

The effect of diazepam on human gastric secretion

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SUMMARY Human basal gastric secretion is markedly reduced after oral administration of 10 mg diazepam. This effect lasts for five hours.

Gastric nocturnal secretion, collected five hours after the last meal, reveals a decline towards the morning hours with an average of 25% in placebo-treated patients. A comparison between placebo and diazepam reveals a significantly greater decrease of 47% in volume after giving parenterally 10 mg diazepam without noticeable side effects.

The functional symptoms arising in the gastrointestinal tract may be caused by disturbance of visceral muscular activity, and of secretion and by alterations in blood flow.

Duodenal ulcer may be due to hyperactivity of gastric motor and secretory function, and one of the premises of the psychosomatic theory is that emotional conflict, mainly anxiety and psychic trauma, may induce such hyperactivity (Beaumont, 1833; Wolf, 1965). With these aspects in mind and the results of previous observations in rats (Birnbaum, 1968), a study on the effect of diazepam on human gastric secretion was initiated.

Methods

In the first series basal gastric secretion in 20 duodenal ulcer patients was studied without and with premedication with diazepam. The patients were tested after a 12-hour fast. Gastric aspiration aiming at complete evacuation preceded the collection period. For one hour aspiration was continued at intervals of two to three minutes and samples were collected every 10 minutes. Diazepam, in a dose of 10 mg, was given by mouth and the collection of gastric secretion was interrupted for 30 minutes. After complete aspiration of the fluid content of the stomach samples were again collected according to the method described above during one hour.

The duration of the pharmacological effect was studied in 19 patients from whom gastric juice had been collected according to the method described.

In a third group, 24 patients, mostly suffering from duodenal ulcer, were studied during the six night hours (11pm-5am) after intubation of the stomach

five hours after the last meal. Gastric content was aspirated and did not contain any food residue. Twelve of these patients received, after a control collection of gastric secretion for one hour, an intramuscular injection of 10 mg diazepam while the control group received at the same time the solvent of diazepam alone.

In another series of 20 duodenal ulcer patients the effect of diazepam on the duration of achlorhydria after 840 mg calcium carbonate was studied. These patients were intubated after a 12-hour fast and the concentration of acid was determined. Calcium carbonate was given by mouth and samples of 1 ml gastric juice were aspirated every five minutes and titrated against 0.05N sodium hydroxide with Töpfer reagent and phenolphthalein as indicators. The disappearance of free acid measures the duration of achlorhydria. Ten mg of diazepam was given by mouth and after 30 minutes the gastric content was aspirated. Acidity was determined and calcium carbonate administered. Achlorhydria was determined according to the method described above.

Results

In our first series of experiments a significant decrease of 32.0 ml/hr \pm 8.61(SE) in volume ($P < 0.01$) and 1.64 mequiv/hr \pm 0.527(SE) in acid output ($P < 0.01$) was observed 30 to 90 minutes after an oral dose of 10 mg diazepam compared with the preceding period of collection of basal gastric secretion during one hour.

The inhibitory effect of diazepam was observed during five hours. Results are summarized in Figure 1. The statistical evaluation of paired data of each hourly collection shows highly significant differences

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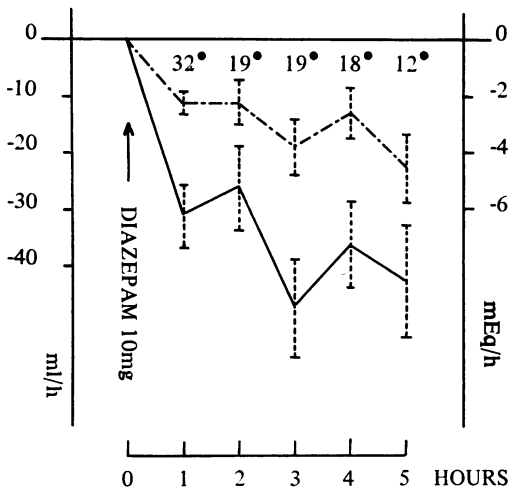


Fig. 1 Variations of mean hourly volume and acid output following diazepam. — Volume; - - - total acid output; O basal secretion; \bar{x} average \pm SE;

● number of patients.

(t values in the range of 2.70 to 5.57 and P values <0.01) for the volume rate and total acid output.

In collections of basal gastric secretion during two to three hours no statistical difference in hourly volume and acid output was observed.

The results obtained in observations on the effect of diazepam or placebo on human night secretion are summarized in Figure 2. The decrease in volume of gastric secretion after parenteral administration of 10 mg diazepam is statistically significant in comparison with that after a placebo (Student's t test; t values from 2.09 to 3.23, all P values <0.05).

Similar variations are observed in total acid output which on the average during five hours shows a decrease in acid output of 52.4% after diazepam, while after placebo an average decrease in acid output of 37.8% was observed. The statistical evaluation of the hourly differences reveals only at the third hour of collection a t value of 2.57 (P < 0.02). Although there exists a difference in total acid output between diazepam and placebo during five hours, this difference is not significant, the fact of which can be explained by the wide variations as well as the relatively small number of patients studied.

The fourth series of observations concerns the effect of diazepam on the duration of achlorhydria following the intake of calcium carbonate. The results of 20 tests compared with those obtained following calcium carbonate without premedication reveal a prolongation of achlorhydria from 22 to 37 minutes (t = 3.09, P < 0.01).

Comment

Diazepam, a benzodiazepine derivative, decreases effectively unstimulated human basal gastric secretion and acid output. A dose of 10 mg produces a significant inhibitory response which lasts up to five hours.

In previous studies (Birnbaum, 1969) we investigated some of the pharmacological effects of diazepam on the gastrointestinal tract. A significant inhibition of basal and stimulated human salivary secretion after oral administration of a dose of 10 mg diazepam was observed (Steiner, Birnbaum, Karmeli, and Cohen, 1970). In rat experiments, a highly significant delay in gastric emptying was noted after diazepam given before a standard meal, though some of the contrast material reached a distance in the

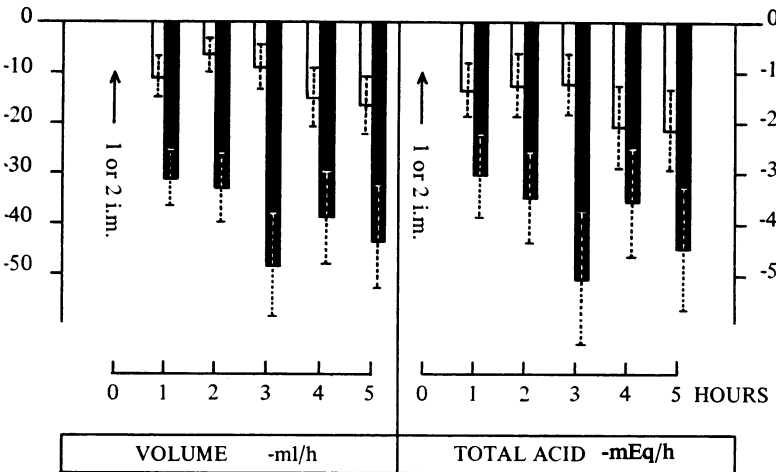


Fig. 2 Comparison of mean hourly volume and acid output following diazepam - 1- and placebo - 2-. ■ Diazepam - 1-; □ placebo - 2-; \bar{x} average \pm SE; O basal secretion.

ileum similar to that in untreated rats. In radiological studies in ulcer patients, serving as their own controls, a delaying effect of gastric and intestinal motility was observed in 10 out of 15 patients (Birnbaum, Ben-Menachem, and Schwartz, 1970).

In view of the delay in motility observed in the radiological study, the possibility of prolongation of achlorhydria induced by a promptly acting antacid was investigated. A statistically significant delay was observed, which, however, is only of minor clinical importance, the duration of achlorhydria being prolonged by 15 minutes only.

Nocturnal gastric secretion starting four to five hours following the last meal provides information on gastric secretory activity in patients who are asleep so that as well as the normal physiological stimuli for gastric secretion being inhibited those in the environment exciting and inhibiting gastric secretion were also excluded.

The investigation on the effect of diazepam on secretion at night was also prompted by the accepted opinion that duodenal ulcer patients secrete a two- to three-fold amount of highly acid gastric juice during the night.

In our group of patients we found variations in the rate of secretion indicating a decline in volume towards the morning hours, averaging in the placebo-treated patients 25.6% while diazepam-treated patients revealed a significantly different decrease of 47% ($t = 2.46$, $P < 0.05$). The results obtained with diazepam on nocturnal gastric secretion in human subjects showed a significant decrease in outputs comparable with those obtained with some anticholinergic drugs at levels causing considerable side effects. Although the inhibition achieved with diazepam at a dose of 10 mg is not equal to that observed following surgical vagotomy (Dragstedt, Palmer, Schafer, and Hodges, 1944), the lack of side effects which are observed with diazepam allows an increase in the dose which may result in a comparable 'medical vagotomy' during the night hours. The decrease in gastric secretion was achieved by a drug which has no anticholinergic effect *in vitro* and the

mechanism of which has to be assumed in its action on higher regulatory structures of autonomic function in the central nervous system. Stimulation of these higher structures under the influence of stressful situations (Miller, Bergei, and Hawk, 1920; Mittelmann and Wolff, 1942; Todd, 1930) of unresolved hostility and anxiety is apparently modified by diazepam which has been shown to inhibit also the effects of stereotactic stimulation of certain areas in the hypothalamus (Morillo, 1967; Schallek, and Zabransky, 1966)

As a result of (unpublished) studies on patients with active duodenal ulcer, based on a clinical evaluation of the drug in 173 duodenal ulcer patients and a controlled double-blind study in 30 patients, diazepam may be considered a beneficial aid in ulcer therapy.

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