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Glucose-6-phosphatase deficiency
growth
lacticaciduria
lipoprotein lipase activity
nocturnal gastric drip feeding
serum lipids

Nocturnal Gastric Drip Feeding in Glucose-6-Phosphatase Deficient Children

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Summary

Six patients with glucose-6-phosphatase deficiency were treated for 12 hr at night with gastric drip feeding (GDF), containing soy milk plus glucose, dextrimaltose, and starch. An alarm system (thermistor), connected to the gastric tube, was devised in case of displacement of the tube by the child. The effects of GDF were as follows. Base deficit and lacticaciduria decreased, but did not normalize. Serum cholesterol levels tended to normalize, but serum triglycerides remained elevated. The hepatic and extrahepatic components of plasma lipoprotein lipase were measured separately 5 and 40 min after iv heparin injection. Hepatic triglyceride lipase activities which were subnormal to normal increased to the lower normal range. Extrahepatic lipoprotein lipase activities, though increasing after GDF, remained abnormally low.

Catch-up growth occurred in all four growth-retarded children. The pronounced liver enlargement of the five patients, not previously treated with GDF, decreased markedly.

Speculation

Nocturnal GDF in glucose-6-phosphatase deficient children, suppresses the tendency for hypoglycemia and acidosis which are causes for stress, catabolism, and anorexia. By suppressing these factors, GDF promotes anabolism and caloric intake, thus accounting for the catch-up growth seen in the patients with growth retardation.

It has recently been demonstrated that continuous GDF at night improves most of the metabolic and clinical abnormalities associated with glucose-6-phosphatase deficiency. The supply of glucose by GDF not only prevented hypoglycemia at night, but also reduced the tendency for lactic acidosis, hyperlipidemia and hyperuricemia, corrected the bleeding tendency, and promoted normal growth (4, 10). In the present study, a complete natural liquid formula consisting of soy milk with glucose, dextrimaltose, and starch was used instead of incomplete feeding (glucose polymers) (4) or elementary feeding (Vivonex) (4, 10). An alarm system was devised (attached to the nasogastric tube) to give a signal if the nasogastric tube was displaced by the child during sleep.

The growth of six patients was followed for 1–3 yr on a regime of 12 hr GDF each night plus frequent daytime feedings. The tendency for lactic acidosis was studied by measuring urinary lactate excretion. Serum lipids were determined regularly and the clearing of triglycerides was evaluated by measuring hepatic and extra hepatic lipoprotein lipase activities.

MATERIALS AND METHODS

PATIENTS

Three girls and three boys (unrelated) were studied. The diagnosis had been confirmed in each patient by the finding of very low or virtually absent glucose-6-phosphatase activity in liver tissue obtained by needle biopsy. All patients showed the characteristic symptoms of pronounced hepatomegaly, tendency for hypoglycemia, hyperlacticacidemia, and hyperlipidemia. Hyperuricemia and bleeding tendency was present in some patients.

At the time of transition to the regime of nocturnal GDF, the patients were 3–8 yr old. The 1st patient, who was in a poor clinical condition, was studied during an initial basal regime (B) of frequent meals around the clock, followed by a first period of nocturnal GDF, a second period with B, and, finally, a permanent regime of nocturnal GDF. The studies were performed during a 6-month stay in the hospital. For the other five patients, the transition to the nocturnal GDF regime required 2–3 wk admission to hospital. The parents were fully informed about the experimental character of the GDF and gave their consent to the diagnostic tests involved.

MANAGEMENT OF THE GASTRIC DRIP

The composition of the diets, the GDF included, is shown in Table 1. The figures within parentheses indicate the calories of the previous 1–2 night meals expressed in percentage of total calories. The GDF consisted of a soy milk formula (Laktopriv, Töpfer, Germany) to which glucose or dextrimaltose and starch were added. We aimed to keep the blood glucose concentration of the patients between 4–6 mM during the 12 hr continuous nocturnal feeding by adjusting the amount of the GDF which varied from 400–500 ml.

It contained: carbohydrates (glucose, dextrimaltose, starch), 69 cal%; protein, 13 cal%; and fat, 18 cal%. The liquid formula was stirred in a bottle by a magnetic stirrer to prevent sedimentation. A PVC nasogastric tube 8 Ch. was positioned every night into the stomach by one of the parents or by the child under their supervision. A connecting system without filter was used to prevent blockage of the flow by undissolved milk powder particles. An Ivac pump was used to control the rate of administration. An extra alarm system came into action, if the child pulled the tube out of his nose during sleep. It consisted of a small thermistor, diameter 1.65 mm, positioned in the nose or esophagus and fixed to the tube with micropore. The thermistor was connected with a Wheatstone bridge (Fig. 1). As soon as the tube and thermistor were withdrawn from the nose, the temperature of the thermistor fell and a voltage drop ensued. This induced a current, which triggered the oscillator via the electronic level switch and an alarm came into action.

The thermistor was used permanently in three children, its use was discontinued in the other three children after 3–6 months due to irritation of the nose by the tip of the thermistor. False positive alarms and breaking of the thermistor wire occurred in the initial phase of experimentation, but these defects were not seen after more experience with the method had been gained. Full details of the system are available on request.

CHEMICAL METHODS

Lactate in urine and blood was determined using lactate dehydrogenase by the Boehringer method (11). Serum triglycerides

Table 1. *Composition of the diet of 6 patients with glucose-6-phosphatase deficiency treated with nocturnal GDF. The data within parentheses represent the calories of the previous night meals as percentages of total calories.*

Patient No.	Sex	Carbohydrate (cal %)	Fat (cal %)	Protein (cal %)	Gastric drip (cal % of total)
1.	♀ E. R.	61	21	16	30 (26)
2.	♀ P. S.	66	18	15	32 (26)
3.	♀ M. B.	60	23	16	34 (10)
4.	♂ D. S.	64	20	16	36 (33)
5.	♂ M. G.	60	19	21	30 (18)
6.	♂ R. S.	67	17	16	35 (22)

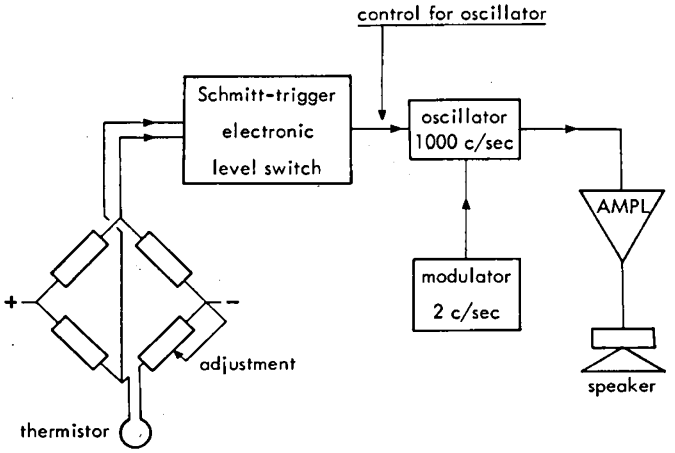

Fig. 1. Schematic presentation of the thermistor alarm system. AMPL: amplifier. For further explanation, see text.

were determined by the Soloni method (18), serum cholesterol by the Huang method (11), and serum phospholipids by the Zilversmit method (22). As regards plasma lipolytic activity, hepatic triglyceride lipase was measured in a medium containing 1.0 M NaCl, and extrahepatic lipoprotein lipase after precipitation of hepatic lipase with a specific antibody against this enzyme, exactly as described by Huttunen *et al.* (13, 14). Plasma samples were obtained at 5 and 40 min after a rapid iv injection of heparin (Vitrum Stockholm) 100 U/kg body weight.

RESULTS

LACTATE EXCRETION, ACID-BASE STATUS

As the 24-hr urinary lactate concentrations reflect the child's metabolic state much better than blood lactate determinations (5), only the former data are shown in the present study.

The effect of the regime with the nocturnal GDF on urinary lactate excretion in patient 1 compared to the basal regime of frequent feedings around the clock (B) is shown in Fig. 2. Assuming the upper limit of normal for lactate excretion to be 0.1 mmoles/24 hr for a child with this body weight (2, 5), a constant slight to moderate hyperlacticaciduria was apparent. Higher and more scattered values were found during both B periods. In patient 3, the marked hyperlacticaciduria decreased precipitously after introduction of GDF. The lactate excretion in the urine per 24 hr amounted to 17.0, 25.5, and 23.2 mmoles during the 3 days before the introduction of GDF and diminished to 1.6, 2.6, 0.7, and 0.9 mmoles on days 4, 6, 11, and 12 after GDF introduction. In this patient, the increase in nocturnal caloric intake from B to GDF feeding was greatest, however (Table 1). In the other patients, the hyperlacticaciduria did not change consistently during GDF when compared to B. Acid-base status was investigated in patient 1 during the 6-month observation period. Blood base excess values were measured with the Astrup method at 9 and 22 hr, during the consecutive B and GDF regimes (Fig. 3). Base excess values were significantly lower during the GDF regime both during the day and at night with the GDF drip, as compared to the B periods (Fig. 3).

SERUM LIPIDS, LIPOPROTEIN LIPASE

Serum triglyceride and serum cholesterol concentrations in patient 1 during the consecutive B and GDF periods are shown in Fig. 4. Serum lipid levels were initially extremely high and decreased markedly during the first basal period. Serum cholesterol even normalized, whereas serum triglyceride concentrations remained above the upper limit of normal (1.5 mM). Serum triglyc-

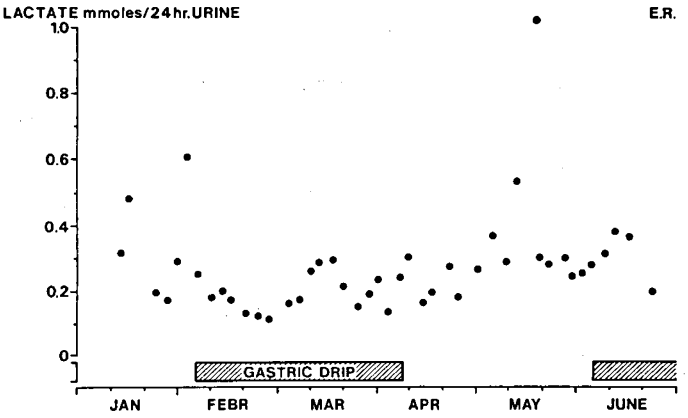

Fig. 2. Lactate excretion of patient 1 during frequent meals around the clock (B), and during GDF for 12 hr at night, combined with frequent meals during the day (GDF, *hatched areas*).

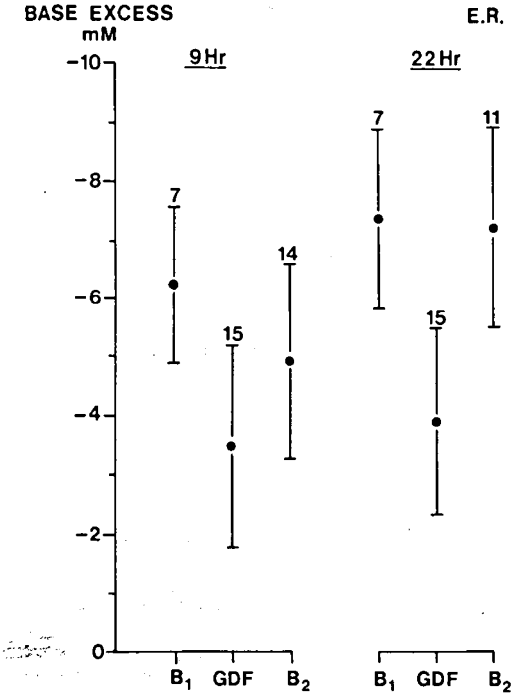

Fig. 3. Blood base excess data of patient 1 during B and GDF periods, measured at 9 and 22 hr. (mean ± SD). Number of measurements above the bars. Base excess at 9 hr is different for B1 and GDF ($P < 0.01$) and for B2 and GDF ($0.05 > P > 0.01$). Base excess at 22 hr is different for B1 and GDF ($P < 0.001$) and for B2 and GDF ($P < 0.0001$).

eride concentrations were lowest during the first GDF period, increased slightly during the second B period, and further gradually increased despite 2½ yr adequate GDF treatment at home. Serum cholesterol generally remained in the normal range. The moderate to marked hypertriglyceridemia of the other five patients changed inconsistently or decreased temporarily. Serum cholesterol levels became or remained normal, except in patient 6. The inconsistent changes of serum lipids during GDF are also shown in Table 2.

Plasma hepatic and extrahepatic lipoprotein lipase activities were measured in three patients before and 14 days after the institution of GDF. The data are also presented in Table 2. Comparing our results with the normal values obtained using the same method in young adults (13), the hepatic triglyceride lipase activity was normal in 1 patient during both B and GDF. In the other two patients, the abnormally low activity increased after GDF, but remained subnormal in one patient. The pre- and posttreatment extrahepatic lipoprotein lipase activity was abnormally low in all patients when compared to the normal adult values given by Huttunen *et al.* (13). Also most 40 min activities were lower than the 5 min activities. In the other three patients, hepatic and extrahepatic lipase activities could only be measured after initiation of GDF. Both hepatic and extrahepatic activity even after 1–2 yr of GDF, are comparable with the data shown in Table 2.

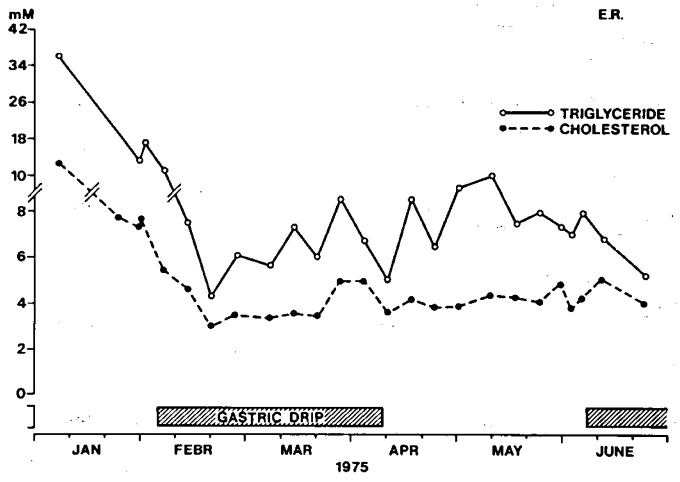

Fig. 4. Serum triglyceride and cholesterol concentrations in patient 1 during B and GDF periods. Upper limits of normal for triglyceride and cholesterol 5.0 and 1.5 mM, respectively.

GROWTH

The data of height, weight, SD score for height (19) related to Dutch standards (20), age at onset, and duration of GDF are given in Table 3.

In patients 1, 2, 3, and 6, SD scores improved after GDF, but, in patient 1, a chronic urinary infection and hematuria caused by a kidney stone, which had to be removed at the age of 8 yr, presumably undid the favorable influence of GDF.

In patient 4, treated alternately with night meals and glucose-containing GDF from the age of 11 months, and in patient 5, treated periodically with 1–2 wk courses of GDF in other pediatric centers, the SD scores were in the low normal range and remained so after institution of our GDF method.

DISCUSSION

The most spectacular effect of nocturnal GDF in patients with glucose-6-phosphatase deficiency is the catch-up growth of those children who were most retarded in growth (patients 1, 2, 3, and 6). Much speculation still exists over the mechanism of the growth retardation on the one hand and of the catch-up growth initiated by GDF on the other hand.

Though no definite explanation has been found for the severe growth retardation in these patients (6), it probably has a multifactorial origin. The tendency to acidemia (6) and the repeated unavailability of glucose for the peripheral tissues (17), accompanied by the tendency for the development of a catabolic state (9) might contribute to the growth retardation. Consequently, the reduction in lactic acid overproduction (3, 9, Fig. 2) and the subsequent normalization of the acid-base equilibrium (Fig. 3.), might be one of the complex factors relating to growth which are influenced by GDF.

Normalization of the sleep pattern, which was observed by the parents of several patients, might be another factor contributing to better growth (21). Children, who slept restlessly with half-closed eyes, sweating excessively during the night, developed a normal sleep pattern during GDF. This was substantiated by the change of the sleep EEG in patient 5, which before GDF was characterized by sleep stages 2 and 3, stage 4, and REM sleep being added during GDF. The change from anorexia to good appetite was observed by us in patient 1 and by the parents of other patients. This factor, presumably due to correction of the acidemia, might lead to a higher caloric intake and, thus, contribute to the catch-up growth of some patients. Other clinical improvements seen were a decrease in liver size in five patients, a finding also reported by others (3, 9), and markedly increased vitality in some patients. The tendency for bruising and epistaxis, apparent in some patients, disappeared after GDF (cf the normalization of the clotting defect after iv nutrition, 1, 7, 15). The

Table 2. *Serum triglyceride (TG), cholesterol (Chol), and phospholipid (PL) concentration, hepatic triglyceride lipase and extrahepatic lipoprotein lipase activity in 3 patients before and after GDF. The 5 min and 40 min postheparin activity is expressed as μmol FFA released from an artificial triglyceride emulsion per min per liter plasma (13). Normal 5 min postheparin activity in young adults is 166–896 for hepatic triglyceride lipase, and 123–382 for extrahepatic lipoprotein lipase (13).*

				Lipase			
				Hepatic		Extrahepatic	
Patient and treatment	TG	Chol	PL	5 min	40 min	5 min	40 min
2. Before GDF	11.2	8.2	7.3	59	92	42	74
After GDF (17 days)	10.1	6.5	6.3	112	95	94	66
3. Before GDF	4.3	3.4	3.9	80	71	66	28
After GDF (14 days)	3.8	4.4	3.1	163	148	104	37
5. Before GDF	5.3	3.8	3.8	249	147	73	15
After GDF (15 days)	11.3	2.9	5.3	266	242	31	15

Table 3. *Age, height, weight, and SDS of 6 patients before and during GDF. SDS was calculated according to Tanner et al. (19) using the data of normal Dutch children (20).*

Patient						GDF		
No.	Sex	Age (yr)	Height (cm)	Weight (kg)	SDS	Age at onset (yr)	Duration (yr)	Remarks
1.	♀ E. R.	1.12	72.3	8.0	−1.92			
		1.39	75.5	9.0	−2.07			
		2.35	79.5	9.6	−3.26			
		3.42	84.5	12.7	−3.90			
		3.81	85.5	12.2	−4.24			
		4.80	88.5	13.5	−4.79			
						4.90		
		5.28	95.3	15.8	−3.74		0.38	
		5.72	100.5	17.4	−3.12		0.82	
		6.54	106.0	17.3	−2.86		1.64	
		7.18	107.2	18.5	−3.24		2.28	Bacteriuria, hematuria, kidney
		7.92	109.4	18.4	−3.47		3.03	stone removed
2.	♀ P. S.	2.04	78.0	11.3	−2.99			
		3.04	86.9	13.7	−2.61			
		3.98	93.1	15.2	−2.66			
		4.99	100.8	17.3	−2.23			
		6.10	105.2	19.3	−2.57			
		6.90	109.5	21.1	−2.54			
		7.42	112.0	21.1	−2.56			
		7.90	114.0	22.0	−2.62			
		8.51	116.4	23.4	−2.70			
						8.73		
		9.01	121.3	24.0	−2.25		0.28	
		9.41	124.8	25.0	−1.96		0.68	
		10.02	128.7	27.5	−1.76		1.29	
3.	♀ M. B.	1.06	70.5	8.1	−2.27			
		2.11	84.6	12.5	−1.20			
		3.14	88.5	15.0	−2.39			
		4.26	95.0	15.2	−2.60			
		5.25	97.0	17.0	−3.34			
		6.10	102.1	16.0	−3.19			
		6.57	103.6	17.1	−3.37			
						6.57		
		7.23	112.8	22.0	−2.23		0.66	
		7.57	118.7	23.5	−1.46		1.00	
		8.36	125.5	26.5	−0.96		1.79	
4.	♂ D. S.	1.72	81.5	12.4	−1.45			GDF (glucose) intermittently
		2.73	92.5	15.0	−0.75			from 11 months
		3.76	98.0	17.2	−1.26			
		4.77	106.0	18.8	−0.87			
						4.77		
		5.73	110.5	21.8	−1.15		0.96	
		6.64	116.9	23.8	−0.93		1.87	
5.	♂ M. G.	1.00	77.0	10.5	0.00			GDF "courses" from 2 yr
		1.68	85.0	13.5	+0.23			
		2.74	92.5	15.2	−0.77			
		3.23	98.2	16.0	−0.28			
		3.68	99.4	17.5	−0.81			
						3.69		
		4.13	104.8	18.7	−0.24		0.44	
		4.77	108.4	19.0	−0.33		1.08	
6.	♂ R. S.	1.82	79.2	10.6	−2.44			
		2.99	85.5	12.3	−3.10			
		4.11	92.5	13.2	−3.04			
		5.30	94.8	14.2	−3.90			
						5.31		
		6.37	106.4	16.7	−2.68		1.06	
		7.18	114.6	19.0	−1.93		1.87	

patients' ages at the beginning of GDF varied from 11 months–16 yr in the various studies in the literature. GDF may be started early depending on the degree of growth retardation and lactic acidemia.

A pronounced improvement in some of the metabolic abnormalities such as hyperlacticacidemia, hyperlipidemia, and hyperuricemia has been observed after institution of GDF (3, 9). We have also observed improvement in these abnormalities. However,

serum triglyceride levels, although decreasing temporarily after the institution of GDF, remained moderately to markedly elevated. The hypertriglyceridemia has already been shown to be the result of both increased liponeogenesis (12) and decreased elimination of triglycerides by lipoprotein lipase (8). In the present study, hepatic and extrahepatic lipase activity was measured separately in three patients before and after institution of GDF in an attempt to obtain some insight into the lipid clearing capacity and the effect of GDF thereon. Hepatic and extrahepatic lipase are the two main components of total lipoprotein lipase in postheparin plasma. Much speculation still exists about the role of hepatic triglyceride lipase in lipoprotein metabolism (13). It appeared, however, that hepatic triglyceride lipase activity was normal in one patient and it increased in the other two patients after institution of GDF, but not quite to normal values. Much more is known about the functions of extrahepatic lipoprotein lipase, which is mainly responsible for the removal of triglycerides from plasma to peripheral tissues (13). The activity of this enzyme was very low in all three patients before and after GDF. Also, in most patients the 40 min postheparin activity was lower than the 5 min postheparin activity. This is the reverse of normal (13) and might reflect insufficient, immediately available, component, which was maximally released from the vascular endothelium 5 min after heparin injection, and also a lower tissue lipase pool as reflected by the 40 min postheparin levels. Extrahepatic lipoprotein lipase activity has been reported to be subnormal after prolonged fasting (14) and in patients with untreated diabetes mellitus (16). The recurrent fasting state with the subsequent hypoglycemia and hypoinsulinemia of patients with glucose-6-phosphatase deficiency might lead to deficiency of extrahepatic lipoprotein lipase by the same mechanism. It is not clear why continuous availability of nutrients from GDF for 12 hr/day does not improve this main component of plasma triglyceride clearing. Although the composition of GDF was not the same in the various studies, the results seem to be equally favorable. We prefer to use a natural feeding without sucrose and lactose (4). Therefore, a liquid formula of soy protein, soy fat, glucose, dextrimaltose, and starch was used instead of the more expensive solutions used by others (glucose polymers (3), Vivonex (1, 3, 9)).

A safety device for timely warning in case of inadvertent displacement of the nasogastric tube by the sleeping child is indispensible. A temperature-sensitive device, such as the thermistor used in our patients, fulfills this purpose. It can be concluded that a 12 hr nocturnal GDF is a safe procedure. It promotes normal growth and reduces liver size. The tendency for acidemia diminishes, though the lacticaciduria does not normalize. The hypertriglyceridemia remains. This is partly due to decreased activity of extrahepatic lipoprotein lipase.

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