

Small bowel function in acute lymphoblastic leukaemia

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SUMMARY Small bowel function before, during, and after treatment for acute lymphoblastic leukaemia was studied in 26 children. A significant impairment of D-xylose absorption was found during treatment. Permeability studies showed a significant decrease in mannitol and a significant increase in lactulose concentrations; five of 20 children tested had evidence of lactose malabsorption, three of whom were symptomatic. Intestinal function abnormalities were greater in children whose methotrexate treatments were separated by 7 day than by 16 day intervals. Only five (19%) children had no abnormal tests. Abnormalities of small bowel function may be treatment induced and this has implications for morbidity from gastrointestinal symptoms, impairment of the mucosal barrier, and malabsorption of both nutrients and drugs leading to malnutrition and suboptimal drug concentrations.

With improvement in the prognosis for childhood acute lymphoblastic leukaemia attention has focussed on treatment complications.¹ One such adverse effect may be overt or latent gastrointestinal damage. Evidence, both in animals and man, suggests that single cytotoxic agents (methotrexate, fluorouracil, and vincristine) may cause morphological alteration of the gastrointestinal mucosa.²⁻⁴ The doses used in many of the animal studies were, however, greater than those used in clinical practice. Corresponding functional changes of active and passive transport and intestinal disaccharidase activity have also been reported.^{2 5-7}

After methotrexate treatment alone small bowel mucosal changes have been observed⁸ and in children with acute lymphoblastic leukaemia impairment of xylose absorption has been shown.⁹⁻¹⁰ In addition, some children have evidence of lactose malabsorption.¹¹ There is, however, conflicting evidence as to whether this damage is cumulative throughout treatment.⁹⁻¹⁰

Detection of impaired small bowel function in children with acute lymphoblastic leukaemia may be important since malabsorption of nutrients, morbidity from gastrointestinal symptoms, and malabsorption of drugs leading to suboptimal treatment could result. With the advent of non-invasive techniques to investigate the gastrointestinal tract it has become ethically possible to study and follow sequentially

larger numbers of children being treated for acute lymphoblastic leukaemia. We have therefore studied various aspects of small bowel function in a group of children with this disease.

Patients and methods

Twenty six children (14 girls and 12 boys) were studied sequentially before, during, and after treatment for acute lymphoblastic leukaemia. Their ages ranged from 2 to 13 years (mean 7.2 years) and duration of treatment from 0 to 36 months. They were treated with one of four regimens; UKALL VI (five patients), a modified UKALL VI (two patients), UKALL VIII (10 patients), and a modified ALGB 6801 (9 patients). The major difference between these is that in the first two regimens maintenance consisted of daily mercaptopurine for 16 days followed by five days oral methotrexate with pulses of prednisone and vincristine. In the latter two regimens oral methotrexate was given weekly and mercaptopurine daily. UKALL VIII was more intensive than ALGB 6801 with more frequent pulses of vincristine and prednisone and higher methotrexate doses. Children treated on UKALL VIII regimen were also studied during the induction period when they received vincristine, prednisone, and asparaginase and some also received daunorubicin.

At the time of study no other drugs were being taken and no complications such as infection were apparent. The studies were performed on the day when the child was next due to take his oral methotrexate; that is either 7 or 16 days after the previous methotrexate dose.

Xylose absorption studies¹² were performed after an 8 hour fast. Five grams of xylose in 100 ml water was ingested and a one hour blood sample taken. Concentrations were assayed and corrected for surface area.

Intestinal permeability was measured by a previously described technique using mannitol and lactulose as probe molecules.¹³ The child drank a moderately hypertonic solution of the two sugars after an overnight fast and the urine was collected for five hours. The child was allowed to eat normally after two hours. The concentration of the sugars in the urine was measured by gas liquid chromatography.¹³

Lactose malabsorption was detected by the hydrogen breath test.¹⁴ After an 8 hour fast the child drank 2 g/kg (maximum 50 g) lactose in a 20% aqueous solution. Samples of end expiratory air were obtained by a modification of a simple Wigan's blow out technique¹⁵ at 0, 30, 60, 90, and 120 minutes and analysed for breath hydrogen using an electrochemical cell.¹⁶ A rise in breath hydrogen of greater than 10 parts/million above the baseline value was taken to indicate lactose malabsorption. Any abdominal pain or loose stools occurring during the 12 hours after the lactose load were noted.

Statistical analysis was by Student's *t* test, χ^2 test, Spearman's correlation coefficient, and non-parametric Wilcoxon test for lactulose and mannitol outputs and their ratios.

Thirty one healthy children (18 boys, 13 girls) aged 2 to 13 years (mean 7.6 years) who had a normal growth pattern and no gastrointestinal or atopic symptoms served as controls for the permeability studies.

Results

Pretreatment, mean corrected, one hour blood xylose concentrations did not differ significantly from values obtained from controls. Xylose absorption was reduced, however, in patients on treatment ($P < 0.001$). (Fig. 1).

Children on treatment excreted less mannitol than normal controls or children before treatment ($P < 0.01$) but they excreted more of the lactulose load than normal children ($P < 0.05$) (Figs. 2 and 3). Expressed as a ratio of lactulose to mannitol the mean value for leukaemic children on treatment was

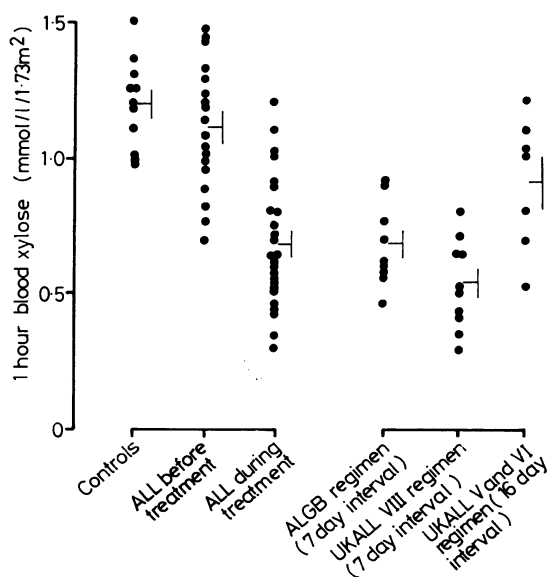


Fig. 1 One hour blood xylose values corrected for surface area in controls and children with acute lymphoblastic leukaemia (ALL) on different treatment regimens.

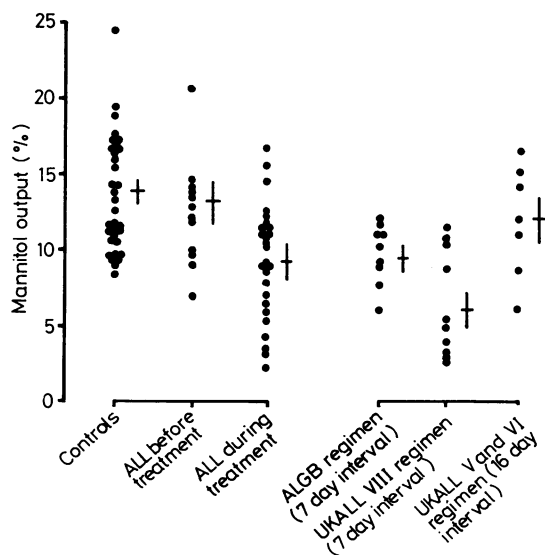


Fig. 2 Percentage mannitol output in controls and children with acute lymphoblastic leukaemia (ALL) on different treatment regimens.

significantly higher than that for normal children ($P < 0.01$) (Fig. 4).

Five of the 20 children tested showed evidence of lactose malabsorption. Three developed loose,

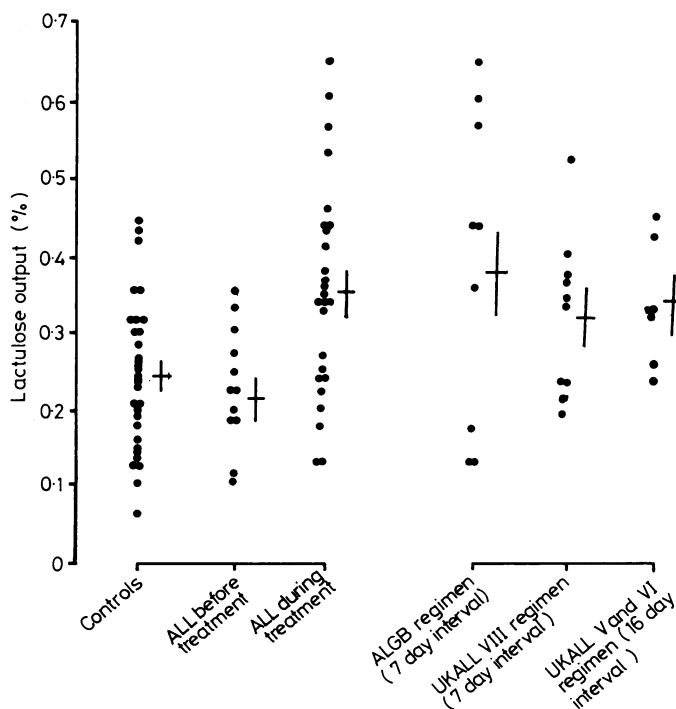


Fig. 3 Percentage lactulose output in controls and children with acute lymphoblastic leukaemia (ALL) on different treatment regimens.

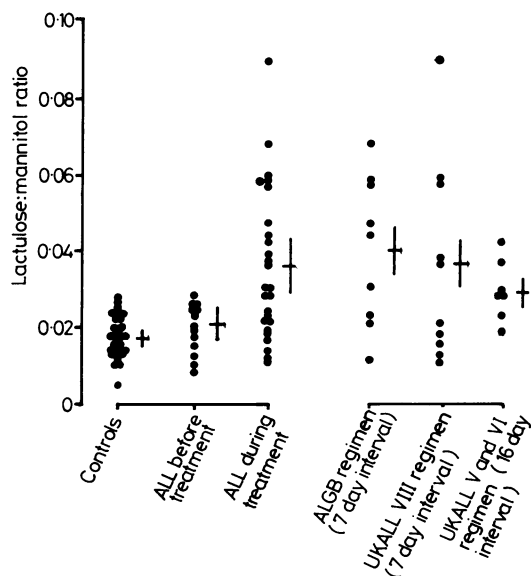


Fig. 4 Ratio lactulose:mannitol output in controls and children with acute lymphoblastic leukaemia (ALL) on different treatment regimens.

watery stools after lactulose ingestion with some abdominal discomfort in two, suggesting lactulose intolerance. Three of these children were tested again after completing treatment for more than two months and showed no evidence of lactulose malabsorption.

There was no correlation between one hour blood xylose, mannitol, and lactulose excretion or their ratio with duration of treatment or with cumulative dose of methotrexate. The one hour blood xylose and mannitol output were significantly higher in children receiving methotrexate separated by 16 day intervals than those with a 7 day interval, while the ratio of lactulose:mannitol output was lower in these children (Figs. 1, 2, 3, and 4). The only significant difference between UKALL VIII and ALGB regimens was lower mannitol excretion. $P < 0.05$ (Figs. 1, 2, 3, and 4).

In a sequential study of lactulose and mannitol absorption maximal abnormality of the permeability ratio was found during the induction period, when it was significantly different ($P < 0.01$) from the values before and after treatment. These latter values did not differ from those obtained from normal children (Fig. 5).

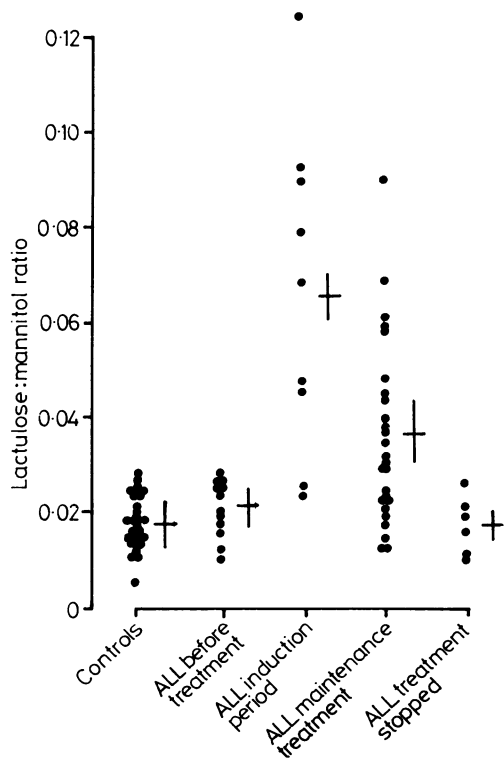


Fig. 5 Ratio lactulose: mannitol output at different stages during treatment for acute lymphoblastic leukaemia (ALL).

Lactose malabsorption usually occurred in younger children; the mean age for children with this was 5 years but was 8 years for those without ($P < 0.05$). There was no relation between lactose malabsorption and the duration of treatment or the cumulative dose of methotrexate. No child treated with methotrexate at 16 day intervals developed evidence of lactose malabsorption. Other aspects of small bowel function, xylose, mannitol, and lactulose absorption were the same between the groups.

The Table shows the number of children who were outside the reference range for each of the tests at some time during the period of the study.

Discussion

This study has shown that most children undergoing treatment for acute lymphoblastic leukaemia will have abnormalities of small bowel function at some stage. We deliberately did not investigate children when they were unwell with infection or when they were receiving drugs other than mercaptopurine. Some children (19%), however, never showed any abnormality, although all children except some with lactose intolerance were asymptomatic.

The finding of reduced one hour blood xylose concentrations confirms previous studies.^{9 10}

Measurement of the differential permeation of non-metabolised sugars has not been reported previously in children receiving treatment for acute lymphoblastic leukaemia. Mannitol is believed to pass transcellularly through aqueous pores in the cell membrane while lactulose passes intracellularly through less abundant areas of tight junctional complexes or extrusion zones.¹⁷ Reduced mannitol permeation of a more noticeable degree has been seen in childhood coeliac disease and this has been interpreted as reflecting a reduction in surface area.¹³ In the children with acute lymphoblastic leukaemia this may also be interpreted as due to a reduced surface area of the small bowel, although previous calculation of the villous area from morphometric studies of the jejunal mucosa in 10 children who were being treated for acute lymphoblastic leukaemia showed no such reduction.⁸ These children, however, had only received methotrexate for the previous 7 days and patchy jejunal changes might have been missed in the sampling. Alternatively methotrexate may have a direct effect upon the cell membrane and therefore reduce permeation through the aqueous pores. Either explanation would be compatible with the D-xylose absorption data in this and other studies.

Enhanced lactulose absorption was noted during treatment. Increased lactulose absorption has previously been noted in childhood Crohn's disease¹³ and increased permeation of lactulose and other larger molecules through the gastrointestinal tract has been noted in coeliac disease, eczema, and in the neonatal period.¹⁸⁻²⁰ It is possible that the

Table Number of abnormal tests of small bowel function in children with acute lymphoblastic leukaemia

Abnormal test	None	Xylose	Lactose	Permeability	Xylose and lactose	Xylose permeability	Lactose permeability	Lactose and xylose and permeability
No	5	2	2	4	1	10	1	1
%	19	8	8	16	4	38	4	4

enhanced lactulose absorption reflects increases in paracellular pathways which also allow the greater absorption of other macromolecules. Support for this concept comes from the finding that the cytotoxic drug fluorouracil causes increased permeation through the bowel of (14C) polyvinyl pyrrolidone (molecular weight 11 000).²¹ This increased lactulose permeation may reflect impairment of the integrity of the gastrointestinal mucosa which normally acts as a barrier to the entry into the body of macromolecules and enteric bacteria and their products. This may therefore be one reason for the not infrequent occurrence of bacteraemia with bowel organisms as both increased permeability and infection are highest at the time of maximal impairment in total body immunity, that is during the induction period.

Lactose malabsorption occurred in some children during treatment for acute lymphoblastic leukaemia indicating damage to the brush border enzymes. Some also had symptoms of loose stools and abdominal pain giving rise to definite morbidity. Lactose deficiency with lactose malabsorption did not seem to correlate with other aspects of small bowel function. It occurred more often in younger children and less often if the methotrexate dosage was separated by 16 days. Parents usually accept episodic loose stools or nausea and abdominal pains during treatment but some of these symptoms could be alleviated by a lactose free diet. Secondary lactase deficiency may occur after various insults to the small bowel mucosa, especially gastroenteritis and has previously been found in a group of children being treated for childhood malignancy.¹¹ One of the children (a non-Caucasian) with evidence of lactose malabsorption was tested again after stopping treatment and no evidence of lactose malabsorption was found suggesting that this was a temporary, secondary lactase intolerance and not a racially associated post-weaning lactose intolerance.

The aetiology of the impairment of the small bowel function is probably multifactorial; methotrexate in high doses is enterotoxic in experimental animals² and has been shown in man to produce morphological changes at the dosage used.⁸ Mercaptopurine may also be important and possibly poor nutrition with folate and other deficiencies may contribute to the changes.²²⁻²⁴ Reasons for the variability in small bowel function in children at the same stage of treatment need elucidation.

The effect of impairment of small bowel function is fourfold; it may result in morbidity from gastrointestinal symptoms, impairment of the gastrointestinal barrier, and occult malabsorption of nutrients possibly causing chronic growth retardation and malnutrition. Perhaps equally important,

however, are the implications of impaired small bowel function on the absorption of cytotoxic drugs in childhood acute lymphoblastic leukaemia. A study correlating small bowel function with methotrexate absorption is now being performed.

These various techniques of studying small bowel function are all non-invasive and simple to apply and can be used to assess gastrointestinal toxicity of various treatment protocols for childhood with acute lymphoblastic leukaemia.

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