Utilization of Intravenously Injected FRUCTOSE *and* INVERT SUGAR *in* NORMAL HUMAN SUBJECTS

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Within recent years increasing recognition has been given to the importance of calories in the intravenous feeding of patients. This recognition arose from the finding that adequate caloric intake is required for optimal nitrogen utilization. Currently invert sugar, fructose, ethyl alcohol, and fat emulsions are being studied in various laboratories as intravenous aliments that may possess advantages over glucose in terms of the number of calories per unit time that can be administered.[1] The present study is concerned with the rate of utilization of fructose and invert sugar to assist in evaluating their possible superiority to glucose.

Plan of the Present Study

In the studies reported here, answers were sought to the following questions: (1) What is the pattern of tolerance, in terms of blood and urinary sugar levels, when fructose and invert sugar are given in amounts comparable to those which would be desirable in the treatment of patients with caloric depletion? Previous investigators, although they have used relatively high rates of infusion, have continued the infusions for only 1 to 1.5 hours, giving a maximum of 150 Gm. of sugar. (2) What are the comparative rates of utilization of fructose and invert sugar? None of the previous investigators has administered these substances to the same group of subjects at the same rates, so as to permit direct comparison. (3) What is the effect of simultaneous administration of fructose on glucose tolerance? As indicated above, studies in animals suggest that simultaneous administration of fructose improves glucose tolerance.

Methods

Nine normal male subjects, ranging in age from 27 to 45 years, each received each of the following infusions on separate days: (1) 141 Gm. of glucose (1500 ml. of 10 per cent glucose in water), (2) 291 Gm. of fructose, and (3) 288 Gm. of invert sugar (the latter two were both in the form of 3000 ml. of 10 per cent solution in water).* The solutions were given at a constant rate over a 3-hour period with the subjects in the fasting state. Blood and urine collections were made just before, each hour during infusion, and for 2 hours after the infusions. Since invert sugar consists of equal parts of glucose and fructose, the rate of administration of glucose was the same in the glucose infusion as in the invert sugar infusion. This permitted an evaluation of the effect on glucose tolerance of simultaneous administration of fructose.

Total reducing substances in blood and urine were determined by the Nelson[2] modification of the Somogyi[3] method. Fructose determinations were done by the method of Roe.[4]

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The opinions expressed in this paper are those of the authors and do not necessarily represent those of any governmental agency.

* 10 per cent glucose in distilled water was kindly supplied by Abbott Laboratories, North Chicago, Ill.; 10 per cent fructose and invert sugar in distilled water by Abbott Laboratories, North Chicago, Ill., and Baxter Laboratories, Morton Grove, Ill.

To provide a basis for calculating the blood and urinary levels of glucose and fructose, a study was made of the comparative reducing power of fructose and glucose in the Nelson method for total reducing substances and the amount of reaction produced by glucose in the Roe method for fructose. It was found that in the Nelson method, fructose produces 88 per cent as much reduction as does an equal amount of glucose. Four different samples of purified fructose,* dried for 48 hours in a vacuum desiccator, all gave the same result. Glucose was found to produce 2 per cent as much reaction in the Roe method for fructose as does an equal amount of fructose. Simultaneous equations were derived to permit calculation of the glucose and fructose content of samples from the results of the Nelson and Roe methods:

$$G_g = 1.018\ G_t - 0.896\ F_t$$
$$F_f = 1.018\ F_t - 0.0204\ G_t$$

where G_t = total concentration of reducing substance (uncorrected value of the Nelson method determination), G_g = that part of G_t due to glucose, F_t = uncorrected value of Roe method determination, F_f = that part of F_t due to fructose.†

For the calculation of the percentage urinary sugar loss the concentration of sugar in the solutions infused was determined by actual analysis, rather than using the values given on the labels. In the case of glucose, the U.S.P. 10 per cent solution is based on the hydrated form of glucose and represents about a 9.4 per cent solution of the unhydrated form. The percentage of sugar (calculated as the unhydrated form), in the solutions infused, as determined by chemical analysis, was found to be:

10 per cent Glucose	9.4 per cent
10 per cent Fructose	9.7 per cent
10 per cent Invert Sugar	
Glucose	4.8 per cent
Fructose	4.8 per cent

Therefore, 1500 ml. of 10 per cent glucose contained 141 Gm., 3000 ml. of 10 per cent fructose 291 Gm., and 3000 ml. of 10 per cent invert sugar 288 Gm.

Results

Figure 1a shows the blood glucose levels, urinary glucose output and urine volume after the administration of 141 Gm. of glucose. The values are the means for the nine subjects and the bars indicate the standard errors. The blood glucose, after reaching an early peak, steadily fell in spite of the continued infusion at a constant rate. Hypoglycemic levels occurred in all subjects following termination of the infusions. The peak of the urinary glucose output was during the second hour of infusion and the maximal diuresis was during the third hour.

Figure 1b shows the blood and urinary values following the administration of 291 Gm. of fructose. There was a slight initial rise in blood glucose followed by a progressive fall during the course of the infusion, thus showing the same general pattern as in the glucose infusion. After the infusion was stopped blood glucose fell to hypoglycemic levels. In contrast, however, the blood fructose level did not fall during the infusion but rose slightly and then fell rapidly when the infusion stopped. The urinary sugar was mainly fructose and the peak of output as well as the maximal diuresis was seen in the third hour.

In Figure 1c, the blood and urinary values after the administration of 288 Gm. of invert sugar are presented. Again a sharp peak in blood glucose occurred with a progressive fall despite the continued administration of the sugar. Blood fructose levels remained rather constant during the infusion but fell rapidly upon termination. Thus, during the second and third hours of the infusion the blood glucose level fell while the blood fructose remained constant, although both glucose and fructose were being infused at constant and equal rates. The urinary sugar was divided approximately

* Kindly supplied by Prof. M. Wolfrom, Ohio State University; Baxter Laboratories; U.S.D.A., Western Regional Research Laboratories; and Pfanstiehl Chemical Company.

† The method of derivation of these equations is presented in the Medical Nutrition Laboratory Report of this work.[22]

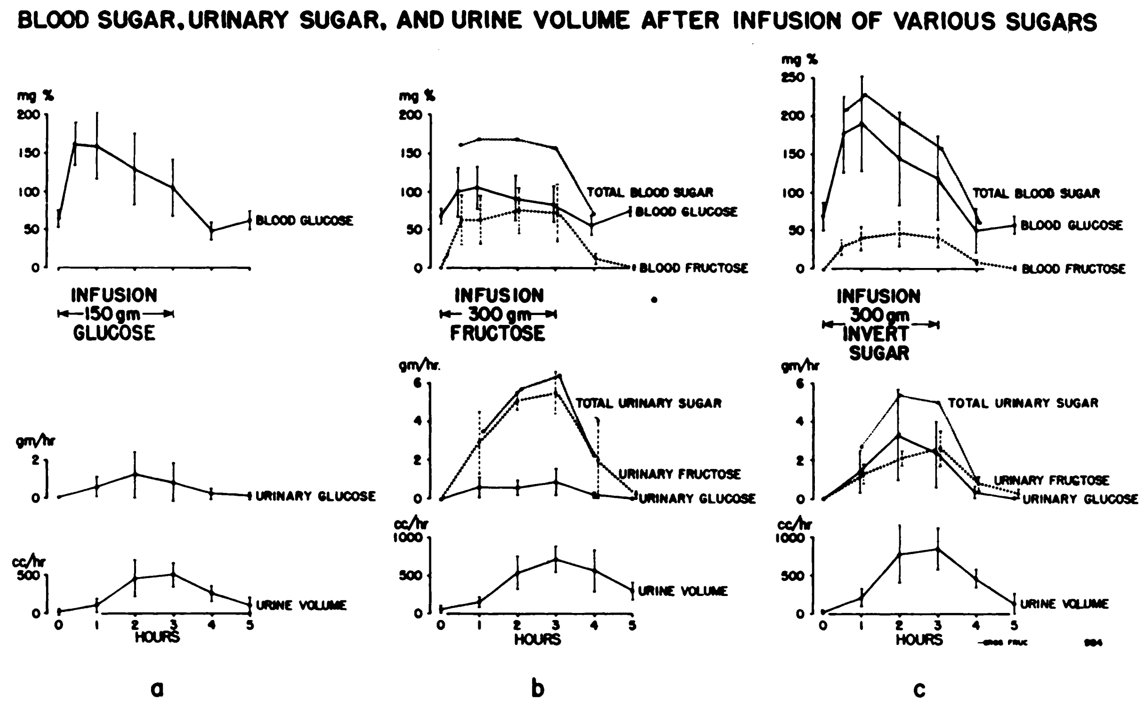

Fig. 1. Blood Sugar, Urinary Sugar, and Urine Volume After Infusion of Various Sugars.

equally between fructose and glucose and the maximal sugar output, as well as the maximal diuresis, occurred during the second and third hours of the infusion.

The mean values for the highest blood glucose, blood fructose, and total blood sugar are given in Figure 2. Blood glucose was highest with the infusion of invert sugar (198 mg. per cent) despite the fact that the rate of administration of glucose was the same as in the glucose infusion, in which the mean highest blood glucose value was 187 mg. per cent. During fructose administration the mean highest blood glucose was 118 mg. per cent.

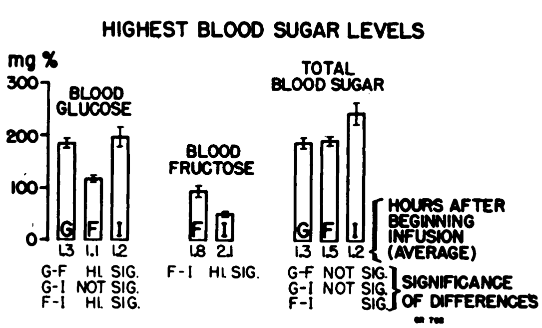

Fig. 2. Highest Blood Sugar Levels.

The mean highest concentration of fructose in the blood was almost twice as great during fructose infusion (92 mg. per cent) as during invert sugar infusion (51 mg. per cent), thus corresponding rather closely with the rate of administration of fructose, which was twice as great in the fructose infusion as in the invert sugar infusion. The peak values for blood fructose occurred somewhat later during the infusion than the peak values for glucose.

The mean highest total blood sugar was greatest with the invert sugar infusion (243 mg. per cent) as compared with the glucose infusion (187 mg. per cent) and the fructose infusion (191 mg. per cent).

The grams of sugar excreted in the urine in 5 hours, including the 3 hours of infusion and 2 postinfusion hours, are given in Figure 3. More glucose was excreted with invert sugar infusions (7.14 Gm.) than with glucose infusions (2.98 Gm.) even though glucose was given at the same rate in the two infusions. Glucose excretion with fructose infusion had a mean value of 2.21 Gm. Fructose excretion was approximately twice as great with fructose administration (15.84 Gm.) as with invert

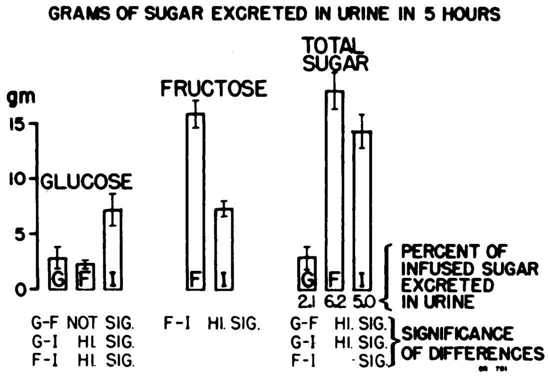

Fig. 3. Grams of Sugar Excreted in Urine in 5 Hours.

sugar administration (7.12 Gm.) and thus was proportional to the rate of administration of fructose because the rate of administration of fructose was twice as great in the fructose infusion as in invert sugar infusion. The total sugar excretion was greatest with fructose infusion (18.06 Gm.) and the amount lost with invert sugar (14.27 Gm.) was more than four times as great as with glucose administration (2.98 Gm.). The mean urinary sugar loss expressed as per cent of sugar infused was 2.12 per cent for glucose infusion, 6.21 per cent for fructose infusion and 4.96 per cent for invert sugar infusion. It will be noted that the urinary sugar loss was greater for fructose infusion than for invert sugar infusion, although the highest total blood sugar levels occurred with the invert sugar infusions.

The mean urine volume for 5 hours (3 hours of infusion plus 2 postinfusion hours) was 1493 ml. for glucose infusion, 2290 ml. for fructose infusion, and 2475 ml. for invert sugar infusion, representing 99, 76, and 83 per cent, respectively, of the volumes infused.

The maximal urinary fructose concentrations were considerably higher than the maximal urinary glucose concentrations. A graph of the data revealed that the slope of the curve relating blood fructose level to urinary fructose output is steeper than the corresponding curve for glucose. Fructose appears in the urine at very low blood fructose levels, confirming the well-known fact that the ability of the renal tubules to reabsorb fructose is much less than for glucose.[5]

During the infusion of the various solutions symptoms occurred in some of the subjects. With the infusion of the fructose solutions, six subjects developed symptoms of severe epigastric and substernal pain, as well as cramping sensations in the abdomen that in several instances radiated through to the back. These symptoms were so severe in one subject that on two occasions the infusion had to be discontinued and the results on this subject, therefore, are not included in the mean values. Milder symptoms of a similar character were seen in four subjects during the infusion of invert sugar. Only one subject noticed any symptoms during the infusion of glucose.

Discussion

These studies were not designed to compare tolerance for glucose with that for fructose and invert sugar, because glucose was given at a lower rate than the other two sugars. The previous studies[7–15] in which this direct comparison was made by the intravenous administration of glucose, fructose, and invert sugar at the same rates have, with one exception,[19] established that invert sugar and fructose produce lower total blood sugar levels and less urinary sugar loss than does glucose.

In the present study glucose was administered at a rate one-half as great as that used for fructose and invert sugar. This was done so that the rate of administration of glucose would be the same in the invert sugar infusion as in the glucose infusion. In the invert sugar infusion fructose was being given at the same rate as glucose. Thus a comparison could be made of the rate of utilization of glucose with and without simultaneous administration of an equal amount of fructose. This comparison revealed that the simultaneous administration of fructose with glucose resulted in higher blood and urinary glucose levels than with infusion alone. This is in contrast to animal studies in which fructose had been shown to improve glucose utilization.[16–18] However, the design of the animal experiments was quite different from the one we have used, and it is possible that under comparable conditions a similar effect might be demonstrated in human subjects.

In the present study larger total quantities of sugar were infused than in previous studies.

Two considerations directed this choice: (a) we wished to make the comparisons under conditions more comparable to the clinical situation in which infusions of large caloric equivalents are desired, and (b) since glucose shows a change in "tolerance" as the infusion is continued,[6] it was considered desirable to determine what influence this delayed effect would have on the comparative tolerance for fructose and invert sugar. Our results, as well as those of previous workers,[6] show that during a continuous infusion of glucose at a constant rate the blood glucose concentration reaches a peak and then progressively declines. This is attributed to the calling into play of mechanisms which increase the rate of removal of glucose from the blood and decrease hepatic discharge of glucose.[6] In contrast, the results of the present study show that the blood level of fructose reaches a maximum and then remains at a plateau level as long as the infusion is continued, indicating that no special mechanisms for fructose metabolism are mobilized as the result of fructose infusion.

The fact that the blood level of fructose remained relatively constant during the infusions of fructose and invert sugar indicates that once equilibrium had been established, the rate of removal of fructose from the blood stream was equal to the rate of infusion. Furthermore, since this plateau level of fructose was approximately twice as high with the fructose infusion as with the invert sugar infusion, and since the rate of fructose infusion was twice as fast in the former, it may be concluded that, within the range studied here, the rate of removal of fructose from the blood stream is proportional to the blood level, which in turn is proportional to the rate of infusion of fructose.

Weinstein[7] found that invert sugar given at a rate of 1.5 Gm. per Kg. per hour produced no more urinary sugar loss than glucose given at a rate of 0.75 Gm. per Kg. per hour. Our rates of administration of these sugars were similar to those of Weinstein, but we found that the mean urinary loss with invert sugar (5.0 per cent of infused sugar) was distinctly greater than with glucose (2.1 per cent of infused sugar). The total quantities of sugar infused were 3 times as great in our studies as in Weinstein's. Also, we used normal subjects, whereas those in Weinstein's series were patients with chronic illnesses. The work of Lawton *et al.*[12] suggests that in debilitated patients the tolerance for glucose is depressed more than that for invert sugar. Drucker *et al.*[20] have also found that in patients in the early postoperative state or ill with acute febrile diseases tolerance for glucose is impaired, whereas tolerance for fructose is not. This, together with the studies on fructose in diabetics,[21] suggests that under conditions in which glucose tolerance is impaired (e.g. "stress" and diabetes), tolerance for fructose may not be impaired.

Fructose infusions resulted in a distinctly lower elevation of total blood sugar than did invert sugar infusions, but the urinary sugar loss was slightly greater with the fructose infusion. The slightly higher urinary sugar loss of fructose as compared with invert sugar (3.8 Gm.), although statistically significant, is unimportant in terms of the additional caloric value of the sugar retained (14 calories).

Subjective symptoms such as were observed in some of our subjects during the infusions have been reported by only one other group of investigators.[13] The mechanism of production of these symptoms is not apparent.

More complete details of this study are presented in the laboratory report which has been published.[22]

Summary and Conclusions

Nine normal male subjects each received the following intravenous infusions lasting 3 hours each on 3 separate days: 141 Gm. of glucose, 291 Gm. of fructose, and 288 Gm. of invert sugar. The mean highest total blood sugar concentrations were 187 mg. per cent for the glucose infusion, 191 mg. per cent for the fructose infusion, and 242 mg. per cent for the invert sugar infusion. The urinary loss of total sugar (glucose plus fructose), expressed as per cent of sugar infused, was 2.1 per cent for glucose infusion, 6.2 per cent for fructose infusion, and 5.0 per cent for invert sugar infusion. Although under the conditions of this study it was found that in normal subjects the

percentage urinary loss is slightly greater for fructose infusions than for invert sugar infusions, there is a possibility that fructose might have specific advantages, other than providing calories, in certain clinical conditions because of its distinctive metabolic effects.

REFERENCES

1. Van Itallie, T. B.: Priorities in parenteral nutrition. *Nutrition Rev.* 9: 193, 1951.
2. Nelson, N.: A photometric adaptation of the Somogyi method for the determination of glucose. *J. Biol. Chem.* 153: 375, 1944.
3. Somogyi, M.: A new reagent for the determination of sugar. *J. Biol. Chem.* 160: 69, 1945.
4. Roe, J. H.: A colorimetric method for the determination of fructose in blood and urine. *J. Biol. Chem.* 107: 15, 1934.
5. Hansen, P. G., Jacobson, E. A., and Peterson, M. F.: Renal excretion of fructose. *Acta physiol. Scandinav.* 6: 195, 1943.
6. Soskin, S., and Levine, R.: *Carbohydrate Metabolism.* University of Chicago Press, Chicago, 1946.
7. Weinstein, J. J.: Intravenous infusions of invert sugar, a preliminary report. *M. Ann. District of Columbia* 19: 179, 1950.
8. Weinstein, J. J.: Parenteral therapy with invert sugar. *Ann. West. Med. & Surg.* 4: 373, 1950b.
9. Weinstein, J. J.: Tolerance of human beings to intravenous infusion of fifteen per cent invert sugar. *J. Lab. & Clin. Med.* 38: 70, 1951.
10. Weinstein, J. J.: Comparative utilization of invert sugar and dextrose in non-diabetic human beings. *M. Ann. District of Columbia* 20: 355, 1951.
11. Weinstein, J. J., and Lane, G. F.: Rapid infusion of invert sugar. *M. Ann. District of Columbia* 20: 186, 1951.
12. Lawton, B. R., Curreri, A. A., and Gale, J. W.: Use of invert sugar solutions for parenteral feeding of surgical patients. *Arch. Surg.* 63: 561, 1951.
13. Frost, D. V., Miller, J. P., and Richards, R. K.: Some considerations regarding invert sugar and dextrose. *J. Applied Physiol.* 4: 793, 1952.
14. Weichselbaum, T. E., Elman, R., and Lund, R. H.: Comparative utilization of fructose and glucose given intravenously. *Proc. Soc. Exper. Biol. & Med.* 75: 816, 1950.
15. Weinstein, J. J., and Roe, J. H.: The utilization of fructose by human subjects and animals. *J. Lab. & Clin. Med.* 40: 39, 1952.
16. Fletcher, J. P., and Waters, E. T.: Effect of fructose on glucose tolerance curve. *Biochem. J.* 32: 212, 1938.
17. Corkill, A. B., and Nelson, J.: Influence of fructose upon peripheral utilization of glucose. *Australian J. Exper. Biol. & M. Sc.* 18: 171, 1940.
18. Corkill, A. B., and Nelson, J.: The influence of fructose on the utilization of glucose by isolated muscle. *Australian J. Exper. Biol. & M. Sc.* 25: 347, 1947.
19. Smith, J. L., Beal, J. M., and Frost, P.: Comparative utilization of intravenous invert sugar and glucose. *Surgery* 31: 720, 1952.
20. Drucker, W. R., Miller, M., Abbott, W. E., Craig, J. W., Jefferies, W. M., Levey, S., and Woodward, H.: The effects of stress on glucose and fructose metabolism. *J. Lab. & Clin. Med.* 40: 794, 1952.
21. Miller, M., Drucker, W. R., Owens, J. E., Craig, J. W., and Woodward, H.: Metabolism of intravenous fructose and glucose in normal and diabetic subjects. *J. Clin. Investigation* 31: 115, 1952.
22. Strub, I. H., Best, W. R., Consolazio, C. F., and Grossman, M. I.: Utilization of intravenously injected fructose and invert sugar in normal human subjects. *Medical Nutrition Laboratory Report* No. 106, 20 Feb. 1953.

Resumen

Utilización de la fructuosa y del azúcar invertido administrado por vía endovenosa en individuos normales

Cada uno de nueve hombres normales recibieron las siguientes infusiones intravenosas de tres horas de duración cada una en tres diferentes días: 141 gm. de glucosa, 291 gm. de fructuosa, y 288 gm. de azúcar invertido. Los niveles máximos de azúcar en la sangre fueron 187 mg. por ciento con la infusión de glucosa, 191 mg. con la de fructuosa, y 242 con la de azúcar invertido. La pérdida urinaria de azúcar total (glucosa + fructuosa) expresada como un porcentaje del azúcar inyectado fué 2,1 por ciento con la infusión de glucosa, 6,2 por ciento con la de fructuosa, y 5,0 por ciento para la de azúcar invertido. Aunque bajo las condiciones de este estudio se encontró que en sujetos normales el porcentaje de pérdida urinaria es ligeramente mayor con las infusiones de fructuosa que con las de azúcar invertido, existe la posibilidad de que la fructuosa tenga ventajas específicas en ciertas condiciones clínicas debido a sus característicos efectos metabólicos.