EFFECT OF PREDNISOLONE ON GASTRIC FUNCTION AND STRUCTURE IN MAN


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Administration of prednisolone in a dosage of 20 mg per day for 1 month caused a modest but significant increase in stimulated gastric acid secretion in a group of 14 healthy, institutionalized male subjects. In contrast, a control group not taking corticosteroids showed no significant change in stimulated acid secretion when tested on two occasions 1 month apart. The increase in stimulated acid output following prednisolone was the result of an increase in acid concentration. Stimulated secretory volume was not significantly altered by prednisolone. Gastric biopsies prior to prednisolone administration revealed chronic superficial gastritis in 5 of the 14 subjects. However, acid production in these subjects did not significantly differ from that in persons with normal gastric histology; stimulated acid concentration increased in both groups during prednisolone administration. Gastric mucosal structure in both normal and gastritic subjects was unchanged by prednisolone, and no ulcers were observed in these subjects in a prospective radiological study.

Several studies of the gastric secretory response to prolonged administration of corticosteroids or adrenocorticotropic in man have yielded conflicting evidence about their effects on acid secretion.1–4

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Some of the disparity in previous reports may lie in the use of basal or submaximal histamine-stimulated secretory studies, both of which give poorly reproducible values for gastric acid secretion.5,6 Only one previous study has utilized the more reproducible maximal histamine test to investigate the effect of corticosteroid drugs on gastric function in man.7

The effect of corticosteroids on gastric mucosal structure in man has received little attention with the exception of recent observations of their effect on the gastric lesion in pernicious anemia.8–11 We can find only one previous report in which the functional and structural response to corticosteroids has been studied in subjects without advanced gastric disease.12

Because of the uncertainty concerning the effect of prolonged corticosteroid administration on gastric acid secretion, and in view of the paucity of information about the effect of these drugs on normal gastric mucosal structure in man, the pres-
ent investigation was undertaken. We have studied the response of 14 asymptomatic subjects to prednisolone (Hydeltra) in an oral dose of 20 mg per day for 1 month. The effects on maximal histalog-stimulated acid secretion, gastric mucosal histology, and X-rays of the stomach and duodenum are described, all studies having been obtained prior to and at the end of 28 days of steroid administration.

**Material and Methods**

**Subjects investigated.** Fourteen healthy male subjects with no previous history of gastrointestinal disease and no medical contraindication to the administration of corticosteroids were selected for study. They were volunteers from a group of prisoners undergoing vocational rehabilitation at the California Medical Facility, Vacaville, California; all studies were carried out at that institution.

The mean age of the 14 subjects was 36 years (range 23 to 45). Ten were Caucasian, 2 were Negro, and 2 were Mexican American.

A control group of 10 volunteers from the Stanford Hospital staff each underwent two maximal Histalog tests, separated by 1 month. Six males and 4 females constituted this group and their mean age was 26 years (range 20 to 33). These studies were performed at the Stanford Medical Center Palo Alto, California. The same technicians were utilized for the secretory studies performed at both institutions.

**Methods.** Acid secretory studies were performed in the fasting state. A no. 16 FR Levin-type stomach tube was passed through the nose, and resting gastric juice aspirated. The subjects were kept in the left semirecumbent position and free flow was established before commencing the test. Saliva was expectorated throughout the test period. Gastric juice was aspirated by intermittent hand suction for two 30-min periods in the basal state. Five 15-min collections were then obtained following an intramuscular injection of betazole hydrochloride (Histalog) in a dosage of 1.5 mg per kg of body weight. The gastric juice from each collection period was centrifuged, and 5-ml aliquots of the supernatant titrated to pH 7.4 using 0.1 N NaOH, a manual burette, and pH meter.

Basal acid output (BAO) was the sum of the outputs obtained during the two 30-min basal collection periods. Basal acid concentration (BAC) was the mean of the concentrations of the two 30-min basal collections. Basal volume was the volume collected over the entire basal hour.

Peak acid output (PAO) was the maximal 30-min output following histalog. Peak volume was the volume of gastric juice collected over this 30-min period. Peak acid concentration (PAC) was the highest concentration achieved in any of the 15-min samples following histalog and mean acid concentration (MAC) the average concentration during the final 60 min of the test.

Serum from each subject was examined for the presence of parietal cell antibodies by immunofluorescence and for intrinsic factor antibodies by radioimmunoassay.

Gastric biopsies were performed with a multipurpose suction biopsy tube. All biopsies were taken under fluoroscopic control from the mid-body of the stomach on the greater curvature. The specimens were oriented on stiff paper and fixed in 10% formalin. Serial sections were stained with hematoxylin and eosin, phosphotungstic acid hematoxylin for parietal cells, and periodic acid-Schiff (PAS), which stains the neutral polysaccharide of epithelial mucus. The sections were coded, examined by light microscopy, and classified independently by each of four observers. The number of biopsies obtained from each subject with one passage of the biopsy instrument averaged three before steroids (range 2 to 6) and two following the administration of the drug (range 1 to 5). All biopsies were recognizable as body of stomach with one exception, which was entirely antral in type. Measurements of the depth of the glandular layer were taken using a calibrated eyepiece micrometer, at two separate sites in each biopsy. Points of reference were the bases of the foveolae and the muscularis mucosae and all measurements were obtained in areas in which the glands were oriented perpendicular to the surface epithelium.

Radiological studies consisted of limited upper gastrointestinal X-rays. The views obtained were supine anteroposterior, prone, and erect right anterior oblique of the stomach; and filled erect right anterior oblique, left anterior oblique, and prone compression films of the duodenal bulb. The completed studies were assigned random numbers and were reviewed independently by two radiologists, who had no knowledge of the functional or histological findings. The results of acid secretory tests were analyzed using Student's t-test.
Results

Initial clinical observations and biopsy findings. All 14 subjects were in good health and had no gastrointestinal symptoms or other medical disease.

The gastric biopsies obtained before commencing corticosteroids revealed that 9 of the 14 subjects had normal gastric histology (fig. 1). The remaining 5 subjects were found to have chronic superficial gastritis. Many of the surface epithelial

Fig. 1. Normal gastric mucosa. × 80.
cells were cuboidal with hyperchromatic nuclei, the foveolae were lengthened and the chronic inflammatory cell content of the lamina propria was increased with focal encroachment into the glandular layer. The glandular layer was otherwise normal with plentiful chief and parietal cells (fig. 2).

Both Negroes in the group had this lesion. Two Caucasians and 1 Mexican-American made up the remainder of the gastritic group. Eight of the subjects with normal biopsies were Caucasian and 1 was Mexican-American. The mean age was 36 years in those with gastritis and 35 years in those with normal biopsies. There was

Fig. 2. Gastric mucosa from patient with chronic superficial gastritis. × 80.
no relationship between the biopsy findings and a history of alcoholism. The diet was similar and coffee drinking and smoking were common to both groups. The sera of all 14 subjects were negative for parietal cell and intrinsic factor antibodies.

Mean values of acid secretion were only slightly lower in the subjects with gastritis than in those with normal gastric histology and the differences were not statistically significant (table 1).

The effect of steroids on gastric function and structure. Because gastritis was unsuspected until biopsies were reviewed and in view of the absence of any significant functional difference between normal and gastritic subjects, the results have been analyzed both for the entire group of 14 subjects and separately on the basis of the biopsy findings.

Effect on acid secretion. Table 1 shows the mean secretory values obtained before and at the completion of 4 weeks administration of oral prednisolone.

When all 14 subjects were analyzed as a group, all parameters showed a mean increase over preliminary values at the end of a month of oral steroids, stimulated acid concentration being the most strikingly altered. This change after administration of the drug was apparent in both normal and gastritic subjects, the only exception being a mean decrease in peak volume in those with gastritis.

In contrast, mean values in the control group (table 2) were slightly lower in the second test compared to the first test performed 1 month earlier. The results in this control group confirm the reproducibility of stimulated secretory values even when the tests are separated by a month and, as expected, basal secretory values were found to be poorly reproducible.

The individual changes in basal and stimulated acid secretion are shown in figures 3 and 4. Values prior to prednisolone administration are compared to those obtained at the end of 4 weeks on the drug.

Basal secretion (fig. 1). Increases in BAO and BAC were more consistent in those subjects with superficial gastritis, than among the subjects with normal gastric

### Table 1

<table>
<thead>
<tr>
<th>Type</th>
<th>Secretery parameter</th>
<th>Entire group (n=14)</th>
<th>Chronic superficial gastritis (n=9)</th>
</tr>
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<tr>
<td></td>
<td>Prednisoloid</td>
<td>Prednisoloid</td>
<td>Prednisoloid</td>
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<tr>
<td>BAO (mEq/L/hr)</td>
<td>1.6 (1.1)</td>
<td>1.6 (1.1)</td>
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<tr>
<td>BAC (mEq/L)</td>
<td>3.8 (0.6)</td>
<td>3.8 (0.6)</td>
<td>3.8 (0.6)</td>
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<tr>
<td>Peak acid output (mEq/30 min.)</td>
<td>100.5 (10.9)</td>
<td>100.5 (10.9)</td>
<td>100.5 (10.9)</td>
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<tr>
<td>Peak acid concentration (mEq/L)</td>
<td>93.3 (15.7)</td>
<td>93.3 (15.7)</td>
<td>93.3 (15.7)</td>
</tr>
<tr>
<td>Basal acid concentration (mEq/L)</td>
<td>100.2 (20.4)</td>
<td>100.2 (20.4)</td>
<td>100.2 (20.4)</td>
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<tr>
<td>Basal volume (mL)</td>
<td>115.9 (28.8)</td>
<td>115.9 (28.8)</td>
<td>115.9 (28.8)</td>
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<tr>
<td>Peak volume (mL)</td>
<td>106.5 (30.1)</td>
<td>106.5 (30.1)</td>
<td>106.5 (30.1)</td>
</tr>
</tbody>
</table>

* No. of subjects in parentheses.
Table 2. Acid secretory values of two maximal histalog tests separated by 1 month in 10 normal control subjects

<table>
<thead>
<tr>
<th>Secretory parameter</th>
<th>Test 1(^a)</th>
<th>Test 2(^a)</th>
<th>CV(^b) (%)</th>
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<tr>
<td>Basal acid output (mEq/hr)</td>
<td>2.5 (1.7)</td>
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<td>Basal acid concentration (mEq/liter)</td>
<td>27.2 (15.5)</td>
<td>24.1 (17.8)</td>
<td>31.1</td>
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<td>Basal volume (ml)</td>
<td>94.9 (20.5)</td>
<td>86.0 (30.3)</td>
<td>20.5</td>
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<td>Peak acid output (mEq/30 min)</td>
<td>9.2 (4.5)</td>
<td>8.6 (4.0)</td>
<td>6.7</td>
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<td>Peak acid concentration (mEq/liter)</td>
<td>98.0 (27.8)</td>
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<td>10.9</td>
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<tr>
<td>Mean acid concentration (mEq/liter)</td>
<td>87.0 (22.6)</td>
<td>83.0 (20.3)</td>
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<tr>
<td>Peak volume (ml)</td>
<td>103.8 (35.5)</td>
<td>103.8 (40.5)</td>
<td>6.2</td>
</tr>
</tbody>
</table>

\(^{a}\) Values given as mean ± sd.

\(^{b}\) CV, mean individual coefficient of variation.

Fig. 3. Basal acid secretory values. Each double bar refers to the study of a single subject. Before prednisolone (■) and after 1 month of 20 mg of prednisolone per day (□).
histology. Five of the 9 normal subjects showed increases in BAO and BAC after corticosteroids, 3 showed a decrease in these values, and 1 subject with basal achlorhydria showed no change. Basal volume changes were inconsistent in both normal and gastritic subjects.

*Stimulated secretion (fig. 2).* Stimulated acid concentration was the most consistently altered parameter of secretion in both normal and gastritic subjects following corticosteroid treatment. Ten of the 14 subjects demonstrated increases in PAC and MAC in excess of that expected from the mean coefficient of variation observed in the control group. The range of increase was wide, being 14 to 92% for PAC and 8 to 104% for MAC.
Only one individual in the entire group had a significant decrease in stimulated acid concentration after corticosteroids. This subject developed an anxiety depressive state with severe anorexia and a weight loss of 36 lbs over the course of corticosteroid administration, which reversed rapidly on withdrawal of the drug. This untoward reaction to prednisolone was not observed among the other subjects.

Stimulated volume changes after corticosteroids were more variable in both normal and gastritic subjects. In normal subjects no consistent pattern emerged, 3 individuals showing an increase, 2 a decrease, and the remaining 4 no change in peak volume. Despite this variability in peak volume change, 6 of the 9 showed significant increments in PAO after administration of steroids.

Of the 5 subjects with gastritis, 3 demonstrated a decrease in peak volume and 1 an increase; the remaining subject showed no change. In this small group no consistent change in PAO was apparent, only 1 individual showing a clear increase after steroids.

Paired analysis of all 14 subjects revealed no significant change in basal secretion after steroids but significant increases in PAC (\(P < 0.01\)), MAC (\(P < 0.01\)), and PAO (\(P < 0.05\)). Peak volume changes were not significant (\(P > 0.1\)). By contrast, paired analysis of the control group revealed that the observed differences in both basal and stimulated secretion in the two tests were not significant at the 5% level.

Further analysis of the group receiving corticosteroids indicated differences between those subjects with normal mucosal histology and those with chronic superficial gastritis. The only parameter of basal secretion in either group which showed a statistically significant increase after steroids was the BAO in those individuals with gastritis (\(P < 0.05\)).

PAO was significantly increased in subjects with normal gastric histology (\(P < 0.05\)) but the individual changes in PAC and MAC just failed to reach significance (\(P < 0.1\)).

In subjects with gastritis the situation was reversed; PAC and MAC were significantly increased after steroids (\(P < 0.05\)) and PAO was not significantly altered.

Neither normal nor gastritic subjects showed any significant alteration of peak volume after steroids (\(P > 0.1\)).

**Histological changes after steroids.** In spite of the observed increase in acid secretion in these subjects, histological alterations were not striking. Of the 5 subjects with gastritis, 1 had to be excluded from the comparative study of biopsy material because the specimen obtained after steroid treatment proved to be entirely antral mucosa. One subject before steroids appeared to have chronic superficial gastritis with some glandular atrophy. The second biopsy, after the course of steroids, revealed chronic superficial gastritis with no glandular atrophy. This subject's functional response was the least striking in the gastritic group and we suspect that the original biopsy was either taken from the junctional zone or that he did have patchy focal glandular atrophy and the second biopsy failed to sample such an area. There was no discernible change in the degree of epithelial abnormality, or cellular infiltration in the remaining subjects having gastritis.

No striking change was observed in the subjects with normal presteroid biopsies. No apparent increase in parietal cells was seen and measurement of glandular depth revealed no significant increase after steroid therapy in either normal or gastritic groups.

The PAS-stained sections did not show any alteration in the degree of staining of surface mucus or epithelial cells after corticosteroids in either group.

**Radiological findings.** Initial X-rays were all negative for ulcer disease of the stomach or duodenum. Minor abnormalities of gastric and duodenal folds were noted but these bore no relationship to either the biopsy findings or the gastric secretory values. No ulcers were detected in either
group after 4 weeks of steroid administration.

Discussion

Acute administration of glucocorticoids for periods of 24 hr or less have been shown to exert no effect on gastric acid secretion in man.2, 7, 16, 17

Our results agree with those of previous investigators who have shown no significant effect of prolonged corticosteroid administration on basal acid secretion in apparently healthy subjects.2 - 4 The results obtained in our control group indicate, however, that tests of basal acid secretion are not reproducible. This makes the assessment of additional factors such as prolonged corticosteroid drug administration, on the basis of change in basal secretion, very difficult.

Crean7 utilized the augmented histamine test18 to study the gastric secretory response to long term administration of cortisone in 6 patients with either Crohn's disease or ulcerative colitis. He found increases in stimulated acid output of from 130 to 500% of control values after corticosteroids. Data on basal secretion and the values of stimulated acid concentration or secretory volume were not included in this report, and gastric structure was not investigated.

The present study indicates a significant increase in histalog-stimulated acid secretion in a group of healthy men who had taken oral prednisolone for 1 month in a dose of 20 mg per day. The degree of increase as reflected by mean and percentage change in PAO is not so great as that observed by Crean.7 However, the dosages used in his patients were variable and often higher than those used in our study and the treatment period also varied, 3 of his 6 patients being restudied after 2 to 3 months of cortisone therapy.

The results in the group receiving corticosteroids clearly differ from those observed in the control group undergoing the same test on two occasions, a month apart, where secretory values were not significantly different, and mean values were slightly lower in the second test.

The increase in stimulated acid secretion observed in the subjects taking corticosteroids appears from our data to be due mainly to an increase in acid concentration. The maximal concentration achieved was significantly increased and concentration throughout the posthistalog period was sustained at a significantly higher level following steroids. In contrast there was an inconsistent effect on the peak volume.

Our observations agree with those reported in dogs undergoing maximal histamine- or gastrin-stimulated acid secretion, following chronic administration of glucocorticoid drugs, where there was a significant increase in stimulated acid output.19, 20 The increased acid secretion from Heidenhain pouches appeared to result from increases in both concentration of acid and volume secreted.19 Dogs treated with Metapirone, a blocker of $\beta$-hydroxylation in the adrenal cortex, which leads to marked lowering of circulating glucocorticoids, demonstrated a significantly reduced acid output from Heidenhain pouches in response to maximal histamine stimulation. This decrease was largely the result of a decrease in acid concentration, with more variable decreases in volume.21 Maximal stimulated secretion from Heidenhain pouches was significantly reduced by adrenalectomy. This was due to a marked reduction in secretory volume with no significant change in acid concentration. However, replacement therapy with glucocorticoids in these animals resulted in an increase in both acid concentration and volume to supranormal levels lasting some days.22

Analysis of the acid secretory results of our subjects on the basis of the gastric biopsy findings revealed differences in the significance of the observed changes in the two groups. Thus, although 6 of the 9 subjects with normal gastric histology showed increases in stimulated acid concentration after steroid administration, this observation did not reach statistical significance. This appeared to be largely due to a striking reduction in peak and mean concentration in 1 individual dis-
cussed in the "Results" section. The marked decrease in body weight during prednisolone administration in this subject may have partly accounted for the decrease in stimulated acid secretion, as recent studies have shown that maximally stimulated acid secretion is significantly correlated with both body weight and lean body mass. The lower dose of histalog given in the second test may also partly explain this individual's response.

The subjects with gastritis failed to show a significant increase in peak output despite striking changes in acid concentration. This appeared to be due to a decrease in peak volume after steroids, which, although consistent, failed to reach statistical significance.

The mechanism of this observed increase in acid secretion in response to chronic glucocorticoid administration is unknown. Chronic glucocorticoid administration to animals has been reported variously to increase, to decrease, or to have no effect on the parietal cell population. No studies of the gastric mucosa in response to corticosteroids have been carried out in normal man. Glandular depth was comparable in 11 of the 14 subjects and was not increased in any biopsy taken after steroid administration and no obvious increase in parietal cell population was seen.

Recent observations on the response of atrophic gastritis to corticosteroids have suggested that regeneration of parietal cells may occur, but little change in the degree of inflammation has been noted. No histological improvement in our subjects with chronic superficial gastritis occurred following corticosteroids.

Histochemical staining of the biopsy specimens for mucopolysaccharide failed to reveal visible alteration in cellular or surface mucus in response to corticosteroids in any of our subjects.

Using a similar technique, Glass et al. described partial disintegration of the mucosal lining and abnormalities in PAS staining following steroid therapy in patients with chronic arthritic disease. Men- guy and Masters reported a decrease in PAS staining of the gastric epithelial cells and a disappearance of surface mucus in rats given cortisone. Species variation in response to corticosteroids may account for the differences between the latter findings and our own. Certainly such variation does occur with respect to the effect of chronic glucocorticoid administration on acid secretion and several studies reviewed by Cooke indicate the absence of a response in the rat.

We cannot explain the difference between our findings and those of Glass et al. Perhaps the presence of chronic disease alters the response of the protective gastric mucosal lining to corticosteroids.

Other recent studies have suggested the existence of back diffusion of hydrogen ions from the gastric lumen in both normal individuals and in patients with both diffuse and focal gastric diseases. It is possible that corticosteroid drugs may inhibit this mechanism thus producing an apparent increase in acid concentration of stimulated gastric juice. Cooke et al., however, found no change in the absorption of hydrogen ion from Heidenhain pouches following adrenalectomy or during replacement therapy with glucocorticoids despite striking alterations in acid secretion.

In a recent review, Cooke concluded that despite good evidence for an ulcerogenic effect of corticosteroids in the experimental animal, the evidence for such an effect in man remains unproven. All previous prospective studies have been performed in subjects with chronic rheumatic, connective tissue, or chronic pulmonary diseases, where the incidence of ulcer may well be enhanced over that seen in the normal population and where, often, other drugs can be equally implicated as a cause of ulceration. Our study makes it clear that orally administered glucocorticoids do enhance gastric acid secretion in normal individuals. Although no ulcers were detected in the prospective radiological study of these 14 subjects, an ulcerogenic effect with higher doses of corticosteroids and/or more prolonged ad-
ministration of these drugs is not excluded, nor can it be in individuals with higher initial levels of gastric acid secretion.

REFERENCES


