Z. Ernährungswiss. **19**, 88–94 (1980)

ISSN 0044-264 X

Nutrition Institute, Moscow, USSR

Xylitol. Experimental and clinical investigations conducted in the USSR (Review)

M. F. Nesterin

(Received October 27, 1979)

Since 1960 in the USSR there have been performed various studies on general effects of xylitol, on its toxicity, its influence upon body functions in experimental animals. Furthermore there are extensive clinical observations in diabetes mellitus, disorders of the hepatobiliary system etc.

Toxicity

Toxicological tests on rats and dogs showed that in animals fed xylitol containing diets (3.7–5 g/kg of body weight) no signs of intoxication were observed. The general status and the behaviour of the animals was not changed compared to the control group. On intravenous injection of xylitol to dogs (1 g/kg of body weight) intoxication did not occur either (*Shillinger* and *Zaicev*, 1966, 13).

According to data obtained in xylitol administration by gastric tubing LD_{50} was 12.5 g/kg for mice; 17.3 g/kg for rats; 25 g/kg for rabbits. 90 days of xylitol administration ($^1/_{10}$ LD_{50}, i.c. 1.73 g/kg) reduced the working capacity of animals. Hexenal tests revealed shortened sleep. In reduced doses (0.5 g/kg) administered for 55 days the author recorded no changes in estrous cycle in females or spermatogenesis in males (14). In tests on mice rapid intravenous administration of 40% xylitol solution (5 sec) LD_{50} was 3.77 g/kg. Beginning with this dose clinical signs (slow respiration, convulsions) were manifested in animals. In slow xylitol administration (2 min) LD_{50} was 9.45 g/kg. Xylitol doses of 9 g/kg induced convulsions 20-40 min after the injection. High doses increased excitability to such stimuli as noise and light. Animals died in manifestations of tetanus in the first six hours after the injection. Intravenous injections of xylitol to rabbits and dogs in the dose of 1 g/kg produced no changes in function of cerebral cortex or arterial pressure (11).

Diabetes mellitus

Clinical studies on xylitol in diabetes mellitus have been conducted over a year in the Central Hospital, USSR Academy of Sciences. For a year 55 patients received a long-term xylitol treatment (15–20 g twice a day) in addition to a diabetic diet. No side-effects were observed, laxative effects were never recorded. To estimate xylitol effects, a series of loading tests

were performed. The maximum increase of blood glucose after xylitol loading (30 g) ranged from + 1 to 40%; it averaged to 17%. After glucose loading it ranged from 65 to 75%. In most patients glycemic curves 2.5 hrs after xylitol loading were lower than initial ones. Xylitol intake produced no effect upon glucosuria. In five cases of severe diabetes, disorders of carbohydrate metabolism disappeared and the patients felt better. It was especially reasonable to prescribe 50–60 g of xylitol to patients suffering from constipations. Xylitol diets were consumed well; pathological symptoms did not occur.

Good tolerance to xylitol was noted in the treatment of children who received 30-35 g for 4 weeks (7).

During a daily intake of 40 g xylitol for a month in diabetic patients fluctuations of blood sugar levels and glucosuria following glucose intake were not observed (30 g xylitol or 50 g glucose). As a result of a continuous intake of xylitol, a favourable course of the disease was observed with lowering of hyperglycemia together with diminution of insulin doses or cutting off taking hypoglycemizing preparations in a number of patients (13).

Coronary atherosclerosis

Xylitol effects upon some metabolic parameters correlated with coronary atherosclerosis were studied in two groups of patients. One group received an antiatherosclerosis diet with 70 g of sugar (40 patients), the other group received a diet with 60 g of xylitol instead of sugar (35 patients). The antisclerotic diet was low in cholesterol, animal fat and sodium chloride. After four weeks of dieting the general condition in both groups of patients improved significantly. The patients fed xylitol got abdominal distention, meteorism, diarrhea. Five or six days later, however, the patients got adapted to xylitol. After treatment the patients fed sugar diet had reduction of lipemia concerning all the lipid components except phospholipids. The contents of cholesterol, total lipids and β-lipoproteins increased with the patients of the xylitol group in comparison with the initial level. The patients suffering from vegetovascular dystonia with inclination for hypertension had a change for the worse in general condition after taking xylitol. According to the author a daily xylitol intake is contraindicated in atherosclerosis accompanied by hypertension and colitis (29).

Gastroenteric diseases

According to some experimental data, xylitol inhibits gastric secretion in dogs, induced by insulin injection (i.e. vagal secretion) (2). In connection with this, observations of duodenal ulcer patients with high level secretion were made. To 19 men in the age of 19–46 15 g of xylitol in solution was introduced by a stomach tube into the duodenum. Before and 2 hours after xylitol application, portions of gastric juice were aspirated. There was a significant reduction of the concentration of basic ingredients of the gastric juice and of their output per hour. No significant changes of gastric juice volume have been found yet. So the concentration of free hydrochloric acid lowered from 38 ± 3 to 20 ± 2 titrimetric units, the total acidity – from 50 ± 3 to 32 ± 2 meq/l, pepsinogen concentration from 30 ± 6 to 19 ±

3 mg/100 ml (4). Introduction of 15 g xylitol into the stomach by a stomach tube resulted in inhibition of gastric secretion stimulated by cabbage juice. At the same time the secretion of free hydrochloric acid was reduced (25 patients were investigated) (9).

The use of xylitol in diseases of the biliary system was studied at the Dnepropetrovsk Gastroenterological Institute, at the clinical hospital of the USSR Academy of Sciences, at the clinical of the Astrakhan Medical Institute, and at the clinical nutrition department of the Nutrition Institute of the USSR Academy of Medical Sciences. Xylitol influences the cholekinetic and choleretic functions of hepatobiliary system. As compared to $MgSO_4$ xylitol causes a more rapid secretion of B-bile and enhances the rate of choleresis (13).

Xylitol was used as a means, which favours the reflex contraction of the gallbladder during drainage and roentgenometric examination of the gallbladder. From 111 patients who received xylitol for diagnostic and therapeutical purposes, 103 reacted with a good contraction of the gallbladder together with secretion of a B-bile portion. In 8 patients the reflex was obtained neither with xylitol nor with $MgSO_4$ (8).

The action of xylitol as a cholekinetic means during roentgenologic examination was studied with 107 patients. The degree of the gallbladder contraction was estimated by comparison of its size with the primary roentgenograms. Analysis of the data reveals that xylitol causes intensive contraction of the gallbladder walls without side-effects. That are the advantages of xylitol as compared to other physiologic stimuli such as yolk of egg, sour cream (8).

Medical effects of 10 g doses of xylitol three times a day 30 minutes before a meal were investigated with 120 patients suffering from chronic combined diseases of the hepatobiliary system and the liver in the unsharp aggravation phase. The treatment of the patients was conducted alongside with the special dieting and lasted for 4 weeks. As a rule the patients easily endured xylitol treatment, and side-effects – such as meteorism and watery stools – occurred seldom. Most of the patients were women at the age of 40 to 60 suffering from gallbladder disease for over 5 years. As a result of the treatment, pain and the feeling of heaviness in the right hypochondrium vanished or considerably abated; dispepsia and painfulness during palpation vanished also. In most cases the liver function and gall drainage normalized (17).

According to the data obtained during the treatment of 63 patients with disease of the hepatobiliary system 20 g of xylitol introduced into the duodenum by a gastric tube enhanced the secretion of C-bile by 30%. At the same time the concentration of bile acids, phospholipids and bilirubin in bile increased by 22–130% (21).

Clinic studies of the Soviet xylitol preparation were conducted at a clinic in Sofia. The cholecystokinetic and choleretic effects of xylitol and $MgSO_4$ were investigated in 25 patients with diseases of the hepatobiliar system. The total quantity of C-bile portion after 20 g dose of xylitol and 33% solution of magnesium was equal; neither was there a difference in the contents of bilirubin in the C-portion. After examination of the B-portion a more pronounced cholecystokinetic effect was observed with xylitol. The volume of the B-portion after application of xylitol made up

153% compared to the effect of magnesium (6). Xylitol introduced 40–45 minutes after $MgSO_4$ causes a good cholagogic effect; this method is recommended for drainage of biliary system (3).

The influence of xylitol the exocrinous function of the liver was investigated in chronic experiments in dogs. 7 dogs had chronic fistulae of the biliary system. 3–4 weeks after the operation bile was obtained by means of a rubber tube introduced into the cystic duct. Bile was collected on an empty stomach for 6 hours and the initial level was determined. Then the effect of xylitol was studied, after application by mouth of doses of 0.3; 0.6; 1.5; 2.0 g/kg body weight. Xylitol caused an increase of bile during the first hours after doses of 0.3-1.5 g/kg body weight. The amount of bile as compared to the control experiments was 2–4 times higher. In a number of cases with increase of bile the concentration of cholic acid and total phosphorus was reduced. However, their total contents in bile obtained during 6 hours were higher.

Thus, xylitol has a real choleretic effect and besides of the increase of bile volume, it causes an increase of the concentrations of cholic acid, phospholipids and bilirubin during the first hours after taking a dose. According to the author, the experiments showed that 2 g xylitol per kilogram of body weight caused in a number of cases vomiting together with oppression of bile secretion (15). The choleretic effect of xylitol in chronic experiments on dogs appeared with 4 g dose per kilogram of body weight; in acute experiments with rats in doses of 2 and 4 g/kg of body weight (1).

One of the properties of xylitol is its laxative effect. It was found during duodenal drainage and during loading in order to study the influence on blood glucose levels (13, 8, 16, 17). There was a special prescription of xylitol in doses of 25–35 g, to the patients with gastritis or ulcer with stable constipation. After having taken xylitol for 30–50 days most of the patients had their stools normalized. Interruption of the treatment with xylitol caused resumption of constipation (13). According to some authors' observations, xylitol causes laxative effects mostly in those patients who had not taken any purgative remedies before. The best way of using xylitol as a purgative is the application of 30 g of xylitol on an empty stomach (18).

Experiments in some other diseases

At the Leningrad Institute of Hematology and Blood Transfusion there was obtained a xylitol-containing preparation – *gelaxil,* which comprises also NaCl and K, $NaHCO_3$ hydrolysate of gelatine.

The therapeutic effectiveness of "gelaxil" was studied in animals (19, 20). In one of the series of experiments with 7 dogs posttransfusion complication was caused by intravenous introduction of human blood in a dose of 20 ml/kg of body weight. Heterogeneous blood infusion in all animals was followed by developing of intoxication, azotemia, hemolysis, bilirubinemia, anuria. Gelaxil infusion was begun 30 minutes after developing of complication by introducing 0.5–1 g of xylitol per 1 kg of body weight. Gelaxil resulted in normalization of hemodynamics and respiration. Anuria changed into diuresis with hydruria (i.e. the urine had a low specific weight). Moreover it resulted in lowering the signs of intoxication and normalizing of liver and kidney functions. In the other

series gelaxil was used as a prophylactic preparation when rats were intoxicated with CCl_4. The experiments without gelaxil resulted in appearing of pro nounced focal necrosis of hepatic lobes and small drop fatty infiltration. After intravenous gelaxil introduction into rats, fatty infiltration reduced con siderably and focal necrosis was less pronounced.

Notable are experiments with gelaxil in hypoxic conditions. The survival time of animals placed into closed vessels was studied in mice. In the experimental group gelaxil was introduced intravenously into mice during 1–5 days before placing them in hypoxic conditions. The xylitol dose was 0.25–0.5 g/kg of body weight. In the control group 11% of the animals perished after 20 minutes of hypoxia, in the experimental group – 50%. After 30 minutes perished 70% of the control group, in the experimental group – 50%. Death of the total amount of animals occurred after 45 minutes in both groups. On the basis of these data the authors drew the conclusion that xylitol exerts a favourable influence on metabolic processes in the brain (19).

In experiments with rabbits the effects of glucose and xylitol on the course of experimental hepatitis caused by CCl_4 were compared. During 2 weeks the rabbits of a first group received xylitol in an amount of 0.5 g/kg of body weight, those of a second group received glucose, a third group served as the control. The levels of protein, sugar, bilirubin, potassium, sodium, calcium, alkaline phosphatase in blood were determined. A bromsulphalein test was made. Xylitol reduced the clinical picture of intoxication. Normalization of biochemical indices occurred faster, except for total protein and cholesterol. Bromsulphalein clearance after xylitol and glucose was 3.2 and 3.7%, in the control group 23.5%. Fatty infiltration of liver tissue decreased (10).

Less pronounced fatty infiltration under the influence of xylitol was noted also in experiments on growing rats that received a choline deficient diet. Rats weighing 50–60 g received a diet consisting of casein, washed with boiling alcohol, meal without bran, lard, saccharose, saline solution and vitamins without choline. In one of the groups saccharose was replaced by xylitol (20%). 15 days later the rats were killed and the histologic structure of liver and kidney was examined. The cytoplasm of hepatocytes of the control group was filled with large droplets of neutral fat. The structure of the lobules was changed. The nuclei contained large nucleoli rich with RNA. Micronecrosis was revealed. In the group which received xylitol a large number of hepatocytes contained no fat in the cytoplasm. The radial structure was preserved. Abundant amount of glycogen was observed in the cytoplasm of the cells. In the kidneys of the control rats pronounced stagnant phenomena in the capillaries of the cortex were observed; in the kidneys of the experimental rats those phenomena were insignificant (12).

In conclusion it should be noted that xylitol was approved by the Pharmacological Committee in our country; and xylitol is used for nutritive and medical purposes (5). Xylitol in accordance with requirements for technical conditions of its production easily dissolves in water, has a melting point of 90–94 °C, pH about 7.5, contains no more than 2% of moisture and no more than 0.1% of reducing substance and ashes. The main consumer of crystalline xylitol is the food industry, which uses

xylitol as a substitute for sugar in the diet of diabetic patients. A group of various dietetic confectioneries was worked out on the basis of xylitol: chocolate, sweets with cream, biscuits, liqueur-bonbons, kind of souffle sweetmeat. The use of xylitol gave the opportunity to considerably reduce (4–6 times) the contents of simple sugars as compared to confectioneries with saccharine (22). At present saccharine is banned in the Soviet Union by the USSR Ministry of Health. There is being produced also a large variety of canned fruits with xylitol for dietetic nutrition and the maintenance of xylitol in prepared products is constantly controlled with appropriate methods (23).

In our country xylitol is produced at hydrolyzate factories. Cotton flakes and corn stumps are used as raw material. The technology of production of crystalline xylitol out of water solutions (24) makes it possible to realize the industrial production of xylitol at Fergana chemical factory of furan preparatus, and at Krasnodar group of chemical enterprises (25).

The level of xylitol output in 1975 was 3300 tons. But the amount of xylitol required in 1980 will be 15 000 tons, while the output will reach only 7500 tons. Thus, the supposed output of xylitol will satisfy only 50% of the requirements (26).

Some ways of increasing the efficiency of xylitol production were proposed, and technical directions for the improvement of xylitol production were determined (28).

Acknowledgement

To Prof. *K. Bässler* my sincere gratitude for the discussion and English correction of the manuscript.

Zusammenfassung

Der Artikel enthält Literaturangaben über die biologische Wirkung, Toxizität im Tierversuch und die Verwendung von Xylit bei der Behandlung des Diabetes mellitus sowie von Störungen des Leber-Galle-Systems.

Auf Grund der Ergebnisse der Untersuchungen des Pharmakologischen Komitees des Gesundheitsministeriums der UdSSR wurde Xylit für die Ernährung und die pharmakologische Verwendung zugelassen. Xylit wird durch Hydrolyse von Pflanzenmaterial hergestellt. Die Verbraucher erhalten das Xylit hauptsächlich durch die Lebensmittelindustrie (Zusatz von Xylit zu Candies und eingedosten Früchten).

References

1. *Bezkorovainaia, N. M.:* The influence of xylitol on intensity of bile secretion and synthesis of bile acids. Bullet. experim. biol. med. **5**, 69–71 (1970). – 2. *Vainshtein, S. G.:* The influence of xylitol on gastric secretion in dogs. Farmakologija i toksicologija **1**, 97 (1971). – 3. *Vainshtein, S. G. D. H. Maksudova, M. I. Pivikova:* Clinical study of xylitol as a cholagoque. Clinicheskaya medicina **1**, 126–128 (1970). – 4. *Vainshtein, S. G., M. I. Pivikova, D. H. Maksudova:* The influence of xylitol on gastric secretion and exocrine function of pancreas in patients with duodenal ulcer. Voprosy pitania **1**, 14–17 (1973). – 5. *Volkind, I. V., I. Ya. Gurevich, O. Yu. Uropov:* Pharmacological manual for doctors and pharmacists. L. 1976. – 6. *Grancharov, V. P.:* Chologon and choleretic effect of the soviet xylitol preparation. Voprosy pitania **6**, 18–20 (1971). – 7. *Dombrovskaia, M. P., M. A. Utkelova:* Some indices of protein metabolism in children ill with eczema and the influence of xylitol-add diet upon them. Pediatria **1**, 21–25 (1977). – 8. *Egorov, M. N., N. M. Isirulnikov, L. R. Novofa-*

stovskaya: Xylitol and its clinical use. Klinicheskaya medicina **4**, 133–135 (1968). – 9. *Zemlanitsina, N. P.:* On xylitol influence on a gastric function. Sbornic nauchno-practicheskih rabot vratchei sanatoriev. p. 74–76 (1973). – 10. *Krasovskaya, A. G., Yu. I. Rafes:* About basis for intravenous applying of xylitol during hepatitis and hepatocirrhosis. Gastroenterologia Kiev, ed. 6th, p. 113–120 (1974). – 11. *Kryshen, P. F., Yu. I. Rafes, A. G. Krasovskaya, G. B. Genbacheva, V. N. Ardelyan:* On xylitol pharmacology. Pharmakologija i toksicologija **3**, 333-335 (1971). – 12. *Marshak, M. S., M. I. Rasumov, G. A. Nyezhdanova, G. A. Fursova:* The influence of xylitol upon liver and kidney during choline deficiency. Veprosy pitania Nol, p. 51–54 (1968). – 13. *Marshak, M. S., I. S. Savoshchenko, V. M. Gamerova:* Nutritional and medico- and prophylactic use of xylitol. Sov. medicine **2**, 123–127 (1962). – 14. *Plitman, S. I.:* Experimental base of tolerable pentaeritritis and xylitol in water of reservoirs. Sanitaria i gigiena **2**, 25–29 (1971). – 15. *Poryadkov, L. F.:* Influence of sorbitol and xylitol on exocrine function of liver. Voprosy pitania **5**, 19–24 (1968). – 16. *Radkov, M. G.:* Xylitol in clinical nutrition of patients with diabetes mellitus in sanatorium. Sbornik nauchno-prakticheskih rabot vrachei sanatoriev. M. 116–121 (1973). – 17. *Rafes, Yu. I., I. I. Shelekstina, V. S. Voroshelyak, Z. S. Kulakova, L. Ya. Melnichenko:* Effects of xylitol on some functions of liver and pancreas with biliar pathology. Vrachebnoye delo **2**, 10–24 (1972). – 18. *Ruban, A. P., A. P. Shchekotolo:* Clinical observations during use xylitol with patients with functional constipation. Sbornik nauchno-prakticheskih rabot vrachei sanatoriev. M. 79–84 (1973). – 19. *Suslov, V. S.:* Xylitol- – penta-atom spirit. See in the book: Mnogoatomnye spirty i ih primenenie v transfuziologii, M. str. 72–84 (1977). – 20. *Filatov, A. N., L. G. Bogomolova, V. S. Suslov:* Disintoxicational solution on basis of xylitol and its studying in experiments. Materialy II resublicanskogo syezda hematologov in transfuziologov Byelorusii. Minsk. 268–272 (1979). – 21. *Shelekstina, I. I.:* Influence of sorbitol and xylitol on exocrine function of liver. Voprosy profilaktiki., diagnostiki i lechenia zabolevanii organov pishehevarenia. Kiev 162–163 (1969). – 22. *Ermakova, I. P., I. B. Golseva:* A new kind of confectioneries with xylitol. Hlebopekarnaya i konditerskaia promyshlennost. **2**, 34–36 (1971). – 23. *Kamneva, Z. P., L. I. Klimenko, A. I. Starkina:* Methods of controlling sorbitol and xylitol in dietetic canned food. Konservnaia i ovoshchesushilnaia promyshlennost. 1972. **4**, 30–31 (1972). – 24. *Soboleva, G. D.:* Investigation of xylitol and working out a scheme of its industrial crystallization. Autoreferat dissert. (kand.) (1966). – 25. *Suslov, B. C.:* Xylitol and ways of its use. Clinicheskaya medicina **3**, 8–15 (1973). – 26. *Belyayer, V. D.:* Development of furfurol and xylitol production in the 10th five-year period. See the book: Isposzovanie pentozansoderzhashchego syria. Riga 1976, 5–9 (1976). – 27. *Glasman, R. N., L. N. Pashkova, I. I. Leonova, D. I. Nikolayev:* The effeciency of production of pure xylitol out of maize stump. See the book: Ispo zevanie pentozansoderzhaeshchego syria. Riga 60–61 (1976). – 28. *Leikin, E. R., Yu. P. Ivanov, M. Yu. Kamenkovich:* The main directions of improving technics and raising economical effectiveness of pure xylitol production. See the book: Ispolsovanie pentozansoderzhaeshhe syria. Riga 98–101 (1976). – 29. *Chunakova, E. P.:* Influence of xylitol on clinical and biochemical indices of coronary atherosclerosis patients. Vrachebnoie delo. **11**, 37–40 (1971).

Author's address:

Dr. *M. F. Nesterin,* Nutrition Institute, Moscow (USSR)