Gut permeability and myocardial damage in paediatric cardiac surgery

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CHAPTER 5

Rhamnitol is a metabolite of rhamnose in man

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Until now rhamnose has been considered an inert sugar not metabolized by the human body. During an investigation on gut permeability in children undergoing cardiac surgery using the dual sugar permeability test[1] (DSPT), we found increased concentrations of rhamnitol, a metabolite of rhamnose, in their urine. Four saccharides, 3-O-methyl-D-glucose, D-xylose, L-rhamnose and lactulose are used in the DSPT. The identity of rhamnitol was established by mass spectrometry. Rhamnitol also increased when an adult volunteer ingested the sugar solution. Our finding provides evidence that, contrary to accepted opinion, rhamnose is not an inert sugar but is partially metabolized into rhamnitol in humans.

Materials and methods

Our initial study[1] involved 34 paediatric patients undergoing cardiac surgery with (n = 17) or without (n = 17) cardiopulmonary bypass (CPB). Anaesthesia was standard for all patients. Two ml kg^{-1} of a sugar solution were instilled through a nasogastric tube after induction of anaesthesia, and again 12 and 24 h later. The test solution contained 3-O-methyl-D-glucose (2 g l^{-1}), D-xylose (5 g l^{-1}), L-rhamnose (10 g l^{-1}) and lactulose (50 g l^{-1}). After each instillation, urine was completely collected through a urinary catheter for 3 h, and stored at –20 ºC until analysis. One infant undergoing cardiac surgery received the sugar solution only once during induction of anaesthesia and urine was collected for 24 h afterwards. A healthy adult volunteer ingested the sugar solution (2 ml kg^{-1}) after overnight fasting and urine samples were subsequently collected at 4 h, 8 h, 16 h and 24 h.

Sugar concentrations in urine were determined by gas chromatography and a full description of the method can be found elsewhere[1]. The identity of rhamnitol was confirmed by comparison of retention time and electron-ionization mass spectrum with that of authentic rhamnitol (Sigma-Aldrich, St. Louis, USA). Data are presented as mean (95% Confidence Intervals). After a natural logarithmic transformation a paired t test was used for statistical analysis.

Results

Table 1 shows the percentage recovery of rhamnose and the percentage of ingested rhamnose metabolized into rhamnitol in urine in the two groups (Table 2 gives the absolute values). As can be seen from the data both parameters increase in the consecutive 3 h urine collections.

The patient's weight (kg) was 4.8 (2.5-15) for the non-CPB group and 6 (4-14) for the CPB group. Rhamnitol was not detectable in the sugar solution supplied by the pharmacy. Rhamnitol was detected in trace amounts (< 0.03 mg/3 h) in urine of paediatric patients investigated for inborn errors of metabolism. In the patient where the sugar solution was administered only once, 12.2% (9.7 mg) of the ingested rhamnose was recovered unaltered and 1.3% (1.03 mg) was recovered as rhamnitol.

	T0	T12	T24
No CPB			
Rhamnose %	0.34 (0.2 – 0.48)	3.4 (1.4 – 5.4)	4.6 (2.5 – 6.8)
Rhamnitol %	0.03 (0 – 0.48)	0.23 (0.1 – 0.37)	0.68 (0.4 – 1)
CPB			
Rhamnose %	0.16 (0.02 – 0.3)	1.4 (0.68 – 2.2)	2.5 (1.3 – 3.7)
Rhamnitol %	0.02 (0.06 – 0.03)	0.13 (0.08 – 0.2)	0.76 (0.4 – 1.1)

Table 1: Percentage of ingested rhamnose recovered in urine and percentage of rhamnose metabolized into rhamnitol found in urine. Values expressed as mean (95% Confidence Intervals).

	T0	T12	T24
CPB	0.03 (0.01 - 0.06)	0.2 (0.07 - 0.33)	0.89 (0.45 - 1.33)
No CPB	0.02 (0.005 - 0.029)	0.23 (0.11 - 0.36)	0.69 (0.42 - 0.95)

Table 2: Total amount of Rhamnitol in mg in urine collected over a three hour period. Values expressed as mean (95% confidence intervals).

In the adult volunteer rhamnitol was present in the urine after the ingestion of the sugar solution. In urine collected 4 h after loading, 5.1% (76.8 mg) of the ingested rhamnose was recovered and 0.11% (1.7 mg) was found to be metabolized into rhamnitol. In the whole 24 h urine these figures were 6.7% (107 mg) and 1.2% (18.3 mg), respectively.

Discussion

Assessment of gut permeability using the DSPT was introduced in the late seventies[2]. The L/R ratio is considered to be a parameter for intestinal permeability. The strength of the test relies on the fact that both are assumed to be inert sugars not metabolized by the organism. In humans, the proportion of rhamnose not excreted in the urine is assumed to be fermented by colonic bacteria into short chain fatty acids (acetate, propionate and butyrate)[3]. Some bacteria metabolize rhamnose into rhamnulose but not to rhamnitol[4].

However we have consistently found rhamnitol in the urine of patients in our study. Traces of rhamnitol were generally found in urine of children who were screened for inborn errors of metabolism. It is likely that the conversion of rhamnose into rhamnitol by the human body follows a pathway similar to what has been proposed for another previously thought inert sugar (L-arabinose)[5]. A possible metabolite such as rhamnoate however was not present. The findings in the adult volunteer as well as the data presented in table 1 indicate that rhamnose is slowly metabolized. Therefore almost certainly the rhamnitol found in the urine of the patients after the second and third instillation is largely a metabolite of the previous dose(s).

Xylitol was also increased in the urine samples of the patients in this study (data not shown), indicating that xylose is also not an inert sugar. The DSPT is used as a research tool in human and animal studies. The addition of rhamnitol to rhamnose can reduce the L/R ratio strongly. Lactulose/Rhamnose ratios (L/R) changed significantly when rhamnitol was added to rhamnose in our previous study; group with CPB ($P < 0.02$) 0.57 (0.24 – 0.91) (without rhamnitol) and 0.49 (0.22 – 0.76) (with rhamnitol). Group without CPB ($P < 0.01$) 0.6 (0.36 – 0.85) (without rhamnitol) and 0.55 (0.32 – 0.78) (with rhamnitol) (normal L/R <0.05). This may be clinically irrelevant when the L/R ratios are as high as in our investigations. However it must be taken into consideration when L/R ratios are close to normal or when urine samples are collected for longer periods after administration.

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