Assimilation of lactitol, an ‘unabsorbed’ disaccharide in the normal human colon

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SUMMARY The fate of orally ingested lactitol, a non-absorbed sugar, was measured in six healthy human subjects by following the three routes of disposal of universally "C-labelled sugar. Lactitol was given as a 20 g daily dose to six healthy volunteers for 14 days and on the seventh day, 10 μCi of L-[U-"C]-lactitol was given with the unlabelled sugar and excretion of the "C in breath, urine and faeces was followed. The peak of "CO2 excretion occurred at six hours and total "CO2 accounted for 62-9 (5-0)\% of isotope given, whilst 6-5 (3-6)\% and 2-0 (0-3)\% of the label were recovered from faeces and urine respectively. These data suggest that lactitol is extensively metabolised in the human colon and that a significant proportion of the bacterial metabolites are available for colonic absorption. Calculation revealed that 54-5\% of the theoretical energy content of this compound was utilised by the subjects. It is suggested that this sugar, and other soluble ‘non-absorbed’ sugars (lactulose, sorbitol, mannitol), may undergo a similar pattern of colonic metabolism and can be considered as reduced calorie compounds.

Lactitol, [4-O(beta-D-galactopyranosyl)-D-glucitol], is a disaccharide alcohol prepared by hydrogenation of lactose. Small intestinal perfusion studies have shown that no significant absorption of lactitol occurs in man. In the light of its favourable physicochemical and taste properties, this would suggest that lactitol could be substituted for sucrose and glucose syrups, as a low calorie, bulk sweetener and humectant for foodstuffs. Dietary carbohydrate entering the colon is salvaged through the action of colonic bacteria, by metabolism to volatile fatty acids (VFA’s) which may be absorbed by the colon. In vitro incubation experiments have confirmed that human faecal bacteria can metabolise lactitol to VFA’s and we have shown that the luminal contents of the right side of the human colon are acidified, following oral ingestion of lactitol.

As VFA’s are avidly absorbed from the colon and utilised as a primary energy substrate by colonic mucosa, and other tissues, metabolic pathways therefore exist, in man, for converting unabsorbed lactitol into utilisable moieties.

The rate of conversion and uptake of lactitol and similar compounds (sorbitol, mannitol, maltitol and palatinin) is poorly defined and it is not known whether they should be considered as a ‘low calorie’ substitute for sucrose and glucose syrups. The aim of the present study, therefore, has been to investigate the fate and quantitative metabolism of lactitol following oral ingestion of the universally "C-labelled sugar at sublaxative doses.

Methods

STUDY DESIGN

In the first part of the study (adaptation), six healthy volunteers (four men, two women, age 25–43 years) who were consuming their normal diet and not on any concurrent medication, received 20 g of lactitol daily (dissolved in 150 ml of water), after breakfast, for seven days. On the eighth day, 10 μCi universally labelled "C-lactitol (D-[U-"C]lactitol, 14 μCi/mmol, Amersham International, Bucks, UK) was given with the unlabelled lactitol and for the next seven
days, 20 g unlabelled lactitol was given daily. Excretion of $^1^3$C in $\text{CO}_2$, faeces and urine were followed over the next seven days. Before the study, the background level of labelling in breath $\text{CO}_2$, faeces and urine was measured.

**CO$_2$ measurements**

Subjects inflated a modified, disposable urine bag (with non-return flap-valve) via a drying tube containing calcium chloride (3–8 mesh). The sample of collected expired air was gently bubbled through 3–0 ml of a solution containing 1–0 ml of hyamine hydroxide (1–0 mol/l), 2–0 ml ethanol and phenolphthalein as indicator, until the solution became colourless, whereupon 5–0 ml of scintillation fluid (Beckman Ready Solv-MP) was added. The $\text{CO}_2$ absorbing capacity of each batch of ethanolic hyamine hydroxide solution was checked by titration against a volumetric solution of 0–1 mol/l HCl. Radioactivity was assayed by liquid scintillation counting (Beckman LS 7500, Beckman, High Wycombe, Bucks, UK) with quench correction by the H-Number method. Breath samples were taken 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 24, 36, 48 hours and 3, 4, 5, 6 and 7 days after $^1^3$C lactitol administration. Steady state $\text{CO}_2$ production rates (normalised to STP) were measured, using an indirect calorimeter, built according to the design of Clugston, to a precision better than $\pm$0.5%.

The steady state $^1^3$CO$_2$ output corrected for incomplete recovery (see below) was calculated as the product of $\text{CO}_2$ specific activity (dpm/$\mu$mol$^{-1}$) and $\text{CO}_2$ output ($\mu$mol/h).

**Urine analysis**

Urine was collected, for 24 hour periods, in containers to which 5 ml 10-0 mol/l NaOH had been added. Samples of the urine (2-0 ml) were neutralised by titration with 0-1 mol/l HCl using phenolphthalein as indicator, 5-0 ml scintillation fluid was added and radioactivity assayed as described.

**Faecal analysis**

Twenty four hour faecal samples were collected in thick walled polyethylene bags and frozen immediately. Each frozen sample was homogenised in an equal volume of distilled water and a 1-0 g aliquot of homogenate was incubated with 2-0 ml of 0-45 mol/l NaOH for two hours at 60°C in a tightly capped scintillation vial. Samples were decolourised by addition of 1-5 ml of 5-0% NaOCl (domestic bleach – Melzone), incubated at 60°C for 20 minutes and excess chlorine removed by brief vacuum treatment. A stable gel was formed by addition of 3-0 ml water and 10 ml Readysolv-MP and scintillation vials were stored in the dark for five days to allow decay of chemiluminescence. This method produces scintillation gels which are stable for more than three weeks (with no detectable loss of $^1^3$C) and avoids the need for expensive combustion apparatus to measure faecal $^1^3$C as $^1^3$CO$_2$. Efficiency of counting was 60% and 80%, partially- and fully-decoloured gels, respectively, and reproducibility was $\pm$0.8% and $\pm$2.0% for samples containing 10000 dpm and 100 dpm, respectively.

**Calculation of results**

The metabolic fate of universally labelled lactitol was followed. During the course of the experiments, the possible routes of $^1^3$C disposal were, breath ($^1^3$CO$_2$), urine and faeces.

Steady state $^1^3$CO$_2$ production (dpm/h) = $\text{CO}_2$ specific radioactivity (dpm/$\mu$mol) × $\text{CO}_2$ output ($\mu$mol/h) × 1/23

**Equation 1**

*Where the factor of 1.23 is used to correct for incomplete recovery of $^1^3$CO$_2$.*

**Results**

Ingestion of 20 g of lactitol during the course of this experiment did not have a cathartic effect. Average stool weight (Table 1) was 306.5 (91.6) g/day (mean (SE)) and it had been noted in a previous study, with the same volunteers, that 20 g bolus dose of lactitol did not exceed the laxative threshold for each subject. The time from ingestion to peak $^1^3$CO$_2$ excretion averaged six hours (Fig. 1) and Table 2

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Average faecal output</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>M</td>
<td>34</td>
<td>142-0 (18-0)</td>
</tr>
<tr>
<td>B</td>
<td>M</td>
<td>35</td>
<td>446-5 (90-1)</td>
</tr>
<tr>
<td>C</td>
<td>M</td>
<td>34</td>
<td>683-0 (28-2)</td>
</tr>
<tr>
<td>D</td>
<td>M</td>
<td>40</td>
<td>240-0 (72-5)</td>
</tr>
<tr>
<td>E</td>
<td>F</td>
<td>30</td>
<td>218-7 (51-0)</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>30</td>
<td>109-0 (27-2)</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td></td>
<td></td>
<td>306-5 (91-6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>Faeces</th>
<th>Urine</th>
<th>Breath</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>2-4</td>
<td>3-2</td>
<td>78-2</td>
<td>83-8</td>
</tr>
<tr>
<td>B</td>
<td>22-5</td>
<td>1-7</td>
<td>44-6</td>
<td>68-7</td>
</tr>
<tr>
<td>C</td>
<td>10-9</td>
<td>2-0</td>
<td>52-6</td>
<td>65-5</td>
</tr>
<tr>
<td>D</td>
<td>2-2</td>
<td>1-8</td>
<td>64-2</td>
<td>68-2</td>
</tr>
<tr>
<td>E</td>
<td>0-8</td>
<td>1-9</td>
<td>69-1</td>
<td>71-8</td>
</tr>
<tr>
<td>F</td>
<td>0-4</td>
<td>1-5</td>
<td>68-6</td>
<td>70-5</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>6-5 (3-6)</td>
<td>2-0 (0-25)</td>
<td>62-9 (5-0)</td>
<td>71-4 (2-63)</td>
</tr>
</tbody>
</table>
summarises the individual values for \(^{14}\)C excretion in breath, faeces and urine over a period of three days. Total recovery of \(^{14}\)C was mean 71.4\% (2.6) and 88.1\% of recovered \(^{14}\)C was in the form of expired CO\(_2\) and 6.5\% in stool (Table 2). Urinary excretion of \(^{14}\)C (2.0\% (0.25) of ingested dose) was not in the form of HCO\(_3^-\), because Na\(_2\)CO\(_3\) addition to samples and subsequent acidification did not reduce \(^{14}\)C content.

There was such rapid clearance of label through all three routes (Table 3) that it was not possible to detect \(^{14}\)CO\(_2\) in breath after two days, at the level of sensitivity of the method (<0.05\% of dose given). As will be discussed, we calculate that of ingested \(^{14}\)C-lactitol, 2\% was passively absorbed in the small bowel (appearing in urine) and 98\% entered the colon. Assuming that bacterial metabolism resulted in loss of 28\% of the lactitol carbon entering the colon as CO\(_2\) (27.4\% of the dose), the remaining \(^{14}\)C (64.1\% of the dose), was either absorbed by colonic mucosa as VFA’s or excreted in faeces (6.5\% of dose). The absorbed fraction was not all metabolised directly to \(^{14}\)CO\(_2\), instead we calculate that 28-6\% of the dose was incorporated into nonlabile whole-body metabolites (the retained fraction) whilst 35-5\% of the dose was completely metabolised, endogenously, to \(^{14}\)CO\(_2\).

### Discussion

The colonic microflora have a large capacity to metabolise malabsorbed dietary carbohydrate and breath hydrogen studies suggest that up to 20\% of starch may be handled in this way.\(^\text{7,10,13,22}\) Even well absorbed carbohydrates, such as glucose, instilled directly into the large intestine, are fermented at a rate exceeding that of passive colonic absorption.\(^\text{24,25}\) As orally administered lactitol promotes acidification of the right colon\(^\text{47}\) in a similar fashion to lactulose,\(^\text{86}\) it can therefore be considered along with other non-absorbed carbohydrates which are metabolised, primarily by colonic fermentation.

Energy balance studies in man have suggested that

### Table 3

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Faeces</th>
<th>Urine</th>
<th>Breath</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24</td>
<td>5.73 (3.58)</td>
<td>1.49 (0.20)</td>
<td>59.33 (4.35)</td>
<td>66.56 (2.75)</td>
</tr>
<tr>
<td>24-48</td>
<td>0.50 (0.16)</td>
<td>0.38 (0.04)</td>
<td>3.55 (1.17)</td>
<td>4.44 (1.12)</td>
</tr>
<tr>
<td>48-72</td>
<td>0.25 (0.10)</td>
<td>0.11 (0.03)</td>
<td>0.36 (0.26)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as \% of ingested dose
Caloric utilisation of lactitol

approximately 50% of the energy content of lactitol is available for endogenous metabolism, compared with sucrose. In this type of study, correction is made for differences in activity patterns between groups of subjects before extrapolating energy expenditure to dietary intakes consisting entirely of the sugars under study. The principles and limitations of this method are discussed in detail elsewhere. We have used an alternative method, with different assumptions and limitations, to calculate the metabolic utilisation of lactitol. In brief, these assumptions are: (1) All 14CO2 produced by endogenous and exogenous metabolism of lactitol must be measured. (2) There should be no significant, undetected, loss of 14CH4 and 14CO2 in flatus. (3) Faecal excretion of intact 14C-lactitol should be minimal. (4) Faecal collection should be complete.

Values for 14CO2 excretion were corrected for incomplete recovery due to hold up in non-labile CO2 pools as described before and shown in Equation 1.

Although the colonic mucosa is only marginally permeable to H2 and CH4 (only 14% H2 appears in breath, the remainder being expelled in flatus), it is likely that CH4 production represents only a small proportion of metabolised carbon. Absorption of CO2 is, however, rapid as observed at colonoscopy and calculation of flatus losses, based on the labelling of the administered lactitol and the rate of flatus production and its CO2 content in subjects consuming a highly flatogenic diet, indicates that less than 3% of CO2 would have been excreted through this route during the first day of the study.

We have assumed that little intact 14C-lactitol was excreted in faeces and presumably, faecal excretion of 14C represents isotope incorporated into the faecal bacterial mass.

Finally, we have assumed that faecal collection was complete. All studies were carried out on motivated volunteers within the hospital and given the small recovery of 14C in faeces, an error here would not significantly affect the estimate of 14C excretion by this route. Finally, the proportion of 14C-lactitol which was excreted in the urine represents the amount absorbed from the gastrointestinal tract by passive diffusion (Fig. 2) and has thus been subtracted from the ingested dose to give the amount which entered the large bowel. The overall stoichiometry of colonic fermentation of carbohydrate has been described, according to the equation:

\[ 34.5 \text{ C}_6\text{H}_{12}\text{O}_6 + 37.0 \text{ H}_2\text{O} \rightarrow 48 \text{ acetate} + 58.0 \text{ CO}_2 + 95 \text{ H}_2 + 11 \text{ propionate} + 5 \text{ butyrate} \]

Equation 2

Thus, 28% of the lactitol carbon would have been released as CO2 during colonic conversion to VFA’s and, because little intact 14C-lactitol was excreted in faeces, 28% of the fermentable 14C-labelled sugar which had entered the colon was released as CO2 by bacterial action. Of the remainder, part would be absorbed as 14C-VFA’s (to undergo further oxidative and interconverting metabolism), part metabolised endogenously by the colonic mucosa to CO2 and non-labile 14C-metabolites, and part incorporated into bacteria or excreted as 14C-VFA’s in the faeces (Fig. 2). The proportion of 14CO2 produced by microbial fermentation of lactitol to VFA’s can be calculated as 27.4% of the ingested 14C dose (Equation 2 and Fig. 2). The remaining 14CO2 must have come from endogenous oxidative metabolism and accounts for 35.5% of ingested 14C-lactitol carbon. A proportion (28.6%) of 14C could not be accounted for, and this may represent 14C-VFA’s absorbed and metabolically incorporated by the colonocytes or by other tissues in the body. On this basis, we would calculate that 64.1% (28.6% + 35.5%) of the 14C of orally ingested 14C-lactitol was available for further metabolism by the subjects themselves. Oxidative metabolism of VFA’s...
produces 15% less ATP per calorie than glucose\(^7\) and the energy yield of absorbed VFA’s in this study was therefore 64·1% x 0·85, or 54·5% of the energy content of lactitol. We believe that this technique is robust if the carbohydrate under test is extensively metabolised in the large bowel. If a test substance undergoes modest colonic metabolism (\(^{14}\)CO\(_2\) output low) and high faecal excretion of \(^{14}C\)\(^3\) the proportion of faecal-\(^{14}C\) present as intact \(^{14}C\)-carbohydrate or \(^{14}C\)-VFA should be measured, so that the value for bacterial \(^{14}CO_2\) production can be subtracted from total \(^{14}CO_2\) in the calculation.

Three points may be made about these results. First, a wide variation in faecal output of \(^{14}C\) was noted which may relate to differences in dietary intake. All subjects were interviewed about their diet and in the case of subject (B), an Indian national who was consuming a vegetarian diet, faecal \(^{14}C\) output was high, whereas a West Indian subject (A), consuming a high fat, low residue diet had small faecal output, low faecal \(^{14}C\) excretion and a high \(^{14}CO_2\) output. The remaining caucasian subjects had intermediate values for faecal \(^{14}C\) and \(^{14}CO_2\) with one exception. The caloric utilisation of lactitol, for any individual, may therefore be influenced by pre-existing dietary habits and fibre intake. Conversely, chronic, sublaxative consumption of lactitol may alter utilisation of natural, malabsorbed dietary carbohydrates since it can alter bowel habit.\(^5\)

Moderate intakes of other non-absorbed sugars decrease transit time and increase faecal output and nitrogen content.\(^14\)\(^19\) Under these circumstances, a loss of energy to the large bowel from VFA’s produced by fermentation of natural dietary carbohydrates may be offset by VFA’s, released by avid metabolism of lactitol itself. The true caloric utilisation of lactitol, under such circumstances may be less than our estimate of 54·5% or 2·2 kcal/g.

Although malabsorbed carbohydrate may have a protective effect on the large bowel,\(^23\) this should be balanced against the effects of ingestion of large quantities of non-absorbed sugars. Substitution of lactitol for sucrose and glucose syrups in confectionery and foodstuffs, may lead to intakes approaching the laxative threshold (up to 70 g/day),\(^3\) and produce symptoms such as bloating, diarrhoea, excessive flatus, and abdominal cramps. Although the strategy of substituting lactitol for sugar in foodstuffs is undoubtedly good for teeth,\(^37\) and the pancreas,\(^39\) it may not produce socially acceptable bowel habits.

We would therefore conclude from the present study that the pattern of small and large bowel handling of lactitol reduced its potential energy yield by 45%. In this respect, it can be considered as a reduced calorie substitute for sucrose and glucose syrups.

We are grateful to Express Dairies (UK) Ltd for financial support and encouragement and to Amersham International for custom synthesis of universally \(^{14}C\)-labelled lactitol.

References

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Caloric utilisation of lactitol


Addendum

A recent study of the energy yield of acetate and propionate instilled in the caecum of pigs, suggests that it may be 21-25% less than glucose, not 15% less as previously proposed. 27 The potential energy yield of lactitol may therefore be closer to 50% than 55%, as suggested above.
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