Possible interactions between dietary fibres and 5-aminosalicylic acid

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Abstract:

Background: Potentially, a binding of 5-aminosalicylic acid (5-ASA) to dietary fibres could reduce the systemic absorption and increase the intraluminal amount. The purposes of the study were to investigate if: (1) dietary fibres can bind 5-ASA *in vitro*, and (2) consumption of dietary fibres is related to disease activity in patients with ulcerative colitis (UC) treated with 5-ASA.

Methods: *In vitro*: 15 g of Ispaghula Husk, wheat bran, citrus-pectin, or wheat flour were incubated in a 37°C buffered solutions of 5-ASA (1 g/l) for 3 hours at pH 6 and 7. The concentrations of 5-ASA were determined before and after the incubation using HPLC. *In vivo*: patients with UC were interviewed two to three times during 6 months. The fibre consumption was estimated and related to the disease activity (CAI, CRP, Faecal-calprotectin) and quality of life (IBDQ).

Results: *In vitro*: 5-ASA was bound to Ispaghula Husk (5.3–10.0 mg/g) and wheat bran (4.6–5.5 mg/g), and to a minor degree to citrus-pectin. No differences were found in relation to pH. *In vivo*: 29 patients completed the scheduled interviews. No significant changes in fibre consumption were observed over time; however, patients consuming a diet high in fibre (>20 g/day) had significantly lower CRP ($p < 0.01$) and faecal-calprotectin ($p < 0.01$) than those consuming less fibre (<20 g/dg).

Conclusions: Patients with a high intake of fibre had a lower disease activity than those with low intake. Ispaghula Husk bound 5-ASA *in vitro*, independent of pH. The effect might be clinically relevant in patients with UC treated with 5-ASA.

Keywords: 5-ASA, bioavailability, dietary fibres, ulcerative colitis

Introduction

Food–drug interactions can be associated with alterations in the pharmacokinetic and pharmacodynamic profiles of various drugs, which can result in increased or decreased bioavailability of the medication and consequently cause unwanted clinical effects or lack of effects [Singh and Malhotra, 2004; Harris *et al.* 2003; Doherty and Charman, 2002; Schmidt and Dalhoff, 2002; Singh, 1999; Melander and McLean, 1983]. This may have consequences for the treatment of the patients and the progress of their disease.

Orally administrated drugs normally dissolves in the stomach or intestinal fluid and are absorbed from these regions of the gastrointestinal canal depending on the physical–chemical properties of the drug, but ingested meals may change these conditions. Localized delivery of the drugs

(e.g. 5-aminosalicylic acid (5-ASA) to the colon rather than absorption in the upper gastrointestinal canal) is essential in the treatment of ulcerative colitis (UC) [Cohen, 2006]. A high intake of dietary fibres has been shown to reduce the effect of lovastatin dramatically and to a clinically relevant degree in patients with hyperlipidemia due to the binding of the drug to dietary fibres in the intestine [Richter *et al.* 1991]. This binding capacity might be a therapeutic gain in the treatment of UC with 5-ASA, as a high local concentration in the colon is wanted, and as side effects of 5-ASA are mainly attributed to the absorbed fraction. The purposes of the study were (1) to investigate if dietary fibres could bind 5-ASA *in vitro*, and (2) to investigate if a relation between consumption of dietary fibres and disease activity could be plausible in patients with UC in long-term treatment with 5-ASA.

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Materials and methods

In vitro experiment

Fifteen grams of Ispaghula Husk, wheat bran, citrus pectin, or wheat flour were placed in a tea bag and incubated for 3 hours at 37°C in 350 ml liquid solution of 1 mg 5-ASA/ml water. Afterwards the solutions were analyzed for changes in the concentration of 5-ASA using HPLC (high performance liquid chromatography). The experiment was carried out at pH 6 and pH 7, respectively, buffered with NaOH. Amount of fibre-bound 5-ASA in excess of fibre-bound water was calculated.

HPLC

HPLC was used to measure the concentration of 5-ASA. The analytical column consisted of 'Eclipse XDB C8, 3.5 µm, 150 × 4.6 mm'. The mobile phase was acetonitrile with 0.2 M potassium citrate buffer pH 6.0 and water (15:5:80 v/v/v) with 2.0 g of tetrabutylammonium hydrogen sulphate added per litre at detection 254 nm and 315 nm. The analysis was carried out at a column temperature at 30°C and with a flow-rate of 1 ml/min.

In vivo clinical investigation

An open-label observational study was conducted at Hvidovre Hospital for a 6-month period. Consecutive patients fulfilling the inclusion criteria were invited to participate. Of the 53 patients showing up in the outpatient clinic, 34 patients (17 males, 17 females) agreed to participate in the study. Baseline characteristics are shown in Table 1.

The patients aged 19–88 (median 42) had been in oral 5-ASA maintenance therapy for at least 1 month prior to the study, but were not treated with steroids at the time of inclusion. The patients were interviewed two or three times depending on the duration of their stay in the study. At the interview, fibre consumption for the preceding 2 weeks was estimated and related to disease activity and quality of life. Disease activity was estimated using Clinical Activity Index (CAI), plasma C-reactive protein (CRP), and F-calprotectin; and quality of life was estimated by use of the Inflammatory Bowel Disease Questionnaire (IBDQ). A retrospective question about relapses during 2008 was added to compensate for the differences in observation times.

Statistic

The Mann–Whitney rank sum test and the Wilcoxon signed rank sum test was used for unpaired and paired comparisons respectively supplemented with the Fishers Exact test. Spearman's rank correlation test was used to analyze for possible correlation between consumption of fibre and disease activity.

Ethics

The investigation was approved by the regional ethical committee, and conducted in accordance with the standards of the Declaration of Helsinki.

Results

The *in vitro* experiment showed a reduction in the amount of 5-ASA in the solution with Ispaghula Husk and wheat bran and a lesser reduction with citrus pectin and wheat flour. No significant

Table 1. Baseline characteristics for patients with ulcerative colitis in long-term treatment with 5-aminosalicylic acid, *n* = 34.

Patient characteristics	Median (range)	Diagnosis and treatment characteristics	Median (range)
Gender		Diagnose	
Male, <i>n</i>	17	Haemorrhagic proctitis, <i>n</i>	10
Female, <i>n</i>	17	Procto-sigmoiditis, <i>n</i>	4
Age, year	42	Left-sided colitis, <i>n</i>	13
	[19–88]	Pancolitis, <i>n</i>	7
Weight, kg	75	Years with the diagnose	10
	[51–132]		[2–44]
Height, m	1.72	Medication	
	[1.53–1.86]	Salazopyrin®/Sulfasalazine, <i>n</i>	5
BMI, kg/m ²	25.3	Dipentum®/Olsalazine, <i>n</i>	1
	[17.6–39.4]	Asacol®/Mesalazine, <i>n</i>	24
		Pentasa®/Mesalazine, <i>n</i>	4
		Doses, mg	2400
			[800–4000]

differences were found between pH 6 and pH 7. Ispaghula Husk reduced the 5-ASA content with 8.6 mg/g and 6.1 mg/g at pH 6 and pH 7, respectively; wheat bran with 4.7 mg/g and 5.2 mg/g; citrus pectin with 1.9 mg/g and 2.0 mg/g; and wheat flour with 1.7 mg/g and 1.3 mg/g. Data are shown in Table 2. The two reference tests incubating empty tea bags showed an increased mean amount of 4.4 mg 5-ASA (1.3%) at pH 6, and a decreased mean amount of 0.3 mg 5-ASA at pH 7 (0.09%), indicating that the choice of bags was without systematic influence on the results.

In vivo investigation

Of the 34 patients included 29 completed more than one of the scheduled interviews. One was excluded because of pregnancy and four patients did not show up for the second interview. Seventeen patients participated in three interviews and 12 patients participated in two interviews. The median observation time was 100 days (range 64–182 days). Based on the patients' daily oral dose of 5-ASA, they were divided into three groups administering doses of 800–1999, 2000–2999 and 3000–4000 mg 5-ASA. No significant changes in fibre consumption over time

was observed, however, the group administering 2000–2999 mg 5-ASA experienced a significant drop in CRP ($p < 0.05$) and CAI ($p < 0.01$) between the first and the second interview. A comparison between patients with high (> 20 g/day) and low (< 20 g/day) total fibre consumption showed a significant lower CRP ($p < 0.01$) and F-calprotectin ($p < 0.01$) in the high-fibre group. The same effect was found in relation to grain fibres, CRP ($p < 0.05$) and F-calprotectin ($p < 0.05$).

Simple comparison between the highest and the lowest fibre consumption in 'total amount', 'fruit/vegetable fibres', and 'grain fibres' indicated that the patients with the lowest consumed amount in 70% (16/23), 52% (12/23), and 48% (11/23) of the cases respectively had a higher disease activity compared to the patients with the highest consumed amount. Data are shown in Table 3.

Discussion

In vitro experiment

A similar *in vitro* experiment has not been published. Accordingly, we constructed our

Table 2. The amount of 5-aminosalicylic acid bound to different kinds of fibres/starch *in vitro* (pH 6/pH 7).

Material	Amount of 5-ASA expected (control deducted), mg	Amount of 5-ASA measured in the solution after incubation, mg	Amount of 5-ASA bound to the fibre/starch, mg	Amount of 5-ASA bound per g fibre/starch, mg/g
HUSK 1	347.5/347.1	240.3/242.9	107.2/104.2	7.1/6.9
HUSK 2	352.5/346.8	203.0/267.1	149.5/79.7	10.0/5.3
Wheat bran 1	345.1/346.0	276.3/262.9	68.8/83.1	4.6/5.5
Wheat bran 2	349.3/347.1	277.1/274.3	72.2/72.8	4.8/4.8
Pectin 1	347.7/346.7	320.0/320.6	27.7/26.1	1.9/1.7
Pectin 2	346.7/348.1	316.6/314.6	30.1/33.5	2.0/2.2
White flour 1	346.8/346.4	320.9/329.9	26.0/16.5	1.7/1.1
White flour 2	347.3/346.8	392.5/323.4	−45.2/23.5	−3.0/1.6

5-ASA, 5-aminosalicylic acid.

Table 3. Incidents where the one *versus* the other level of intake indicate increased disease activity; 23 incidents in each case.

	Total intake of fibre		Intake of fibre from fruit and vegetable		Intake of fibre from grain products	
	High intake	Low intake	High intake	Low intake	High intake	Low intake
800–1999 mg 5-ASA	3	4	2	3	2	4
2000–2999 mg 5-ASA	1	6	1	6	2	2
3000–4000 mg 5-ASA	2	6	5	3	1	5
Total numbers of incidents	6	16	8	12	5	11

5-ASA, 5-aminosalicylic acid.

own design. The amount of 5-ASA used (1 g/l) is clinically realistic, as daily doses in the relevant patients vary from 800 mg to 4 g. The amount of 5-ASA bound to fibres is determined by at least two factors, the ability to bind water and the specific binding of 5-ASA by ionic bonding, water bonding or other kinds of linkage. We have assumed that the concentration of 5-ASA in water was the same, whether the water was in the solution or bound to fibres. This was not verified in the experiment. Calculating the amount of 5-ASA no longer in the solution and after adjusting for the amount of water bound in the fibres, we found major differences between the types of fibres. The reduction was highest in the samples with Ispaghula Husk and wheat bran, which also had the largest binding of water. The net binding of 5–10 mg/g fibre could be clinically relevant, if the binding is sufficiently strong to prevent absorption of 5-ASA. This question cannot be answered by the present experiments. The sample sizes in the experiments were small, so the results are sensitive to confounders of many kinds, but the design was chosen to explore whether it might be worthwhile to continue this line of thinking. The tea bags with Ispaghula Husk were expanded after the incubation due to the high water-binding capacity, which might have impeded contact between the solution of 5-ASA and Ispaghula Husk, and thereby underestimated the binding of 5-ASA. The binding was highest in the samples with Ispaghula Husk followed by wheat bran, pectin and wheat flour in descending order.

In vivo investigation

The observational study was intended as a screening for major effects as a reference to the experimental results. The disease activity was established both by questionnaire and measurements in blood and faeces, but the number of patients was too small to detect relevant correlations, or the observation period and number of measurements per patient too short, as patients did not change their intake of fibres spontaneously. Accordingly, we were unable to observe a direct relationship between activity in the disease and the intake of fibres within the same patient. A larger number of patients were not available in the period of time due to a combination of many factors including nurses' strike and reorganization of the health system. Intervention studies will be necessary to answer the questions about clinical relevance, and such studies would be both clinically and ethically

justified on the basis of our preliminary results. Among the many problems with observational studies in this field are the heterogeneous patient population both concerning extension of disease, activity of disease, compliance to medication, concomitant rectal treatment, additional therapies (i.e. herbs) and others. Low compliance, with only 20–50% administering the prescribed medication, was estimated in a study with patients having UC in remission [Kane *et al.* 2008]. Our results showed no relationship between the daily intake of dietary fibres and the disease activity between patients. But a simple comparison between the extremes related to intakes of dietary fibres (highest *versus* lowest intake) indicated that a higher intake of dietary fibres was related to less disease activity. A coherence between the intake of dietary fibres and disease activity has been found in interventions studies with patients with UC and oral treatment with 5-ASA. In these studies they used other outcome measurements like maintaining of remission in 12 months [Fernandez-Banares *et al.* 1999] and occurrence of specific symptoms for the disease [Hallert *et al.* 1991].

This possible coherence between the intake of dietary fibres and disease activity is not necessarily caused by an increased delivery of 5-ASA to the inflamed area in colon because of binding of 5-ASA to dietary fibre. It may also be due to increased production of short chain fatty acids (SCFA) in the colon.

The risk of side effects such as interstitial nephritis caused by systemic absorption of 5-ASA restrains the use of high doses for treatment [Frandsen *et al.* 2002; Riley *et al.* 1992; Staerk Laursen *et al.* 1990]. About 30% of an oral administration dose of 5-ASA (coated, time-released or azo-bound) is absorbed, and can potentially cause side effects [Klotz, 1985]. If our experimental results are valid in patients, and the binding is linear, an amount of 87.7–122.9 g Ispaghula Husk (pH 6 and pH 7 respectively) is theoretically needed to bind a dose of 720 mg 5-ASA (30% of a dose of 2400 mg 5-ASA). This is three to four times the recommend daily dose of Ispaghula Husk and would require a very large intake of water. An intake of the usually recommended 30 g HUSK could theoretical bind 7–11% of a 2400 mg dose of 5-ASA. Whether this is sufficient to reduce the risk of side effects of 5-ASA to a relevant degree is not known.

Results from intervention studies in which patients with UC were treated with 20 g Plantago seed and 1500 mg Claversal[®] [Fernandez-Banares *et al.* 1999] or 4 g Vi-Siblin[®] (3.52 g Ispaghula Husk) where 70% of the patients were administered Sulphasalazine[®] [Hallert *et al.* 1991] have shown beneficial effect in maintaining remission and a significant reduction in disease-specific symptoms.

Riley studied the effect of 7 g Ispaghula Husk together with a diet rich in fibres on pharmacokinetics in patients treated with Asacol[®] [Riley *et al.* 1991]. They found no significant changes but the median excretion of 5-ASA and Ac-5-ASA were reduced by 28% and 21% and by 1% and 10% in urine and faeces respectively. Both randomized trials and investigations of pharmacokinetics are needed to elucidate if the binding of 5-ASA to dietary fibres is clinically relevant.

Conclusions

We conclude that Ispaghula Husk, wheat bran, citrus pectin, and wheat flour bound 5-ASA content *in vitro* and Ispaghula Husk to a level that might be clinically relevant. In patients with UC and in long-term treatment with 5-ASA we found significantly lower concentrations of CRP ($p < 0.01$) and faecal-calprotectin ($p < 0.01$) in patients consuming a diet with a high content of fibre *versus* a low content. We found no direct correlations between fibre consumption and disease activity.

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Conflict of interest statement

No conflict of interests exists for any of the authors.

References

- Baumgart, D.C. and Sandborn, W.J. (2007) Inflammatory bowel disease: Clinical aspects and established and evolving therapies. *Lancet* 369: 1641–1657.
- Cohen, R.D. (2006) Review article: evolutionary advances in the delivery of aminosalicylates for the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 24: 465–474.
- Doherty, M.M. and Charman, W.N. (2002) The mucosa of the small intestine {-} how clinically relevant as an organ and drug metabolism? *Clin Pharmacokinet* 41: 235–253.
- Fernandez-Banares, F., Hinojosa, J., Sánchez-Lombrana, L., Navarro, E., Martínez-Salmerón, J.F., García-Pugés, A. *et al.* (1999) Randomized clinical trial of Plantago ovata seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. *Am J Gastroenterol* 94: 427–433.
- Frandsen, N.E., Saugmann, S. and Marcussen, N. (2002) Acute interstitial nephritis associated with the use of mesalazine in inflammatory bowel disease. *Nephron* 92: 200–202.
- Hallert, C., Kaldman, M. and Peterson, B.G. (1991) Ispaghula Husk may relieve gastrointestinal symptoms in ulcerative colitis in remission. *Scand J Gastroenterol* 26: 747–750.
- Harris, R.Z., Graham, R.J. and Tsunoda, S. (2003) Dietary effects on drug metabolism and transport. *Clin Pharmacokinet* 42: 1071–1088.
- Kane, S.V., Brixner, D., Rubin, D.T. and Sewitch, M.J. (2008) The challenge of compliance and persistence: focus on ulcerative colitis. *J Manag Care Pharm* 14: 2–15.
- Klotz, U. (1985) Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-aminosalicylic acid. *Clin Pharmacokinet* 10: 285–302.
- Melander, A. and McLean, A. (1983) Influence of food intake on presystemic clearance of drugs. *Clin Pharmacokinet* 8: 286–296.
- Richter, W.O., Jacob, B.G. and Schwandt, P. (1991) Interaction between fibre and Lovastatin. *Lancet* 338: 706.
- Riley, S.A., Lloyd, D.R. and Mani, V. (1992) Tests of renal function in patients with quiescent colitis: effects of drug treatment. *Gut* 33: 1348–1352.
- Riley, S.A., Travares, I.A., Bishai, P.M., Bennett, A. and Mani, V. (1991) Mesalazine release from coated tablets: effect of dietary fibre. *Br J Clin Pharmacol* 32: 248–250.
- Schmidt, L.E. and Dalhoff. (2002) Food-drug interactions. *Drugs* 62: 1481–1502.
- Singh, B.N. (1999) Effects of food on clinical pharmacokinetics. *Clin Pharmacokinet* 37: 213–255.
- Singh, B.N. and Malhotra, B.K. (2004) Effects of food on the clinical pharmacokinetics of anticancer agents. *Clin Pharmacokinet* 43: 1127–1156.
- Staerk, L.L., Stokholm, M., Bukhave, K., Rask, M.J. and Lauritsen, K. (1990) Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values, and urinary excretion. *Gut* 31: 1271–1276.