Ranitidine, diarrhoea, and lymphocytic colitis

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Abstract

A 69 year old woman developed chronic diarrhoea while being treated with ranitidine. Sigmoidoscopy was performed after six weeks and showed typical histological features of lymphocytic colitis. Ranitidine was withdrawn and the diarrhoea resolved. Eight months later, a 72 hour oral rechallenge period of ranitidine, was performed immediately preceded (period 1) and followed (period 2) by sigmoidoscopy and biopsy. Diarrhoea recurred during the rechallenge period and resolved again within one day after drug withdrawal. The mean (SEM) intraepithelial lymphocyte count was not significantly different between periods 1 and 2 (11.9 (0.6) and 13.1 (0.4) per 100, respectively). An immunopathological study of 30 serial sections of biopsy specimens was performed for both periods 1 and 2. The expression of HLA-DR by the rectal epithelium was mild or absent in all sections from period 1, and was considerable in 25 of 30 sections from period 2 ($p < 10^{-9}$). It is suggested that the oral intake of ranitidine was responsible for the diarrhoea and induced the immunopathological signs of activation of the rectal mucosal immune system during the rechallenge period.

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Lymphocytic colitis, previously termed 'microscopic colitis',¹⁻³ is a clinicopathological syndrome of chronic water diarrhoea, diffuse colonic mucosal inflammatory changes, and an increased intraepithelial lymphocyte count despite normal endoscopic tests.⁴

The cause of most cases of lymphocytic colitis is unknown. Lymphocytic colitis may be drug induced, however, as in the three cases of lymphocytic colitis with protracted diarrhoea secondary to the longterm use of Cyclo 3 Fort, a phlebotonic drug used in France, which we reported previously.⁵ We describe here the case of a woman who developed chronic diarrhoea while being treated with ranitidine and who, after six weeks, was found to have lymphocytic colitis. Eight months after the withdrawal of ranitidine and the cessation of diarrhoea, we performed a 72 hour rechallenge test with ranitidine given orally, preceded and followed by rectal biopsy. Based on the clinicopathological results of this test, we suggest that the diarrhoea was drug induced. Furthermore, we show that the oral intake of ranitidine in itself can induce an activation of the rectal mucosal

immune system. We cannot conclude, however, whether lymphocytic colitis was ranitidine induced or ranitidine exacerbated, as persistent histological features of lymphocytic colitis were seen before the drug rechallenge.

Case report

A 69 year old woman was admitted to our department in February 1993 for intense epigastric pain. She had a past history of subtotal thyroidectomy for toxic multinodular goitre at age 16, and she had been treated intermittently for 10 years with non-steroidal anti-inflammatory drugs for psoriatic arthritis. At the time of admission, she was receiving diclofenac 100 mg daily for low back pain. Her physical examination was unremarkable, except for epigastric pain provoked by palpation of the abdomen. An upright film of the abdomen was normal. Upper gastrointestinal endoscopy showed a duodenal ulcer. Non-steroidal inflammatory drugs were definitively withdrawn. The patient received omeprazole 20 mg daily and reported relief of epigastric pain within the first 72 hours of this treatment. Six weeks later, omeprazole was replaced with ranitidine 150 mg daily in the evening. During all this period, the patient continued to receive levothyroxin for postsurgical thyroid insufficiency and paracetamol for lumbar pain.

At the beginning of the ranitidine treatment, the patient had two to four formed stools per week with no past history of intermittent or sustained diarrhoea. After one week receiving ranitidine, her stools became soft and more frequent. After 10 days of treatment, she had persistent diarrhoea (five to seven liquid stools per day, including two to three stools during the night). An initial flexible sigmoidoscopy was performed six weeks after the onset of diarrhoea (period 0). Endoscopic examination showed normal colonic mucosa. Three biopsy samples were taken from the rectum and fixed in Bouin's solution. Paraffin wax sections were stained with haematoxylin and eosin. The intraepithelial lymphocyte count was assessed by estimating their number per 100 epithelial cells, 100 to 300 enterocytes being counted at each section level. The intraepithelial lymphocyte count was evaluated in three sections from each biopsy specimen - that is, for nine section levels. The subepithelial collagen layer was measured in 10 intercryptal spaces in nine well oriented sections.

The mean (SEM) intraepithelial lymphocyte count was 20.4 (1.2) per 100 epithelial cells. Patchy surface epithelial detachment was seen in most of the sections. There was moderate infiltration of the lamina propria by mononuclear cells, but not by neutrophils or

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eosinophils (Fig 1 (A)). The thickness of the subepithelial collagen layer was within the normal range, from 0 to 7 μm in all the sections. All these histological features were consistent with the diagnosis of lymphocytic colitis.

Ranitidine was withdrawn, whereas levothyroxin and paracetamol were continued. Diarrhoea disappeared within 48 hours and the bowel habit returned to its previous normal state. Omeprazole 20 mg three times a week was then introduced as a maintenance treatment for the duodenal ulcer. Eight months later, the patient was seen at our unit in an ambulatory setting, and reported no recurrence of diarrhoea. We suggested a 72 hour ranitidine rechallenge period with flexible sigmoidoscopy and biopsy specimens obtained immediately before (period 1) and after (period 2) the rechallenge. The aims of the test were to assess the state of the colon by histological examination after the drug had been withdrawn for some time and to detect the first immunopathological events induced by the drug on rechallenge. The patient gave her informed consent to the test. Omeprazole was withdrawn, and ranitidine given orally at a dose of 150 mg daily for three days. During each sigmoidoscopy, three biopsy specimens were obtained and fixed in Bouin's solution. Paraffin wax sections were cut and stained with haematoxylin and eosin. The intraepithelial lymphocyte count was assessed in 10 sections from each biopsy specimen – that is, in 30 sections per period – as described above, and in one section from rectal specimens of 10 adult controls with a histologically normal colon. The pathologist was unaware whether the sections were from period 1 or 2. The mean intraepithelial lymphocyte counts were compared using variance analysis, and differences between the pairs of means compared by the Newman-Keuls test.

During each sigmoidoscopy in periods 1 and 2, three additional biopsy specimens from the rectum were taken and immediately frozen, and then stored at -80°C until cryostat sections were obtained. A three stage indirect immunoperoxidase staining technique using anti-CD 25 and anti-HLA-DR monoclonal antibodies was used on these sections. CD 25 is an interleukin 2 receptor and its expression is a marker of activation of a number of cell types, including T cells, B cells, and macrophages. HLA-DR is normally expressed by antigen-presenting cells – that is, macrophages of the lamina propria – but it is not or barely expressed by colonic epithelial cells.^{6,7} The expression of HLA-DR by the epithelial cells in crypts and intercryptic spaces was scored as absent or mild (no or a few positive cells) or considerable (numerous positive cells) in 30 different sections for each time period. Again, the pathologist was unaware of the period. Similarly, the expression of CD 25 by mononuclear cells of the lamina propria was scored as absent or mild (none or a few positive cells) or considerable (numerous positive cells) and assessed in 30 different sections for each period. The expression of HLA-DR and CD

Figure 1: Histological appearance of: (A) the rectal mucosa after six weeks of treatment with ranitidine and with continued diarrhoea (period 0); (B) the rectal mucosa eight months after ranitidine withdrawal (period 1) (haematoxylin and eosin; original magnification $\times 25$). Note the partial regression of the lamina propria infiltration by mononuclear cells between periods 0 and 1.

25 was compared between periods 1 and 2 by the χ^2 test.

Diarrhoea recurred on the second and third day of ranitidine rechallenge, and disappeared again within one day after drug withdrawal. The endoscopic appearance of rectal mucosa was normal before as well as after rechallenge.

Intraepithelial lymphocyte count of rectal mucosa in the patient for the three periods, and in 10 controls

	Intraepithelial lymphocyte count (%, mean (SEM))
Patient	
At the time of diarrhoea (period 0, n=9 sections)	20.4 (1.2)*
Just before rechallenge (period 1, n=10 sections)	11.9 (0.6)†
At day 3 of rechallenge (period 2, n=10 sections)	13.1 (0.4)‡
Controls (n=10)	7.4 (1.1)§

*Significantly different from † and ‡; † not different from ‡, †, and ‡ significantly different from §.

The Table gives the mean intraepithelial lymphocyte counts. Intraepithelial lymphocyte counts for periods 1 and 2 did not differ significantly, but both were significantly lower than the period 0 intraepithelial lymphocyte count ($p < 10^{-5}$), and significantly higher than controls ($p < 0.01$). There was a mild lamina propria infiltration by mononuclear cells in both periods (Fig 1 (B)). The subepithelial collagen layer thickness was within the normal range, from 0 to 7 μm in all the sections from both periods 1 and 2.

The expression of HLA-DR by the epithelium was mild or absent in all 30 sections during period 1 (Fig 2 (A)) and was considerable in 25 of the 30 sections from period 2 – that is, after ranitidine rechallenge (Fig 2 (B)). This difference was highly significant ($p < 10^{-9}$). CD 25 expression by mononuclear cells of the lamina propria was more often marked during period 2 (21 of 30 sections) than during period 1 (13 of 30 sections, $p < 0.05$).

Discussion

Microscopic colitis is now regarded as an 'umbrella' term covering any case of colitis in which there is histological but not colonoscopic or barium enema abnormality.^{8,9} The histological abnormalities encountered when our patient was taking ranitidine met all the diagnostic criteria of lymphocytic colitis and not those of collagenous colitis.¹⁰ At this point, the diagnosis of idiopathic lymphocytic colitis was the most likely for the following reasons. Firstly, like most patients with lymphocytic colitis, our patient was a middle aged woman, with associated arthritic symptoms. Secondly, there was no evidence of drug induced lymphocytic colitis. As a matter of fact, the longterm use of non-steroidal anti-inflammatory drugs has been pointed out as a possible cause of collagenous colitis^{11,12} but not lymphocytic colitis.

Eight months after stopping ranitidine, we performed a 72 hour rechallenge test with oral ranitidine preceded and followed by rectal biopsy. Although the patient had experienced no recurrence of diarrhoea after the ranitidine was stopped, the rectum was still histologically abnormal before the drug rechallenge. This result shows that lymphocytic colitis can be seen histologically in the absence of diarrhoea. Clinicopathological discrepancy has been reported in the case of collagenous colitis¹³ but, to our knowledge, not in the case of lymphocytic colitis.

Diarrhoea recurred during the 72 hour rechallenge period and it resolved again soon

Figure 2: HLA-DR antigen expression by rectal mucosa cells immediately before (A, period 1) and after (B, period 2) a 72 hour period of drug rechallenge. Note the absence of HLA-DR antigen expression by epithelial cells before rechallenge (A) and the considerable HLA-DR antigen expression of epithelial cells after rechallenge (B) (immunoperoxidase staining with monoclonal antibody directed against HLA-DR non-polymorphic determinants, original magnification $\times 20$).

after withdrawal of ranitidine. This feature strongly suggested that ranitidine was the cause of the diarrhoea. This suggestion is not in itself original, as diarrhoea was previously reported as the most common side effect of ranitidine.¹⁴

The immunopathological study of rectal biopsy specimens performed immediately before and after the 72 hour rechallenge period allowed us to show the existence of early immunopathological changes induced by the oral intake of ranitidine. These changes – that is, augmentation of CD 25 expression by lamina propria mononuclear cells and appearance of diffuse HLA-DR expression by epithelial cells – were consistent with activation of mucosal immune cells.^{15 16} The site and the mechanism of this activation are not specified by our model, nor could we discover if the drug itself or its metabolites are responsible for this activation. Nevertheless, it can be hypothesised that the histological appearance of lymphocytic colitis seen after six weeks of diarrhoea and ranitidine intake was partly or totally related to the chronic immune activation of the rectal immune system secondary to ranitidine. It could not be stated in our case, however, whether the lymphocytic colitis was drug induced as has been shown for Cyclo 3 Fort,⁵ or simply a 'drug exacerbated' idiopathic colitis. As a matter of fact, histological features consistent with a minor aspect of lymphocytic colitis were still seen in our patient eight months after ranitidine had been withdrawn. Moreover, our patient exhibited an underlying condition (that is, middle age and arthritic disease), usually seen in patients with idiopathic lymphocytic colitis.¹⁰

Our finding suggests that some drugs could have a role in the pathogenesis or the exacerbation of some cases of lymphocytic colitis, or both. We propose that all recent and concurrent drug treatments should be noted when lymphocytic colitis is diagnosed. Withdrawal should be attempted if possible when the role of a drug is suspected because of previous findings. When a drug has not been implicated previously in published works, we suggest that a short-term rechallenge should be considered, using our immunopathological model. In that

way, early immunopathological changes induced by the drug may be detected, long after the drug has been stopped.

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