Hospital Topics

Is the Xylose Test still a Worth-while Investigation?

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Summary

In a retrospective survey the results of a D-xylose absorption test have been assessed in relation to jejunal morphology and final diagnosis in 152 adult patients with various types of gastrointestinal disease. Neither urine excretion rates nor serum concentrations alone provide an adequate separation between patients with definite mucosal lesions and those without evidence of gut disease or with other types of gastrointestinal pathology.

It is suggested that when a jejunal biopsy can readily be performed the xylose test serves little useful purpose in routine practice and can be positively misleading. It may still be useful as a screening test for referral for jejunal biopsy, provided that strict criteria of normality are applied.

Introduction

Absorption of the pentose sugar D-xylose is the standard test of jejunal mucosal function in the U.K. It is used both in the diagnosis of specific mucosal diseases, such as adult coeliac disease, and in the assessment of general absorptive function in patients with various gastrointestinal and other disorders. For diagnosis it has been superseded by the now widely available technique of jejunal biopsy, but it may still have a role when a biopsy cannot readily be undertaken. In this retrospective survey the results of a standard routine xylose test performed without special supervision were assessed in a group of patients with normal jejunal biopsy findings and a group with a frankly abnormal mucosa, mainly untreated adult coeliac disease. The object was to assess the use of the test as an indicator of mucosal disease and as a screening test for jejunal biopsy. In a larger group of patients with Crohn's disease the test was also assessed as an indicator both of jejunal involvement with disease and of the contribution of malabsorption to such common features as loss of weight and anaemia.

Many earlier reports showed a broad separation of results obtained in patients with mucosal disease and patients with other types of malabsorption,¹⁻⁴ but no recent reports have indicated the value of the test in the assessment of individual patients or the need to retain the test at all now that biopsy techniques are so widely used. It is well known that delayed urinary excretion can invalidate the test and that blood levels

may overcome this problem, yet assessment of jejunal function in routine practice is often based on urine excretion data alone. In this survey the serum concentration one and a half hours after a 25-g load of xylose was assessed in relation to the usual five-hour urine collection.

Subjects and Methods

All patients who had a technically satisfactory xylose test together with a jejunal biopsy in the gastrointestinal unit at St. Bartholomew's Hospital during 1967-71 were included in the survey. In addition patients with Crohn's disease were included, although they did not routinely undergo jejunal biopsy. Thus in most of the patients a direct comparison could eventually be made between the results of the xylose test and the jejunal mucosal histological picture.

The xylose test was performed on inpatients after an overnight fast. A 25-g dose of D-xylose was taken in 200 ml of water after emptying the bladder and discarding the urine. A further 200 ml of water was given one and two hours later in order to ensure an adequate urine flow. Urine volumes of less than 100 ml in five hours were considered unsatisfactory, and such tests were excluded from the survey. The urine collected in the first five hours was measured and a sample was retained for estimation. A sample of venous blood was taken one and a half hours after ingestion of xylose and the serum was separated. Evidence from other sources suggests that peak serum levels are reached between one and two hours after administration.¹⁻⁶ Xylose was estimated in serum and urine by the method of Roe and Rice.⁷ On the basis of available evidence in the literature lower limits of normal were arbitrarily selected as 30 mg/100 ml for serum xylose and 4.0 g for the five-hour urine sample.^{1-5, 8, 9} No formal assessment was made of renal function but at least one estimation of blood urea was available for each patient.

Jejunal biopsy material was obtained with the Crosby capsule¹⁰ positioned under radiological control just beyond the duodenojejunal junction. The specimens were laid flat on ground glass slides, immersed in 10% formol-saline, examined under the dissecting microscope, and then prepared for conventional light microscopy.

CLASSIFICATION OF PATIENTS

The patients were classified as follows according to the final diagnosis.

Group A comprised 38 patients with normal jejunal biopsy specimens. Indications for biopsy included unexplained diarrhoea, non-specific abnormalities on barium follow-through examination, and evidence of low folate status. No evidence of organic disease was found after full investigation, including radiography of the small and large bowel.

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Group B comprised 26 patients also with normal biopsy specimens but in whom there was definite gastrointestinal pathology or other possibly relevant disease outside the gastrointestinal tract. This group included patients with pancreatic insufficiency (4), ulcerative colitis (2), ileostomy dysfunction in the absence of Crohn's disease (2), postvagotomy diarrhoea (3), postgastrectomy diarrhoea or nutritional problems (4), and one case each of pernicious anaemia, small-bowel ischaemia, small-bowel diverticula, distal small-gut resection, nodular lymphoid hyperplasia, oesophageal stricture, purgative abuse, thyrotoxicosis, nutritional folate deficiency, drug-induced diarrhoea, and giardiasis. The specimen from the patient with giardiasis showed trophozoites in the intervillous spaces, but the villous structure and surface cells appeared normal and there was no excess cellular infiltrate in the lamina propria.

Group C comprised 52 patients with Crohn's disease. Most of these patients did not have a jejunal biopsy. In each case the diagnosis was considered definite on the basis of the usual pathological or radiological criteria. Evidence of jejunal involvement was sought from available radiological and/or surgical information. Only five patients had extensive jejunal involvement and none had had any jejunum resected.

Group D comprised 36 patients with a frankly abnormal jejunal biopsy specimen. Out of 31 patients with untreated adult coeliac disease 30 had the typical flat mucosa of subtotal villous atrophy and only one had the lesser changes of partial villous atrophy. All showed a satisfactory clinical and histological response to a gluten-free diet. Four patients were considered to have chronic tropical sprue on the basis of a history of residence in the tropics, partial villous atrophy with intense cellular infiltration into the lamina propria, impaired vitamin B₁₂ absorption, and a good clinical and haematological response to either folic acid or antibiotics or both. One patient had proved Whipple's disease and responded well to tetracycline. The present results all relate to the period before treatment.

Thus the jejunal biopsy specimens from patients in groups A and B were normal, whereas specimens from group D were abnormal. Patients in group C (Crohn's disease) did not have biopsies performed, but most had no macroscopic evidence of jejunal involvement.

Results

The individual urine excretion rates in the four groups of patients are shown in fig. 1, together with the number of patients in each group excreting less than 4.0 g of xylose in five hours. There was a considerable overlap of results, but no patient with a normal jejunal biopsy specimen (groups A and B) excreted less than 1.9 g and no patient in group D excreted more than 5.3 g in five hours.

The individual serum xylose concentrations one and a half hours after ingestion are shown in fig. 2, together with the number of patients having serum levels of less than 30 mg/100 ml. In groups A and C the incidence of subnormal serum results was much less than that of subnormal urinary excretion. However, the reverse applied to group B patients, and among patients in group D a similar number had normal urine excretion and normal serum concentrations. The two very high serum levels in patients with adult coeliac disease are surprising and may represent laboratory error; but they were not repeated.

In an attempt to improve the discriminatory value of the test urine excretion and serum concentrations were compared in individual patients, and the results are shown in figs. 3-6. A subnormal urine excretion and serum concentration in the same patient can be regarded as a strictly abnormal result. On this basis there were no abnormal results in group A,

FIG. 1—Individual urinary xylose excretion rates in the four clinical groups of patients. In group D, O refers to patients with chronic tropical sprue, and Δ refers to the patient with Whipple's disease. Horizontal line represents arbitrarily selected lower limit of normal.

FIG. 2—Individual serum xylose concentrations. Details as in legend to fig. 1.

FIG. 3—Relation between urine xylose excretion and serum concentration in patients in group A. Vertical and horizontal lines represent arbitrarily selected lower limits of normal.

FIG. 4—Relation between individual urinary excretion and serum concentration in patients in group B.

FIG. 5—Relation between urinary excretion and serum concentration in patients in group C. Arrows indicate serum concentrations greater than 80 mg/100 ml.

FIG. 6—Relation between urinary excretion and serum concentration in patients in group D. The symbols are explained in the box.

compared with 25 abnormal results in the 36 patients in group D. There was, however, an appreciable minority of abnormal results in the other groups of patients.

In group B 4 of the 26 patients gave a strictly abnormal response to the xylose tests although their jejunal specimens were known to be normal. The diagnoses were: postvagotomy diarrhoea (1), ileostomy dysfunction (1), small-bowel ischaemia (1), and thyrotoxicosis (1).

In group C (Crohn's disease) only 5 of the 52 patients gave strictly abnormal results; one had evidence of duodenal but not extensive jejunal involvement, two had ileocolonic disease, and in two the disease was apparently confined to the colon. An unusually large number of patients in this group (14) had normal or even high serum concentrations in association with subnormal urinary excretion.

The value of this stricter definition of abnormality as an indication of jejunal mucosal disease is offset by the fact that 11 of the 36 patients in group D did not give a strictly abnormal result. This number could be reduced to 8 if the lower limit of urinary excretion were taken as 5.0 g rather than 4.0 g, as in common clinical practice. This would not affect the number of abnormal results in the other groups. None of these patients had both normal serum and normal urinary values.

Discussion

The direct intubation studies of Fordtran *et al.*¹¹ showed that xylose is absorbed from a 25-g dose almost exclusively by the jejunum. Patients with normal jejunal biopsy specimens and with predominantly non-jejunal Crohn's disease (groups A, B, and C in this study) would therefore be expected to show normal absorption, whereas patients with abnormal specimens (Group D) might show evidence of impaired jejunal function.

In this study a very wide range of urinary excretion rates were obtained in patients in groups A, B and C with many apparently abnormal results. However, in a comparable number of normal subjects Texter *et al.*⁹ observed urinary excretion rates ranging from 2.4 to 8.5 g/5 hr in persons aged less than 60 years and 2.3 to 4.5 g/5 hr in those aged 60 years or over. Reduced excretion in the elderly is the result of impaired renal function rather than impaired absorption.¹² Many of the subnormal results in the present study can probably be attributed to delayed renal excretion rather than impaired absorption. Estimation of serum concentration should obviate the problem of delayed renal excretion, and in groups A and C the incidence of subnormal serum levels was appreciably less than that of subnormal urinary excretion. Nevertheless, the value of the serum concentration alone was greatly reduced by the important minority of patients with untreated coeliac disease (6 out of 31) who had normal or, in two cases, high values.

If serum and urine results are considered together in individual patients a stricter definition of abnormality can be employed, and this should largely overcome the problem of variable renal handling of xylose. Indeed, on this basis no patient in group A gave an abnormal result, confirming this postulate. However, a minority of patients in groups B and C gave abnormal results.

There are several possible explanations of an abnormal xylose test result in a patient with a normal jejunal mucosa, normal renal function, and an adequate urine volume during the test. Rapid intestinal transit can reduce xylose absorption by limiting the contact time available.¹¹ This may explain abnormal results in patients after gastric surgery, although the reported incidence of this is variable.^{13,14} In this series only one such patient (with "postvagotomy diarrhoea") gave an abnormal result. In the patient with ileostomy dysfunction rapid transit may have been responsible for impaired absorp-

tion and was suggested by carmine marker studies. There is evidence that enteric bacteria proliferating in the upper small bowel can metabolize xylose in quantitatively significant amounts even after a 25-g load.¹³ In group B one patient had jejunal diverticulosis with gross bacterial overgrowth, but her response to the xylose test was normal. In group C 10 patients had detailed bacterial studies on small-bowel contents, and these have been reported elsewhere.¹⁵ Three of these patients had significant bacterial overgrowth in the upper small-bowel, and although all gave rather borderline results in none were they strictly abnormal. Of the five patients in this group who gave an abnormal response to the xylose test bacterial studies were performed in only one, and showed minimal overgrowth in the lower jejunum. Small-gut ischaemia may have impaired xylose absorption in the one patient who died soon afterwards from massive small-gut infarction. Other causes of reduced renal excretion of xylose, such as hypothyroidism¹⁴ and ascites,⁶ are not relevant to this survey.

In relation to Crohn's disease malabsorption is often invoked as an explanation for loss of weight, anaemia, and other deficiencies. In this study urine excretion data alone suggest that jejunal malfunction was common in these patients. However, in most the serum levels were normal and a strictly abnormal result was uncommon. In contrast to most of the patients in the other groups these patients were generally ill enough to warrant admission to hospital for consideration of specific medical or surgical treatment of their disease. Most had lost weight and many were anaemic, yet jejunal malfunction as judged by a strictly abnormal response to the xylose test was rare. Presumably many of these patients had occult renal dysfunction to account for the subnormal urinary excretion, yet only three patients in this group were aged over 60 and only one other had a moderately raised blood urea (40 mg/100 ml). On the basis of an earlier study, which included some of these patients, Dyer and Dawson¹⁶ also concluded that malabsorption was uncommon in Crohn's disease and that the findings of the xylose test were easily misinterpreted in this context. Moreover, even a strictly abnormal xylose test result does not necessarily indicate frank jejunal involvement by the disease. In this series only five patients had evidence of extensive jejunal disease and they all gave a normal response to the test, although in two the results were borderline.

In patients without evidence of other gastrointestinal lesions a strictly abnormal result will usually indicate a significant mucosal lesion. For the non-specialist, who may have to refer patients elsewhere for jejunal biopsy, this may provide a useful and simple screening test. However, its value is offset by the fact that almost a third of the patients in group D in this study gave results that were not strictly abnormal. This may reflect a milder functional abnormality and may be a frequent observation now that jejunal biopsies are increasingly performed on patients without gross generalized malabsorption. Nevertheless, no patient in this group gave a strictly normal response—that is, both values within the normal range. In our experience more useful indications for

jejunal biopsy include any prolonged and unexplained diarrhoea, non-specific abnormalities on barium follow-through examination, evidence of folate depletion, and, rarely, Howell-Jolly bodies in the red cells¹⁷ and unexplained osteomalacia. It cannot be stressed enough that a diagnosis of coeliac disease and the institution of a gluten-free diet should ideally never be based on any of these indirect assessments but solely on the evidence of jejunal morphological change and its subsequent response to treatment.

In conclusion, using strict criteria an abnormal response to the xylose test is found in the majority of patients (but not all) with a significant jejunal mucosal lesion and in a small minority of patients with Crohn's disease and assorted other gastrointestinal conditions. Its diagnostic usefulness as a screening test for jejunal biopsy is therefore limited. Evidence based on urinary excretion data alone can be very misleading in that malabsorption will be incorrectly diagnosed in many patients with Crohn's disease and in many with a perfectly normal jejunal mucosa. In the majority of such patients normal serum concentrations indicate that the fault lies in the disposal and not the absorption of xylose. There seems to be no reason to retain the xylose test as used in this survey in centres where a jejunal biopsy can readily be performed.

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