The Potential Use of Xylitol in Glucose-6-Phosphate Dehydrogenase Deficiency Anemia

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ABSTRACT NADP-linked xylitol dehydrogenase has been found to be present in human red blood cells. This enzyme activity is normal in most glucose-6-phosphate dehydrogenase (G6PD)-deficient red cells. Xylitol was explored as a potential agent for treatment of hemolysis in patients with G6PD-deficiency. Intracellular GSH (glutathione, reduced) was first converted to its oxidized form by incubation of the erythrocytes with acetylphenylhydrazine or by pretreatment with methyl phenyldiazene-carboxylate. The addition of 0.15 M xylitol was shown to be more effective than 0.15 M glucose in maintaining the levels of GSH in G6PD-deficient red cells during such oxidative challenge. Rabbit erythrocytes contain less activity of G6PD and glutathione reductase compared with the normal human adult values, but have an active xylitol dehydrogenase. The rabbit erythrocyte is sensitive to acetylphenylhydrazine and primaquine phosphate. In both *in vivo* and *in vitro* experiments, xylitol was found to partially prevent acetylphenylhydrazine induced acute hemolysis of the rabbit red cell and GSH content was found to be preserved. The intravenous injection of xylitol (0.5 g/kg body weight per 6 hr) for 6 days, seemed to be nontoxic to the animal. The results suggest that xylitol should be further investigated as an agent for the treatment of G6PD-deficient patients during acute hemolytic episodes.

INTRODUCTION

Red blood cell glucose-6-phosphate dehydrogenase (G6PD)¹ deficiency is a widespread genetic disorder. About 3% of the world population is estimated to be affected. 10% of American Negroes have been found to carry such genetic defect. Hemolysis, resulting

from G6PD-deficiency can be expressed in five ways depending on the clinical setting; (a) drug induced hemolytic anemia; (b) hemolytic anemia in infectious and other febrile illness; (c) chronic nonspherocytic hemolytic anemia; (d) favism; and (e) neonatal jaundice. Drug induced hemolysis is usually a self-limited disease, but among enzyme-deficient patients, 2% have a chronic hemolytic anemia in the absence of drug challenge (1). The disease is characterized biochemically by a low or almost absent G6PD-activity. Secondly, the GSH is unstable on *in vitro* incubation of such red cells in the presence of oxidizing agents. There are many enzyme variants, and clinical expression correlates both with enzyme activity, and, directly or indirectly, with the type of enzyme. The mechanism of hemolysis is still far from clear. It has been presumed that a normal GSH concentration plays an important role in the maintenance of the integrity of the red cell. Treatment with either ACTH (adrenocorticotropin) (2) or cortisone (3, 4), appears to be of no value for the congenital nonspherocytic hemolytic anemia secondary to G6PD-deficiency. Splenectomy is much less effective than in hereditary spherocytosis. In fact, no adequate treatment of such disease has thus far been developed. Transfusion is the only method known to maintain the patient during acute hemolytic crises.

Recently, we were able to demonstrate the presence of a triphosphopyridine nucleotide (NADP)-linked xylitol dehydrogenase (XDH) in the human red blood cell. The red cell hemolysate can utilize xylitol and produce L-xylulose and NADPH (reduced form of triphosphopyridine nucleotide) (5). It thus seems possible that xylitol might be able to replace glucose-6-phosphate for the maintenance of NADPH in the G6PD-deficient state. In such a way, the intracellular GSH concentration could be restored in the deficient cells, thereby protecting red cells from oxidative injury as shown in the Scheme 1. The purpose of this report is to present evidence from both *in vitro* and animal experiments which

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¹Abbreviations used in this paper: APH, acetylphenylhydrazine; G6PD, glucose-6-phosphate dehydrogenase; GSSG-R, glutathione reductase; PVC, packed cell volume; XDH, xylitol dehydrogenase.

Maintenance and restoration of intracellular GSH by xylitol. Xylitol is actively metabolized by red cells and has been shown to stimulate lactate formation (19) and methemoglobin reduction (20, 21). Xylitol can restore GSH in sodium nitrite-treated normal erythrocytes (22). The permeability of xylitol to the red cell was evaluated by Asakura et al. (22), and a simple diffusion mechanism has been suggested. Xylitol passes through the red cell membrane easily and equilibrates in less than 1 min. Long-term storage with xylitol as an additive to red cells has been shown in our laboratory to help the maintenance of the 2, 3 DPG-level.² A direct demonstration of the effectiveness of xylitol in restoring GSH in both normal and G6PD-deficient cells has been made by using APH and methyl phenyldiazene-carboxylate.

Fig. 1 gives the results of a representative experiment with APH. Fig. 1A shows that glucose could maintain the GSH level better than xylitol in normal red cells. However, Figure 1B demonstrates that xylitol preserved more intracellular GSH in the G6PD-deficient cells. In the normal cells, glucose maintains 90% GSH and xylitol 55% after 4 hr incubation. In the deficient cell, glucose preserved only 26% and xylitol 35%. This result was reproducible on multiple experiments and the difference is significant ($P < 0.05$). Fig. 2 shows similar results of a representative experiment using the azoester. Fig. 2A illustrates that glucose is far better than xylitol in GSH-recovery in the normal blood cells, in which, glucose restores 85% GSH and xylitol 56%. In the G6PD-deficient cell xylitol shows better ability to regenerate GSH as shown in Fig. 2B. Xylitol restores 65% of GSH and glucose only 48%. The difference is reproducible on multiple trials and is significant ($P < 0.05$). A 100% recovery is not likely to be reached, since the GSSG has been reported to leak out of the red cells (23). Even without an oxidant challenge, xylitol maintained GSH better than glucose in the G6PD-deficient cells. This is shown in the top curve of Figs. 1B and 2B. In red cells from persons heterozygous for G6PD-deficiency (around 55 IU per 100 ml RBC) the benefit of xylitol was much less marked.

Glucose and xylitol at final concentrations of 0.015 M, which is 10 times lower than that used in the experiments described, gave similar results to glucose and xylitol at 0.15 M.

The effect of xylitol on rabbit erythrocytes in vitro. There is no suitable animal model for G6PD-deficient studies. The rabbit was chosen because it is known to be drug sensitive. In a preliminary experiment the levels of the pertinent enzymes were measured. Table II gives the G6PD, GSSG-R, and XDH activities in the rabbit red cell hemolysates. With the average of 4.3%

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FIGURE 1 The maintenance of intracellular GSH in human erythrocytes during APH stress. Fig. (A) refers to normal cells and (B) to G6PD-deficient cells. The following symbols are used: solid lines indicate control, i.e. without APH, and dotted lines represent experimental samples to which APH is added; (O) control, i.e. no xylitol or glucose added; (□) 0.15 M xylitol, and (Δ) 0.15 M glucose.

reticulocytes, GSSG-R activity was found to be half that of the normal human level; G6PD was also lower when considered relative to the per cent reticulocytes. Rabbit XDH-activity has been found the same as human values. The average activity in five samples was around 8.6 ± 1.3 nM NADPH/min per g Hb. compared to 7.0 ± 0.8 nM/min per g Hb. in humans. The Michaelis-Menten constant of xylitol for the rabbit XDH is estimated to be 5.4×10^{-3} M. In the GSH instability test, rabbit red cells were more drug sensitive than normal human red cells under the same experimental conditions. Xylitol helped in maintenance of intracellular GSH, though glucose was shown to be better. In experiments in which primaquine phosphate was

FIGURE 2 The regeneration of intracellular GSH in human erythrocytes after azoester stress. (A) Normal cells, (B) G6PD-deficient cells. The same symbols are used as described in Fig. 1 except that azoester instead of APH was used as described in the text.

TABLE II
Comparison of G6PD-, Glutathione Reductase (GSSG-R)-, and XDH-Activities and Reticulocyte Percentage in Human and Rabbit Erythrocytes

	Human	Rabbit
G6PD IU/100 ml RBC	153.5 $\pm$ 15.3 (8)*†	166.0 $\pm$ 15.2 (5)
GSSG-R IU/100 ml RBC	95.8 $\pm$ 15.4 (5)	54.9 $\pm$ 9.1 (5)
XDH nM NADPH/min per Hb	7.0 $\pm$ 0.8 (8)	8.6 $\pm$ 1.3 (5)
Average reticulocytes, %	1	4.3

* Mean $\pm$ 1 SD.

† Figure in parenthesis indicates the number of subjects.

added, the same results were obtained. Fig. 3 shows a representative experiment.

Optimal dose of APH-induction of *in vivo* hemolysis. Fig. 4 shows the percentage hemolysis after different doses of APH were injected intraperitoneally. 40% hemolysis was observed consistently after 72 hr when more than 20 mg APH per kg body weight was injected into rabbits. Some animals died with a dosage exceeding 25 mg APH per kg body weight. There was a drastic decrease of the GSH content along with a severe drop of PCV and hemoglobin concentration. The reticulocyte count rose proportionately. A 70% reticulocyte count was observed in one rabbit before death. Serum hemoglobin was found increased occasionally. 10 mg APH per kg body weight was chosen to be a reasonable dose and is therefore, the one used in the following long-term animal experiments.

FIGURE 3 The maintenance and regeneration of intracellular GSH in rabbit erythrocytes. A) During APH-stress, B) After azoester challenge, C) During primaquine phosphate treatment. The same symbols are used as shown in Fig. 1.

Administration of xylitol to rabbits with APH-induced hemolysis. Fig. 5 gives the result in a long-term xylitol treatment of animals anemic from an APH-injection. PCV, hemoglobin concentration, reticulocyte counts, and GSH content of single animals are shown. Rabbits in each group followed a similar pattern in their hematological values. While there are no observable changes in control animals, animals to which only xylitol was given intracellular GSH content increased slightly. The value returned to normal at the end of experimental period. In animals to which only APH was administered, the PCV dropped from 36 to 24%, the hemoglobin concentration fell from 12.8 to 8.6 g per 100 ml in 120 hr. GSH content showed an 18% decrease. With the injection of xylitol and the administration of APH, the animal showed only an absolute drop in PCV of 6%, while hemoglobin fell only from 12.2 to 10.3 g per 100 ml blood. GSH measured within normal range. An increase of reticulocyte count was seen after the 5th day. In the animals of the control and xylitol treated group, the reticulocyte counts increase slightly, which is likely due to the continued withdrawal of 2-3 ml blood from the animals daily.

Fig. 6 summarizes the average differences of PCV- and GSH-content in per cent of initial value among the four groups. The baseline value is set at 100%. Fig. 6A indicates the differences in PCV among groups. Fig. 6B demonstrates that GSH has been conserved by the treatment of xylitol in the APH-treated animals. It seems clear that the production of NADPH by xylitol maintained the intracellular GSH content.

Toxicity of xylitol to the rabbit. Xylitol and glucose levels in three animals after a single xylitol intravenous injection (0.5 g xylitol per kg body weight in a 20% solution) are shown in Fig. 7. The values are expressed in mg per 100 ml. The plasma xylitol declines rapidly five min after intravenous infusion. The mean half disap-

FIGURE 4 APH-dose response in rabbit. The oxidant was given intraperitoneally. The percentage hemolysis was then measured at 72 hr by the decrease of packed cell volume from the baseline.

pearance rate, $t_{1/2}$ of xylitol is estimated to be about 20 min. The decay constant of xylitol in plasma is computed to be 3.3% per min. The results are in agreement with the results of the elimination study in human blood (24).

The xylitol content in the red cell has been found elevated after xylitol injection. Fig. 7A points out that xylitol is higher in whole blood than plasma after 6 hr. Red cell xylitol reached about 13 mg per 100 ml. The glucose concentration in both whole blood or plasma was not significantly altered by the injection of xylitol. The parallel curve between plasma and whole blood glucose indicates that red cell glucose was maintained unchanged. The fall of glucose at 60 min might be caused by an

FIGURE 5 The hematological alterations in representative animals during a long-term animal experiment. The following symbols are used: (●) control group, (○) xylitol group, (▲) APH-group, (△) experimental group to which both APH and xylitol were given. APH at dose of 10 mg per kg body weight was injected intraperitoneally at zero time. Xylitol, in a 20% solution, was injected four times a day for 6 days. 0.5 g xylitol per kg body weight was injected over 4 min each time through an ear vein.

FIGURE 6 Hematological changes in rabbits expressed as per cent of initial values. The same symbols are used as described in Fig. 5. Baseline values were used as 100%. Each point represents an average of three animals ± 1 sd.

increase of insulin in the plasma (25). Fig. 8 shows the time course of the plasma xylulose after an intravenous xylitol injection. The ketopentose formation reached a peak around 5 min after the injection. The total conversion to xylulose was estimated to be only 4% of the xylitol injected. It is likely that the ketopentose is L-xylulose. However, the plasma ketopentose was not characterized.

Serum bilirubin has been determined in two animals who received xylitol only. There was no elevation of serum bilirubin in 24 or 48 hr during chronic xylitol administration.

No deterioration has been observed in the group which received only xylitol and all animals survived throughout the study.

FIGURE 7 A) Xylitol; B) glucose concentration in whole blood and plasma after a single xylitol injection (a 20% solution at 0.5 g xylitol per kg body wt). (○) refers to whole blood; and (△) to plasma. Each point indicates an average of three animals ± 1 sd.

FIGURE 8 Time course of xylitol disappearance and ketopentose formation in whole blood after a single xylitol injection. (○) refers to xylitol concentration and (△) to ketopentose concentration. Each point indicates an average value of three animals.

DISCUSSION

The results show that xylitol might be useful to patients with severe hemolytic episode. The *in vitro* data obtained on human red cells indicate the usefulness of xylitol to restore or maintain the GSH-content in the G6PD-deficient state either when challenged or in chronic nonspherocytic hemolytic anemia. The long-term animal experiments prove that xylitol infusion could protect rabbits from acute hemolysis induced by acetylphenylhydrazine. The GSH is also conserved by continuing treatment with xylitol. It is, of course, possible that the comparatively small drop of GSH-concentration in APH-treated animals might not be the major cause for the acute hemolysis. In addition to being the intermediate in maintenance of a normal level of GSH, NADPH may be directly involved in the maintenance of hemoglobin and other functional or structural proteins in a reduced active form after oxidative injury. However, the state of hemoglobin as well as the total sulfhydryl concentration was not measured. Methemoglobin reductase has been shown to use both NADH and NADPH. Xylitol is uniquely suited to maintain ferrous hemoglobin because it can generate both reduced coenzymes readily (5). Since APH may not be solely an oxidative challenge to the red cell (26), the action

of xylitol may be a general one in other cells besides the erythrocyte. In patients with G6PD-deficiency this enzyme may also be decreased in liver (27), platelets (28), leucocytes (29), skin (30), and in lens tissue (31, 32). The NADP-linked xylitol dehydrogenase has been found in almost all the organs of mammals (33). Therefore, the potential usefulness of xylitol may not be limited to the erythrocyte.

Xylitol has been introduced for clinical application 10 yr ago as an adjuvant in parenteral alimentation. It has been reported that xylitol is independent of insulin for transport (34). It is also an adequate calorie source (35). Xylitol has been used in the human in Germany (36), Japan (37), Russia (38, 39), Italy (40), and South Africa (25). Besides normal subjects, it has been used to treat patients with diabetes (41), bile duct and liver disease (38), renal disease (25), ketonemia (42), pulmonary tuberculosis (43), and for parenteral nutrition during and after surgery (36). No harmful effect has been observed in these published series. Recently, however, Donahoe and Powers (44) reported that the hyperuricemia, hyperuricosuria and hyperbilirubinemia have occasionally been observed in normal subject with xylitol doses of 1.22–3.13 g per kg body weight. The infusion time was not indicated in this note. Similar adverse effects were also reported by an Australian group (45). Once again, the xylitol dose and the infusion time were not mentioned. At a lower dose, 1.5 g xylitol per kg body weight Forster, Meyer, Ziege (46) reported transient rise in serum uric acid and serum bilirubin though remaining within the normal range, in normal subjects after rapid xylitol infusion. SGOT- and SGPT-levels were not influenced by the xylitol administration. Our experience with xylitol in rabbits showed no clinical toxicity, and no serum bilirubin elevation, though the literature did mention xylitol toxicity in rabbits (47).

The plasma and whole blood glucose was found unchanged for 6 hr after a single xylitol injection. Similar results were found in dogs (48), rabbits (49), and humans (50) with different xylitol dosage. Therefore, the maintenance of the hematocrit was not due to increased serum glucose, but likely from the effect of xylitol *per se*. The xylitol concentration was estimated to be 13 mg per 100 ml red blood cell after a single injection of xylitol. The NADP-linked xylitol dehydrogenase has a low K_m for xylitol (5). Although the xylitol content of the red cell increased after repeated injection, it is unlikely that the intracellular xylitol concentration reached saturating levels for the enzyme. Even so, saturation is not necessary if the NADPH formed is rapidly utilized to reduce GSSG.

The liver is the major organ which metabolizes xylitol. The major products, except L-xylulose are similar

to that of glucose. The excess L-xylulose will be excreted through the urine, and is likewise a harmless substance, as shown by pentosurics who are asymptomatic in spite of the excretion of gram quantities of that sugar (51). A mild increase of lactate was reported (25, 42, 50) in the blood after intravenous xylitol administration. The serum concentration of xylulose was very low in our experiments.

For the time being human experiments are excluded. The Australian groups reported multiple cases of death from xylitol infusion although the presence of a contaminant in the xylitol solution was strongly suspected (52). Since these observations are at present not published but only informally reported, a decision must await more details.

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