

Evaluation of SeHCAT test in determining ileal involvement and dysfunction in Crohn's disease

LAWRENCE WOROBETZ, MD, ALEX WILKINSON, MD, CHESTER CHMIELOWIEC, MD, LEONARD TAN, MB, PHD

L WOROBETZ, A WILKINSON, C CHMIELOWIEC, L TAN. Evaluation of SeHCAT test in determining ileal involvement and dysfunction in Crohn's disease. *Can J Gastroenterol* 1993;7(8):597-601. In view of the imperfect methodology that exists for the detection of terminal ileal disease, the authors examined the ability of the SeHCAT test to detect ileal involvement and dysfunction in patients with inflammatory bowel disease. An attempt was also made to correlate the 23-selena-25-homotaurocholate retention (SeHCAT) test with disease activity, extent of ileal disease, presence of diarrhea and response to cholestyramine. Forty-three patients were studied, including 12 controls - 22 with Crohn's disease limited to the small bowel and nine with ulcerative or granulomatous colitis. The mean SeHCAT retention values were 25, 4 and 47%, respectively, all significantly different from each other ($P < 0.05$). This gave a sensitivity of 91%, a specificity of 81% and an accuracy of 86%. No correlation could be established between the SeHCAT retention value and disease activity, extent of ileal disease, presence of diarrhea or response to cholestyramine.

Key Words: Bile salts, Crohn's disease, SeHCAT test

Évaluation d'un test au SeHCAT pour l'identification des lésions iléales dans la maladie de Crohn

RÉSUMÉ : Étant donné l'imperfection des méthodes qui permettent de déceler la maladie iléale terminale, les auteurs ont examiné le potentiel du test au SeHCAT dans le dépistage des lésions iléales dysfonctionnelles chez les patients atteints de maladie intestinale inflammatoire. Une tentative a également été faite pour établir une corrélation entre les tests de rétention du 23-sélénia-25 homotaurocholate et l'activité de cette maladie, l'étendue de la lésion iléale et la présence de diarrhée, ainsi que la réponse à la cholestyramine. Quarante-trois sujets ont été étudiés, dont douze témoins, 22 atteints de la maladie de Crohn

Departments of Medicine, Nuclear Medicine and Community Health and Epidemiology, University of Saskatchewan, Saskatoon, Saskatchewan

Correspondence and requests: Dr LJ Worobetz, Department of Medicine, Royal University Hospital, Saskatoon, Saskatchewan S7N 0X0. Telephone (306) 966-7964

Received for publication May 21, 1992. Accepted January 2, 1993

CROHN'S DISEASE IS A CHRONIC inflammatory disorder potentially involving any level of the gastrointestinal tract but with a predilection to involve the terminal ileum. The methods that presently exist for detecting disease of the terminal ileum are imperfect. The Schilling's test is neither sensitive for limited ileal disease nor specific (1). The C14-conjugated bile acid excretion with fecal collection is more specific and sensitive than the bile acid breath test (2-6); however, it is difficult as a routine clinical test. Barium examination underestimates the presence of terminal ileal disease and is not a test of ileal function (7-9). Endoscopic examination and biopsy of the terminal ileum are technically demanding and, again, are not tests of ileal function.

An available method is the selenium-labelled synthetic conjugated trihydroxy bile acid called 75-SeHCAT (75 se-23-selena-25 homotaurocholic acid) (10,11). The absorption and excretion of SeHCAT is similar to cholic acid being absorbed by the terminal ileum and excreted solely by the biliary system. By virtue of the gamma ray emissions, it can be measured by whole body counting and by uncollimated gamma camera measurements (12). It

limitée à l'intestin grêle et neuf porteurs de colite ulcéreuse ou granulomateuse. Les valeurs de rétention moyenne du SeHCAT ont été entre 25,4 % et 47 % respectivement, toutes nettement différentes les unes des autres ($P < 0,05$). Cela a conduit à un degré de sensibilité de 91 %, de spécificité de 81 % et de précision de 86 %. Aucune corrélation n'a pu être établie entre la valeur de rétention du SeHCAT et l'activité de la maladie, l'étendue de l'atteinte iléale, la présence de diarrhée ou la réponse à la cholestyramine.

has been proposed that measurement of SeHCAT retention is a simple and acceptable test for investigating ileal function, especially in inflammatory bowel disease (13-20). The purpose of this study was to evaluate the ability of the SeHCAT test to determine ileal involvement and dysfunction in patients with inflammatory bowel disease. An attempt was also made to correlate the SeHCAT retention with the extent of terminal ileal disease, the Crohn's disease activity index (CDAI), the presence of diarrhea and its response to cholestyramine, a bile acid resin used in the treatment of bile salt catharsis.

SUBJECTS AND METHODS

The study was approved by the University of Saskatchewan Advisory Committee of Ethics in Human Experimentation. All subjects gave informed signed consent.

Study population: Forty-three subjects were studied (26 males and 17 females), with age ranging from 25 to 69 years (mean 37). Of these 43, 12 were healthy controls (10 males and two females) with no symptoms to suggest gastrointestinal disease, no history of biliary or intestinal surgery and normal bowel habits. A normal bowel habit was defined as passage of formed stool fewer than three times a day with no recent change, and with the person considering their habit as normal. The ages of these controls ranged from 24 to 42 years (mean 32).

Twenty-four of the subjects, aged from 22 to 56 years (mean 31), were diagnosed as having Crohn's disease (confirmed by positive biopsy and/or typical radiological appearance). Of these, two had disease limited to the colon as verified by radiology and colonoscopy with ileoscopy, eight had active terminal ileitis and 14 had prior

terminal ileal resection (10 of these with recent recurrence proximal to the ileocolic anastomosis). Presence and extent of terminal ileal involvement or removal was determined by radiological, surgical and/or pathologic means.

Seven patients, aged from 25 to 69 years (mean 37), had left-sided or panulcerative colitis proven by biopsy, and appropriate endoscopic and radiological studies. Of these seven, four had clinically active disease.

Procedures: The isotope procedure included the oral administration of 0.37 MBq of $^{75}\text{SeHCAT}$ in capsule form after a 3 h fast. The initial count was measured 3 h after the intake of the isotope with the patient supine and then prone beneath an uncollimated gamma camera at a distance of 42 cm from the table top, centred to the patient's umbilicus. The activity of the $^{75}\text{SeHCAT}$ was measured using a 20% window around the 266 KeV photon peak. All counts were for 300 s. The geometric mean of the anterior and posterior counts was then calculated. The mean of the two background counts was subtracted from the geometric mean to give the final patient count. The second measurement was performed on day 7 in a similar fashion with no intervening dietary or activity changes. The measurement was corrected for decay and a percentage of the retained activity calculated with values equal to or greater than 19% was considered normal.

In those patients with known Crohn's disease, the CDAI was calculated for the week the test was being performed. All patients with clinical diarrhea (defined as unformed stool more than three times per day) were offered cholestyramine following the SeHCAT study at an initial dose of 4 g/day, increased to 8 g/day after one week if no response. The clinical response was compared with the

SeHCAT value, with clinical response being defined as a stool becoming formed with a frequency of less than three times per day. A correlation was also sought between the SeHCAT test and the amount of the terminal ileum resected or involved with Crohn's disease.

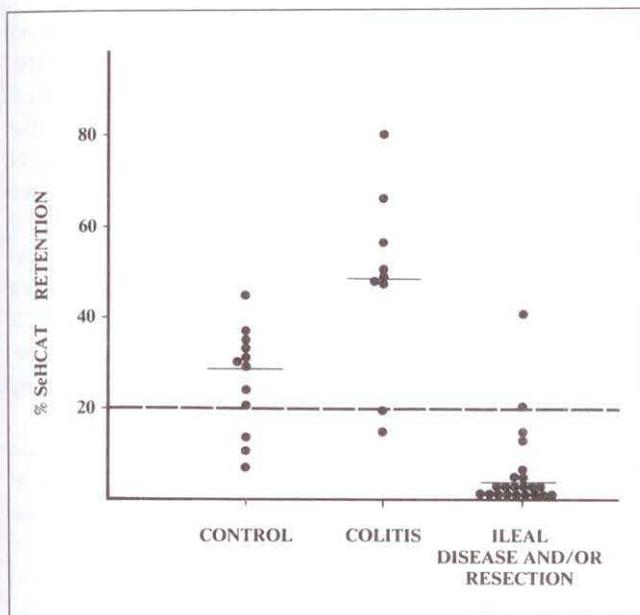
Statistical analysis was carried out by using the nonparametric Mann-Whitney test of analysis.

RESULTS

The mean \pm SE SeHCAT retention for the control group of 12 normal individuals was $25.0 \pm 3.2\%$. In this group, three individuals had abnormally low SeHCAT retention values (14, 11 and 6%), representing apparent false positives. One individual with a false positive result was verified by repeat SeHCAT study (14 and 12%). In all three, the Schilling's test and radiological study of the terminal ileum were normal. All three continue to remain well without diarrhea or other intestinal symptoms after one year follow-up.

In patients with Crohn's disease, the overall mean SeHCAT retention value of those with terminal ileal disease and/or resection was $5.0 \pm 2.0\%$, significantly different from the control group ($P < 0.01$). This group included two false negatives with SeHCAT values of 20 and 29%; one patient had 11 cm of terminal ileum resected with 10 cm of recurrent proximal disease and the other had 25 cm of terminal ileal involvement. Neither had evidence of colonic involvement.

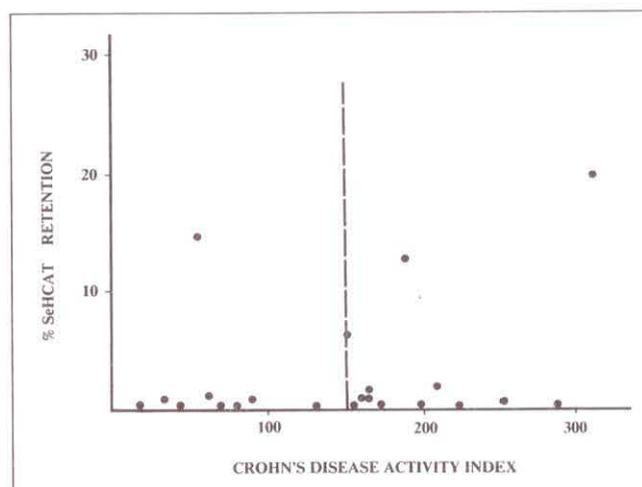
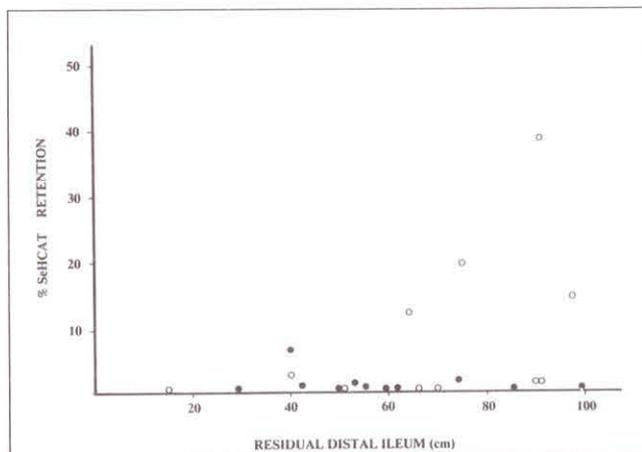
The mean SeHCAT value in patients with ulcerative or granulomatous colitis was $47.5 \pm 6.7\%$ which was significantly higher than the mean for the terminal ileal disease group ($P < 0.01$). It was also significantly higher than the mean for the control group ($P < 0.05$) (Figure 1). In this group of colitis patients, there was one false positive, a patient labelled as left-sided ulcerative colitis whose SeHCAT value was 15% and, after a one-year follow-up, continues to demonstrate a radiologically normal terminal ileum and Schilling's test. The two highest values in this group (79 and 64%) were individuals with active panulcerative colitis.



Top left: Figure 1 Percentage retention of SeHCAT on day 7 for the groups of control, colitis and ileal disease and/or resection. The solid horizontal lines represent the mean of the group. The dotted horizontal line represents the lower limit for normal SeHCAT retention

Top right: Figure 2 Correlation between the percentage retention of SeHCAT on day 7 and the residual length of the terminal 100 cm of ileum. The coefficient of correlation was 0.457 ($P=0.163$) for patients with ileocecal valve present (open circles) and -0.134 ($P=0.742$) for those with resected ileocecal valve (filled circles)

Bottom right: Figure 3 Percentage retention of SeHCAT on day 7 in relation to the Crohn's disease activity index (CDAI). The dotted vertical line separates clinically active from inactive disease groups (CDAI = 150)



Thus, in the group of 43 patients, there were 20 true positives, four false positives, two false negatives and 17 true negatives. This gives a sensitivity for the SeHCAT test of 91%, a specificity of 81% and an accuracy of 86%.

Assuming the distal ileum to be 100 cm, a relationship was sought between the percentage retention of SeHCAT and the residual distal ileum. However, using correlation analysis, no correlation was found overall (Figure 2). Of the 11 patients with retained ileocecal valve, the mean SeHCAT retention was $8.7 \pm 3.7\%$ with mean residual ileal length of 68.0 ± 7.5 cm (correlation coefficient = 0.457, $P=0.163$). Five of these 11 patients had diarrhea. Of the 11 patients without ileocecal valve, the mean SeHCAT retention value was $1.1 \pm 0.8\%$, with a mean residual ileal length of 48.0 ± 8.1 cm (correlation coefficient -0.134 , $P=0.742$). Nine of 11 patients had diarrhea.

In patients with terminal ileal dis-

ease and/or resection, 20 of 22 patients also had a low SeHCAT retention value; of this group, 13 (65%) had diarrhea while seven (35%) did not. In the group with diarrhea, only seven (54%) responded to the cholestyramine therapy. Thus, a low SeHCAT retention value (less than 19%) in patients with terminal ileal Crohn's disease did not reliably predict the presence of diarrhea or the clinical response of those with diarrhea to cholestyramine.

There was no correlation established between the CDAI and the SeHCAT retention values (correlation coefficient -0.25). The mean of those with active Crohn's disease (CDAI more than 150) was $4.0 \pm 1.2\%$ while the mean of those with inactive disease (CDAI less than 150) was $3.0 \pm 1.8\%$ (Figure 3).

The mean length of terminal ileal involvement/resection in those with diarrhea was 45.8 ± 4.1 cm (range 25 to 75) which was significantly different

from those without diarrhea, the mean being 23.9 ± 10.8 cm (range 2 to 84) ($P<0.05$). In those who clinically responded to cholestyramine, the mean length of involvement/resection was 35.3 ± 5.4 cm (range 25 to 50) and in those who did not respond it was 46.4 ± 6.1 cm (range 25 to 75). The difference was insignificant [$P=0.29$]).

DISCUSSION

The SeHCAT test is a test of bile salt absorption and has been proposed as a test of ileal function. In this study, it appears that in patients with Crohn's disease, a low SeHCAT retention value strongly correlates with ileal involvement. However, the sensitivity of 91% and specificity of 81% for the SeHCAT test in this study are not as high as previous studies quoting as high as 94% sensitivity and 100% specificity. The reasons for this are unclear. In our study, a value of greater than 19% for SeHCAT retention at day 7 was con-

sidered normal. Values between 12 and 19% have previously been defined as equivocal. If, for this study, the values of 12% or lower were defined as abnormal, this would have the effect of reducing the sensitivity to 82%, increasing the specificity to 90% but not changing the accuracy of 85%. Recent observations claim improved sensitivity with three-day retention readings or analysis of activity versus time monoexponential curves calculated by the least squares method. Recently shown is that data uncorrected for colonic retention overestimate SeHCAT absorption to a variable degree with a resulting reduction in accuracy of the test. This would likely be of importance in those without diarrhea.

Indeed, the true sensitivity and specificity of the SeHCAT test is difficult to determine as we do not have a gold standard for diagnosing ileal dysfunction against which to compare. However, the sensitivity and specificity values in this study of patients with morphological evidence of Crohn's disease limited to the ileum are equal to or better than the reported values for other ileal function tests, including the Schilling's test, bile acid breath test and the C14-conjugated bile acid stool collection. In view of this and of the simplicity of the test, the SeHCAT test could be considered an appropriate investigation for diagnosing ileal involvement in Crohn's disease, espec-

ially in distinguishing those with isolated large bowel involvement from those with isolated ileal involvement. The highest retention values were achieved by patients with active pancolitis. Although up to 30% of the daily bile salt load can be absorbed by the healthy colon, the handling of bile salts by the inflamed colon is unknown. In this study, given that the SeHCAT retention values are significantly elevated in active colitis versus control values, this implies an enhanced absorption of bile salts by the inflamed colon which could potentially lead to a false negative SeHCAT retention value in patients with both ileal and extensive colonic involvement.

As would be expected, the SeHCAT values do not correlate with disease activity as measured by the CDAI, but correlates with the presence of ileal involvement, whether active, inactive or surgically removed. No correlation could be established between the SeHCAT value and the amount of terminal ileal remaining, which may represent a type II error as prior studies have suggested such a relationship. As the majority of SeHCAT retention values for terminal ileal disease/resection are very low, it is possible that earlier readings on day 3 or calculation of the area under the retention curve may be more accurate in quantitating the rate of bile salt loss and, thus, more accurately correlate with the extent of ileal disease/resection.

In agreement with prior studies is

the observation that patients with an intact ileocecal valve have a greater retention of bile salts and less diarrhea. This may be explained in part by the fact that those with intact ileocecal valves usually have less ileum diseased or resected. Alternatively, the ileocecal valve may function sufficiently to slow fecal flow in the ileal area to allow more efficient absorption of bile salts. This would support the belief that the ileocecal valve should be preserved during surgery whenever possible.

Low SeHCAT retention values do not predict the presence of diarrhea, as 35% of those with terminal ileal disease and low SeHCAT retention values had normal bowel habits with no clinical evidence of bile salt catharsis. Furthermore, a low SeHCAT retention value in those with diarrhea and with Crohn's disease limited to the terminal ileum is not clinically useful in predicting the clinical response to cholestyramine therapy. Clearly the SeHCAT test is able to demonstrate bile salt loss but the test is unable to establish a causal relationship between bile salt malabsorption and diarrhea. This is understandable given the multiple mechanisms in Crohn's disease besides bile salt catharsis that may contribute to diarrhea. Thus it appears simpler to give an empiric trial of cholestyramine than to investigate the symptomatic patient with a SeHCAT test to determine whether bile salt catharsis is of importance clinically.

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