Colonic bicarbonate output as a test of disease activity in ulcerative colitis

WEW ROEDIGER,* MJ LAWSON,† V KWOK,‡ A KERR GRANT,† PR PANNALL‡

From the *Department of Surgery, University of Adelaide, the †Department of Gastroenterology, Queen Elizabeth Hospital, and the ‡Department of Clinical Chemistry, Queen Elizabeth Hospital, Woodville, Australia

SUMMARY No available test objectively measures impairment of function of the inflamed colonic mucosa in ulcerative colitis. To study function we assessed rectal bicarbonate output by rectal dialysis in the presence of water and bacterial fatty acid (n-butyrate) in 21 controls, 18 patients with acute ulcerative colitis, 12 patients with ulcerative colitis in remission, and 12 patients with other forms of colitis. In acute ulcerative colitis, compared with controls, bicarbonate output and pH was reduced (p < 0.001); stimulated bicarbonate output with bacterial fatty acid (incremental bicarbonate output) was reduced by 80% in acute ulcerative colitis (p < 0.01). Results indicate that bicarbonate output is a useful and selective test of mucosal function in acute ulcerative colitis. A diminished incremental bicarbonate output with n-butyrate supports the view of inadequate oxidation of bacterial fatty acids in vivo by the mucosa in ulcerative colitis. Whether the test will prove to be an index of prognosis or will aid choice between medical or surgical therapy requires further study.

Disease activity in ulcerative colitis is currently graded on clinical, sigmoidoscopic, or histological criteria.1 A rapid and repeatable test of functional impairment and disease activity of the colonic mucosa is not yet available and would be useful to monitor clinical progress, results of treatment, or possibly to determine which treatment modality (medical or surgical) is best. We describe a test based on measurement of colonic bicarbonate, which normally appears in high concentrations in solutions placed in the colon.2 Values of 45 mmol/l have been reported, measured by means of rectal dialysis.3 Physiologically, bicarbonate exchanges for luminal chloride anion in a process that helps maintain luminal pH at 7-4.4 Addition of bacterial fatty acids further stimulates luminal appearance of bicarbonate,5 an effect which we used in our investigations.

In secretory diarrhoea due to viruses, toxigenic Escherichia coli,6 or cholera, appearance of colonic bicarbonate is increased, leading to a systemic acidosis. Little is known about bicarbonate secretion in ulcerative colitis and no information is available which relates disease activity to bicarbonate output.

We wished to determine by rectal dialysis whether colonic bicarbonate output was altered in ulcerative colitis, whether a change in bicarbonate output was important for ulcerative colitis or other inflammatory bowel conditions, and whether stimulated bicarbonate output was impaired in colitis.

Material and methods

Sixty three subjects were studied: 21 control subjects with haemorrhoids or irritable bowel syndrome, in whom mucosal disease was excluded by mucosal appearances at sigmoidoscopy but not by biopsy; 30 patients with ulcerative colitis, of whom 18 were studied during an acute attack and 12 during remission. Known cases of ulcerative colitis had to have symptomatic, sigmoidoscopic, and histological features (at least mucus cell depletion, crypt abscesses, and increased inflammatory cells) before they were included in the category of acute colitis. A further 12 patients acted as disease controls: six with Crohn's disease, and three each with pseudomembranous or bacterial colitis. None of the disease control patients was taking oral or rectal steroids, but nearly all the patients with ulcerative colitis were taking sulphasalazine both during an acute attack and

Accepted for publication 15 February 1984

Colonic bicarbonate output as a test of disease activity in ulcerative colitis

in remission.

Dialysis tubing (Visking ¼"), tied off at each end with 0 silk, was placed by proctoscope in the rectum, which was cleared of faecal contents with cotton swabs. Segments of tubing, 3 cm, contained either 1·5 ml of distilled water or 1·5 ml of 40 mM sodium n-butyrate together with ¹⁴COOH—dextran (4 × 10⁴ counts/ml) as a non-dialysable marker for volume correction at the end of a 60 min rectal placement. This time interval was chosen as previous reports indicated that equilibration occurred over this period.³⁸ Wherever possible bicarbonate output was determined with water and n-butyrate in each case. If this was not possible patients were studied with butyrate alone. Dialysate was discarded when faecal pigments were observed, which indicated excessive bacterial presence. pH and pCO₂ of the dialysate were measured by micro gas analysis within 3 min of collection, and bicarbonate concentration was derived from these values. Radioactivity was measured by scintillation counting, and volume was calculated from initial and final counts. Bicarbonate output was expressed as mmol/h (volume after 60 min × bicarbonate concentration) and the incremental bicarbonate output designated the difference between bicarbonate output obtained with water and that with n-butyrate.

Results

The procedure was tolerated well by all patients and none of them sustained macroscopic mucosal damage. The mean bicarbonate output with distilled water was 45·1 ± 3·6 (n = 21), which increased significantly to 65·3 ± 3·1 (p < 0·01, Wilcoxon’s paired rank sum test) with n-butyrate (Figure). The pH increased from 7·53 ± 0·03 (n = 21) with distilled water to 7·64 ± 0·03 with butyrate in the dialysis bag (p < 0·01 Wilcoxon’s paired rank sum test).

Bicarbonate output (mmol/h), pH, and incremental bicarbonate output with butyrate (40 mmol/l) in healthy and disease controls and in patients with colitis

<table>
<thead>
<tr>
<th></th>
<th>Bicarbonate output</th>
<th>pH</th>
<th>Incremental bicarbonate output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>65·3 ± 3·1 (21)*</td>
<td>7·64 ± 0·03 (21)</td>
<td>19·9 ± 3·2 (21)</td>
</tr>
<tr>
<td>Disease controls</td>
<td>51·3 ± 7·7 (12)</td>
<td>7·43 ± 0·06 (12)</td>
<td>9·0 ± 6·9 (10)†</td>
</tr>
<tr>
<td>Acute ulcerative colitis</td>
<td>23·3 ± 1·7 (18)</td>
<td>7·15 ± 0·04 (18)</td>
<td>3·8 ± 1·4 (16)$$</td>
</tr>
<tr>
<td>Quiescent ulcerative colitis</td>
<td>57·1 ± 3·7 (12)</td>
<td>7·56 ± 0·06 (12)</td>
<td>13·9 ± 4·8 (9)†</td>
</tr>
</tbody>
</table>

Values given as mean ± SEM of the number of cases in parentheses.

*One tailed analysis of variance.

F = 24·27; dfₙ = 3 dfₓ = 59.

healthy control v disease control p < 0·001.

acute colitis v disease control p < 0·001.

healthy control v quiescent colitis 0·1 < p < 0·001.

acute colitis v quiescent colitis 0·5 < p < 0·01.

Compared with healthy controls (Wilcoxon’s rank sum test)

Not significant.

†Not significant.

Compared with healthy controls (Wilcoxon’s rank sum test)

§Not significant.

Increased bicarbonate output in rectal dialysate with n-butyrate in the control group. Wilcoxon’s paired rank sum test p < 0·01 (water v butyrate).

Bicarbonate output was significantly lower in patients with active ulcerative colitis compared with healthy and disease controls (Table). The incremen-
nal bicarbonate output was notably smaller in patients with acute ulcerative colitis than in controls. A trend towards lower values of bicarbonate output was also noted in the disease controls, but this was not significant.

Discussion

Our study has confirmed that there is normally considerable bicarbonate secretion into the colon of man, the rate of which we have termed "bicarbonate output." Values of bicarbonate secretion in our control cases were slightly higher than those reported by McNeil et al; this may be due to differences between volume corrections obtained with a radioactive, non-dialysable marker and those obtained by weighing dialysis bags.

In ulcerative colitis the bicarbonate output was significantly reduced, and this is in keeping with previous investigations. Breuer et al found higher levels of chloride anion in the colons of patients with ulcerative colitis compared with controls, indicating that the normal luminal to mucosal exchange of chloride for bicarbonate was impaired. In another study with orally ingested dialysis bags the luminal pH in ulcerative colitis was low in the presence of normal concentrations of bacterial fatty acids. Excess bacterial fatty acids has in the past been implicated as the cause of acidic stools, especially in infant diarrhoea. Our findings of low pHs indicate that a failure of bicarbonate secretion rather than excessive bacterial fermentation is the cause of lowered luminal pH of the colon with ulcerative colitis.

Bicarbonate output in other forms of colitis was noticeably different. In Crohn's colitis Breuer et al found that the luminal levels of chloride were within the normal range, which, together with our results, suggests an impaired exchange of chloride for bicarbonate. In contrast with our pH values in the large bowel in disease controls, the pH of the small bowel in patients with Crohn's disease was higher than in patients with healthy mucosa. Thus in general bicarbonate secretion, at least in Crohn's disease, is not grossly altered, though some impairment of mucosal production does exist as our stimulated bicarbonate output was not optimal. Overall, a lowered bicarbonate output in ulcerative colitis appears to occur mainly in the acute condition.

We have confirmed that bicarbonate output is stimulated by n-butyrate, an observation first shown in man with acetate by McNeil et al and Ruppin et al. Whether stimulation of bicarbonate output was maximal needs to be established by further work. Bicarbonate secretion is mediated by carbonic anhydrase, which is located in the columnar epithelial cells of the superficial epithelium of the human colon. Butyrate could either alter the activity of this enzyme directly or exert its action indirectly through metabolism of n-butyrate to CO₂ in the colonic epithelium. The CO₂ on which carbonic anhydrase acts is usually considered to be of metabolic origin, though generation of CO₂ by bacteria could be an alternative source. We tried to exclude bacterial CO₂ as much as possible by performing dialysis in rectums cleared of luminal contents. Previous in vitro investigations with isolated epithelial cells of the colon showed diminished production of CO₂ from n-butyrate in ulcerative colitis. We have confirmed these findings in vivo by showing a reduced incremental output of bicarbonate in response to butyrate. Observations of the present and other studies show that the colonic mucosa in ulcerative colitis is unable to oxidise short chain fatty acids.

The value of bicarbonate output in determining prognosis of ulcerative colitis is unclear. We did not correlate bicarbonate output with histological activity, but 12 of 18 patients had moderate disease activity on sigmoidoscopy, indicating that diminished bicarbonate output occurred in the early phase of acute ulcerative colitis. Two of the lowest bicarbonate values were recorded within two weeks of urgent surgery for previously controlled colitis. We are hoping to determine by long term follow up whether low bicarbonate output is an indicator of prognosis in ulcerative colitis.

References

Colonic bicarbonate output as a test of disease activity in ulcerative colitis


Requests for reprints to: Dr W E Roediger, University Department of Surgery, The Queen Elizabeth Hospital, Woodville, South Australia 5001, Australia.

The May 1984 issue

The May 1984 issue contains the following papers:

Varied light and scanning electron microscopic appearances of barium sulphate in smears and histological sections  DA LEVISON, PR CROCKER, A SMITH, AJ BLACKshaw, CI BARTRAM

Unusual histological appearances of barium sulphate—a case report with scanning electron microscopy and energy dispersive x ray analysis C WOMACK

Cortical microcystic disease of the kidney with dominant inheritance: a previously undescribed syndrome SC MELNICK, DB BREWER, JS OLDHAM

Tumour-associated eosinophilia in the bladder D LOWE, CDM FLETCHER, RL GOWER

Primary chorionicarcinoma of the bladder evolving from a transitional cell carcinoma PM DENNIS, AG TURNER

Relation between intragastric bile acid concentration and mucosal abnormality in the stomach after vagotomy and gastroenterostomy for duodenal ulcer PCH WATT, JM SLOAN, TL KENNEDY

Relation between gastric histology and gastric juice pH and nitrite and N-nitroso compound concentrations in the stomach after surgery for duodenal ulcer PCH WATT, JM SLOAN, JOAN DONALDSON, G CAMPBELL, TL KENNEDY

Crohn’s disease of the gall bladder J MCCLURE, SS BANERJEE, PS SCHOFIELD

A quantitative study of mast cells in Hodgkin’s disease J CROCKER, PJ SMITH

Antithrombin III metabolism in patients with liver disease EAR KNOT, JW TEN CATE, HR DRUFHOUT, LH KAHLE, GN TYTGAT

Pepsinogen synthesis and secretion in isolated gastric glands J DEFIZE, G PALS, RR FRANTS, BD WESTERVELD, SGM MEUWISSEN, AW ERIKSSON

Collagen stimulating factors from lung in experimental paraquat poisoning demonstrated in vitro and in vivo WD THOMPSON, RS PATRICK

Collagen stimulating factors in hepatic fibrogenesis A FALLON, JF BRADLEY, J BURNS, J O’D MCGEE

Patterns of chronic liver disease in Kuwait with special reference to localisation of hepatitis B surface antigen MS AL ADNANI, SM ALI

Widespread distribution in human tissues of an antigenic determinant of granulocytes AJ HOWIE, G BROWN, AMANDA G FISHER, M KHAN

Localisation of factor XIII in human tissues using an immunoperoxidase technique JD FEAR, PJ JACKSON, C GRAY, KJA MIŁOSZEWSKI, MS LOSOWSKY

Chronic lymphocytic leukaemia terminating in acute myelofibrosis ANNE L LENNAJD, SJ PROCTOR

Effect of volume of blood cultured on detection of Streptococcus viridans bacteraemia DC SHANSON, F THOMAS, D WILSON

Anomalous results using countercurrent immunoelectrophoresis for the detection of pneumococcal antigen in Bactec blood culture media WENDY CHAN CHIANG, GS TILLOTSON, MAEV G LEANEY, LEELA A GANGULI

Evaluation of a commercial antibody capture enzyme immunoassay for the detection of rubella specific IgM J HODGSON, P MORGAN-CAPNER

Prospective study of the human polyomaviruses BK and JC and cytomegalovirus in renal transplant recipients SD GARDNER, EFD MACKENZIE, C SMITH, AA PORTER

Rectal organ culture as a model for the investigation of bacterial adhesion and invasion RJ DICKINSON, WJ BRANCH, RE WARREN, G NEALE

The bacteriology of infected malignant ulcers VO ROTIMI, FA DUROSINMI-ETTI

Technical method

Automated method of nitrite estimation in gastric juice PCH WATT, JOAN D DONALDSON

Letters to the Editor

Book reviews

Some new titles

Notice

Correction

Copies are still available and may be obtained from the PUBLISHING MANAGER, BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON WC1H 9JR, price £5.00, including postage.
Colonic bicarbonate output as a test of disease activity in ulcerative colitis.
W E Roediger, M J Lawson, V Kwok, A K Grant and P R Pannall

doi: 10.1136/jcp.37.6.704

Updated information and services can be found at:
http://jcp.bmj.com/content/37/6/704

**Email alerting service**

*These include:*

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/