variable names.) "NA" in the datafile denotes cases missing data for some variables.

The variables measured in the dataset are as follows:

ptid	Patient identification number
tx	Treatment arm (0= Placebo, 1= Study drug)
age	Age at randomization (years)
sex	Sex (0= Female, 1= Male)
height	Height (cm)
weight	Weight (kg)
durdis	Days between diagnosis with PBC and randomization
stage	Stage (histologic stage of liver disease (1,2,3,4)) reported by local
splen	Splenomegaly (1= Absent, 2= Present, 3= Unknown)
bili	Total bilirubin (mg/dl)
alb	Albumin (g/dl)
alkphos	Alkaline phosphatase (U/l)
alt	ALT (U/l)
ptsec	Prothrombin time (sec)
chol	Serum cholesterol (mg/dl)

plt	Platelets (1000 cells / cu mm)
dlcoBsln	DLCO - diffused lung carbon monoxide- at randomization (ml / min / mmHg)
dlcoFnl	DLCO at the time study drug or placebo discontinued (ml / min / mmHg)
dlcoMin	Minimal DLCO measured while taking study drug or placebo (ml / min / mmHg)
stopdrug	Days between randomization and the patient stopping intake of study drug or placebo
obsprog	Days between randomization and the earlier of progression or subject last follow-up
progress	Indicator that progression of disease was observed (0= no, 1= yes)
obsdeath	Days between randomization and the earlier of death or subject last follow-up
death	Indicator that death was observed on study (0= no, 1= yes)