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Specialist Interest Articles

Aggressive Chemotherapy for Acute Leukaemia Frequently Causes Intestinal Protein Leakage

Simon Daenen, Frits A.J. Muskiet, Jan Marrink and M. Ruud Halie

Cytostatic drugs are known to produce disturbances in intestinal absorption of carbohydrates. To further explore the gastrointestinal (GI) toxicity of cytostatic therapy, 37 patients with acute leukaemia were investigated during and/or after remission induction courses by the use of the differential sugar absorption test (DSAT) and the intestinal clearance of alpha-1-antitrypsin (Cl_{AAT}). The ratio of the lactulose to the mannitol excretion in the urine was found abnormal in 44% of the tests. The Cl_{AAT} was increased in 74% of tests. The test results differed considerably from patient to patient and depended on the chemotherapy course; correlation between the tests was low, probably indicating that unrelated pathophysiological processes were measured. After haematological regeneration, abnormal test results normalised. It is concluded that aggressive chemotherapy not only causes a reduction in the absorption of sugars, but commonly also protein leakage. These GI side-effects are reversible, and the application of both tests in combination provides a practical and reproducible method for investigation of GI toxicity in patients treated with cytostatic drugs.
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INTRODUCTION

TREATMENT WITH cytostatic drugs can lead to moderate to severe gastrointestinal (GI) side-effects [1–3]. Some of these, such as nausea, vomiting and diarrhoea, are easily recognised and the clinical situation mostly suggests a direct relation with the cytostatic therapy. Impairment of the intestinal mucosa is less well explored, especially when aggressive anti-leukaemia type chemotherapy is administered. Invasive methods of investigation are not applicable when the patient is deeply pancytopenic. Breath hydrogen tests, as used by Hyams *et al.* [4], are of limited value when antibiotics are given prophylactically, or otherwise. Other investigators [5] used the xylose absorption test and found a trend towards an increasing incidence of life-threatening infections when xylose absorption was decreased. Parrilli *et al.* [6] investigated early changes in intestinal permeability to lactulose; they concluded that this test was more sensitive than other absorption tests, or even biopsy.

We studied the differential absorption of sugars (differential sugar absorption test, DSAT) and the intestinal clearance of alpha-1-antitrypsin (Cl_{AAT}) in 37 evaluable patients treated with aggressive chemotherapy for acute leukaemia. Until now, DSAT is used mainly for diagnosis and follow up of mucosal damage in coeliac disease [7–9]. Abnormal DSAT is based on a reduction of the active absorption via the aqueous pores of a monosaccharide, mostly mannitol [10], and/or an increase of the permeability via an intercellular pathway of a disaccharide, mostly lactulose. When the number of cells and the absorptive surface are reduced by the cytostatic drugs, absorption of mannitol is expected to decrease; when the tight junctions of the cells in the mucosal lining are damaged or subendothelial structures lie bare altogether, passive diffusion of lactulose can be expected to increase.

The anti-enzyme AAT is normally secreted in small amounts in the intestinal lumen. Since it is not degraded by intestinal

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Table 1. GI toxicity, measured by DSAT and Cl_{AAT} during aggressive chemotherapy in 28 patients with acute leukaemia

Patient	Age	Mannitol	Lactulose	L/M	Cl_{AAT}	Complaints
OPA scheme						
1 a	17	–	–	0.057	100	
b		–	–	0.046	143	
2	37	1.90	0.080	0.042	–	
3	57	–	–	0.040	14	
4	55	2.43	0.081	0.033	10	
5	20	0.72	0.031	0.043	[1.9 mg/g]	
6	40	0.74	0.023	0.031	33.5	Nausea (1)
7	22	1.20	0.043	0.036	[3.3 mg/g]	Sore throat
8 a	32	0.73	0.138	0.189	15	
b		0.77	0.021	0.027	16.5	
9	22	–	–	–	16	
AraC-DNR scheme						
10	19	–	–	–	76	Stomatitis (2), hyperperistalsis
11	31	6.96	0.023	0.003	21	Abdominal cramps, diarrhoea (1)
12	61	–	–	0.310	148	Nausea, anorexia, diarrhoea (2–3)
13	22	2.12	0.037	0.017	9	Diarrhoea (1)
14	62	1.01	0.010	0.010	–	
15	45	1.40	0.030	0.021	–	
16	43	2.73	0.362	0.133	116	Hyperperistalsis
17	29	–	–	–	22	
18	17	1.23	0.108	0.088	5.2	Nausea, diarrhoea
19	50	0.75	0.061	0.081	43	Dysphagia (3)
20	60	0.10	0.004	0.040	59	Diarrhoea (1)
21	35	2.11	0.133	0.063	42	Anorexia(1)
22	36	2.26	0.123	0.054	51	
AraC-AMSA scheme						
11	31	9.95	0.054	0.005	7	Abdominal cramps, mucositis (1)
12	61	0.95	0.048	0.051	10.5	Nausea, diarrhoea
14	62	1.12	0.061	0.054	–	
15	45	1.05	0.246	0.234	23	Nausea, vomiting
18	17	1.23	0.108	0.088	[2.5 mg/g]	Nausea, diarrhoea
20	60	0.96	0.009	0.009	–	
21	35	–	–	0.150	6	
23	47	1.25	0.285	0.228	10.5	Anorexia (1), diarrhoea (1)
24	24	1.13	0.007	0.006	11	Vomiting (2–3), diarrhoea (2–3)
25	26	–	–	–	140	Oesophagitis (3), diarrhoea (1)
26	56	0.27	0.000	0.000	8.5	Diarrhoea (1)
27	24	0.64	0.097	0.152	–	Diarrhoea (1), mucositis (2)
28	50	0.25	0.049	0.196	137	Diarrhoea (3), abdominal distention
29	49	0.28	0.010	0.036	15	
30	67	–	–	–	152	Vomiting, diarrhoea, nausea, distention
31	30	3.36	0.100	0.030	16	
32	26	0.93	0.027	0.029	8.5	Abdominal cramps, diarrhoea (2)

Employed chemotherapy schemes: OPA: vincristine 1.5 mg/m²/day intravenously days 1, 8, 15; prednisone 60 mg/m²/day orally days 1–21; doxorubicin 40 mg/m²/day intravenously days 2–4.
AraC-DNR: cytarabine 200 mg/m²/day continuous intravenous infusion × 7; daunorubicin 45 mg/m²/day intravenously days 1–3.
AraC-AMSA: cytarabine 1000 mg/m²/12 h intravenously × 12; amsacrine 115 mg/m²/day intravenously days 1–3.
OPA was used in patients with ALL. AraC-DNR and AraC-AMSA were used as first and second chemotherapy course for remission induction and/or consolidation of patients with AML. DSAT = differential sugar absorption test; L/M = ratio of lactulose to mannitol excretion (ref: 0.000–0.047); Cl_{AAT} = intestinal clearance of alpha-1-antitrypsin (ref: up to 10 ml/d); – = not done, or not given because of inadequate sampling (in some cases L/M could still be determined); (1–4) indicates grading of complaints, according to WHO criteria. The concentration of AAT in faeces when no clearance could be calculated (ref: < 2.6 mg/g dry weight) is shown in square parentheses.

enzymes, its faecal content may be used as a measure for protein leakage from the circulation into the GI tract [11]. There is a good correlation between the faecal excretion of AAT, expressed as the intestinal clearance (Cl_{AAT}), and faecal loss of IV-injected ^{51}Cr-labelled albumin [12]. Although protein loss has not been reported in patients with cancer chemotherapy until now, it is easily conceivable that cytostatics-induced mucosal injury can lead to intestinal protein leakage.

PATIENTS AND METHODS

Patients

37 patients admitted to the haematology ward for aggressive chemotherapy of acute myeloblastic (AML) or acute lymphoblastic leukaemia (ALL) were eligible for the study. Patients with severe nausea or vomiting for any cause, patients with diabetes mellitus, and patients in critical clinical condition due to infections or haemorrhage were excluded. Abnormal kidney function was not a reason for exclusion when it was not a contraindication for aggressive chemotherapy *per se*, since changes in renal handling were expected to affect both sugars in the same way and not to interfere significantly with the outcome of DSAT. When patients could not be treated immediately because of circumstances not related to this study, the tests were performed before the start of chemotherapy. All patients were tested 10–12 days after the start of the chemotherapy. When the patient was still in the hospital at the time of complete regeneration, the tests were repeated at that time.

Treatment

Patients treated with chemotherapeutic schemes given in the footnote to Table I were selected for the study. All received

oral antibiotics prophylactically. Supportive care was given according to standard practice, including platelet transfusions, and systemic antibiotics in case of established or suspected infection.

Differential sugar absorption test (DSAT). After an overnight fast, patients were given 2 g mannitol and 5 g lactulose with 40 g of sucrose in water (150 ml). Sucrose was added to increase the osmolarity of the solution, thereby improving the absorption and as a result the sensitivity of the test [13]. Urine was voided at the start of the test and then collected for 5 hours. Patients were instructed to drink plain water. They were not allowed to take food or other beverages during the test. Drugs interfering with intestinal motility or secretory activity were temporarily withheld. Sugars in the urine were determined by a capillary gas chromatographic method [14]. Reference values for mannitol were 1.114–4.118 mmol/l/5 h, for lactulose 0.000–0.089 mmol/l/5 h, and for the lactulose:mannitol (L/M) ratio 0.000–0.047. A solitary decrease of mannitol without increased lactulose and with normal L/M ratio was considered to result from inadequate urine collection and was not counted as abnormal.

Alpha-1-antitrypsin clearance (Cl_{AAT}). Faeces were collected for three consecutive days, pooled and freeze-dried. AAT was determined by the F Behring Nephelometer-Analyser (Behringwerke AG, Germany) and expressed in mg/g. On days 1 and 3, AAT was also measured in plasma by the same nephelometric assay. The mean was used in a clearance formula $Cl_{AAT} = AAT_F \times W_F / AAT_{PL}$, in which: AAT_F = concentration of AAT in pooled faeces, in mg/g faeces; AAT_{PL} = mean concentrations of AAT in plasma in mg/ml; W_F = mean 24 h faecal weight, in g/d. Reference value of Cl_{AAT} was up to 10 ml/d. When faecal volume was to low for measurement of the clearance, AAT was expressed in mg/g faeces. Reference value was < 2.6 mg/g dry weight.

RESULTS

Feasibility of the test

Most patients tolerated the sugar solution surprisingly well. 7 patients (19%) complained of nausea. 2 vomited after drinking the test solution and refused to take it later on. 5 patients (13.5%) had passage of one or two soft stools, and 12 (32.4%) had a transient increase in bowel sounds. None of the patients had severe renal function abnormality. However, in this study population only few tests could be performed before the start of the chemotherapy because treatment cannot be delayed 3 days in case of acute leukaemia. After regeneration the number of tests was low because at that time most patients are not willing to undergo an unnecessary examination and because it is unethical and uneconomical to keep the patient in the hospital.

DSAT and Cl_{AAT} in acute leukaemia before aggressive chemotherapy

10 patients underwent DSAT before any cytostatic drug was given. In 1 with B-cell ALL and an abdominal mass, urinary excretion of lactulose (0.161 mmol/5 h) and L/M ratio (0.132) was increased without obvious reason. All other values were in the normal range.

Pretherapeutic Cl_{AAT} could be measured in only 3 patients. In 1 with AML following a myelodysplastic preleukaemic phase Cl_{AAT} was found to be increased (22 ml/d), without clinical signs, nor apparent cause.

Table 2. Results of DSAT and Cl_{AAT} in patients after haematological recovery from remission induction therapy for acute leukaemia

Patient	Mannitol	Lactulose	L/M	Cl_{AAT}
A. Patients with abnormal test results during chemotherapy (see Table 1)				
1 a	–	–	0.046	6.5
8 a	0.05	0.003	0.060	10
12	–	–	0.035	15
22	2.48	0.057	0.023	11
25	–	–	–	4
26	1.93	0.040	0.021	3
29	2.24	0.027	0.012	10
B. Additional patients*				
33	2.41	0.045	0.019	–
34	0.41	0.008	0.019	11
35	0.74	0.010	0.013	4.5
36	–	–	0.040	3
37 a	0.90	0.017	0.019	–
b	1.41	0.012	0.009	–

* Not tested during chemotherapy or abnormal on deviant chemotherapy.

DSAT and Cl_{AAT} during aggressive chemotherapy

Table 1 gives the test results, subdivided according to chemotherapy regimen. Also indicated are GI complaints, which occurred in the aplastic phase. Patients were tested 10–12 days after aggressive chemotherapy. Complaints were documented during the whole chemotherapy course and in most cases were not present during the test. 5 h urinary excretion (mmol/l) of mannitol (reference values: 1.114–4.118 mmol/l); and of lactulose (ref: 0.000–0.089 mmol/l) are shown). Mucosal damage as measured in these tests, varied considerably from patient to patient, and from one kind of chemotherapy to the other. 26 of 32 patients (81%) examined following a chemotherapy course showed abnormalities in one or both tests. The outcome of the two tests was concordant in only 57% (37% both abnormal, 20% both normal) and there was no correlation between the tests in the individual patient. Cl_{AAT} was more often disturbed than DSAT (74 vs 44%). In 8 cases mannitol was decreased but L/M normal, probably indicating that urine collection was inadequate (see Materials and Methods). In 2 patients the same chemotherapy course (OPA) was given twice: Cl_{AAT} was about the same in both courses, but the L/M was more affected during the first than during the second course.

On 30 of the 42 occasions both DSAT and Cl_{AAT} were performed simultaneously after a chemotherapy course. 6 (20%) were normal in both tests, 3 (10%) had abnormal DSAT only, 9 (30%) abnormal Cl_{AAT} only, and 12 (40%) both abnormal DSAT and abnormal Cl_{AAT}.

DSAT and Cl_{AAT} after haematological recovery from aggressive chemotherapy

Table 2 gives the results for DSAT and Cl_{AAT} after haematological regeneration in 7 of the patients with abnormal test results following chemotherapy. In addition, Table 2 shows results after regeneration for 5 additional patients who were not tested during chemotherapy, or whose results were not included in Table 1 because of deviant chemotherapy courses. For some (8a, 34, 35 and 37a) mannitol remained decreased, but with one exception (8a), lactulose and L/M were in the normal range. As

mentioned earlier this might indicate inadequate urine collection rather than mucosal damage. For 3 (11, 22 and 34) Cl_{AAT} remained marginally increased but apparently much less so than immediately after chemotherapy.

DISCUSSION

The GI toxicity of current aggressive chemotherapy for acute leukaemia has not been studied extensively. This is probably due to practical constraints caused by the disease, and by the chemotherapy itself: patients are often in bad condition and have an increased risk of infections and haemorrhage. Nevertheless, it would be important to gain insight into the pathogenesis and the extension of intestinal damage. Toxicity to the GI tract may enhance infectivity, interfere with adequate feeding, and become more and more the limiting factor for the further intensification of chemotherapy.

In the present study, we combined a test which measured simultaneously active intestinal absorption of mannitol and passive diffusion of lactulose, with one that estimated intestinal protein loss. All patients were deeply pancytopenic for a prolonged time. The tests were tolerated remarkably well, although they were performed only a few days after commencement of chemotherapy, which could cause severe nausea and vomiting by itself. 2 patients refused to swallow the test solution because it caused abdominal discomfort. Some had a transient increase in bowel sounds and even diarrhoea, obviously caused by the 5 g of lactulose in the test solution. This was never so severe as to incite reconsideration of the feasibility of the study.

The tests measure different pathophysiological processes. Our results showed that their combination detected mucosal damage more effectively and more sensitively than any of them separately. The correlation between Cl_{AAT} and DSAT appeared even to be low. This could mean that each test explored different parts of the alimentary tract which were not affected to the same extent, e.g. absorption of mannitol mainly in the upper small bowel, diffusion of lactulose throughout the small bowel, and protein loss over the entire GI tract from mouth to rectum. Another explanation could be that the observed lack of correlation was caused by differences in the capacities to compensate for reduced absorption of M, or loss of protein, in parts of the bowel which were less affected.

Absorption of the monosaccharide xylose has been studied most extensively, with variable outcome. Craft *et al.* [15] documented a progressive increase of intestinal methotrexate toxicity in children with ALL. On the other hand, Pegues *et al.* [5], and Reis *et al.* [16] did not observe consistent changes in patients in remission from AML, or in different solid tumours, respectively. However, Pegues [5] found an increased incidence of infections when xylose absorption was decreased. In the DSAT we replaced xylose by mannitol, which is metabolically more inert [7]. We did not find a correlation between impaired mannitol absorption and infections (data not shown), probably because all our patients received prophylactic antibiotics aimed at the elimination of *Staphylococcus aureus*, gram negative bacteria, and yeasts from the gut [17].

Parilli *et al.* [6] examined 9 lymphoma patients with a test similar to our DSAT. They observed early increases in the intestinal permeability to lactulose and suggested that lactulose absorption was the most sensitive test for the detection of GI side-effects of cytostatic drugs. Our patients were treated more aggressively and tested later than those of Parilli, at a moment considered to be optimal for the detection of cellular damage. The addition of mannitol to lactulose in the test solution had the considerable advantage of making it possible to calculate the L/M ratio. Variations in bowel transit time, inadequate collection of urine, and impairment of renal function influenced the GI absorption as well as the urinary excretion of both sugars similarly. Therefore, a ratio greatly reduced the problems of interpretation which arose when abnormal values were found in cases where either or both substances were measured alone.

The frequent derangement of the Cl_{AAT} indicated that cytostatic drugs often led to protein loss from the gut. To our knowledge, this has not been reported before. In fact, the Cl_{AAT} was even more frequently deranged than the L/M ratio and thus might be a more sensitive assay to document bowel toxicity of cytostatic drugs. Recently, intestinal infections such as *Clostridium difficile* [18] and cytomegalovirus [19] have also been recognised as possible causes of protein leakage. We screened for these organisms routinely when our patients developed diarrhoea but they were never demonstrated, so were probably not the cause of the protein loss in this study. The possibility that the protein loss was due to occult bleeding was not investigated systematically, but was not documented when occasionally searched for.

After haematological regeneration the test results normalised in the majority of patients. In addition, some patients (1, 8, 11, 12, 20) showed a better outcome when tested during the second (OPA or AraC-AMSA) than during the first (OPA or AraC-DNR) chemotherapy course, which also seems to indicate that the mucosal damage *can* be reversible. However, others did not show much difference (18, 20) or were more severely affected (11, 14, 15, 21) during the second course. The latter could point to cumulative toxicity, which would hamper the use of these assays for comparison of GI toxicity of sequentially administered cytostatic drugs in individual patients. Even so, the tests could be useful to compare the GI toxicity of different chemotherapy regimens in groups of patients.

There was no strict correlation between the test results and clinical signs or complaints of GI toxicity. It seems that the information gained by these tests is complementary, and more specifically directed at the small and to a lesser extent the large bowel. They have the advantage that the intestinal damage can be quantitated objectively and reproducibly. They are easy to perform and cause minor trouble for the patient, except for the most severely ill. They offer more information than the ^{51}Cr-EDTA absorption test (a measure for the intercellular pathway only) and the faecal excretion of ^{51}Cr-labelled albumin (which cannot be combined with the former), without the problems related to the use of radioactive substances. Polyethylene glycols have also been used for the study of intestinal absorption and seem to be suited especially for the study of the aqueous pores because their molecular size can vary widely. However, they are difficult to assay [7] and require complex mathematical calculations whose value is still questionable [20].

In conclusion, the DSAT and the Cl_{AAT} are relatively simple and reproducible tests, which in combination are well suited for the measurement and follow up of GI toxicity due to cytostatic drugs. These cytostatic drugs often induce intestinal protein loss which, together with other side-effects, appears largely reversible. The tests may be useful for the investigation and comparison of the GI toxicity of different cytostatic drugs and drug regimens.

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Palliative Surgery of Metastatic Bone Disease: a Review of 83 Cases

B. Bono, P. Cazzaniga, V. Pini, S.M. Zurrida, R. Spagnolo, L. Torelli, C. Corona and A. Bono

Of a total of 83 patients with metastatic bone disease, surgery was performed in 17 cases at the prefracture stage, in 54 cases after complete fracture and in 10 cases to decompress the spinal cord. Positive short-term results were obtained in 75% of cases. 7 patients presented mild complications. In 2 cases, the patients had to be reoperated. 55% of the patients were still alive after 6 months, 31% after 12 months and 10% after 2 years.
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INTRODUCTION

THANKS TO the advances in cancer therapy and supportive therapy, the survival of patients with metastatic carcinoma has increased and their quality of life has significantly improved in recent years [1–3]. In the 1960s survival after onset of bone metastases was estimated at less than a year, but many patients today enjoy a life expectancy of over 2 years even after pathological fracture [4–7].

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Bone metastases are very frequently observed in patients with carcinoma of the breast, lung, prostate gland and other sites, and although a grave occurrence, they are no longer considered to mark the beginning of the terminal phase of the illness. Pain, pathological fracture, neurological deficit and forced immobility, however, all significantly reduce patients' quality of life [8, 9].

When used in conjunction with other palliative therapies, "palliative surgery" of bone metastases is beginning to play an important role in providing both physical and psychological relief to these patients [10, 11].

The present study reports on more than 10 years of surgical treatment of bone metastases at a large general hospital.

MATERIALS AND METHODS

A retrospective study was carried out on 349 patients with skeletal metastases hospitalised at the Divisione II di Ortopedia