A Comparison of the Effects of Tolbutamide and Insulin on Infused Pentoses

A Study in Man

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Insulin has been shown to facilitate the transport of sugars into muscle under a variety of experimental conditions. Since the original observation of Goldstein and collaborators[1] that insulin increased the volume of distribution of D-xylose and L-arabinose in the eviscerate nephrectomized dog, several investigators have demonstrated that insulin increases intracellular pentose levels in the eviscerate rat, [2, 3] intact cat,[4] perfused rat heart[5] and isolated rat diaphragm.[6] Such observations have resulted in the concept that the peripheral action of insulin, facilitating the transport of certain pentoses into muscle cells, reflects a similar peripheral action of insulin on glucose.

The precise mode of action of the sulfonylurea compounds is not known. It has been suggested that they produce hypoglycemia by causing insulin release from the pancreas[7] or inhibiting insulin degradation,[8] thus increasing circulating insulin and enhancing peripheral utilization of glucose, or by altering hepatic glucose metabolism.[9, 10, 11] Recently, it has been shown that the increase in peripheral utilization of glucose caused by exogenous insulin in man is paralleled by the increased disappearance from blood of the infused pentoses D-xylose and L-arabinose.[12] Therefore, experiments were undertaken to study the effects of tolbutamide on these insulin responsive pentoses to ascertain the existence of any dissimilarities between the effect of insulin and tolbutamide which would more clearly define the mode of action of the sulfonylureas.

METHODS

All studies were performed in normal subjects ranging in age from eighteen to twenty-one years. Each individual was maintained on a high carbohydrate diet. Prior to each study the subjects were fasted for fourteen to eighteen hours. An in-dwelling plastic needle was employed in one arm as a means of providing frequent and reliable blood samples. The opposite arm was used to administer all other materials required in a particular test. Twenty-gram quantities of pentose, as a 10 per cent solution, were infused intravenously. A blood sample was drawn at the end of the infusion and a period of twenty-five to thirty minutes was permitted to elapse, in order to insure adequate mixing of the sugar in the body fluids. At the end of this period blood samples were drawn at five- or ten-minute intervals for twenty-five to thirty minutes. At this time (fifty to sixty minutes after the end of the pentose infusion), when enough blood values had been obtained to establish a curve of the falling blood levels, 0.1 unit of crystalline insulin per kg. of body weight or sodium tolbutamide (25 to 40 mg. per kg. body weight) was injected intravenously. Blood specimens were drawn at five- to fifteen-minute intervals for another 90 to 110 minutes.

D-xylose and L-arabinose were obtained from Pfanstiehl Laboratories, Inc., Waukegan, Illinois. The sugars were prepared for intravenous use by autoclaving as a 10 per cent solution, and were found to be sterile and pyrogen-free prior to use. Sodium tolbutamide (Orinase, sodium) was supplied as a sterile powder by the Upjohn Company. The material was put in solution with isotonic sodium chloride such that the final concentration was 10 per cent. The material was injected intravenously over a two- to three-minute interval.

Blood glucose was measured with glucose oxidase according to the method of Wyngaarden, Segal and Foley;[13] blood pyruvate by the Friedemann-Haugen method.[14] Plasma phosphate was determined by the Fiske and Subba Row method.[15] Plasma levels of sodium tolbutamide were measured, using the method of Miller and co-workers.[16] Blood pentose values were determined by the orcinol technic, using blood filtrates in which glucose had been destroyed by treatment with glucose oxidase.[13]

RESULTS

The rapid, single administration of sodium tolbutamide (20 to 40 mg. per kg. body weight) intravenously in

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normal subjects produced a reduction in blood glucose which appeared promptly and which was maximal in thirty to forty minutes. The degree of hypoglycemia ranged from 40 to 60 per cent and corresponds to the hypoglycemia produced by 0.1 unit per kg. body weight of intravenous insulin. Once the intravenous dosage of sodium tolbutamide was determined which produced a 40 per cent or greater lowering of the blood glucose in thirty minutes, this amount was used in all subsequent studies in the particular individual concerned. The proper dosage must be determined individually.

Figure 1 demonstrates the effect of sodium tolbutamide and insulin on the disappearance of 20 gm. of infused D-xylose from the blood of a normal subject. As has been described,[12] when 0.1 U/kg. insulin is given intravenously, there is a phase of enhanced disappearance which appears promptly and lasts about thirty minutes. At that time the disappearance slows, and a curve with a rate constant similar to the one in the initial phase is established. In the post-insulin phase the disappearance is enhanced three times and the xylose level thirty minutes after insulin is 40 per cent lower than that expected from the original phase of disappearance. In contrast to this effect is that observed with 2.0 gm. of intravenous sodium tolbutamide. After administration of the latter only the slightest suggestion of an effect on pentose disappearance is observed.

Figure 2 shows the effects of insulin on L-arabinose disappearance in another normal subject. As with D-xylose the disappearance is increased three-fold. This was compared with the effect of tolbutamide on L-arabinose and D-xylose in the same subject. Tolbutamide is seen to increase L-arabinose disappearance not at all. The D-xylose curve is similarly essentially unaffected.

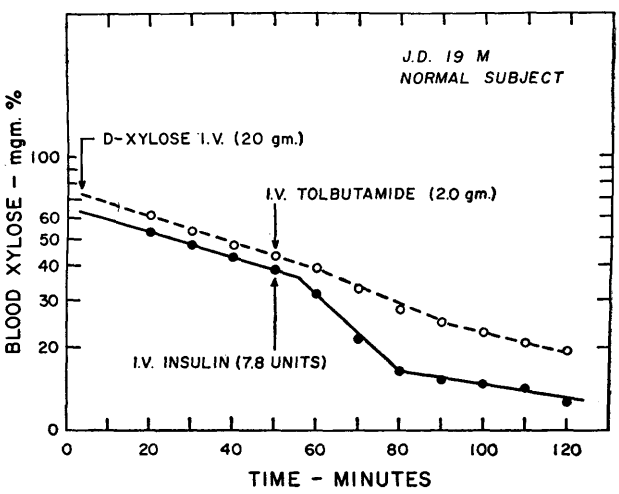

FIGURE 1

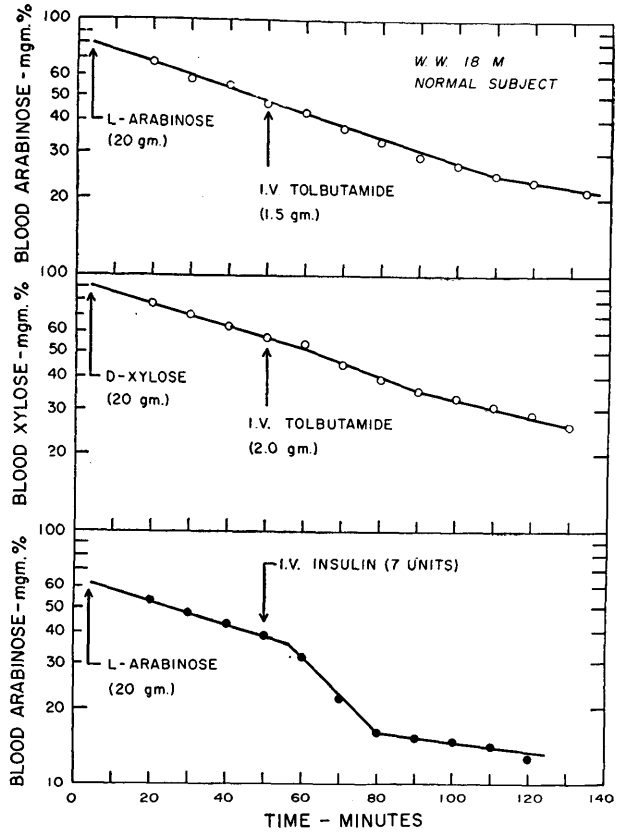

FIGURE 2

Figure 3 indicates that, although D-xylose responds to tolbutamide minimally, there was a definite fall in blood sugar of 45 per cent and a fall of phosphorus of 32 per cent, both of which indicate that the tolbutamide was producing its characteristic hypoglycemic and hypophosphatemic effects. In addition a rise in blood pyruvic acid occurred following the period of hypoglycemia. Thus the marked metabolic effects of tolbutamide are not paralleled by the effect on the xylose disappearance curve.

In order to determine whether a dose of insulin lower than 0.1 U/kg. affects xylose blood levels the study shown in figure 4 was performed. In this study 0.05 U/kg. was given intravenously, after the xylose disappearance curve had been established. Even with this small insulin dose the disappearance was enhanced three times but the degree of lowering of the blood level is only 26 per cent as compared to 40 per cent obtained in figure 1.

DISCUSSION

The studies with infused pentoses point to a major difference between the mode of action of insulin and

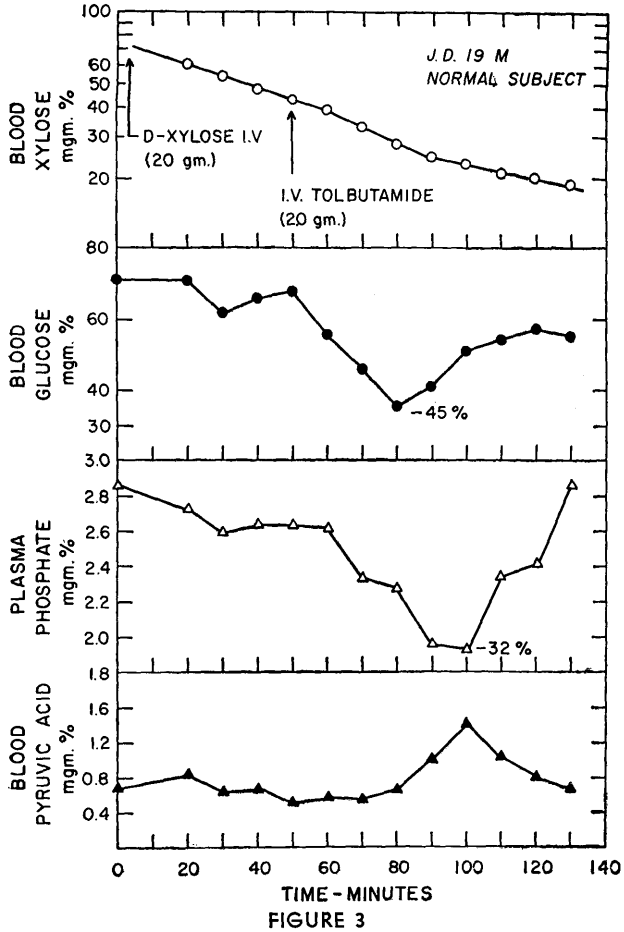

FIGURE 3

tolbutamide. Although both insulin and tolbutamide in the doses used cause comparable decreases in blood glucose within the same period of time after administration, only insulin causes appreciable changes in the rates of disappearance of the pentoses D-xylose and L-arabinose from blood. Should the effects of tolbutamide on blood glucose be associated with an increase in peripheral utilization of glucose resulting from an increase in circulating insulin or an enhanced activity of normally circulating amounts, one would expect to find an appreciable effect of tolbutamide on pentose disappearance. This is not the case. The results here suggest that tolbutamide does not cause hypoglycemia primarily by enhancing the peripheral utilization of glucose due to hyperinsulinism.

Other differences between tolbutamide and insulin effects have been observed. Tolbutamide causes a delay in return of blood glucose to control levels[11] and a fall in blood pyruvic acid.[17, 18] In reported studies of the effect of tolbutamide on glucose A-V differences there was no increase in the A-V difference which is known to follow insulin administration.[19]

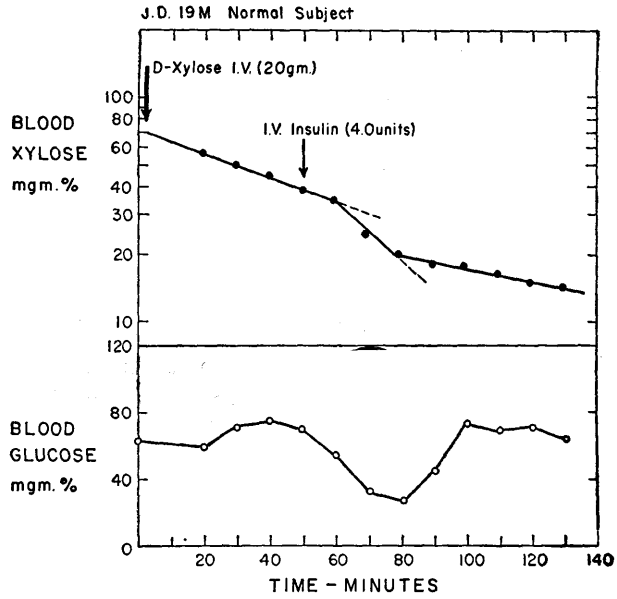

FIGURE 4

Effects of sulfonylureas on hepatic glucose metabolism have been noted.[10,20] These compounds have been shown to increase hepatic glycogen,[21] inhibit hepatic glycogenolysis[11, 20] and to impair the conversion of fructose and galactose to glucose.[9] The lack of enhanced peripheral insulin activity due to tolbutamide, as demonstrated by the pentose studies in man, as well as the effects on hepatic glucose metabolism have prompted us to propose that the hypoglycemic action of tolbutamide may be attributed to a marked enhancement of endogenous insulin action on the liver without a similar degree of effect on peripheral insulin activity.

SUMMARY

A comparison has been made of the effects of insulin and tolbutamide on the disappearance from blood of infused pentoses D-xylose and L-arabinose in man. In contrast to the enhanced disappearance due to insulin, little or no response was observed after tolbutamide. These results suggest that tolbutamide action is not associated primarily with an enhanced peripheral activity of insulin.

SUMMARIO IN INTERLINGUA

Comparation del Effectos de Tolbutamido e de Insulina Super Pentosas Infundite in Humanos

Esseva studiate comparativemente le effectos de insulina e tolbutamido super le disparition ex le sanguine human de infusiones del pentosas D-xylosa e L-arabinosa. Per contrasto con le acceleration de lor disparition causate per insulina, pauc o nulle responsa esseva observate

post administrationes de tolbutamido. Iste resultatos suggere que le action de tolbutamido non se associa primarimente con un promotion del activitate peripheric de insulina.

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Carbohydrate and the Heart

The previous discussion of carbohydrate as the most efficient fuel for muscular exercise and of the muscle glycogen as an important emergency source of contractile energy applies in even greater measure to cardiac muscle than it does to skeletal muscle. The latter can in some measure accommodate itself to a decreased supply of carbohydrate by decreasing its work. The heart cannot stop to rest. A temporary reduction in the supply of sugar to the normal heart (as in induced attacks of hypoglycemia) has little apparent effect on the organ, although a definite change in the electrocardiogram may be noted.[1] The apparent lack of influence of hypoglycemia on the heart may be due to the normally good glycogen stores to be found there. But in the heart which has been damaged by disease and in which the initial glycogen stores are poor, hypoglycemia may precipitate stenocardial symptoms with angina and even result in death. This has been noted in diabetic[2] as well as in nondiabetic cardiac patients; both, it has also been observed, are likely to do better when the blood sugar is somewhat elevated, even above the normal range. High-carbohydrate therapy has been successfully used on this basis.[3]

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