

Progress report

Glucocorticoids and the gastrointestinal tract: current status

Since their introduction into clinical medicine 20 years ago, the glucocorticoids have become therapeutic agents of major importance. They have become associated with numerous clinical consequences involving every system of the body¹, including the gastrointestinal tract^{2,3}. It now seems pertinent and valuable to review critically the clinically relevant consequences of glucocorticoid therapy for the gastrointestinal tract. This study will concentrate upon those sequelae that can be attributable to the glucocorticoids *per se* rather than to the possible effects of the basic underlying disease for which the steroids were prescribed, or to their possible androgenic and/or mineral corticoid actions.

Stomach

The precise relationship of glucocorticoid therapy to peptic ulcerative disease in the stomach is still unclear^{4,9}. There is, however, a widely held clinical impression that incidence of gastric peptic ulcer is actually increased after glucocorticoid therapy, which appears to be particularly strong amongst those investigators treating rheumatoid arthritis, who have had the longest and largest experience with chronic glucocorticoid therapy^{5,9,10}. The steroid and gastric ulcer association gains further support from its impressive incidence in children in whom ulcer diseases are rare¹¹.

The classic description of the 'steroid ulcer'⁶, is of a relatively painless, 'silent' process, often acute or rapidly developing, commonly presenting with melaena, massive haemorrhage, or perforation¹². The ulcers are typical but not exclusively pyloric or prepyloric in location. Pathologically¹³, they are described as being soft, pliable, almost rubbery in consistency with relatively little fibrous reaction. However, upon close scrutiny of the available clinical data, convincing demonstration of such a steroid ulcer is lacking⁷.

INCIDENCE OF STEROID ULCER

Despite numerous studies, the precise incidence of gastric peptic ulcer as a complication of glucocorticoid therapy is still uncertain. As stressed by Cooke in his critical review⁵, most attention has been given to patients with rheumatoid arthritis. Retrospective studies of these patients treated with glucocorticoids in various dose schedules and for varying periods of time have shown an ulcer incidence ranging widely from 0% to 38%. If 23 series of rheumatoid arthritis patients treated with glucocorticoids are pooled, 4,298 cases were at risk (some overlap may have occurred since two studies also reviewed the previous literature), and a total of 286 cases of peptic ulcer was found. This overall incidence, 6.7%, is not strikingly different from the

often cited incidence of peptic ulcer in the general population of 5 to 10%. In a particularly careful retrospective study, Kearn, Clark, and Lukens¹⁴ described well documented gastric ulcers in 12.5% of 169 cases, and 4.4% in those receiving only glucocorticoids at the time the ulcer diagnosis was made. However, it should be emphasized that retrospective studies in general probably would underestimate the frequency of such a complication since the criteria for its diagnosis and the intensity of the search to document peptic disease varies widely from clinic to clinic.

Several prospective studies of glucocorticoid-treated rheumatoid arthritis patients, evaluated with periodic barium examinations, have been carried out^{11,15}. The ulcer incidence ranged from 3% to 31% and is suggestive of a high incidence rate. However, it seems well established that rheumatoid arthritis patients not receiving glucocorticoid therapy also have high incidence rates of gastric ulcer^{15,16}. Since many of these arthritic patients were also treated with aspirin, phenylbutazone, and indomethacin, the role that these gastric irritants¹⁷ may have played was usually not considered or established in the above series. These other drugs undoubtedly constitute very important additional variables. In a prospective study¹⁸, patients with collagen diseases treated with glucocorticoids also had a high incidence of peptic ulcer (27% of 63 cases) but 12.7% were known to develop an ulcer while on treatment since their pretreatment x-ray studies were negative. The roles that the collagen diseases played *per se* are unknown, however. An increased incidence of peptic disease in rheumatoid arthritis and patients with collagen diseases seems likely, but the role of glucocorticoids alone is uncertain.

On the other hand, the relatively low incidence of gastric peptic ulcer as a complication of glucocorticoid therapy in other, non-arthritic disorders seems to argue strongly against a fundamental ulcerogenic property of the glucocorticoids. Schwartz¹⁹ in asthma, Baldwin, Dworetzky, and Isaacs²⁰ in allergic disorders, Stevenson²¹, and Sanders, Brodey, and Nelson²² in bullous dermatological lesions, notably pemphigus, and Kirsner²³ in ulcerative colitis, have reported that glucocorticoid therapy is infrequently associated with peptic ulcers. Prospective studies of patients before commencing chronic glucocorticoid therapy are needed. It would seem particularly interesting to establish at the outset also which of these subjects are hypersecreters of gastric acid to conventional stimuli.

EFFECTS OF GLUCOCORTICOIDS ON GASTRIC FUNCTION

Although the pathogenesis of peptic ulcer is still poorly understood, considerable investigative interest has focused on gastric acid, pepsin, mucus, and the gut wall without clearly defining the roles of each. Studies of the physiological effects of glucocorticoids on stomach function do not establish a means by which a possible ulcerogenic mechanism may be operative.

The relationship between gastric acid, pepsin secretion, and glucocorticoids was recently critically examined by Cooke²⁴ who concluded that present information is largely inconclusive except for a permissive effect, especially well documented in animals. The handful of subsequent studies has largely failed to resolve the inconsistencies. The untreated Addisonian patient²⁵ usually has hypochlorhydria and a suboptimal response to maximal histamine stimulation. Although usually corrected with replacement therapy, the hypochlorhydria may persist²⁶. The roles that atrophic gastritis²⁷ or antibodies to gastric parietal cells²⁸, the incidence of which is both increased in idiopathic Addison's disease patients, may play in the failure of glucocorticoids to restore their gastric function to normal need to be further studied. The association of active peptic ulcer and untreated Addison's disease is very rare and these patients deserve careful study. In animals, adrenalectomy seems to reduce gastric acid secretion significantly²⁴ which is

usually restored^{29,30} within several hours after the replacement of glucocorticoids. Glucocorticoids seem necessary to maintain gastric acid secretion in animals, and they probably also exert such a permissive effect in man.

Numerous studies in man and animals with intact adrenals of gastric acid and pepsin responses to ACTH or glucocorticoids have produced inconsistent and conflicting results²⁴. Only some of the discrepancies can be related to dose, duration of treatment, or species differences. The conditions of the gastric analyses are of great importance, that is, 24-hour collections are known to vary widely from day to day; basal conditions, if rigidly controlled, can be standardized, but they only represent one phase of circadian gastric acid secretion. Submaximal stimulation may reproduce more fairly the conditions in the waking phase of the day-night cycle, but its significance for a full 24 hours is difficult to interpret. On the other hand, maximal stimulation currently induced with histamine, gastrin, their derivatives or analogues, before and after glucocorticoids, produce valid data on the maximal secretory capability of the stomach; however, their physiological relevance to the 'steroid' ulcer problem is uncertain.

In animals, the short-term administration of steroids produced no change in acid secretion. Longer term administration studies on dogs under basal³¹, submaximal³², and maximal^{29,33} stimulation showed that acid secretion usually rose, unlike in the rat where no changes were observed. In man, acute administration also produced no change³⁴. However, after several days of glucocorticoids under basal conditions evidence both for^{6,34,35,36} and against^{8,35,36,37} increased acid secretion has been reported. Submaximal stimulation³⁸ showed no significant change after glucocorticoids whereas under maximal histamine stimulation striking increases following glucocorticoids were observed⁴ but inconsistent results after ACTH. Further studies of human responses are clearly needed.

Augmentation of maximally stimulated gastric acid secretion with hydrocortisone when it occurs may differ according to the stimulatory agent employed.^{29,39,40} It seems unlikely that an increase in total parietal cell mass is responsible, since an increase in total secreting elements would not be expected to differentiate between histamine and gastrin. An effect of glucocorticoids on stomach absorption of hydrogen ions merits detailed investigation.

Since gastrin secretion and mucosal blood flow are reported⁴¹ to be closely related, increased gastric acid secretion might result from an increase in mucosal blood flow secondary to a microcirculatory effect of glucocorticoids⁴². However, Jacobson⁴¹ disassociated an increase in acid secretion in dogs due to hydrocortisone from its variable effect on blood flow. It would seem unlikely that the glucocorticoid effect on acid secretion is a result of a primary change in mucosal blood flow.

Another possible mechanism suggested by Hirshowitz, Streeten, Pollard, and Baldt³⁵ is a quantitative change in the gastric mucosal barrier. The viscosity and quantity of mucus secreted appears to fall after ACTH or cortisone in dogs^{43,44}. Qualitative changes with reduced fucose and fucosid content have been observed in dogs treated with hydrocortisone⁴⁵, and may affect the protective function of gastric mucus.

Since the gastric epithelial cell is rapidly turned over and replaced, another possible mechanism might involve a reduction in the rate of epithelial cell formation leading to a stomach wall more susceptible to peptic disease. This argument is supported by the work of Rasanen⁴⁶ who observed a reduced frequency of mitosis in stomach glandular epithelium of ACTH- or glucocorticoid-treated rats. The significance of these findings for human disease merits further study. This approach may be particularly promising.

A direct topical ulcerogenic action of glucocorticoids would appear to be excluded by Smith⁴⁷ who noted that the application of prednisone directly

to the mucosal surface produced no reaction. Nevertheless, a possible locus of glucocorticoid action on the stomach wall has been attributed to an impairment of wound healing in the gastrointestinal tract⁴⁸.

Small Intestine

The frequency of peptic ulceration in the duodenum and its attendant complications are often stated to be higher, but not convincingly demonstrated to be so in glucocorticoid-treated patients^{3,49}. It seems clear that in steroid-treated subjects the relative incidence of duodenal versus gastric ulcer is much less, producing a high gastric to duodenal ulcer ratio or a complete reversal of the usual ratio in the non-steroid ulcer population. Although the pathogenesis of duodenal ulcer is also not well understood, many of the observations of glucocorticoid effects on gastric function already cited should be applicable to duodenal peptic ulcer as well.

The frequency of small bowel perforation may be increased with glucocorticoids³ but convincing evidence is lacking. It may occur uncommonly in patients with such small intestinal diseases as regional enteritis.

There is a widely held but undocumented clinical impression that glucocorticoids may mask the usual signs of peritonitis after perforation of an abdominal viscus, leading to a relatively 'clean' or silent perforation⁵⁰. This important problem deserves careful study. If such a glucocorticoid masking effect occurs, what role their inhibition of the inflammatory response⁵¹, lysosomal stabilization⁵¹, reduction in the polymorphonuclear leucocytic migration⁵², prevention of kallikrein release⁵³, or hypothalamic antipyrogenic effect⁵⁴ may play may help to illuminate the basic pathogenesis in peritonitis.

Gastrocolic fistula, very rare in the absence of carcinoma, surgery, radiation, or inflammatory disease of the bowel, has been observed twice^{55,56} in glucocorticoid-treated patients, apparently secondary to silently perforated gastric ulcers.

Interest in the effects of glucocorticoids on small intestinal function has recently been revived⁵⁷. Although data on motility and secretory activities are lacking, the absorptive functions of the small intestine appear to be directly influenced by glucocorticoids. In the adrenalectomized animal reduced rates of xylose, glucose, glycine, and galactose⁵⁸ absorption are observed. The content of ATP, hexokinase, and alkaline phosphatase⁵⁹ in these animals is reduced in the gut wall. In untreated Addisonian patients, whose intestinal functions need much more documentation, steatorrhea appears to be not uncommon⁶⁰. From animal studies, lack of glucocorticoids has been postulated to induce a defect in lipid transport across the gut wall⁶¹; however, more recent studies⁶² showed normal transport of lipids and appear to locate the site of the defect to the esterification of fatty acids to triglycerides, probably as a result of reduced microsomal enzyme activities. Pancreatic exocrine insufficiency to account for the steatorrhea solely appears excluded as absorption of both free fatty acids and triglycerides in the adrenalectomized animal was impaired. Since these absorptive disturbances were corrected by replacement glucocorticoid therapy, a permissive action of glucocorticoids on absorption seems well established in animals.

Perhaps the most important effect of pharmacological doses of steroids on small intestinal absorption in the intact subject is their antagonism to the vitamin D-related calcium transport mechanism. The effects of glucocorticoids on other small intestinal absorptive pathways needs further study.

Colon

In the clinical literature there are occasional reports of perforation of the

caecum⁶⁵, diverticuli⁶⁴, and the colon in general⁶⁵ in association with glucocorticoids, particularly in patients with underlying inflammatory disease of the large bowel^{66,67}. Rectal and colonic ulcerations and proctitis have also been reported².

Recent studies indicate that adrenal steroids exerted an important effect on colonic cation absorption rates⁶⁷. Although it is considered to be primarily a mineralocorticoid function, nevertheless, cortisol administration *per se* markedly decreased the faecal excretion of sodium and increased faecal potassium levels. Since spironolactone, an aldosterone antagonist, blocked the Na-K effects of aldosterone but not those of cortisol, there may be differences between the mineralocorticoid and glucocorticoid cation absorptive mechanisms in the colon.

Although the precise pathogenesis of toxic dilatation of the colon, a rare and serious complication of ulcerative colitis, is unknown, an increased incidence with glucocorticoid therapy has been claimed^{66,67,68}. However, more recently the role of glucocorticoids appears to be more coincidental⁶⁹.

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