

Effects of tixocortol pivalate on gastrointestinal disease in systemic mastocytosis: a preliminary study

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Summary

Tixocortol pivalate is a steroid reportedly without significant adrenal–pituitary axis suppression when administered via the gastrointestinal tract. To determine whether this steroid would suppress the gastrointestinal manifestations of systemic mastocytosis, we performed an open clinical trial for safety and efficacy with tixocortol pivalate in four patients for periods of 8–15 weeks. All patients showed a decrease in the symptoms of abdominal pain and frequency of stools. Laboratory parameters of malabsorption improved in parallel with symptom relief. Histopathologic abnormalities of the small bowel improved in one patient. There was no significant suppression of the pituitary–adrenal axis. Two patients developed fluid retention while on tixocortol pivalate, which was attributed to a mineralocorticoid effect. One patient had a fall in AM cortisol. In summary, this study strongly suggests that tixocortol pivalate, when administered orally, has gastrointestinal anti-inflammatory activity comparable to conventional steroids, but may not be entirely without adrenal-suppressive effect and may lead to fluid retention in some patients. Further studies are warranted to assess the value of tixocortol pivalate in the therapy of inflammatory diseases of the upper gastrointestinal tract.

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Introduction

Mast cell disorders are a closely related group of diseases in which there is an abnormal accumulation of mast cells in one or more organ systems. These disorders are most commonly grouped under the spectrum of ‘mastocytosis’ and include indolent mastocytosis (formerly benign mastocytosis), which is divided into two subgroups: those with isolated skin involvement, and those with systemic disease; mastocytosis with an associated hematologic disorder; mast cell leukaemia; and lymphadenopathic mastocytosis with eosinophilia [1,2]. Indolent systemic mastocytosis is characterized by extracutaneous mast cell hyperplasia with or without cutaneous involvement. The most prominent extracutaneous tissues involved are the bone marrow, skeletal system, gastrointestinal (GI) tract, lymph nodes, liver, and spleen. GI involvement is often found in patients with indolent systemic mastocytosis

[3,4]. The most common gastrointestinal problems are abdominal cramping, gastric hypersecretion, peptic ulcer disease, and malabsorption. Malabsorption is associated with diarrhoea, abdominal pain, nausea, vomiting, and steatorrhoea. One study found that malabsorption occurred in 34% of patients with systemic mastocytosis [3]. Symptoms have been attributed to the release and generation of mast cell mediators, such as histamine and prostaglandin D₂, and to direct organ infiltration by mast cells [5–7].

The malabsorption seen in some patients with systemic mastocytosis is often the most difficult of the GI manifestations of disease to control. H1 and H2 antagonists, anticholinergics, and disodium cromoglycate are of limited value in this disease [8]. In mastocytosis patients with severe malabsorption, systemic steroids have been shown to be effective, which can partially be explained by their anti-inflammatory effects [3,4]; however, their use is often complicated by their effects such as osteoporosis and gastroduodenal ulcers which, in patients with mastocytosis, aggravate a predisposition to develop these problems

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from their underlying disease [2]. A novel corticosteroid, tixocortol pivalate (Sandoz, East Hanover, NJ), which reportedly lacks significant adrenal-pituitary axis suppression when administered via the GI tract and yet has potent local anti-inflammatory activity, has been shown to be more effective than hydrocortisone retention enemas (Cortenema®) in the treatment of certain patients with ulcerative colitis [9]. On the basis of this study, we postulated that the topical GI mucosal effects of tixocortol pivalate would help control malabsorption in patients with mastocytosis. We report here an open clinical trial of tixocortol pivalate in patients with indolent systemic mastocytosis. Our results suggest that this agent has GI anti-inflammatory activity comparable to conventional steroids but is not without side effects.

Subjects and methods

Three women and one man with indolent systemic mastocytosis and known GI involvement were enrolled in this study under a protocol approved by the Clinical Research Subpanel of the National Institute of Allergy and Infectious Diseases (Protocol no. 87-I-182). This was an open prospective clinical trial in which patients received from 250 mg of an oral suspension of tixocortol pivalate twice daily to 500 mg four times daily. The drug was dispensed by the Pharmaceutical Development Service of the National Institutes of Health. Symptoms were recorded daily by the patients in a diary. Symptoms evaluated by the patient were general well-being, scored on the following scale: 0, well; 1+, slightly under par; 2+, poor; 3+, very poor; and 4+ terrible. Abdominal pain was scored as follows: 0, none; 1+, mild; 2+, moderate; and 3+, severe. Additionally, patients recorded the number and character of their stools daily. An increased frequency of stools was defined as > 3 bowel movements per day.

Prior to initiating tixocortol pivalate, patients had their histories recorded and underwent a physical examination. Blood was obtained for complete blood count, serum chemistries, and 8 AM cortisol. To assess GI absorptive function, all patients had stool collected for 72 hr and the daily faecal fat output determined after the patients had been on a 100 g fat diet for at least 3 days [10]. The collection was obtained while anti-secretory agents, anti-diarrhoeal agents, and antacids were withheld. Malabsorption was said to be present if steatorrhea was present (> 7 g/day of faecal fat). A D-xylose test was performed with determination of serum D-xylose concentration 2 hr after ingestion of 25 g of D-xylose in water and determination of D-xylose excreted in urine collected 5 hr following the oral D-xylose load [11]. Malabsorption of D-xylose was said to be present if either the urinary or

serum D-xylose concentration was decreased (urinary, < 4 g/5 hr; serum, < 20 mg/dl at 2 hr).

Esophagogastroduodenoscopy was performed in each patient with an Olympus GIF-XQ fiberoptic panendoscope (Olympus Corporation of America, New Hyde Park, NY). Two biopsies were taken from the stomach antrum and fundus and the duodenum, fixed in both 10% formalin and Carnoy's fixative, paraffin-embedded, and stained with haematoxylin and eosin, as well as special stains to identify mast cells: Giemsa, toluidine blue, and chloroacetate esterase [1]. Results from endoscopy were routinely sent for pathology, where they were assessed for evidence of active disease (ulceration, moderate to severe gastritis or duodenitis, moderate to severe erythema, or nodularity of the mucosa). Histopathologic abnormalities included acute or chronic inflammation, abnormal villous architecture, or increased numbers of mast cells. All studies were repeated after the patient received 6–12 weeks of tixocortol pivalate.

Results

Four patients aged 31–68 years, with the diagnosis of indolent systemic mastocytosis for 10–50 years were entered in the study (Table 1). The diagnosis of indolent systemic mastocytosis was based on classic histopathologic lesions in the bone marrow and skin [1,12]. Patients had presented initially with urticaria pigmentosa. GI symptoms developed 5–24 years after the onset of urticaria pigmentosa. All patients had episodic crampy abdominal pain, alcohol intolerance, malabsorption and diarrhoea. Patient 1 had an upper GI haemorrhage secondary to a large hiatal hernia 8 years prior to beginning this study. Patient 2 had a gastric ulcer diagnosed by endoscopic examination 20 months prior to beginning this study, which was successfully treated with medical therapy. All patients had pruritus and bone pain. Patients 2 and 3 had frequent headaches and persistent fatigue. Patients 1 and 4 had splenectomies with histologic documentation of mast cell infiltration within the spleen, and hepatomegaly documented on physical examination and liver-spleen scan.

Patients 1 and 2 had never received systemic steroids prior to the study (Table 1). Patient 3 had been on systemic steroids for 10 years. Her maintenance dose of prednisone (10 mg every other day) was tapered, then stopped 1 week prior to starting tixocortol pivalate. Patient 4 had been on systemic steroids for 3 years and required a maintenance dose of prednisone at 20 mg every other day; as with patient 3, prednisone was tapered and discontinued 1 week prior to starting tixocortol pivalate.

Patients 1, 2 and 3 completed the protocol. Patient 1 had daily crampy abdominal pain (score 2+) with bouts of

Table 1. Patients participating in this study

Patient no.	Age (years)/sex	Disease duration (years)	GI symptom duration (years)	Historical features GI	Other	Prestudy corticosteroid
1	68/M	50	26	Alcohol intolerance, crampy abdominal pain, diarrhoea alternating with constipation, upper GI bleed, splenectomy	Pruitis, flushing, bone pain	No
2	31/F	10	5	Alcohol intolerance, crampy abdominal pain, diarrhoea, gastric ulcers	Pruitis, flushing, fatigue, headaches, bone pain	No
3	64/F	33	17	Alcohol intolerance, crampy abdominal pain, diarrhoea	Pruritis, fatigue, headaches, bone pain	Yes (10 years)
4	59/F	23	13	Alcohol intolerance, crampy abdominal pain, diarrhoea, colonic AV malformations, multiple GI bleeds, splenectomy	Pruitis bone pain, fatigue	Yes (3 years)

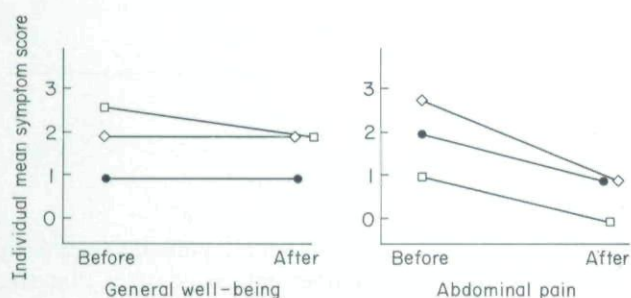


Fig. 1. Cumulative mean patient symptom scores before tixocortol pivalate therapy began, and after receiving 8–15 weeks of tixocortol pivalate. Symptoms were scored daily by the patient utilizing the following scale: general well being; 0, well; 1+, slightly under par; 2+, poor; 3+, very poor; and 4+, terrible. Abdominal pain was scored as follows: 0, none; 1+, mild; 2+, moderate; and 3+, severe. The line connects the symptom scores for the same patient: ●, patient 1; □, patient 2; ◇, patient 3.

severe diarrhoea (> 3 stools/day) intermixed with constipation. He received tixocortol pivalate for 15 weeks. His general sense of well-being remained unchanged. Abdominal pain and diarrhoea improved by 50% (Figs 1 and 2) within 10 weeks of tixocortol pivalate therapy. This patient continued to have intermittent bouts of constipation, but bowel movements became less watery and abundant. The faecal fat decreased by 74%; D-xylose

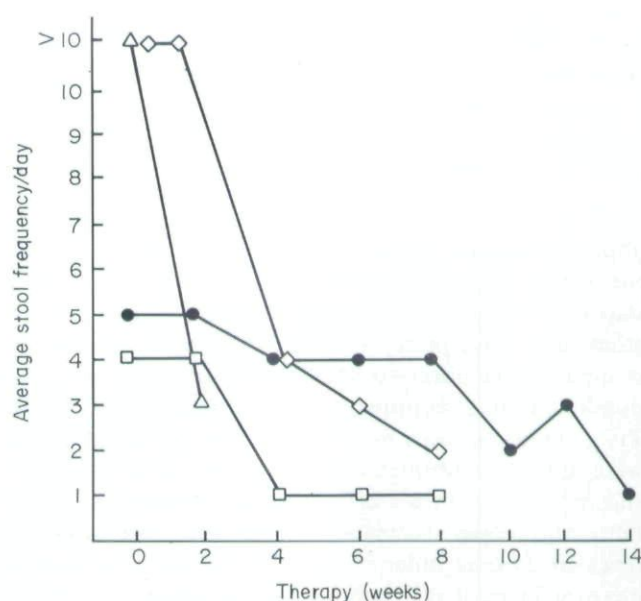


Fig. 2. Stool frequency before and after tixocortol pivalate therapy. The average stool number was determined for each patient before receiving tixocortol pivalate (time 0) and weekly while on therapy. ●, patient 1; □, patient 2; ◇, patient 3; △, patient 4.

Table 2. Malabsorption data prior to and after receiving tixocortol pivalate

Patient no.	Faecal fat (g/day)* before/after	D-xylose test†		Serum B12‡ before/after	Abnormal endoscopy before/after
		Urine (g/5 hr) before/after	Serum (ml/dl) before/after		
1	10.1/2.6	1.3/1.8	11/32	229/307	Yes/No
2	5.2/1.1	5.1/3.9	28/28	673/518	No/No
3	20.0/6.6	2.4/4.9	12/30	526/729	Yes/Yes
4	1.4/ND	2.7/ND	25/ND	195/ND	Yes/No

* Normal value < 7 g/day of faecal fat.

† Normal value: urine, 4 g/5 hr; 2-h serum concentration, 20 mg/dl.

‡ Normal value 215–800 pg/ml.

ND, not done.

Table 3. AM cortisol/electrolytes and blood cell counts before (B) and after (A) tixocortol pivalate

Patient no.	8 AM cortisol*		Glu† mg/d		K ⁺ meq/l		Na meq/l		WBC 10 ³ /mm ³		Neutrophil %		Lymphocyte %		Monocyte %		Eosinophil %	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	7.4	2.5‡	87	77	3.7	3.8	142	139	10.9	8.5	46	30	39	51	12	11	2	8
2	14.5	9.4	84	85	4.1	4.3	141	139	10.3	12.2	41	40	49	52	5	5	4	2
3	18.0	20.0	79	103	4.0	4.5	143	145	6.7	10.0	60	65	28	25	4	5	7	4

* Normal value 6–26 µg/dl.

† Fasting

‡ ACTH cortisol stimulation test normal.

improved by 38% in the urine analysis and normalized in the serum analysis (Table 2). Prior to therapy with tixocortol pivalate, the initial endoscopy revealed the stomach to have prominent linear folds from the gastro-esophageal junction to the lesser curvature, and the duodenum had multiple nodules and enlarged folds. Tissue biopsies taken from the stomach prior to therapy were considered normal. Giemsa and toluidine blue stains showed scattered mast cells without increased numbers. Duodenal biopsy specimens obtained prior to study drug revealed chronic inflammation. There was a subjective increase in mast cell numbers in the stomach and the duodenum relative to normals. Follow-up endoscopy 8 weeks later showed normalization of the appearance of the stomach and duodenal mucosa. Histologic specimens showed a loss of inflammation, and a subjective decrease in the number of mast cells.

Patient 2 had abdominal discomfort which was described as mild crampy daily pain (score 1+) and was associated with diarrhoea (> 3 stools/day). After tixo-

cortol pivalate therapy, abdominal pain decreased to none (score 0), and diarrhoea improved such that the patient was having one to two normal stools twice a week (Fig 1 and 2). Although the 72-hr faecal fat was normal prior to starting tixocortol pivalate, there was a 79% decrease in the amount of fat excreted at the conclusion of the study. D-xylose remained normal. Endoscopic studies done both prior to and at 8 weeks of tixocortol pivalate were normal grossly and histopathologically.

Patient 3 had moderate crampy abdominal pain (score 2+) with frequent bouts of severe diarrhoea (> 10 stools/day) (Figs 1 and 2). This patient received 8 weeks of tixocortol pivalate. Abdominal pain scores improved by 60% and diarrhoea scores improved by 80%, with the average frequency of stools decreasing to two per day (Figs 1 and 2). There was improvement in malabsorptive studies, with the 72-hr faecal fat decreasing from 20.0 to 6.6 g/day (67% decrease) and normalization of the D-xylose test (100% improvement). The endoscopic examination remained abnormal, showing multiple scattered

small (2 mm) polyps, with nodularity and erythema of the duodenal mucosa in both bulbar and post-bulbar area. Histologic examination gave evidence of chronic inflammation both before and after study drug. Stomach mast cells were normal in number before and after treatment. Duodenal mast cells were subjectively increased before treatment, and there was a decrease in number after tixocortol pivalate therapy.

Patient 4 initially received 500 mg of tixocortol pivalate every 6 hr for 4 days and developed shortness of breath with orthopnea and pedal oedema. This patient had no history of heart disease. Tixocortol pivalate was discontinued and the patient was hospitalized by her physician for congestive heart failure, documented by pulmonary oedema and cardiomegaly on a chest X-ray, and an echocardiogram which revealed a small pericardial effusion and left ventricular hypokinesis. Electrocardiograms, cardiac enzymes, AM cortisol, serum glucose, electrolytes, and complete blood counts were normal. She was successfully managed with medical therapy, and follow-up studies 3 weeks after the event showed normal results. Tixocortol pivalate was reinstituted at a lower dose of 125 mg twice a day for 4 days without difficulty, and then increased to 250 mg twice a day. The patient received this dose for 2 weeks and had a marked improvement in abdominal pain from a score of 3+ to 0, and a decrease in frequency of stools from 10 to 15 loose watery stools per day to two to three normal formed stools per day (Fig. 2). Despite this improvement, the patient elected to discontinue the tixocortol pivalate due to myalgias in her shoulders which led to her fear she was having a recurrence of the congestive heart failure. Her private physician repeated a chest X-ray and electrocardiogram at this time, and both were normal. Prednisone at 20 mg on alternate days was resumed following discontinuation of tixocortol pivalate with return to her baseline state of symptomatology and stool frequency.

Baseline studies to assess adrenal function were obtained prior to starting tixocortol pivalate (Table 3). ACTH stimulation tests were not performed on patients 3 and 4, as their chronic use of systemic steroids would have made their response abnormal. All patients, including those who had been receiving chronic alternate-day prednisone, had normal baseline studies. Patient 1 had a fall in AM cortisol level to a nadir of 2.5 µg/dl after receiving 8 weeks of tixocortol pivalate. This patient developed mild weight gain and pedal oedema during the first 2 weeks of the study, during which an ACTH stimulation test, serum electrolytes, glucose, and total leucocyte count including differential were normal. The oedema responded to diuretic therapy, and tixocortol pivalate was continued at the same dose for 4 weeks without further evidence of glucocorticoid or mineralo-

corticoid effects (Table 3). Patients 2 and 3 maintained normal adrenal function while receiving tixocortol pivalate for 8 weeks.

Discussion

The treatment of the GI manifestations of systemic mastocytosis is complex. There is considerable variability in the anatomic distribution of GI involvement associated with a variety of problems, from gastric acid hypersecretion to impaired small intestinal absorption. The dyspeptic abdominal pain caused by gastric acid hypersecretion is common and well controlled with H₂-receptor antagonists [3]. This is in contrast to patients who have crampy lower abdominal pain associated with bloating. This pain is not relieved by foods, antacids, or histamine H₂-receptor antagonists. This latter group of patients often suffer from diarrhoea associated with varying degrees of malabsorption. In previous studies, malabsorption was considered to be unusual in patients with systemic mastocytosis [13]. In a recent study [3], malabsorption was found in 31% of patients with systemic mastocytosis. The proposed mechanism for this malabsorption includes small intestine mucosal dysfunction, which is supported by pathologic findings of blunted villi with increased mucosal mast cells on jejunal biopsies [3]. The only therapy that has been found to be beneficial in treating both the abdominal pain and diarrhoea/malabsorption in this group of patients has been systemic steroids [3,4]. Unfortunately, steroids may contribute to the pathologic features of systemic mastocytosis, including osteoporosis, and must be used with caution and have been reserved for patients with severe malabsorption. For these reasons, a safety and efficacy study using a novel corticosteroid, tixocortol pivalate, was undertaken in four patients with GI involvement of mastocytosis. In previous studies, tixocortol pivalate has been reported to lack pituitary-adrenal axis suppression [14]. When taken orally, it is rapidly absorbed and has local anti-inflammatory activity equivalent to or greater than hydrocortisone. Tixocortol pivalate undergoes extensive and rapid metabolism and has a high volume of distribution and a low oral bioavailability, all of which contributes to the lack of systemic activity [14,15].

Due to the small available patient number, and lack of previous experience with tixocortol pivalate, an open clinical trial was performed to determine drug safety and efficacy. Symptom scores, laboratory studies of GI malabsorption and histologic data from esophagogastroduodenoscopy were used to evaluate the drug (Table 2). Function of the pituitary-adrenal axis was also assessed (Table 3).

Patient symptom scores showed improvement in both

abdominal pain and diarrhoea in all patients (Figs 1 and 2). The effects were present in patients who had never received systemic steroids and in those who had been on chronic systemic steroids. Malabsorption decreased and paralleled the symptom relief (Table 2). Faecal fat analysis on standardized fat intake improved from 67% to 79%, and urine D-xylose improved from 38% to 100%.

GI small bowel biopsies in patients with malabsorption secondary to mastocytosis may show a variety of mucosal abnormalities including partial villous atrophy, mucosal oedema, and a mild to moderate chronic inflammatory infiltrate in the lamina propria [4]. Mast cell numbers in the GI tract are difficult to quantitate and may be increased in a variety of inflammatory conditions. Therefore, unless dense cell infiltrates are present, mast cell hyperplasia is not sufficient to make the diagnosis of mastocytosis in the GI tract [1]. Patient 1 had complete normalization of GI pathology on both gross and histologic examination after 8 weeks of treatment with tixocortol pivalate. The nodular mucosa associated with chronic inflammation and mast cell hyperplasia was felt to be representative of mastocytosis. This patient had never received systemic steroids and was extremely sensitive to the tixocortol pivalate. Patient 3 had been receiving systemic steroids for 10 years prior to the study. Her endoscopic examination had been abnormal for 10 years, and even on daily systemic steroids, never normalized. The persistent GI pathology after 8 weeks of tixocortol pivalate was thus not surprising. Despite this continued abnormality, malabsorptive studies improved significantly (Table 2). Patient 2 began the study with a normal endoscopy and normal malabsorptive studies, which remained normal after 8 weeks of tixocortol pivalate; however, symptoms of abdominal pain and diarrhoea improved.

Patient 1 had a fall in AM cortisol while on tixocortol pivalate (Table 3) and experiences weight gain which was managed with diuretics. Patient 4 had fluid retention while on 500 mg of tixocortol pivalate every 6 hr. While this was not associated with a decrease in AM cortisol level in patient 4, we feel that fluid retention was a mineralocorticoid effect. When this patient was given tixocortol pivalate at a lower dose, no fluid retention occurred. The myalgias she experienced with the second course of tixocortol pivalate were attributed to withdrawal of oral systemic steroids. These observations together suggest that the use of tixocortol pivalate is not without side effects that may limit its use in some patients.

We conclude that tixocortol pivalate seems to be useful in patients with GI manifestations of systemic mastocytosis who require steroid therapy, and may be of use in other inflammatory diseases of the upper GI tract. Further studies are warranted.

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