Galactose Absorption after Oral Administration of Lactose in Neonates

Ryozo OKAMOTO1,* Makoto MINO,1 and Masaki HAYASHI2

1Department of Pediatrics, Osaka Medical College, Takatsuki, 569, Japan
2Department of Pediatrics, Osaka Rosai Hospital, Sakai, 591, Japan

(Received March 22, 1989)

Summary
1. A lactose tolerance test was performed in infants and children. The majority of the infants showed a good response with serum glucose elevations, while there were poor responders among children more than 2 years old. During this test, serum galactose usually was nondetectable, even in the good responders.
2. After simultaneous loading with a constant amount of galactose and varying amounts of glucose in neonates, the degree of elevation of serum galactose levels decreased with increasing amounts of glucose, and loading with equal amounts of galactose and glucose resulted in no elevation of serum galactose levels.
3. In a 6-year-old galactosemic child, serum galactose levels were markedly and continuously elevated after lactose loading.
4. After galactose loading with simultaneous intravenous glucose loading in neonates, elevation of serum galactose was markedly suppressed, as compared with that after galactose loading alone, while it was higher than that after oral loading with the equal doses of galactose and glucose.

From the above, the fact that no increase was observed in serum galactose concentration when lactose was loaded orally in neonates is ascribable partially to inhibited absorption of galactose by glucose in the intestine but in the most part to accelerated metabolism of galactose by the glucose absorbed.

Key Words lactose, galactose, glucose, carbohydrate absorption, infant, galactosemia

Galactose, which is the c-4 epimer of glucose, is well known to occur naturally in lactose, milk sugar. It is an important infant nutrient, because galactose is the major source of carbohydrates in infants (1). However, there have been few reports that the oral intake of galactose accompanied by glucose in human adults suppresses serum galactose elevations, as compared with that of the same dosage of galactose.
alone (2). With respect to infant nutrition, the behavior of circulating glucose after a meal or sugar intake is well documented, while the behavior of galactose in neonatal blood is not yet thoroughly understood because serum galactose level is not routinely determined in clinical practice. However, it has been reported that galactose metabolism plays a role in regulating carbohydrate metabolism (3, 4), and the galactose metabolism in the neonatal liver is more rapid than in adults' (5). On the other hand, galactose is a constituent of proteoglycans and mucopolysaccharides, which are components of biomembrane and other tissues. In these compounds, galactose is incorporated and strictly discriminated from glucose. During the period of rapid development, the galactose requirement increases in neonates and infants. However, it is generally recognized, based on the investigations of galactosemic infants (6), that no detectable levels of circulating galactose exist in healthy neonates and infants, even when lactose is their major carbohydrate source. How galactose is handled after galactose or lactose ingestion in healthy neonates and infants has not been investigated. This study focused on examining serum galactose changes after galactose loading in neonates in association with glucose load.

MATERIALS AND METHODS

Subjects. The subjects enrolled in this study were 47 children, 0 to 14 years old (mean, 6.5 years), including 21 boys and 26 girls. These children had been brought to our university clinic for evaluation of equivocal symptoms including autonomic dysfunction and headache, nausea, abdominal discomfort or pain, and dizziness, but without evidence of organic or metabolic disease, or other conditions which could adversely affect gastrointestinal function. In addition, five healthy full-term neonates without problems and one galactosemic patient with galactose-1-phosphate uridyl transferase deficiency also were enrolled in this study. For the neonates, the study was started after 7 days of life, when they had recovered from their physiological weight loss. The studies were performed after informed consent was obtained from the parents.

Tolerance tests of carbohydrate metabolism

1) Lactose-loading test. After an overnight fast, a sample of blood was obtained as the control, and 2 g/kg of lactose (not to exceed 50 g) as a 10% solution was administered orally. Blood samples were obtained every 30 min for 120 min after loading, and glucose and galactose concentrations were determined.

2) Galactose-loading test. In the neonates, 1 g/kg of galactose, which is the amount of the sugar contained in 2 g/kg of lactose, was administered as a 10% solution after a 4-h fast. Serum galactose and glucose concentrations were determined every 30 min for 120 min after loading.

3) Galactose-plus-glucose-loading test. In order to examine the effect of glucose on galactose absorption, 1 g/kg of galactose was administered together with 1 g/kg of glucose to the neonates after a 4-h fast. This dosage of galactose and glucose corresponded to 2 g/kg of lactose. After loading, serum glucose and galactose
were determined. Subsequently, mixtures of a constant amount of galactose (1 g/kg) together with amounts of glucose varying from 0 to 1 g/kg were administered to determine the effect of glucose on galactose absorption.

4) Galactose-loading test with a simultaneous intravenous infusion of glucose. To examine the affect of hyperglycemia on serum galactose levels after oral galactose loading, 1 g/kg of galactose was administered simultaneously with an intravenous infusion of 10% glucose solution for 2 h (0.5–1.0 g/kg/h) in neonates to keep their intravenous glucose concentration above 120 mg/100 ml.

Analysis.
1) Galactose. A UV-method with galactose dehydrogenase (7) was used.
2) Glucose. A UV-method with hexokinase and glucose-6-phosphate dehydrogenase (8) was used.

The galactose and glucose reactions catalyzed by the above enzymes simultaneously formed NADH and NADPH, respectively, in proportion to the amount of each sugar. Therefore, quantitation of these sugars was carried out by measuring the amount of NADH or NADPH generated using the Roto Chem (Amin Co.) equipment.

RESULTS AND DISCUSSION

1. Lactose-loading test

1) Changes in serum glucose. It is generally accepted that the normal response to lactose loading is an elevation of the serum glucose by more than 20 mg/dl over the fasting level within 90 min. However, 25 of the subjects showed a poor response to lactose loading (Table 1). In addition, a relationship existed between the maximum response and the age of the subjects examined (Fig. 1 and Table 2). The maximum increase in the serum glucose after lactose loading decreased with age, and it was less than 20 mg/dl in the majority of children more than 10 years old, whereas in all of the infants less than one year old, a good response was shown, and the glucose level rose more than 30 mg/dl. This is in agreement with many previous reports (9–11) which found that lactase activity in the intestine decreases with age. However, reports by other authors have indicated that the decrease in intestinal lactase activity with age seems to relate neither to the amount of milk consumed nor the duration of milk feeding, but is related to genetic factors (9, 10). Among Japanese, the decrease in lactase activity with age has been observed to be greater than among Caucasians (11).

2) Changes in serum galactose. When these examinees were divided into two

Table 1. Results of lactose-tolerance test in infants and children.

| Total numbers of subjects | Maximum increase in serum glucose: |
|---------------------------|-----------------------------------|
|                           | 20 mg/100 ml or more              |
|                           | less than 20 mg/100 ml             |
|                           | 52                                |
|                           | 27 (51.9%)                        |
|                           | 25 (48.1%)                        |

Vol. 35, No. 5, 1989
Fig. 1. Maximum rise of serum glucose levels after lactose loading as a function of age. Lactose was administered orally at a dosage of 2 g/kg of body weight.

Table 2. Relation between the maximum increase in serum glucose after lactose loading and age in children.

| Age   | Numbers | Maximum increase in serum glucose (M + SD) | Numbers of subjects with a poor response (< 20 mg/100 ml) |
|-------|---------|--------------------------------------------|----------------------------------------------------------|
| Neonates | 5       | 55 ± 15                                    | 0 (0%)                                                    |
| -1 yr  | 6       | 45 ± 11                                    | 0 (0%)                                                    |
| -6 yrs | 12      | 22 ± 13                                    | 6 (50%)                                                   |
| -10 yrs| 21      | 17 ± 10                                    | 11 (52%)                                                  |
| -14 yrs| 8       | 10 ± 5                                     | 8 (100%)                                                  |

groups, good responders (glucose elevation of 20 mg/dl or more after lactose loading) and poor responders (less than a 20 mg/dl increase), there was no documented elevation of serum galactose levels in either the good responders or poor responders (Fig. 2). In the good responders, ingested lactose must have been adequately hydrolyzed and cleaved into glucose and galactose and effectively absorbed through the gut, given the consistent elevations in the serum glucose levels. Therefore, the problem arises as to whether or not galactose derived from lactose in the intestine is absorbed.

*J. Nutr. Sci. Vitaminol.*
GALACTOSE METABOLISM IN INFANTS

Fig. 2. Changes in serum glucose and galactose levels in good and poor responders after lactose loading. The good responder showed a glucose elevation of 20 mg/dl or more after lactose loading, and poor responder showed an increase of less than 20 mg/dl.

Fig. 3. Changes in serum galactose and glucose levels after galactose loading of (1 g/kg) in infants.

2. Galactose-loading test

To examine galactose absorption, galactose alone was given orally to the infant group. The dosage was 1 g/kg, which is the amount derived from 2 g/kg of lactose after complete digestion. As shown in Fig. 3, serum galactose levels increased.
significantly, while little changes occurred in the serum glucose levels. This indicates that ingested galactose is absorbed effectively through the gut and is not converted immediately into circulating glucose. Therefore, the elevated serum glucose levels after lactose loading must not be attributable to metabolized galactose, but represent glucose absorbed directly. This fact suggests a possible significance of preventing precipitous elevation of blood glucose in infants who are taking milk. On the basis of this result, the lack of an elevation in serum galactose levels after lactose loading might be explained by one of two mechanisms, i.e., 1) competition between glucose and galactose for absorption, or 2) more glucose supply to produce the UDP-glucose which is essential for the metabolism of galactose along the Leloir pathway (12).

3. Galactose-loading test together with glucose loading

First, changes in serum galactose after simultaneous loading with equal amounts of galactose and glucose were investigated. Since the 1 g/kg of galactose load in the previous examination reliably raised serum galactose levels, 1 g/kg each of galactose and glucose (equivalent to a 2 g/kg of lactose load) were administered simultaneously to neonates to eliminate the role of the intestinal digestion of lactose. After loading, only the serum glucose level increased, and no significant elevation of galactose occurred (Fig. 4). This result indicates that oral glucose loading may play a role in limiting serum galactose elevation after oral galactose loading.

Therefore, another study was carried out, administering 1 g/kg of galactose orally together with varying amounts of glucose, 0, 0.2 g/kg, 0.5 g/kg, and 1 g/kg, (Fig. 5). The maximum elevation in serum galactose after loading decreased as the loading dose of glucose 1g/kg BW + galactose 1g/kg BW (n=5)

![Galactose-loading test](Fig. 4. Changes in serum galactose and glucose levels after loading with 1 g/kg each of galactose and glucose in neonates.)

J. Nutr. Sci. Vitaminol.
Fig. 5. Changes in serum galactose and glucose levels after loading with a constant amount of galactose (1 g/kg) plus different amounts (0–1 g/kg) of glucose in neonates.

amount of glucose increased, and again no significant elevation in serum galactose levels was found with equal amounts of glucose and galactose (1 g: 1 g). This finding may suggest in part that these sugars compete with each other for absorption through gut, but glucose absorption takes place preferentially.

There have been many reports relating to competition for intestinal absorption between glucose and galactose, i.e., competition between the two sugars for the intestinal transport carrier (13–15).

Given these findings, the question still remains to what extent serum galactose elevation is suppressed by the presence of glucose after lactose intake, or whether no galactose is absorbed after lactose loading. To resolve this question a lactose-loading test was performed in a galactosemic child, who had no problem with sugar absorption but was unable to metabolize only galactose after its absorption.

4. Lactose-loading test in a galactosemic child

In contrast to normal children, the serum galactose level increased gradually and reached a level of 78 mg/dl at 120 min after administering a lactose load of 2 g/kg, while little change occurred in the serum glucose levels (Fig. 6). This elevation in serum galactose after lactose loading was not seen in non-galactosemic children (Fig. 2). If the galactosemic child had no problems with sugar absorption through the gut, a significant elevation in serum galactose after lactose loading would indicate that galactose absorption occurred in the presence of glucose, and the absorbed galactose accumulated in the serum probably because of a failure to metabolize it. Thus, we may assume that galactose must be absorbed in healthy
neonates and children, but the absorbed galactose is constantly being metabolized without any detectable galactose in the serum. From this fact, it was considered that competition between galactose and glucose in the absorptive process is not the main cause for the absence of increase in the serum galactose concentration after loading of lactose in the normal neonates. Then, the elevated serum concentrations of glucose seem likely to have suppressed the serum galactose levels after oral galactose intake. There have been some reports that hyperglycemia may influence the serum galactose levels after oral galactose loading (16, 17).

To examine this in human neonates, an oral galactose-loading test was performed in association with a simultaneous intravenous infusion of glucose, thus bypassing the intestinal transport system.

5. Galactose-loading test with the simultaneous intravenous infusion of glucose

During 2 h of intravenous glucose infusion, which resulted in a maximum glucose concentration of 195 mg/dl and usually more than 120 mg/dl levels (Fig. 7, right), only a 15 mg/dl increase in serum galactose ensued after oral loading with 1 g/kg galactose; this elevation was much lower than the level following oral loading with the same dose of galactose without any glucose infusion (Fig. 7, left). However, after simultaneous oral loading with the equal amounts (1 g/kg) of glucose and galactose, serum galactose levels were not detectable during the experimental period, as shown in the figure. Thus, hyperglycemia could markedly suppress the serum galactose elevation after oral galactose loading to a great extent, but not completely.
All of these results in infants agree with previous investigation in adults, although the possibility that galactose absorption competes with glucose remains. Morgan et al. (16) have investigated the effect of oral galactose loading on GIP and insulin secretion in adults and reported that oral galactose loading causes the release of GIP, which is powerfully insulinotropic in the presence of moderate hyperglycemia. The lower GIP and galactose levels observed following oral galactose administration in the presence of intravenous glucose may be accounted for either by postulating that insulin inhibits the absorption of oral galactose, or that insulin exerts negative feedback control on GIP release and accelerates galactose disposition in the body. Williams et al. (17) also have conducted a similar investigation in adults and assumed that insulin release is not related to this phenomenon, while it is unlikely that this effect occurs solely as a consequence of competition for absorption between the two sugars. However, our findings of reduced galactosemia when glucose accompanies galactose loading could not be explained by a single mechanism, either that hyperglycemia enhances galactose metabolism after absorption to prevent galactosemia, or that competition occurs between the two sugars during absorption. The sugar load in our study corresponded to a dose from 30ml/kg of human milk, a physiological lactose dose for infant nutrition. Therefore, both mechanisms may be operative in galactose metabolism in neonates and possibly in infants. From the above, the fact that no increase was observed in serum galactose concentration when lactose was loaded orally in neonates is ascribable partially to inhibited absorption of galactose by glucose in the intestine but in the most part to accelerated metabolism of galactose by the glucose absorbed.
This study was supported by Grant-in-Aid (58770710) for Scientific Research from the Ministry of Education, Science and Culture of Japan

REFERENCES

1) Yamamoto, Y., Yonekubo, A., Iida, K., Takahashi, S., and Tsuchiya, F. (1978): The composition of Japanese human milk. I. Macro-nutrient and mineral composition. Shoni-Hoken-Kenkyu (in Japanese), 40, 463–475.

2) Holdsworth, C. D., and Dawson, A. M. (1964): The absorption of monosaccharides in man. Clin. Sci., 27, 371–379.

3) Sparks, J. W., Lynch, A., Chez, R. A., and Glinsmann, W. H. (1976): Glycogen regulation in isolated perfused near term monkey liver. Pediatr. Res., 10, 51–56.

4) Kliegman, R. M., Miettinnen, E. L., Kahlhan, S. C., and Adam, P. A. J. (1981): The effect of enteric galactose on neonatal canine carbohydrate metabolism. Metabolism, 30, 1109–1118.

5) Segal, S., Roth, H., and Bertoli, D. (1963): Galactose metabolism by rat liver tissue. Influence of age. Science, 142, 1311–1313.

6) Segal, S. (1983): Disorders of galactose metabolism, In The Metabolic Basis of Inherited Disease, 5th Ed., ed by Stanbury, J. B., Wyngaarden, J. B., Fredriokson, D. S., Goldstein, J. L., and Brown, M. S. McGraw-hill Co., New York, pp. 167–191.

7) Beutler, H. (1984): Lactose and D-galactose. UV-method, In Methods of Enzymatic Analysis, ed. by Bergmeyer, H. U., Verlag Chemie, Weinheim, Vol. 6, pp. 104–112.

8) Kunst, A., Draeger, B., and Ziegenhorn, J. (1984): D-Glucose, UV-method with hexokinase and glucose-6-phosphate dehydrogenase. In Methods of Enzymatic Analysis, Vol. 6, ed. by Bergmeyer, H. U., Verlag Chemie, Weinheim, Vol. 6, pp. 163–172.

9) Sahi, T. (1974): The inheritance of selective adult type lactose malabsorption. Scand. J. Gastroent., 9: Suppl. 80, 11–58.

10) Aoki, K. (1986): A stochastic model of gene-culture coevolution suggested by the “culture historical hypothesis” for the evolution of adult lactose absorption in humans. Proc. Natl. Acad. Sci. USA, 83, 2929–2933.

11) Nose, O. (1978): Carbohydrate absorption capacity in children by the breath hydrogen analysis.—Effect of age on lactose malabsorption in Japanese population—Acta Pediatr. Jpn., 82, 896–901.

12) Rogers, S., and Segal, S. (1981): Changing activities of galactose-metabolizing enzymes during perfusion of suckling rat liver. Am. J. Physiol., 240, E333–E339.

13) Crane, R. K. (1960): Studies on the mechanism of the intestinal absorption of sugars. III. Mutual inhibition, in vitro, between some actively transported sugars. Biochim. Biophys. Acta, 45, 447–482.

14) Annegers, J. H. (1968): Absorption of glucose, galactose, and xylose in the dog. Proc. Soc. Exp. Biol. Med., 127, 1071–1074.

15) Coombe, N. B., and Smith, R. H. (1973): Absorption of glucose and galactose and digestion and absorption of lactose by preruminant calf. Br. J. Nutr., 30, 331–344.

16) Morgan, L. M., Wright, J. W., and Marks, V. (1979): The effect of oral galactose on GIP and insulin secretion in man. Diabetologica, 16, 235–239.

17) Williams, C. A., Phillips, T., and Macdonald, I. (1983): The influence of glucose on serum galactose levels in man. Metabolism, 32, 250–256.

J. Nutr. Sci. Vitaminol.