RADIORESPIROMETRIC STUDY OF CARBOHYDRATE METABOLISM IN CHILDHOOD LIVER DISEASE

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The need for a suitable parameter to evaluate patients with chronic liver disease has been felt for some time, especially in order to judge the response to surgical shunts and the influence of certain drugs and diets on the liver. Since the liver is a major organ for carbohydrate metabolism, it was decided to analyze the in vivo oxidation of such substrates as glucose and galactose labeled with ^{14}C. Moderately advanced "Indian childhood cirrhosis" and idiopathic fatty hepatic infiltration were selected to represent diffuse chronic liver disease. Oral administration of ^{14}C-U-glucose or ^{14}C-1-galactose was followed by analyses of $^{14}CO_2$ in breath by liquid scintillation counting. Conversion of ^{14}C-glucose to $^{14}CO_2$ was accelerated by both diseases. On the other hand, oxidation of ^{14}C-galactose was slowed in fatty infiltration and was markedly subnormal in Indian childhood cirrhosis.

The liver stores large amounts of carbohydrate in the form of glycogen, and patients with liver disease are known to show glucose intolerance and insulin resistance (*1*). Decrease in galactose tolerance is a superior parameter for the evaluation of liver disease (*2*). We chose, therefore, to see whether any abnormalities in the metabolism of such pertinent labeled substrates as ^{14}C-galactose and ^{14}C-glucose (*3*) occurred in patients with histologic diagnosis of Indian childhood cirrhosis or idiopathic fatty hepatic infiltration. A test of substrate oxidation for exhaled $^{14}CO_2$ could be particularly useful clinically.

PATIENTS AND METHOD

Children aged 10 months to 11.5 years were examined. Histology of the liver indicated Indian childhood cirrhosis in 27 patients (*4*) and idiopathic fatty infiltration in 14 other patients. Nine subjects were controls. Each patient received ^{14}C-1-galactose orally (20 μCi per square meter of body surface area) as 0.25 gm galactose/kg in 3.5% aqueous solution on the first day and ^{14}C-U-glucose (10.5 $\mu Ci/m^2$) as 0.5 gm glucose/kg in 3.5% solution 2 days later.

The children exhaled into liquid-scintillation vials containing 1 ml of 1 *M* hyamine hydroxide and 2 ml of ethanol, with a drop of 1% phenolphthalein as

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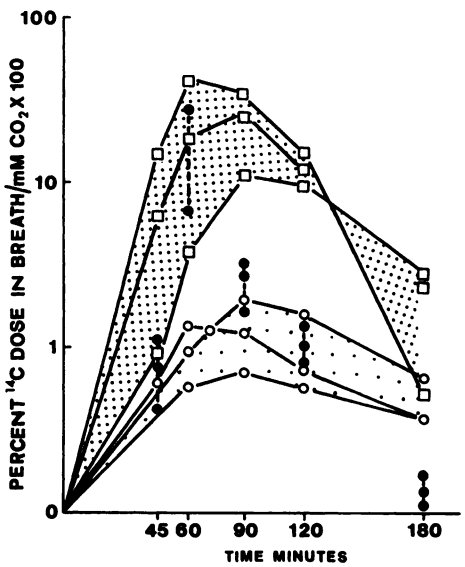

FIG. 1. Exhaled $^{14}CO_2$ values after oral administration of ^{14}C-U-glucose to 9 controls (open circles), 14 patients with fatty hepatic infiltration (closed circles), and to 27 patients with Indian childhood cirrhosis (boxes). Mean values and those for patients with maximum and minimum peaks in each group are plotted.

indicator, until the solution decolorized (*5*). This endpoint indicated saturation with one millimole of carbon dioxide. Nine breath samples were collected at 30-min intervals over a 4-hr period. Each vial was subsequently counted and the $^{14}CO_2$ counts per millimole of exhaled carbon dioxide were expressed as a percentage of the administered activity.

RESULTS AND DISCUSSION

Figures 1 and 2 depict the 4-hr breath curves of $^{14}CO_2$ per millimole carbon dioxide, expressed as percentages of the administered ^{14}C-glucose and ^{14}C-galactose, respectively. The mean values of each group as well as the curves of the individual patients who obtained the highest and the lowest peak activities (at t_{max}) are shown.

The tenfold increase over normal peak values for ^{14}C-glucose (Fig. 1) cannot easily be attributed to liver disease and we are at present unable to offer an explanation for this observation. Galactose catabolism (Fig. 2) is markedly diminished in cirrhotic patients during the initial 4-hr observation period. Children with fatty hepatic infiltration attain normal peak values, albeit after a longer time interval (t_{max}).

Since galactose metabolism initially depends to a great extent on hepatic cell enzymes, oxidation of this sugar is a more specific and direct reflection of the capacity of the liver and integrity of the liver cells (*2*). The marked (30-fold) reduction in oxidation of ^{14}C-galactose to $^{14}CO_2$ in Indian childhood cirrhosis (Fig. 2) could relate to the marked diminution of blood flow and extensive hepatic fibrosis characteristic of this severe liver disease. No similar impairment is seen with idiopathic fatty infiltration. However, the late time peak of $^{14}CO_2$ activity for the latter group is similar to that seen in a study of oxidation of labeled galactose in American patients with alcoholic cirrhosis (*6*).

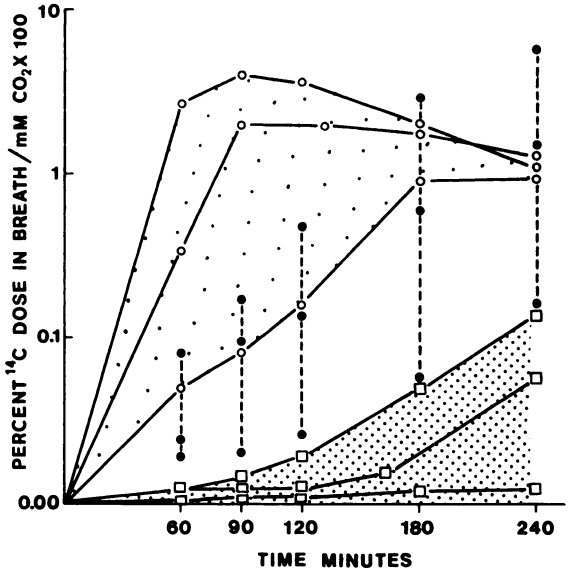

FIG. 2. Exhaled $^{14}CO_2$ values after oral administration of ^{14}C-1-galactose to 9 controls (open circles), 14 patients with fatty hepatic infiltration (closed circles), and 27 patients with Indian childhood cirrhosis (boxes). Mean values and those for patients with maximum and minimum peaks in each group are plotted.

Although considerable variation is found within each group, the results suggest the feasibility of this technique for monitoring patients with liver disease and justify proceeding to the second stage of such a trial wherein an individual patient is re-evaluated at various phases of his illness. The vial technique of breath analysis is simple enough to lend itself to clinical application. It can be performed at the patient's bedside and is more sensitive and less prone to instrumentation problems than the automated ionization chamber system used by us earlier (*3,7*).

In children with severe liver illness, whose clinical management may be affected by the test findings, the use of amounts of ^{14}C (about 20 μCi) delivering no more than 50–100 mrads of whole-body dose (*8,9*) can be considered an acceptable risk. Eventually the substitution of ^{13}C in such diagnostic applications (*6*) would obviate the concern about radiation dosage from ^{14}C.

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