Diagnostic value of a guaiac occult blood test and faecal alpha 1-antitrypsin

A Moran, D Husband, A F Jones, P Asquith

Abstract
This study evaluates the diagnostic accuracy of a faecal occult blood test and faecal alpha 1-antitrypsin in the investigation of patients with gastrointestinal symptoms or iron deficiency anaemia. One hundred and seventy nine patients with either iron deficiency anaemia (n=67), changed bowel habit and aged >39 years (n=107), or a history suggestive of melaena (n=5) provided faecal samples. After investigation, 32 patients had a diagnosis of possible gastrointestinal bleeding and 139 patients had no evidence of gastrointestinal bleeding. Eight patients had a cause of enteric protein loss in the absence of gastrointestinal bleeding and were excluded from subsequent analysis. The faecal alpha 1-antitrypsin test was diagnostically more accurate than the guaiac test in identifying probable gastrointestinal bleeding (82% and 72% respectively, p<0.05). This faecal alpha 1-antitrypsin test was also more specific (83% and 72% respectively, p<0.05), but was not significantly more sensitive (78% and 72% respectively). The sensitivity of these tests was insufficient to recommend their use for most patients in this study.

(Gut 1995; 36: 87–89)

Keywords: guaiac occult blood test, faecal alpha 1-antitrypsin.

Guaiac faecal occult blood tests continue to be used by many clinicians to assist in the investigation of patients with gastrointestinal symptoms or with iron deficiency anaemia. This is despite inherent deficiencies of these tests, with interference caused by faecal degradation of haemoglobin, dietary pseudoperoxidases, and observer error of the colour change. Measurement of faecal alpha 1-antitrypsin is a possible alternative as most of the diseases causing occult gastrointestinal bleeding are also potential causes of increased enteric protein loss. This protease inhibitor is comparatively resistant to degradation in faecal samples and is measured by a specific immunoassay. Preliminary evidence suggests that faecal alpha 1-antitrypsin measurement may be diagnostically more accurate than guaiac faecal occult blood tests. There is a need to extend the validity of guaiac faecal occult blood tests in these selected patients and to develop improved tests. This prospective study assesses the diagnostic value of a guaiac faecal occult blood test and compares it with faecal alpha 1-antitrypsin measurement in selected patients.

Patients and methods
Patients with iron deficiency anaemia, a history suggestive of melaena, or aged >39 years with changed bowel habit, were asked to provide three faecal samples. Patients with known causes of gastrointestinal bleeding or protein losing enteropathy, or with overt gastrointestinal bleeding were not recruited. Patients with iron deficiency anaemia were investigated by colonoscopy, gastroscopy, and distal duodenal biopsy. Patients aged >39 years with changed bowel habit had either a colonoscopy or a rigid sigmoidoscopy and barium enema. A colonoscopy and gastroscopy were performed if there was a history suggestive of melaena.

Faecal samples were analysed with a guaiac faecal occult blood test, Okokit II, and faecal alpha 1-antitrypsin was measured by radial immunodiffusion. Okokit II (Hughes and Hughes, Romford, Essex) is claimed to be sensitive to 5 ml blood/200 g faeces. The detection limit of faecal alpha 1-antitrypsin is 10 mg/l, with a between batch coefficient of variance of 6.4%. A faecal alpha 1-antitrypsin concentration >0.58 mg/g wet faecal weight from any sample was regarded as positive. This cut off value was derived from the 95th centile of faecal alpha 1-antitrypsin concentrations of an asymptomatic control group (n=91, median age (range) 44 (19–70) years). After diagnostic investigations, patients were classified using conventional criteria as probably having gastrointestinal bleeding or as not having gastrointestinal bleeding. To avoid diagnostic bias, the results from each patient were reported by randomly assigning 'test A' or 'test B' to each sample.

TABLE 1 Clinical diagnoses of patients with probable gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>4</td>
</tr>
<tr>
<td>Colorectal adenoma*</td>
<td>6</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>4</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>4</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>1</td>
</tr>
<tr>
<td>Infective haemorrhagic colitis</td>
<td>1</td>
</tr>
<tr>
<td>Cancer of head of pancreas</td>
<td>1</td>
</tr>
<tr>
<td>Osseophageal cancer</td>
<td>1</td>
</tr>
<tr>
<td>Reflux oesophagitis</td>
<td>1</td>
</tr>
<tr>
<td>NSAID gastropathy</td>
<td>4</td>
</tr>
<tr>
<td>Gastric antral vascular ectasia</td>
<td>2</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
</tbody>
</table>

*1.5–3 cm diameter.
NSAID=non-steroidal anti-inflammatory drugs.
B' as the designated name for each of the two faecal tests. Ethical approval was obtained from the Birmingham Heartlands Hospital ethical committee.

Faecal $\alpha$-1-antitrypsin concentrations from the two diagnostic groups were compared using the Mann-Whitney U test. The diagnostic value of the faecal occult blood and faecal $\alpha$-1-antitrypsin test results were compared using McNemar's $\chi^2$ test with continuity correction. The comparative likelihood of gastrointestinal bleeding in patients with changed bowel habit was compared with patients with iron deficiency anaemia using the $\chi^2$ test with Yates's correction factor. Confidence intervals were obtained from statistical tables using the binomial distribution ($n<100$) and from a formula based on the normal distribution ($n>100$).

## Results

One hundred and seventy nine of 207 patients returned faecal samples, with 90% providing three faecal samples. Gastrointestinal bleeding was diagnosed as probable in 32 patients (for diagnosis, see Table I). Probable gastrointestinal bleeding was significantly more frequent ($p<0.005$) in those with iron deficiency anaemia (20 of 67, 30%) than in those with changed bowel habit (12 of 107, 11%). None of the patients with a history suggestive of melaena had a diagnosis of probable gastrointestinal bleeding.

In 139 patients there was no evidence of recent gastrointestinal blood loss. Seventy four per cent of the patients with changed bowel habit were diagnosed as having either irritable bowel syndrome or diverticular disease, and 60% of the patients with iron deficiency anaemia were diagnosed as having either menorrhagia, dietary deficiency or a previous gastrointestinal bleed.

Eight patients had a diagnosis of increased enteric protein loss in the absence of gastrointestinal bleeding (six with coeliac disease, one with contaminated bowel, and one with primary biliary cirrhosis). These patients were not included in the statistical analysis as their detection by the faecal $\alpha$-1-antitrypsin test is of potential benefit despite the absence of gastrointestinal bleeding.

The maximum faecal $\alpha$-1-antitrypsin concentrations of those with probable gastrointestinal bleeding were significantly greater than in those without gastrointestinal bleeding ($p<0.0001$, Fig 1). Table II shows the sensitivity, specificity, accuracy (true results/all results), and positive predictive value of the faecal occult blood test and faecal $\alpha$-1-antitrypsin test results.

Twelve patients had gastrointestinal neoplasia. Four patients had colorectal cancer and three were detected by the faecal $\alpha$-1-antitrypsin test compared with only one by the faecal occult blood test. Six patients had colorectal adenomatous polyps (1.5–3 cm diameter) and four of these were detected by the faecal occult blood test and four by the faecal $\alpha$-1-antitrypsin test. Two patients had upper gastrointestinal cancer, both having positive faecal $\alpha$-1-antitrypsin and faecal occult blood tests.

Figure 2 shows a receiver operating characteristic curve for faecal $\alpha$-1-antitrypsin, including a plot of the faecal occult blood test result for comparison. The true positive rate represents sensitivity and the false positive rate=100 minus specificity (%). The receiver operating characteristic curve plots the performance of a quantitative test throughout a range of cut off values. Using a low cut off concentration, most disease should be detected by a test, such that the true
positive rate will be high. Conversely, a low cut off concentration may increase the number of false positive results, such that the false positive rate is also high. As the cut off concentration is increased, the true positive rate would be expected to decrease and the false positive rate decrease. The receiver operating characteristic curve of an ideal test should reach as close as possible to the top left hand corner of the graph (100% true positive rate and 0% false positive rate). The area under the receiver operating characteristic curve will also provide an indication of the performance of a test and can be used to compare quantitative tests.

**Discussion**

Seventeen per cent of these selected patients had a diagnosis of probable gastrointestinal bleeding and this diagnosis was more frequent in those with iron deficiency anaemia than in those with changed bowel habit. Twelve of 32 (37%) patients with probable gastrointestinal bleeding had neoplastic disease, although none were <40 years. The prevalence of significant gastrointestinal abnormality in these patients was sufficient to warrant tests of high sensitivity. The faecal occult blood and faecal α-1-antitrypsin tests could not be considered to have sufficient sensitivity for patients >39 years because of the risk of gastrointestinal neoplasia. Two of the patients with colorectal neoplasia had negative results with both tests.

This study has also shown that the faecal α-1-antitrypsin test was diagnostically more accurate than the faecal occult blood test in this selected group of patients. The quantitative aspect of the faecal α-1-antitrypsin test may be an additional advantage because a concentration >1-0 mg/g wet faecal weight shows a very high probability of significant gastrointestinal disease. The faecal α-1-antitrypsin test may not only detect protein present in blood loss but also that resulting from mucosal oedema and epithelial sloughing. The faecal α-1-antitrypsin test is, however, more expensive and time consuming than guaiac faecal occult blood tests and dietary restriction may have improved the specificity of the faecal occult blood test. The combined use of the faecal occult blood and faecal α-1-antitrypsin tests would have increased the sensitivity to 94% but with a corresponding fall in specificity to 66%. The receiver operating characteristic curve for faecal α-1-antitrypsin passed above and to the left of the plot for the faecal occult blood test used in this study, consistent with its greater diagnostic accuracy. Receiver operating characteristic curves are affected by the prevalence of disease, however, such that these results cannot be applied to groups at lower risk of occult gastrointestinal bleeding.

In most patients, the likelihood of having significant gastrointestinal disease (due to symptoms, age or haematological results) warranted gastrointestinal investigations without recourse to the use of faecal tests. Faecal tests, however, may yet be found to be of clinical value in patients at a lower risk of gastrointestinal neoplasia such as (a) young female patients with iron deficiency anaemia, (b) young patients with changed bowel habit, (c) patients with negative initial gastrointestinal investigations in whom further tests were being considered, and most importantly (d) asymptomatic patients >40 years as a method of screening for colorectal neoplasia. The HemeSelect test (an immunological test for faecal human haemoglobin) may also be of value in these patients, although this test will be affected to a greater extent by delayed colonic transit, proximal site of lesion, and delays in sample analysis.

In conclusion, neither the faecal occult blood nor the faecal α-1-antitrypsin test provided a satisfactory sensitivity for those patients at high risk of colorectal neoplasia and their routine use in these patients cannot be supported. The faecal α-1-antitrypsin test was significantly more accurate and specific than the faecal occult blood test used in this study and may be more suitable for use in subjects at lower risk of gastrointestinal neoplasia. The HaemoQuant test (a measure of haem-derived faecal porphyrins) and Haemoccult tests have proved to have low sensitivity for colorectal cancer in asymptomatic subjects, and the sensitivities of faecal α-1-antitrypsin and HemeSelect have yet to be assessed in this context.

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