Hereditary Fructose Intolerance

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Fructose "idiosyncrasy" was first reported in 1956 by Chambers and Pratt (1) in a single adult patient. In 1957, Froesch et al. (2) described hereditary fructose intolerance as an inborn error of metabolism in four children, including a brother and sister pair, and suspected a deficiency of a fructose-metabolizing enzyme as its cause. The enzyme defect was characterized in 1961 by Hers and Joassin (3), who demonstrated that the patients' liver aldolase had lost the ability to split fructose 1-phosphate. Since then, a few hundred cases, mainly from Europe and North America, have been reported in the literature. The inheritance of the disorder is autosomal recessive. Its frequency is estimated at approximately 1:20,000, but as discussed below, the true incidence may be higher. In this chapter the clinical symptoms, diagnostic tests, enzyme defect, pathophysiology, and treatment of hereditary fructose intolerance are reviewed. The toxicity of fructose for normal subjects is also discussed, owing to its general medical importance and because its study has contributed substantially to the understanding of the pathophysiology of hereditary fructose intolerance. For a more extensive review on fructose metabolism and its disorders, the reader is referred to ref. 4.

CLINICAL PICTURE

Subjects with hereditary fructose intolerance do not present any symptoms of the enzyme defect as long as they do not ingest foods containing fructose. Typically, babies do well during breast feeding. Symptoms appear on introduction of cow’s milk formulas sweetened with sucrose (composed of a molecule of fructose linked to a molecule of glucose) or at weaning, when fruits and vegetables are given (5). In infants and small children, the first signs are those of gastrointestinal discomfort and hypoglycemia following meals containing fructose. Nausea, vomiting, pallor, sweating, trembling, lethargy, and eventually jerks and convulsions may be observed. If the condition is not recognized and fructose excluded from the diet, failure to thrive, liver disease manifested by hepatomegaly, jaundice, bleeding tendency, eventually edema and ascites, and proximal renal tubular dysfunction appear. The
younger the child and the higher the intake of fructose, the more severe the clinical picture, which when its cause it not recognized, may lead to liver and kidney failure and eventually to death.

In some cases, hereditary fructose intolerance is recognized and adequately treated by suppression of fructose-containing nutrients, although not medically diagnosed. Certain mothers quickly learn that their baby does not tolerate certain foods and suppress these from the diet, so that the infant develops normally. Older children acquire a distinct aversion toward foods containing fructose. This aversion protects them, but is at times considered anomalous behavior.

Although hereditary fructose intolerance is a rare inborn error of metabolism, it should always be considered a diagnostic possibility in an infant with the clinical signs and symptoms listed above. Occasionally, diagnosis is established during preschool or school age, following the finding of hepatomegaly of growth delay. Other cases are diagnosed only after life-threatening perfusions with fructose (6) or sorbitol. Because approximately half of the adults with hereditary fructose intolerance are completely free of caries, diagnoses have also been made by dentists. All these observations indicate that subjects with hereditary fructose intolerance remain undiagnosed in the general population.

**DIAGNOSTIC TESTS**

When hereditary fructose intolerance is suspected, an intravenous fructose tolerance test should be performed after some weeks of fructose withdrawal. Oral loading tests are not recommended because they provoke more ill effects and are less reliable. Fructose should be administered as a 20% solution, at the dose of 200 mg/kg body weight (7). Blood glucose and serum phosphate should be measured, preferably at two 1-min time intervals before the administration of fructose, and 10, 20, 30, and 45 min thereafter (Fig. 1). In normal children, a slight, 5–20 mg/dl increase in blood glucose is recorded, with little change in serum phosphate. In affected children, glucose diminishes progressively, by 30–50 mg/dl over 30–45 min, whereas phosphate decreases more rapidly, by 1–2 mg/dl over 10–20 min. It is thus useful to include serum phosphate among the variables measured during a fructose tolerance test. Other modifications that can be measured during the test include an increase in serum magnesium (Mg²⁺), which is not observed in normal children, and an increase in serum urate, which is more pronounced in patients than in normal children (Fig. 1).

Other laboratory findings in patients with hereditary fructose intolerance, in whom fructose intake has not been suppressed, are those of liver disease (elevations of serum transaminases and bilirubin, depletion of blood clotting factors) and of proximal tubular dysfunction (proteinuria, melituria, generalized hyperaminoaciduria, metabolic acidosis).
FIG. 1. Fructose tolerance tests. Fructose (200 mg/kg) was given intravenously at 0 min in 10 children with hereditary fructose intolerance and in 16 control children. The shaded areas depict mean ± 1 SD of the controls. Bars represent mean ± 1 SD of the patients. Open symbols indicate overlap between the two groups. From Gitzelmann R, et al. (4).

ENZYMES OF FRUCTOSE METABOLISM

Fructose is metabolized predominantly in liver, kidney cortex, and small intestinal mucosa, owing to the existence in these tissues of a specialized pathway, discovered by Hers (8), and composed of three enzymes: fructokinase, aldolase type B, and triokinase (reviewed in refs. 4 and 9). This enzyme sequence converts fructose into intermediates of the glycolytic-gluconeogenic pathway (Fig. 2). Fructokinase catalyzes the phosphorylation of fructose to fructose-1-phosphate. Adenosine triphosphate (ATP) is the main phosphoryl donor, but as recently demonstrated (10), gua-
FIG. 2. Pathway of fructose metabolism in the liver. DHA, dihydroxyacetone; G, glucose; GAH, d-glyceraldehyde; F, fructose; P, phosphate; P_i, inorganic phosphate; 2-P-G, 2-phosphoglycerate. (1) fructokinase, (2) aldolase B, (3) triokinase, (4) sorbitol dehydrogenase, (5) glycogen phosphorylase, (6) phosphohexose isomerase, (7) glucokinase (and hexokinase), (8) glucose-6-phosphatase, (9) fructose-1,6-bisphosphatase, (10) phosphofructokinase. The aldolase B defect is depicted by both the solid and the dotted bar. Also shown are fructokinase deficiency and fructose-1,6-bisphosphatase deficiency.

Inosine triphosphate (GTP) can also be utilized. Fructokinase has a high affinity for fructose (K_m is around 0.5 mM) and a particularly high V_max (about 10 μmol/min per g of liver at 37°C). Aldolase B catalyzes the splitting of both fructose-1-phosphate into d-glyceraldehyde and dihydroxyacetone phosphate, and that of fructose-1,6-bisphosphate into dihydroxyacetone phosphate and d-glyceraldehyde-3-phosphate. Aldolase B also has a high V_max of about 10 μmol/min per g of liver, which is about the same with fructose-1-phosphate and with fructose-1,6-bisphosphate. This is in contrast with the isozymes aldolase A (found in muscle) and aldolase C (found in brain), which have a 50- and 10-fold lower V_max with fructose-1-phosphate than with fructose-1,6-bisphosphate. Triokinase converts d-glyceraldehyde into d-glyceraldehyde-3-phosphate, thereby allowing the nonphosphorylated product of the cleavage of fructose-1-phosphate to reach the glycolytic-gluconeogenic pathway. Triokinase utilizes ATP preferentially as phosphoryl donor, but other nucleoside triphosphates, such as GTP, can also be used. The maximal activity of triokinase
reaches around 1.5 μmol/min per g of liver and is thus markedly lower than that of fructokinase and aldolase B.

Alternative pathways in the metabolism of fructose have been proposed (reviewed in ref. 11). These include utilization of d-glyceraldehyde by two possible enzyme sequences: (i) reduction to glycerol by alcohol dehydrogenase or aldose reductase, followed by phosphorylation to glycerol-3-phosphate, and oxidation to dihydroxyacetone phosphate; and (ii) oxidation to d-glycerate and phosphorylation to 2-phosphoglycerate. Both pathways have been ruled out by kinetic studies of the glyceraldehyde-metabolizing enzymes and by isotope studies in vivo. Recently, it has been claimed that fructose-1-phosphate can be directly converted into fructose-1,6-bisphosphate, without being split by aldolase (12). This proposal is based on studies performed with uniformly labeled [13C]fructose. These have shown that about 50% of infused [13C] fructose was recovered as uniformly labeled [13C]glucose in blood. Owing to the cleavage of the fructose molecule by aldolase and its recombination with unlabeled triose molecules, one would have expected only C1-C2-C3- and C4-C5-C6-labeled glucose to be found. Conversion of fructose into blood glucose by way of phosphorylation to fructose-6-phosphate by hexokinase, followed by isomerisation to glucose-6-phosphate, was ruled out because conversion of uniformly labeled [13C]fructose into uniformly labeled [13C]glucose did not occur in patients with fructose-1,6-bisphosphatase deficiency (13). Although challenging, these studies are, nevertheless, difficult to interpret, because at the amounts used, [13C]fructose cannot any more be considered as a tracer.

In recent years, the molecular biology of the aldolases has been investigated extensively, particularly because it offers the opportunity to study the genetic mechanisms that regulate the expression of isozymes (reviewed in ref. 4). The human aldolase B gene is located on chromosome 9 and has been sequenced (14). It is 14,500 base pairs long and contains nine exons. The corresponding cDNA has also been sequenced and encodes a 364-amino-acid protein (15).

ENZYME DEFECT

In patients with hereditary fructose intolerance, the capacity of aldolase B to split fructose-1-phosphate is reduced, on average to a few percent of normal (3,7). There is also a distinct but less marked reduction of the activity of the enzyme toward fructose-1,6-bisphosphate. As a consequence, the ratio of the $V_{\text{max}}$ toward fructose-1,6-bisphosphate versus the $V_{\text{max}}$ toward fructose-1-phosphate, which is approximately 1 in control liver, is increased to 2 to 8 in patients. Kinetic studies have shown that the mutant aldolase B has an abnormally high $K_m$ for both fructose-1-phosphate and fructose-1,6-bisphosphate (16). The defect of aldolase B has been most extensively investigated in the liver of the patients, but can also be demonstrated in their kidney cortex (7) and jejunal mucosa (17). The activities of aldolase A and C are normal.

Hereditary fructose intolerance is genetically heterogeneous. This is evidenced by
several observations: (i) clinically, certain patients are very sensitive to fructose, whereas others can tolerate moderate intakes of fructose (up to 250 mg/kg-day, compared to an average intake of 1–2 g/kg-day in Western societies); (ii) the activity of aldolase B toward fructose-1-phosphate may vary from undetectable to 15% (7) and even 30% of normal (6); and (iii) immunologically reactive aldolase B is detectable in all affected tissues, but the amount of cross-reacting material found may vary from less than 3% to 100% of controls (18). However, up to now, only one molecular lesion of the aldolase B gene has been identified (19). The mutation is a G to C base change in exon 5, which results in the substitution of an alanine by a proline residue at position 149 of the protein. The mutation also creates a new recognition site for the restriction enzyme AElall, which renders it easily detectable. The same mutation was found in four unrelated subjects with hereditary fructose intolerance. Obviously, more patients will have to be analyzed to verify if this genetic lesion is the prevailing one in hereditary fructose intolerance or if, as observed for instance in the deficiency of hypoxanthine-guanine phosphoribosyltransferase (20), the heterogeneity of the clinical syndrome can be explained by a variety of mutations.

PATHOPHYSIOLOGY

All the manifestations of hereditary fructose intolerance can be traced back to the buildup, upon ingestion or infusion of fructose, of fructose-1-phosphate in the tissues that possess the specialized fructose pathway. The accumulation of fructose-1-phosphate results from its formation by fructokinase, combined with the inability of aldolase B to catalyze its splitting. In turn, the accumulation of fructose-1-phosphate provokes depletion of ATP, GTP, and inorganic phosphate. The loss of ATP and GTP is caused by their utilization as phosphoryl donors in the fructokinase reaction. The depletion of inorganic phosphate is due to its consumption in the mitochondria to regenerate ATP (Fig. 2). These modifications, which were first demonstrated in studies of the effects of fructose loads in animals, reviewed in the next section, were for a long time only indirectly documented in patients. The loss of ATP is manifested by an elevation of serum and urinary uric acid, and of serum Mg\(^{2+}\) (Fig. 1). The depletion of inorganic phosphate is reflected by a decrease of serum phosphate. In recent years, however, noninvasive \(^{31}\)P nuclear magnetic resonance spectroscopy has allowed the demonstration of the accumulation of fructose-1-phosphate and of the depletion of ATP and inorganic phosphate, in the liver of patients \textit{in vivo} (21).

The characteristic rapidly progressive hypoglycemia induced by fructose in hereditary fructose intolerance can be explained by the combined operation of three mechanisms: (i) a block of glycogenolysis; (ii) an inhibition of gluconeogenesis; and (iii) probably also a stimulation of the uptake of glucose, as evidenced by recent studies of glucokinase. The block of glycogenolysis is evidenced both by the absence of dilution of infused radioactive glucose by endogenous glucose (22) and by the inability of glucagon to raise blood glucose during fructose-induced hypoglycemia (23). Detailed investigations of the effects of fructose on the glycogenolytic mech-
anism (24, reviewed in ref. 25) have shown that fructose administration (i) decreases the capacity of the liver to form cyclic AMP; and (ii) provokes an inhibition of the activity of phosphorylase a. The decreased capacity to form cyclic AMP is explained by the loss of ATP, the substrate of adenylate cyclase, and evidenced by a marked reduction of the glucagon-induced urinary excretion of cyclic AMP. The decreased formation of cyclic AMP is, however, not sufficient to explain the absence of response to glucagon since the fructose-induced hypoglycemia can also not be corrected by dibutyryl cyclic AMP. The explanation for the block of glycogenolysis was found to be an inhibition of liver phosphorylase a, caused by the accumulation of fructose-1-phosphate, combined with the depletion of inorganic phosphate, one of the substrates of the enzyme.

The decreased activity of aldolase B toward fructose-1,6-bisphosphate in hereditary fructose intolerance has no clinical consequences on gluconeogenesis in the sense that patients do not display fasting hypoglycemia in the same way as patients with defects of gluconeogenesis (e.g., fructose-1,6-bisphosphatase deficiency). During fructose-induced hypoglycemia an inhibition of gluconeogenesis is, nevertheless, evidenced by the fact that glycemia cannot be corrected by dihydroxyacetone, which enters the glycolytic-gluconeogenic pathway by way of triokinase. The inhibition of gluconeogenesis is explained by the inhibitory effect of fructose-1-phosphate on glucose-6-phosphate isomerase (26), and on the condensation of the triose phosphates to fructose-1,6-bisphosphate by aldolase (Bally C, Leuthardt F, unpublished data cited in ref. 4). Inhibition of gluconeogenesis probably plays a determining role in the hypoglycemic effect of fructose in the fasting state.

Recent studies of the phosphorylation of glucose by isolated rat hepatocytes (27) have shown that it is stimulated by low concentrations of fructose. At 200 μM concentration, fructose stimulates the phosphorylation of a physiological concentration of glucose, namely 5 mM, two- to fourfold. Fructose acts by increasing the apparent affinity for glucose of glucokinase, the only glucose phosphorylating enzyme in liver parenchymal cells. \( V_{\text{max}} \) is not modified. Further studies (28) have led to the discovery of a protein regulator of glucokinase, which inhibits the enzyme by decreasing its affinity for glucose. The inhibitory effect is greatly potentiated by the presence of micromolar concentrations of fructose-6-phosphate. It is, however, antagonized by similar concentrations of fructose-1-phosphate. The accumulation of fructose-1-phosphate, resulting from the intake of fructose, may thus contribute to the hypoglycemia of hereditary fructose intolerance, by relieving the inhibition exerted on glucokinase by the synergic action of its protein regulator and fructose-6-phosphate. In addition to its importance for the pathophysiology of hereditary fructose intolerance, this effect of fructose-1-phosphate may also explain the repeat observation that fructose stimulates the synthesis of glycogen from glucose (reviewed in ref. 9), and the long-standing belief that small amounts of fructose may be beneficial to diabetic patients.

The other toxic effects of fructose recorded in hereditary fructose intolerance—the hepatic and renal dysfunction and the gastrointestinal discomfort—are most likely explained by the loss of ATP and GTP in the fructose-metabolizing tissues.
ATP and GTP, "energy currencies" of the cell, are indeed required for many cellular functions, and their depletion causes several disturbances, as reviewed in the next section.

TOXICITY OF FRUCTOSE IN NORMAL ORGANISMS

After the discovery of hereditary fructose intolerance, fructose toxicity was first thought to be restricted to individuals with a deficiency of aldolase B. However, the development of parenteral nutrition led to the recognition, in the late 1960s of deleterious effects of intravenous fructose in normal humans. The main findings were lactic acidosis (29) and hyperuricemia (30, reviewed in refs. 4, 9, and 11).

Intravenous infusion of fructose may increase blood lactate by two- to fivefold, whereas intravenous glucose on the average does not increase blood lactate more than twofold. The more rapid conversion of fructose into lactate, as compared to glucose is explained by several factors: (i) the approximately 10-fold higher $V_{\text{max}}$ of fructokinase as compared to the maximal glucose phosphorylating capacity of glucokinase; (ii) the fact that fructolysis bypasses phosphofructokinase, the principal regulatory enzyme of glycolysis; and (iii) the stimulation by fructose-1-phosphate of pyruvate kinase, another regulatory enzyme of the glycolytic pathway. In addition, fructose may, under certain conditions (31), increase the concentration of fructose-2,6-bisphosphate, the main stimulator of liver glycolysis (32), and thereby increase the production of lactate from glucose. The fructose-induced increase in lactic acid may provoke metabolic acidosis, which may become life threatening, particularly in liver failure (33).

Hyperuricemia and hyperuricosuria following the intravenous administration of fructose have been repeatedly documented, not only in subjects with hereditary fructose intolerance, but also in patients without the aldolase B defect. In the latter, they become generally apparent at infusion rates above 1.0 to 1.5 g/kg·h. Explanation of the increased production of uric acid induced by intravenous fructose in normal organisms requires an understanding of the factors that determine the velocity of the metabolism of fructose in normal liver. As said before, the $V_{\text{max}}$ of both fructokinase and aldolase reaches about 10 μmol/min per g of liver. This is severalfold more than the $V_{\text{max}}$ of triokinase, which reaches only 1.5 μmol/min·g, or those of the fluxes through the glycolytic and gluconeogenic pathways, which do not exceed 2 μmol of C6 units/min·g. Fructose-1-phosphate can thus easily accumulate, owing to the fact that the velocity of its formation can markedly surpass the rate of its further metabolism. The formation of fructose-1-phosphate is, however, determined not only by the kinetic characteristics of fructokinase. It is also dependent on the transport of fructose inside the hepatocyte. This transport system has a $K_m$ value that reaches around 100 mM (as compared to about 0.5 mM for fructokinase) and a $V_{\text{max}}$ equal to about 30 μmol/min·g of liver (34). After an oral load of fructose, the concentration of fructose in the portal vein reaches maximally about 2.5 mM. During intravenous infusion of fructose at the rates 0.5, 1.0, and 1.5 g/kg·h, fructosemia
reaches 2.3, 4.8, and 7 mM, respectively (35). Intravenous fructose thus results in a higher rate of entry of fructose in the liver, which allows fructose-1-phosphate to accumulate to toxic levels. These can be defined as those that result in depletion of ATP, GTP, and inorganic phosphate.

The decrease in ATP induced by fructose is not accompanied by a commensurate increase in AMP, as observed, for example, in anoxia, but by a loss of adenine nucleotides as a whole. This loss can be explained as follows. The catabolism of the adenine nucleotides ATP, ADP, and AMP, which are maintained in equilibrium by adenylate kinase (Fig. 3), originates from AMP. The catabolism of AMP can, in theory, be initiated by two different reactions: either deamination by AMP deaminase, or dephosphorylation by cytosolic 5'-nucleotidase(s). Studies of the catabolism of the adenine nucleotides in isolated rat hepatocytes have shown that the initial catabolism of AMP, leading to the formation of uric acid and/or allantoin (the terminal purine catabolite in lower mammals), proceeds exclusively by way of AMP deaminase (36, reviewed in ref. 9). Dephosphorylation of AMP takes place but does not contribute to the production of allantoin, because the resulting adenosine is continuously recycled by adenosine kinase (37). Liver AMP deaminase has complex kinetic
properties and is strongly influenced by various metabolites: ATP is a potent stimulator, whereas inorganic phosphate and GTP are inhibitors. At physiologic concentrations of substrate and effectors, the enzyme is 95% inhibited (38). The accumulation of fructose-1-phosphate, by decreasing not only ATP but also GTP and inorganic phosphate, thus causes deinhibition of AMP deaminase. This results in a loss of the adenine nucleotide pool as a whole, which is manifested by hyperuricemia and hyperuricosuria. The increased production of uric acid induced by fructose is thus not a harmless phenomenon, but an indication of the degradation of ATP, the main "energy currency" of the cell. Owing to the potent Mg$^{2+}$ chelating effect of ATP, its loss results in a decrease of Mg$^{2+}$ in the liver, and in an increase of plasma Mg$^{2+}$ (Fig. 1). In the fructose-metabolizing tissues, depletion of ATP results in a series of disturbances. These include inhibition of the synthesis of RNA and protein, disaggregation of ribosomes, and ultrastructural lesions (reviewed in refs. 4, 9, and 11).

From the above it appears that fructose is a potentially dangerous compound in parenteral nutrition, not only for undiagnosed fructose-intolerant children and adults, but also for patients with normal aldolase B. The same holds true for the mixtures of glucose and fructose, known as invert sugar, and for sorbitol, which is converted into fructose in the liver by sorbitol dehydrogenase (Fig. 2). The use of fructose and related compounds as substitutes for glucose in parenteral nutrition has therefore been strongly discouraged by several authors (4,33,39).

TREATMENT

Treatment of hereditary fructose intolerance consists in the elimination of all sources of fructose from the diet. This involves suppression of all foods in which fructose and/or sucrose and sorbitol occur naturally or have been added intentionally. The major natural sources of fructose are fruits, particularly apples, pears, grapes, and sweet cherries, and certain vegetables, such as beets and carrots. Lists of the fructose content of various foodstuffs are available (40). The presence of fructose in medications and in infant formulas, although declining, should also be checked. A fructose-free diet should be instituted as soon as hereditary fructose intolerance is suspected. The beneficial effect of the diet is usually seen within days of its initiation and provides a first clue to the diagnosis. Fructose tolerance tests and the assay of aldolase B in a biopsy of liver or, alternatively, of small intestine, should only be performed when the clinical status has improved.

Despite adequate treatment, small children with hereditary fructose intolerance usually display hepatomegaly for months and even years (41). The reason for this is unclear and has been linked to a too strict, as well as to an insufficiently stringent, limitation of fructose intake. An insufficient restriction of fructose was apparently the cause of the isolated growth retardation recorded in two boys aged 5 and 4 years who displayed no symptoms of fructose toxicity on a self-imposed diet, resulting in an average intake of fructose of approximately 160 mg/kg body weight per day (42).
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Indeed, when a stricter diet was prescribed, providing them with only 20 to 40 mg of fructose/kg body weight per day, catch-up growth was recorded. The intake of fructose should thus, at least in childhood, not be determined by its subjective tolerance, but a diet should be prescribed composed of foodstuffs with no or very low fructose content. Needless to say, patients (and their parents) should be made aware of the fact that infusions containing fructose, sorbitol, or invert sugar are life threatening for them, and they should report fructose intolerance on any hospital admission.

REFERENCES


**DISCUSSION**

**Dr. Mannacerta:** You said that the \( K_m \) for the hepatic fructose transport system is 100 mM and that during an intravenous fructose infusion portal concentrations of 7 mM are reached. This would mean that the transport system is operating at less than 7% of its \( V_{\text{max}} \), which would be less than the \( V_{\text{max}} \) of the gluconeogenic pathway, or is it possible that under certain circumstances you would reach higher fructose concentrations, which would then become dangerous?

**Dr. Van den Berghe:** I agree with you. Figures for \( V_{\text{max}} \) (30 \( \mu \)mol/min · g) and \( K_m \) (approximately 100 mM) of fructose transport were taken from data obtained by Sestoft and Fleron (1) in perfused rat liver. Parameters of fructose transport are, however, difficult to measure, owing to its very rapid metabolism. More recent investigations of fructose transport into isolated rat
her hepatocytes (2) have given a value of 291 mmol/min per ml of cell water for \( V_{\text{max}} \), and of 212 mM for \( K_m \). With these figures, one can calculate that the rate of transport of fructose will be higher than the capacity of the glycolytic-gluconeogenic pathway.

**Dr. Endres:** I found some different figures concerning the self imposed fructose restrictions in adults. Newbrun et al. (3) reported some adults with hereditary fructose intolerance (HFI) who did not know that they had this disease and who had a daily intake of about 2.5 g sucrose (i.e., 1.25 g of fructose) and with an average weight of 60–70 kg that is about 15–20 mg/kg. In a retrospective study in Germany we investigated 56 patients. Interestingly, the first exposure to fructose in 45 of 56 patients was below 6 weeks of age and you could conclude from these figures that a high proportion of patients will never be detected because there must be many more newborns who will not receive fructose or sucrose within these first weeks of life. Concerning the clinical symptoms observed in our patients, there is one symptom that has not been reported in the literature, and that is diarrhea. This has been reported in 80% of our patients. Concerning routine laboratory investigations, it became evident that hypophosphatemia, hyperuricemia, and hypoglycemia are found mainly during the fructose loading test rather than in the chronic state. Between patients who received fructose immediately after birth and those who received it later, there was a statistically significant difference in the development of cirrhosis, while no correlation was found between the amount of fructose ingested and the development of liver cirrhosis. Hence it is not important how much they received, but it is very important how early they received it. Nine of 10 patients who developed liver cirrhosis received fructose-containing formulas immediately after birth; however, there are other infants who had also been fed fructose who did not develop cirrhosis. In summary it can be said that fructose-containing formulas already fed in the neonatal period lead to cirrhosis of the liver in one third of all HFI patients regardless of the amount ingested, and among patients with HFI receiving small amounts of fructose a mild clinical course can be observed five times more often than a severe one. Two of 10 patients suffering from cirrhosis due to HFI died soon after diagnosis during the first months of life.

This is my recommendation: Don’t use fructose-containing formulas in any infant below 3 months of age. There is no advantage of giving fructose or sucrose in comparison to lactose, glucose, or its polymers. The intake of fructose should be restricted to amounts less than 1 g per day.

**Dr. Van den Berghe:** With respect to the sensitivity to fructose, I would like to comment that it has been well documented that some patients are ignorant of their hereditary fructose intolerance until a sometimes dramatic incident occurs. For example, Lamere et al. (4) have reported a 21-year-old Belgian patient in whom hereditary fructose intolerance was only diagnosed following the infusion of invert sugar as part of the treatment of viral meningitis. This was followed by life-threatening acute icterus, complicated by severe gastrointestinal bleeding, hypoglycemia, and proximal renal tubular acidosis. Analysis of a liver biopsy showed that aldolase B activity was 30% of normal. This high residual activity probably explains why hereditary fructose intolerance had remained undiagnosed.

**Dr. Vis:** I suppose that everybody will agree that we should not give fructose to an infant before 3 months of age. Indeed, commercially available infant formulas do not contain fructose. But what about drugs? Some syrups contain fructose; sorbitol is present in some suppositories. We should ask, in all countries, as is already the case in some, that fructose be withdrawn from drug preparations for young infants.

**Dr. Schaub:** Fatty infiltration of the liver cell is a common feature of fructose intolerance, even in well-treated patients. Do you have any explanation for this formation of fat in the liver cells? We have a family with two children, where the second child was diagnosed in the first
week of life; after 14 months of fructose- and saccharose-free treatment this child had mild steatosis of the liver cells.

**Dr. Van den Berghe**: To my knowledge there is no satisfactory explanation for the fatty acid infiltration in the liver of patients with hereditary fructose intolerance. Fructose is known to favor triglyceride synthesis, most likely because it increases glycerol-3-phosphate, which is formed from dihydroxyacetone phosphate and is the cosubstrate of long chain fatty acyl-CoA in the synthesis of triglycerides. However, when aldolase B is deficient there is no conversion of fructose into dihydroxyacetone phosphate.

**Dr. Schaub**: Is it possible that this fat formation in the liver cell is independent of fructose intake?

**Dr. Odièvre**: This is a difficult problem. In our experience liver steatosis remains present in all patients until 6–7 years of age despite good compliance to the restricted diet. The steatosis seems to disappear when the child is placed on a self-imposed diet, possibly less restricted than the previous one. I know several patients in whom the fructose intolerance was only diagnosed at 7 or 8 years after several years of self-imposed diet; these patients had no steatosis at the time of diagnosis. The amount of fat contained in the fructose-free diet is from a caloric point of view relatively high; in some patients about 50% of their energy intake is represented by fat. A last, somewhat provocative remark can be made: When we perform a liver biopsy in young babies not intolerant of fructose and who are receiving only human milk there is some discrete degree of steatosis in the liver. This finding raises the question as to whether fructose could possibly be an essential carbohydrate for human beings; in that case, an overrestricted diet in fructose intolerance might favor the persistence of steatosis.

**Dr. Van den Berghe**: Perhaps I might add that fructose remains a very active and exciting field of investigation. Fructose-2,6-bisphosphate was only discovered in 1980, and the finding of regulatory effects of fructose esters on glucokinase opens additional perspectives.

**Dr. Saudubray**: I have a general question on physiology. Fructose is classically considered as a carbohydrate that does not induce insulin secretion. Is this true, and why?

**Dr. Van den Berghe**: The classical theory is that fructose by itself does not stimulate the secretion of insulin, but that it potentiates the effect of low concentrations of glucose. Since the pancreatic β cell also contains glucokinase, the regulatory effects of the fructose esters on the latter enzyme might play a role in this potentiation.

**Dr. Mowat**: Is there any evidence that the liver disease progresses when patients are on a fructose-free diet? Do they, for example, develop malignancy in the liver?

**Dr. Van den Berghe**: I am not aware of a tendency to develop malignancy. On the other hand, several people with hereditary fructose intolerance are known to have reached very old age, and with excellent teeth!

**Dr. Odièvre**: One adult patient, who probably had fructose intolerance because he presented typical manifestations when he was young and had complete aversion to sweets throughout his life, died at 49 years with a hepatoma. I think it would be interesting to ask our colleagues for a history of aversion to sweets when they see hepatoma in adults. I have a second comment. If you give fructose intravenously in normal patients you observe a peak of insulin during the first minutes after injection; this early peak is not seen in patients with fructose intolerance given a fructose load.

**Dr. Van den Berghe**: This may be due to the fact that in normal individuals fructose is converted into glucose, but not in patients with hereditary fructose intolerance.

**Dr. Eggermont**: When H. G. Hers discovered the aldolase defect in a patient with fructose intolerance, he also measured the enzymes involved in the degradation of glycogen and found glucose-6-phosphatase to be very high. Subsequently, he measured the aldolase activity in liver
biopsy specimens with high glucose-6-phosphatase activities and was able to detect several other patients with fructose intolerance.

Dr. Van den Berghe: The high glucose-6-phosphatase activity in livers of patients with hereditary fructose intolerance has been attributed to the stabilizing effect of their elevated glycogen content (6). The high glycogen is explained by the inhibition of the glycogenolytic mechanism.

Dr. Odievre: Do you think that a block of glycogenolysis and neoglucogenesis associated with a stimulation of glucose uptake by the liver can explain the abrupt character of hypoglycemia induced by fructose?

Dr. Van den Berghe: The rapidity and the degree of hypoglycemia will depend both on the amount of fructose administered and on the metabolic state of the patient: a low glycogen reserve and a low rate of gluconeogenesis would increase the sensitivity to fructose.

Dr. Saudubray: A general statement in the classical textbooks is that one should not use fructose in cases of hepatocellular insufficiency, not merely in fructose intolerance, but in general. I am not sure that this statement has a real foundation. I have investigated three or four patients with very severe hepatocellular dysfunction of unknown origin in neonatal period, presenting with lactic acidemia and severe hypoglycemia after 2, 3, or 4 h of fast. I tried investigating the hypoglycemia by giving various gluconeogenic substrates—lactate, alanine, dihydroxyacetone and fructose after 2–3 h of fasting. To my surprise with fructose we got a marvelous increase in blood glucose, each time, contrasting with the very severe hepatocellular dysfunction and with a complete absence of response with alanine and lactate. My feeling is that the toxic effect of fructose is very specific for fructose intolerance in the hereditary fructose intolerance, but I am not sure whether in a nonspecific sense it is true.

Dr. Van den Berghe: Fructose is normally rapidly converted to glucose. In fact, it is one of the best gluconeogenic precursors because it enters the gluconeogenic pathway above the limiting steps which are found at the level of the so-called “pyruvate crossroads,” through which lactate and alanine have to go. That fructose is very rapidly converted into glucose does not mean that it cannot have toxic effects. First, it is also very quickly converted to lactate and may thus contribute to lactic acidosis. The other toxic effects of intravenous fructose can be related to the decrease in ATP it induces. That these effects on liver ATP often do not seem to impress clinicians may be explained by the fact that ATP cannot be measured by routine clinical chemistry. The introduction of (expensive) NMR equipment could change this. I also would like to warn against overextrapolation of experimental, in vitro, data on clinical situations. For example, in liver perfused in the absence of oxygen, fructose but not glucose was found to be protective against cell damage (6). This may be explained because anaerobic fructolysis is more rapid than glycolysis, and thus allows some preservation of ATP. These are, however, short-term experiments performed in extreme conditions which are difficult to compare with clinical situations.

Dr. Vis: What is the real incidence of disease? Is one out of 20,000 newborns not an optimistic figure? Is it not more than that?

Dr. Van den Berghe: The frequency of 1:20,000 is the one that is classically given by Gitzelmann and his co-workers for Switzerland. I have been told that it may be lower in North America and in England.

Dr. Odievre: The figure is probably higher; many cases are not diagnosed because patients die from apparently unexplained hepatic failure after birth. I disagree with Professor Saudubray because fructose intolerance is a classic cause of acute liver insufficiency, so that we have to be very cautious about fructose administration until fructose intolerance is excluded.

Dr. Saudubray: Yes, I agree with you.
Dr. Odèvre: We saw several cases of fructose intolerance many years ago when the babies were fed with milk containing sucrose. Since they are now fed milk without sucrose, fructose intolerance seems less frequent. In fact, the symptoms appear later and are more discrete, but the frequency of the disease remains the same.

Dr. Van den Berghe: Maybe we could obtain figures by asking school children if they like sweets... .

REFERENCES


3. (from Dr Endres)

