Gut, 1989, **30**, 1236–1240

Are activity indices helpful in assessing active intestinal inflammation in Crohn's disease?

G CRAMA-BOHBOUTH, A S PEÑA, I BIEMOND, H W VERSPAGET, D BLOK, J W ARNDT, I T WETERMAN, E K J PAUWELS, AND C B H W LAMERS

From the Department of Gastroenterology, and Diagnostic Radiology, Division of Nuclear Medicine, University Hospital, Leiden, The Netherlands

SUMMARY **We have investigated the correlation of 24 h and 48 h faecal Indium-111 excretion with each other and with several clinical activity indices for Crohn's disease (CD): Crohn's disease activity index (CDAI), activity index (AI), simple index (SI), Oxford score, and laboratory parameters, such as ESR, serum albumin, orosomucoid, C-reactive protein, alpha-1-antitrypsin (α_1-AT) faecal concentration, and α_1-AT clearance in 58 CD patients (37 with small bowel and 21 with colonic disease). A significant correlation was found between 24 and 48 h faecal Indium-111 excretion for small bowel ($r=0{\cdot}708$, $p<0{\cdot}0001$) and colonic disease ($r=0{\cdot}994$, $p<0{\cdot}0001$). The median faecal Indium-111 excretion for colonic involvement (4%; 0·15–50% median and range) was significantly ($p<0{\cdot}0005$) higher than that for small bowel disease (0·45%; 0·03–2·9%). No significant correlation was found between faecal Indium-111 excretion and any activity index in the patients with small bowel disease, while in the group of patients with colonic localisation only the AI showed a significant correlation ($r=0{\cdot}593$, $p<0{\cdot}02$). Faecal Indium-111 excretion was significantly correlated with α_1-AT clearance ($r=0{\cdot}712$, $p<0{\cdot}0001$) and faecal α_1-AT concentration ($r=0{\cdot}750$, $p<0{\cdot}0001$) in small bowel and in colonic localisation ($r=0{\cdot}530$, $p<0{\cdot}02$ and $r=0{\cdot}444$, $p<0{\cdot}05$). Serum albumin was significantly correlated only in the group of patients with colonic disease ($r=-0{\cdot}593$, $p<0{\cdot}05$). The present study shows poor agreement between activity indices, serum parameters of activity and faecal Indium-111 excretion. As a good correlation was found with the α_1-clearance, which reflects losses into the gut, these results may suggest that faecal Indium excretion does not only reflect activity of inflammation, but may relate to the extent of intestinal ulceration.**

Crohn's disease is a chronic relapsing disease in which the clinical presentation varies considerably. Difficulties arise in accurately assessing the disease activity which is important in the management of the patient and in analysing prospective trials. Laboratory variables such as erythrocyte sedimentation rate (ESR), serum albumin, C reactive protein and orosomucoid concentrations have been used but are not always reliable because they lack specificity for Crohn's disease.

Address for correspondence: Dr A S Peña, Department of Gastroenterology, University Hospital, 2333 AA Leiden, The Netherlands.

Accepted for publication 24 January 1989.

During the last decade a number of clinical indices have been developed to try to standardise disease activity[1–4] but because most are based on a subjective grading of signs and symptoms, none is considered as the final ideal index.

Measurement of clearance and faecal concentration of alpha-1-antitrypsin (α_1-AT) has been successfully used to estimate the degree of intestinal inflammation.[5]

More recently, the quantification of faecal excretion of intravenously administered autologous Indium-111 tropolonate labelled granulocytes has been introduced as a highly specific parameter for bowel inflammation, independent of the subjective

complaints, and not influenced by the presence of possible coexisting diseases.[6–10]

This prospective study was undertaken to investigate the correlation of the 24 h and 48 h faecal Indium-111 excretion and with several established activity indices, such as, the CDAI (Crohn's disease activity index),[1] AI (activity index),[2] SI (simple index),[3] and Oxford scores,[4] and with the following laboratory parameters, clearance and faecal concentration of α_1-AT, ESR, serum albumin, orosomucoid, and C-reative protein.

Methods

PATIENTS

Fifty eight patients with Crohn's disease (34 women) with a median age of 35 years (range 16–60) were studied. The diagnosis was based on standard clinical, endoscopic and histopathologic features. Thirty seven patients had small bowel involvement only, and 21 colitis. In the group of 37 patients with small bowel disease, 21 had undergone surgery (20 an ileocoecal resection, three of whom also had a subtotal colectomy and one a proctocolectomy). Twelve patients were receiving corticosteroids.

Of the group of 21 patients with colonic involvement, 18 had extensive or total colitis, (of whom three had undergone a segmental colonic resection) and three patients had left sided colitis. Fifteen patients were receiving corticosteroids at the time of the study.

Forty eight hour faecal Indium-111 excretion was available in 25 patients with small bowel disease and in 12 patients with colonic involvement.

The Medical Ethics Committee of the University Hospital Leiden approved this investigation and informed consent was obtained from each patient.

ACTIVITY INDICES

The following activity indices for CD were used according to the published definitions given: Crohn's disease activity index (CDAI),[1] activity index (AI),[2] simple index (SI),[3] Oxford score.[4] The following laboratory parameters were measured: ESR, serum albumin, orosomucoid, C-reactive protein, alpha-1-antitrypsin (α_1-AT) faecal concentration, and α_1-AT clearance.[5]

GRANULOCYTE LABELLING AND EXCRETION OF INDIUM-111

Autologous granulocytes were separated and labelled with Indium-111 tropolonate, as previously described.[11] An average of 200 μCi (7·4 MBq) was injected in each study. Indium-111 activity of stools was measured in a gammacounter and expressed as per cent of the injected dose after correction for decay. Faecal Indium-111 excretion and α_1-AT were measured in identical stool samples. Assessment of activity indices, stool, and blood collection were carried out on the same day.

DETERMINATION OF ALPHA-1-ANTITRYPSIN (α_1-AT)

Serum and 24 h stools were collected for α_1-AT measurements. After weighing the total amount of wet faeces, two aliquots (200-500 mg) were taken at random and lyophilised. The dried aliquots were weighed, suspended in saline and homogenised. After centrifugation the α_1-AT concentration in the supernatant and in the serum were measured by radial immunodiffusion (for faeces, LC Partigen plate, Behring Werke AG, Marburg, FRG; for serum, Endoplates, Kallestad, Austin, Tx, USA). The α_1-AT clearance was calculated as follows:

$$\text{clearance (ml/24 h)} = \frac{P\,C_f}{C_s}$$

where P is the product of the wet weight of the 24 h faecal sample and the ratio dry weight/wet weight. C_f is the concentration of α_1-antitrypsin in lyophilised faeces (mg α_1-AT/g dry faeces) and C_s is the concentration in serum (mg α_1-AT/ml).

SERUM LABORATORY PARAMETERS

Serum albumin was determinated by automated bromocresol green method and was expressed in g/l. Human α_1-glycoprotein (orosomucoid) and C reactive protein were measured by radial immunodiffusion and expressed in g/l and in mg/l, respectively.

STATISTICAL ANALYSIS

Results are expressed as median and range. They were analysed for statistical significance using the non parametrical two tailed Wilcoxon's rank-sum test.

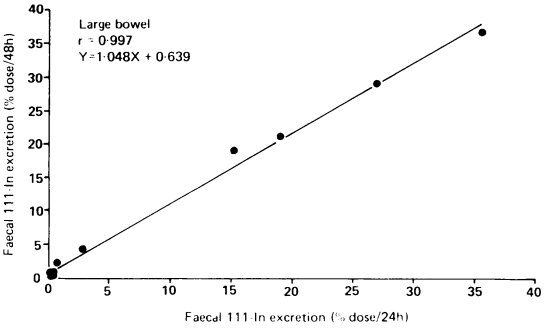

Fig. 1 *Correlation between 24 h and 48 h faecal Indium-111 excretion in patients with colonic involvement of Crohn's disease (n=12) (r=0·994) (p <0·0001).*

Correlation was evaluated using the two tailed Pearson's correlation coefficient.

Results

As shown in Figures 1 and 2 a significant correlation was found between 24 and 48 h faecal excretion for colonic disease (r=0·994) and for small bowel localisation (r=0·708). We therefore used 24 h faecal Indium-111 excretion for the analysis of our results.

The median 24 h Indium-111 faecal excretion was significantly higher (p<0·0005) in patients with colonic involvement (median 4%, range 0·15–50%) than in the group of patients with small bowel disease (0·44%, 0·03–2·9%).

Table 1 shows the correlation between Indium-111 faecal excretion and the activity indices CDAI, AI, SI and Oxford score in the groups of patients with colonic and small bowel localisation separated and combined. As shown in this Table no significant correlation was found between Indium-111 excretion and any activity index for patients with small bowel disease. A significant correlation with the AI (p<0·05), however, was found for colonic localisation and when the groups were analysed combined (p<0·001).

Table 2 shows the correlation between faecal Indum-111 excretion and the various laboratory parameters (ESR, C-reactive protein, serum albumin and orosomucoid), the α_1-AT clearance, and α_1-AT faecal concentration. A significant correlation was found with α_1-AT clearance and faecal concentration in patients with either localisation (p<0·002) (Figs. 3,4).

The α_1-AT clearance and α_1-AT faecal concentration were higher in the group with colonic disease (median 193, range 100–426 ml/24 h; median 8, range 7·0–26·0 mg–g) than in the group with ileal involve-

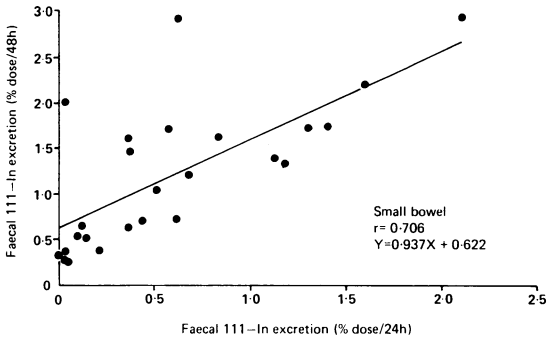

Fig. 2 *Correlation between 24 h and 48 h faecal Indium-111 excretion in patients with small bowel involvement of Crohn's disease (n=25) (r=0·708) (p <0·0001).*

Table 1 *Coefficients (r) and p-values of the correlation between Indium-111 faecal excretion and activity indices for Crohn's disease*

	Faecal Indium-111 excretion					
Localisation	*Small bowel (37)*		*Large bowel (21)*		*Combined (58)*	
	r	*p*	*r*	*p*	*r*	*p*
CDAI	−0·314	0·075	−0·042	0·870	0·160	0·267
SI	−0·303	0·086	0·022	0·931	0·130	0·365
Oxford score†	0·113	0·653	0·108	0·782	0·386	0·046
AI	0·189	0·284	0·593	0·012*	0·524	<0·001*

*statistically significant; †calculated in 18 patients with small bowel and nine with large bowel CD.

Table 2 *Coefficients (r) and p-values of correlation between Indium-111 faecal excretion and various laboratory parameters*

	Faecal Indium-111 excretion					
Localisation	*Small bowel (37)*		*Large bowel (21)*		*Combined (58)*	
	r	*p*	*r*	*p*	*r*	*p*
ESR	0·060	0·732	0·135	0·782	0·291	0·035*
C-reactive protein	0·025	0·894	−0·088	0·719	0·073	0·622
Albumin	0·210	0·226	−0·593	0·012*	−0·528	<0·001*
Orosomucoid†	0·281	0·132	0·322	0·178	0·369	0·009*
α_1-AT clearance	0·712	<0·0001*	0·530	0·019*	0·413	0·002*
α_1-AT faecal concentration	0·750	<0·0001*	0·444	0·044*	0·425	0·002*

*statistically significant; †measured in 30 patients with small bowel and 19 with large bowel localisation.

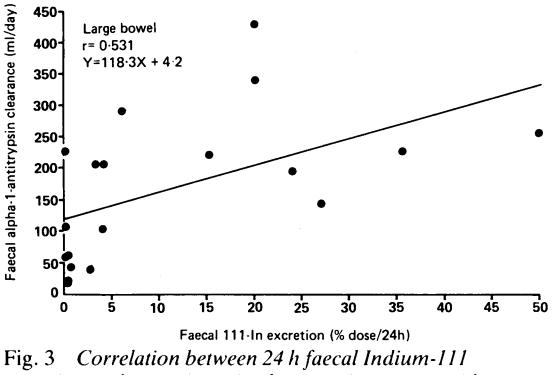

Fig. 3 *Correlation between 24 h faecal Indium-111 excretion and α_1-antitrypsin clearance in patients with colonic involvement of Crohn's disease (n=21) (r=0·530) (p<0·02).*

ment (median 76, range 7–365 ml/24 h; median 4·7, range 0·3–46·7 mg–g) but the difference did not reach statistical significance.

A significant negative correlation between faecal Indium-111 excretion and serum albumin was found only for patients with colonic involvement ($p<0·05$) or when the groups were analysed combined. Furthermore serum orosomucoid correlated significantly with faecal Indium-111 excretion only when both localisations were taken together ($p<0·05$).

Discussion

In the present study 58 CD patients, 37 with small bowel and 21 with colonic disease (CD) have been studied using several clinical indices of activity and laboratory parameters.

Because we have shown an excellent correlation between the 24 h and 48 h faecal Indium-111 excretion, the results of the 24 h faecal collection were used to compare the results obtained with other parameters. As far as we know previous studies using Indium-111 labelled granulocytes reported the results of faecal excretion of both localisations together.[6 10 12] Saverymuttu *et al*[6] showed a significantly higher four days faecal Indium-111 excretion in a group of 28 CD patients with active inflammation than in 25 patients with the irritable bowel syndrome. Leddin *et al*[12] studied a series of 16 patients with CD, 13 with UC, and 14 with other gastrointestinal diseases. All patients with active inflammation had a faecal Indium-111 excretion higher than 0·70%. In the present study, we found that faecal Indium-111 excretion in colonic disease was significantly higher than in small bowel disease. This may be the result of the different extent of inflammation in both localisations.

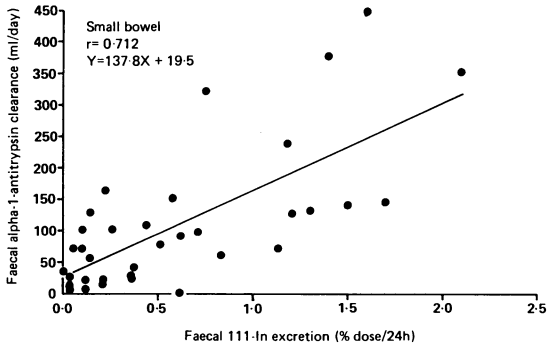

Fig. 4 *Correlation between 24 h faecal Indium-111 excretion and α_1-antitrypsin clearance in patients with small bowel involvement of Crohn's disease (n=37) (r=0·750) (p<0·0001).*

We have also found different correlations for the small and large bowel localisation. These results indicate that the disease behaves differently and therefore both groups should be analysed independently. This has been previously recorded in studies using Indium-111 granulocytes scintigraphy, where different results were found for colonic and small bowel disease.[11]

A significant correlation was found between faecal Indium-111 excretion and α_1-AT clearance in either localisation. Fischbach *et al*[13], however, found no correlation between these two tests and the discrepancy may be because of differences in patient's selection, as they have mainly studied outpatients. Our results are in agreement with the findings of Meyers *et al*,[5] showing that the measurement of α_1-AT concentration and clearance is a reliable method to assess active inflammation of the bowel.

Leddin *et al*[12] and Fischbach *et al*[13] found a significant correlation between the AI and the faecal Indium-111 excretion in their patients. We found that this is true only for colonic localisation, and in fact, their material was based on patients with predominantly colonic disease.

Saverymuttu *et al*[14] found a significant correlation between Indium-111 excretion and the CDAI, which was not confirmed in this study. From all activity indices used in this study, the AI appears to be the best for reflecting gut inflammation in colonic disease. Another explanation for this discrepancy may be observer variation in calculating various indices for estimating the severity and activity of CD. De Dombal and Softley[4] found that the AI had less interobserver variation than other indices.

It is not surprising that in colonic disease a significant correlation is also found for albumin as this biochemical parameter gives a special weight to the calculation of the AI.

Park *et al*[14] have recently shown a very poor

correlation in 19 patients with CD between activity demonstrated by Indium-111 oxine mixed leucocyte scintigraphy, clinical scores, and different laboratory parameters, including ESR, C-reactive protein, and $^{51}CrCl_3$ gastrointestinal protein loss test.

Fischbach *et al*[13] found a significant correlation between Indium-111 excretion and serum orosomucoid in 27 CD patients. We also found a significant correlation in our patients but when the patients were analysed according to localisation no significant correlation was observed.

The faecal Indium-111 excretion showed a poor correlation with the activity indices or serum parameters of activity, such as ESR, CRP, and orosomucoid. A good correlation was found, however, with the α_1-AT clearance, which reflects losses into the gut. These results may suggest that faecal Indium-111 excretion does not only reflect activity of inflammation, but may be also related to the extent of intestinal ulceration.

Future prospective studies should be designed to assess the different contribution of degree of inflammation and extent of ulceration on the faecal excretion of Indium-111 and the clearance of α_1-AT.

G E Crama-Bohbouth was supported by a grant of De Nederlandse Lever Darm Stichting. The authors would like to acknowledge the technical assistance of R I J Feitsma Ing, and Miss Loes Niepoth for typing the manuscript.

References

1 Best WR, Becktel JM, Singleton JW, Kern F, Jr. Rederived values of eight coefficients of the CD activity index (CDAI). *Gastroenterology* 1979; **77:** 843–6.
2 Van Hees PAM, van Elteren Ph, van Lier HJJ, van Tongeren JHM. An index of inflammatory activity in patients with Crohn's disease. *Gut* 1980; **21:** 279–86.
3 Harvey RF, Bradshaw JM. A simple index of Crohn's Disease Activity. *Lancet* 1980; i: 514.
4 De Dombal FT, Softley A. IOIBD report no. 1: observer variation calculating indices of severity and activity in Crohn's disease. *Gut* 1987; **28:** 474–81.
5 Meyers S, Wolke A, Field STP, Feuer EJ, Johnson JW, Janowitz HD. Fecal alpha-1-antitrypsin measurement: an indicator of Crohn's disease activity. *Gastroenterology* 1985; **89:** 13–8.
6 Saverymuttu SH, Peters AM, Lavender JP, Pepys MB, Hodgson HJF, Chadwick VS. Quantitative faecal Indium 111-labeled leukocyte excretion in the assessment of disease in Crohn's disease. *Gastroenterology* 1983; **85:** 1333–9.
7 Keshavarzian A, Price YE, Peters AM, Lavender JP, Wright NA, Hodgson HJF. Specificity of Indium-111 granulocyte scanning and fecal excretion measurement in inflammatory bowel disease – an autoradiographic study. *Dig Dis Sci* 1985; **30:** 1156–60.
8 Segal AW, Ensell J, Munro JA, Sarner M. Indium[111]-tagged leucocytes in the diagnosis of inflammatory bowel disease. *Lancet* 1981; ii: 230–2.
9 Saverymuttu SH, Peters AM, Lavender JP, Hodgson HJF, Chadwick VS. Imaging diseased bowel with Indium[111] labelled leucocytes. *Br J Radiol* 1981; **54:** 707.
10 Saverymuttu SH, Camilleri M, Rees H, Lavender JP, Hodgson HJF, Chadwick VS. Indium 111-Granulocyte scanning in the assessment of disease extent and disease activity in inflammatory bowel disease. *Gastroenterology* 1986; **90:** 1121–8.
11 Crama-Bohbouth GE, Arndt JW, Peña AS, *et al*. Value of Indium-111 granulocyte scintigraphy in the assessment of Crohn's disease of the small bowel. *Digestion* 1988; **40:** 227–36.
12 Leddin D, Paterson W, DaCosta L, *et al*. Indium-111 labeled autologous leukocyte imaging and fecal excretion. *Dig Dis Sci* 1987; **32:** 377–87.
13 Fischbach W, Becker W, Mössner J, Koch W, Reiners C. Faecal alpha-1-antitrypsin and excretion of [111]Indium granulocytes in assessment of disease activity in chronic inflammatory bowel diseases. *Gut* 1987; **28:** 386–93.
14 Park RHR, McKillop JH, Duncan A, MacKenzie JF, Russell RI. Can [111]indium autologous mixed leucocyte scanning accurately assess disease extent and activity in Crohn's disease? *Gut* 1988; **29:** 821–5.