

Treatment of distal ulcerative colitis with lidocaine

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S BJÖRCK, A DAHLSTRÖM, H AHLMAN. Treatment of distal ulcerative colitis with lidocaine. *Can J Gastroenterol* 1993;7(2):179-181. Treatment with lidocaine is gentle, with a high success rate and without observed side effects. Most of the refractory cases in this study responded to such treatment, even patients with severe chronic symptoms. Lidocaine seems to offer a good treatment alternative to conventional treatment and in cases with refractory distal colitis.

Key Words: Lidocaine, Local anesthetics, Mucosal inflammation, Procto-sigmoiditis, Topical treatment, Ulcerative colitis

Traitement de la colite ulcéreuse distale avec de la lidocaïne

RÉSUMÉ: Le traitement à la lidocaïne agit doucement; il s'accompagne d'un taux de réussite élevé, sans effets secondaires observés. Dans cette étude, la plupart des cas rebelles ont répondu à un tel traitement, même les sujets atteints de symptômes chroniques graves. La lidocaïne semble représenter une bonne solution de rechange par rapport au traitement classique et dans les cas de colite distale rebelle.

DISTAL ULCERATIVE COLITIS IS confined to the rectum or recto-sigmoid. The extension of disease can be assessed by rigid sigmoidoscopy and colonoscopy, and the estimated limits usually are based on macroscopic signs of inflammation.

The incidence of distal colitis has increased to between 40 and 70% in patients with ulcerative colitis (1). Patients with distal colitis are, in general, 10 years older at disease onset than patients with ulcerative colitis (aged 30 to 40 years). The treatment of distal colitis varies, but most patients

are treated topically with corticosteroid enemas and sulphasalazine perorally or topically with the new 5-aminosalicylic acid compounds. Those patients with distal colitis who do not respond to treatment within six to eight weeks are referred to as having refractory distal colitis. The reason for this refractory state is unknown (2). In this paper the authors present a new approach to treat the mucosal inflammation in distal colitis with local anesthetics.

An imbalance of the autonomic nervous system in the pathophysiology of ulcerative colitis was suggested many

years ago (3,4). Such an imbalance with adrenergic preponderance might produce both increased epithelial turnover and increased vasomotor tone of the small vessels, resulting in mucosal damage. Several studies (5-8) have reported morphological changes of the enteric nervous system in ulcerative colitis. The authors (9) confirmed hyperplasia of the mucosal adrenergic innervation in ulcerative colitis as previously reported by Kyösola et al (10). Studies of various gastrointestinal diseases over the past few years have pointed out altered distribution of enteric nerves and changed expression of transmitters within these nerves (11-13). Several reports have recently focused on the interaction between enteric nerves and the immune system (neuroimmunomodulation) (14).

To date the authors have treated almost 200 patients with limited or extensive ulcerative colitis with a lidocaine gel. The initial hypothesis was that hyperactive local nervous reflexes were of pathogenetic importance in ulcerative proctitis. Blockade of enteric nerves by a local anesthetic seemed to reduce the inflammatory response. Topical application of a lidocaine gel resulted in good symptomatic relief and restored mucosal integrity in these patients (9,15). Circumstantial evidence that local anesthesia has direct inhibitory effects on the inflammatory response and the proliferation of T cells also exists (16,17).

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PATIENTS AND METHODS

Seventy-seven consecutive patients with histopathologically proven distal colitis were treated with topical lidocaine. Twenty-eight patients (eight males, 20 females, mean age SD: 33 ± 13 years) had proctitis; of these, 22 had chronic symptoms (refractory disease). Forty-nine patients had proctosigmoiditis (31 males, 18 females, mean age SD: 42 ± 13 years); of these, 32 had refractory disease.

Topical treatment: Enemas containing 400 mg lidocaine hydrochloride was given twice a day as a gel preparation. Patients with proctitis (less than 15 cm above the dentate line) applied a 2% lidocaine gel (Astra, Södertälje, Sweden) intrarectally 20 mL twice a day; the others received 100 mL of gel twice a day (400 mg lidocaine in each dose). Patients on peroral sulphasalazine medication were allowed to continue such treatment with an unchanged dose. Patients on medication with cortisone enemas had this treatment withdrawn for a two-week period prior to onset of lidocaine therapy.

Clinical examination: Endoscopy with rectal biopsies was performed before the onset of treatment and at regular intervals every two to six weeks. The mucosal appearance and the mucosal vasculature, as well as the presence of contact bleedings, ulcers, mucus and pus, were described.

Histochemical procedures: The mucosal biopsies were studied immunocytochemically. Slides were incubated using the indirect method of Coons using fluorescein isothiocyanate-labelled secondary antisera. Adrenergic and peptidergic nerves were demonstrated using well-characterized antisera against tyrosine hydroxylase, neuropeptide Y, vasoactive intestinal peptide, substance P, somatostatin and delta sleep-inducing peptide. An antiserum against the Schwann cell protein (S100) was also used to label nerve structures and polydendritic cells. The mucosal infiltration with OKT4⁺ and OKT8⁺ lymphocytes, and plasma cells was investigated using monoclonal antibodies (15).

Histological criteria for improvement of inflammation: Treatment with

lidocaine was continued until two independent examiners could verify a clear reduction of subset of lymphocytes (OKT4⁺ and OKT8⁺) and plasma cells in the lamina propria. This usually occurred in conjunction with a reduced number of polydendritic cells, and with restitution of epithelial height and mucus production. No obvious changes in the hyperinnervation pattern could be seen.

RESULTS

Clinical results: There were no complaints about side effects of treatment despite continuous therapy over several months in certain cases. Many patients reported an almost prompt relief of symptoms (within the first few days). No patient had fecal incontinence or experienced any problems in evacuating the rectum during treatment. In patients with proctitis, the discharge of blood and mucus gradually disappeared within the first seven to 10 days of treatment. In patients with tenesmus, symptoms were usually reduced or abolished within the first week of treatment.

Proctitis: All 28 patients with proctitis responded to treatment, with disappearance of symptoms and gradual improvement of mucosal histology. All patients went into remission, including the 22 patients refractory to other treatments. The proctitis patients were treated for 5.7 ± 0.3 weeks and were followed for 20.0 ± 1.9 months. During this observation, 68% of patients recurred (mucosal inflammation and symptoms).

Proctosigmoiditis: Clinical remission was achieved in 41 of 49 patients treated. Two patients did not respond to treatment; one developed fulminant total colitis and the other responded to subsequent cortisone therapy. In six patients, objective histological improvement was not achieved according to study criteria, but the patients still experienced symptomatic relief that made them continue with treatment. This patient group was treated for 3.5 ± 0.3 months. During the 15.6 ± 1.1 months of total observation, 42% of the patients recurred (mucosal inflammation).

Histological findings: The submucosa and mucosal innervation varied individually between patients, probably reflecting the severity of disease and the degree of inflammatory response. Early in the disease process, hyperplasia of adrenergic nerves and neuropeptide Y immunoreactive nerves was obvious (enlarged varicose nerve terminals and thickened nerve bundles). The most prominent finding in chronic cases (refractory disease) was hyperplasia of substance P and vasoactive intestinal peptide-immunoreactive nerve fibres and terminals. These nerve terminals appeared to innervate the mucosa in a patchy pattern. Usually the innervation pattern was not changed during treatment. The total innervation pattern of the submucosa and mucosa was assessed from the distribution of S100-immunoreactive fibres. This antiserum also labels polydendritic antigen-presenting cells; these cells were abundant in the diseased mucosa, usually located subepithelially along crypts, but with healing and restitution of the epithelium during treatment, they disappeared from the mucosa.

T cells (OKT4⁺ and OKT8⁺) were found in a very low number in healthy controls, but invaded the lamina propria and epithelial lining massively during active disease. These subsets of lymphocytes were part of the inflammatory response in cryptitis and crypt abscesses. During treatment with lidocaine the number of lymphocytes gradually disappeared, starting from the luminal side of the mucosa. The treatment was continued until the number of lymphocytes was markedly reduced and confined to vessels within the lamina propria. The number of plasma cells in the lamina propria was reduced almost in parallel with the lymphocytes.

DISCUSSION

A new approach to treat distal colitis, both in acute and chronic (refractory) phases, has been presented, ie, topical treatment of the inflamed mucosa with a local anesthetic. The rationale for this treatment was to block hyperreactive nervous reflexes and inhibit transmitter release from hy-

periplastic enteric nerves within the mucosa and submucosa. It cannot be concluded whether the changed innervation in ulcerative colitis is secondary to the mucosal inflammation or whether it is a pathogenetic step in the development of mucosal inflammation. Besides nervous blockade, lidocaine can influence immune functions, eg, lymphocyte proliferation and macrophage migration (16,17). The beneficial effect of lidocaine observed in ulcerative colitis (symptoms, endoscopy and histology findings) may be a summation effect in which nerves, inflammatory cells and cell products (lymphokines) all are influenced by treatment in a therapeutic way. Most patients have experienced very rapid relief of symptoms, even patients with refractory disease. However, it must be emphasized that it is much easier to treat patients with the early acute phase compared with the chronic phase (characterized by distorted architecture and low resistant cuboidal epithelium).

The lower recurrence rate observed after treatment for proctosigmoiditis, compared with proctitis, may reflect

the relative importance of long term therapy rather than differences between disease entities. In this series, patients with proctosigmoiditis had a longer duration of symptoms (four times longer) than patients with proctitis alone. Patients with proctitis had a relapse rate of 68% over an observation time of 20 months in accordance with earlier reports (18). The recurrence rate for patients with proctosigmoiditis was 40% over 16 months, which is a good result with respect to the high percentage of patients with refractory disease in this series.

Parameters reflecting the degree of inflammation were easy to follow, ie, T lymphocyte infiltration, and presence of polydendritic and plasma cells within the lamina propria and epithelium. The polydendritic cells are antigen-presenting cells (19). Since these cells are localized subepithelially in the mucosa during active disease, this may indicate that the epithelium has a decreased resistance, with leakage of antigens into the lamina propria. One important function of plasma cells is to produce secretory immunoglobulin A

to cover and protect the luminal surface of the intestine from pathogens, and this function seems to be enhanced in the damaged mucosa (19). These cell types all decreased during treatment with lidocaine. The general morphological features of the diseased mucosa (ie, a low and disrupted epithelium, reduced mucous contents of goblet cells, and shortening and branching of crypts) were also restituted to a high degree during treatment.

CONCLUSIONS

Treatment with lidocaine is gentle, with a high success rate and without observed side effects. Most of the refractory cases in this study responded to such treatment, even patients with severe chronic symptoms. Lidocaine seems to offer a good treatment alternative to conventional treatment and in cases with refractory distal colitis.

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