Secretion of water and electrolytes into the duodenum in normal subjects and in patients with cirrhosis: The response to secretin and pancreozymin

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SUMMARY The increased volume of duodenal juice secreted by cirrhotic subjects in response to secretin was confirmed in 10 patients when their response was compared with that in eight normal subjects. This volume increase was associated with an increased sodium and chloride output while bicarbonate output was normal. The increment in volume of juice secreted by the cirrhotic patients was thus made up of an isotonic sodium chloride solution. The differences in anion concentrations and outputs are similar to reported changes produced in normal subjects given increasing doses of secretin. On the basis of these observations it is suggested that the increased output of duodenal juice in cirrhotic patients may be due to the infused secretin exerting a greater effect than in normals, possibly consequent upon an impaired secretin removal rate in the abnormal liver.

It has been noted by several workers that the volume of fluid secreted into the duodenum in response to secretin is significantly greater in patients with cirrhosis of the liver than in normal subjects (Gross, Comfort, Wollaeger, and Power, 1950; Van Goidenhoven, Henke, Vacca, and Knight, 1963; Sun, Albacete, and Chen, 1967; Turnberg and Grahame, 1970). In an attempt to explain the mechanism for this increased volume of juice we have made observations on electrolyte secretion in patients with cirrhosis. A significant difference in anionic secretion occurred in response to secretin, with higher chloride and lower bicarbonate concentrations in association with the increased volume of duodenal juice in cirrhotic subjects.

Methods

Eight control subjects, age range 26-58, were studied. These were patients without hepatic disease, in hospital for investigation of upper abdominal pain, and tests of pancreatic function were performed as part of their routine investigation.

Ten subjects with cirrhosis, nine with cryptogenic, macronodular cirrhosis, and one with alcoholic, micronodular cirrhosis were also studied. The diagnosis was made on clinical and biochemical findings and confirmed on liver biopsy in all cases. Patients were fasted from 6.00 p.m. and intubated at 8.00 to 9.00 a.m. the following morning. A double-lumen Portex PVC tube with a rubber bag containing 2 ml of mercury tied to one end was swallowed and allowed to pass through the pylorus until the end reached a point just beyond the junction of the second and third parts of the duodenum and its position was confirmed radiologically. Juice was aspirated by continuous suction from the duodenum through one lumen of the tube lying adjacent to the ampulla of Vater. An 'air-bleed' PVC tube, 2 mm diameter, inserted into the most distal hole of the duodenal tube and open to the atmosphere at the other end, prevented the development of too great a negative pressure during suction and facilitated collection. Gastric juice was aspirated with intermittent hand suction by syringe through the second lumen of the tube sited in the stomach. During aspiration a 0.5% solution of the non-absorbable marker, polyethylene glycol (PEG 4000), was infused at a rate of 1.39 ml per minute through a separate, loosely attached, tube opening 2 cm above the duodenal aspiration site. Recovery of juice was calculated from the proportion of the infused PEG recovered from the duodenum and the volumes

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collected were 'corrected' for these recovery figures. Recovery estimated in this way was greater than 80% in all cases and there was no consistent difference between recoveries in the two groups of subjects.

Duodenal juice was collected during separate consecutive 10-minute periods, and after three resting periods, gallbladder contraction was induced by an intravenous injection of cholecystokinin/pancreozymin (C/P) 100 units in 20 ml water given slowly over five minutes. A further three 10-minute collections were made and then an intravenous infusion of secretin in a dose of 3 units per kg body weight per hour was started. The infusion was continued for 60 to 70 minutes while further collections were made.

Polyethylene glycol was measured by the turbidimetric method of Hyden (1956), sodium and potassium on the AutoAnalyzer, chloride with a chloridometer, and bicarbonate by the Van Slyke method.

# Results

The mean volume of juice was greater in the group of cirrhotic patients than in the normal group in all but one of the 10-minute collections (fig 1). This difference reached statistical significance during most of the period of secretin infusion. The maximal response to the C/P injection was delayed until the second collection period after injection in the cirrhotic patients compared with the normal group in which the maximal response occurred promptly after injection.

The concentrations of sodium and potassium in the specimens obtained during secretin infusion were similar in both groups of patients with mean values of 140 and 4·5 m-equiv/l respectively. In the basal collections mean sodium concentrations in both groups were lower than during the secretin infusion at 120 m-equiv/l and mean potassium concentrations were higher at 7·1 m-equiv/l. In the normal group the mean concentration of sodium rose after C/P to 153 m-equiv/l while in the cirrhotic group it rose only slightly to 130 m-equiv/l but this difference was not statistically significant. Potassium concentrations were similar in both groups after C/P at 5·4 and 5·6 m-equiv/l.

Since the cation concentrations were similar in both groups the increased volume during secretin administration was associated with an increased output of sodium and potassium in the cirrhotic group (fig 2a and b).

While the patterns of cation secretion into the duodenum were similar there were clear differences in the patterns of anion secretion in the two groups. The concentrations of bicarbonate were lower and of chloride higher in the cirrhotic patients and the differences from normal reached statistical significance during secretin infusion (fig 3a and b). The mean bicarbonate concentrations during the last three 10-minute collection periods of the secretin infusion were 95, 105, and 111 m-equiv/l in the normal group and 74, 78, and 66 m-equiv/l in the cirrhotic patients, and the differences between these groups are significant (p < 0·05). The mean chloride concentrations in the normal group were between 28 and 53 m-equiv/l and between 62 and 77 m-equiv/l in the cirrhotic group during the secretin infusion and these were also significantly different from each other (p < 0·05 to < 0·01). The outputs of bicarbonate in the two groups were similar, while the outputs of chloride were significantly higher in the cirrhotic than in the normal groups (fig 4a and b). In the normal group the output of chloride lay between 1·3 and 1·0 m-equiv/10 minutes and in the cirrhotic group between 2·1 and 3·6 m-equiv/10 minutes (p < 0·05 to < 0·01). The chloride concentrations

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**Fig 1** Volume of fluid secreted into the duodenum in response to pancreozymin/cholecystokinin (P) and secretin in eight normal subjects and 10 patients with cirrhosis. In this and each subsequent figure mean values ± 1 SEM are shown for each 10-minute period. *Indicates p values < 0·05 and ** indicates p values < 0·01 for the significance of the difference between the two groups.
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Fig 2a

Sodium and potassium output (m-equiv/10 minutes) for each period in normal subjects and patients with cirrhosis.

Fig 2b

Fig 3a and b
Concentrations of bicarbonate and chloride (m-equiv/l) in each 10-minute collection in the two groups of subjects.
Fig 4a and b  Bicarbonate and chloride outputs (m-equiv/10 minutes) in each period in the two groups of subjects.

Discussion

Current concepts of fluid secretion envisage a simple passive movement of water across epithelia, usually in answer to osmotic pressure gradients set up by the transfer of solutes across the epithelial membrane (Sperber, 1965; Schultz and Curran, 1968). Since electrolytes form the large majority of the osmotically effective solutes in biliary and pancreatic secretion in response to secretin it seems likely that the enhanced volume response in cirrhotic patients is secondary to an effect on electrolyte secretion. The concentration of sodium does not vary appreciably with changes in the volume of the fluid secreted so that the output of sodium should bear a direct linear relationship with volume (fig 5). Similarly the output of total anion should bear a linear relationship with sodium output and with volume. It is presumably variation in the secretion of sodium and accompanying anion, the active transport step, which is responsible for the differences in volume of fluid secreted.

The most obvious difference in electrolyte secretion between the two groups lay in the patterns of chloride and bicarbonate secretion during secretin stimulation when the differences in volume were most obvious.

In the cirrhotic group bicarbonate concentrations were lower and chloride concentrations higher than in the normal group and these changes, taken in conjunction with the increased volume of juice, were associated with a normal output of bicarbonate but a greater than normal output of chloride in the cirrhotic group. These findings suggest that the increment in electrolyte and water secreted in cirrhosis is made up by secretion of an isotonic sodium chloride solution. It is of interest to compare these observations with the results of studies reported in normal subjects given varying doses of secretin (Wormsley, 1968). Wormsley showed that as the dose of secretin was increased, bicarbonate output reached a maximal value while the volume of juice secreted continued to rise, the net result being a reduction in bicarbonate concentration at the higher secretin doses. The concentration of chloride, and its output, rose as the
bicarbonate concentration fell at the higher doses. This suggests that after maximal bicarbonate secretion had been reached the increase in volume of fluid secreted in response to higher doses of secretin was made up by a sodium chloride solution. Thus the difference between the volume and anion secretion patterns in the cirrhotic and normal subjects are similar to those produced by increasing dosages of secretin in normal subjects. The cirrhotic subjects behave as if they had received a higher dose of secretin than the normal subjects. One possible explanation for the difference could be that secretin removal was slower in the cirrhotic patients, due for instance to reduced breakdown in the abnormal liver, thus maintaining a higher effective plasma level in these patients compared with the normal group. This suggestion, originally put forward by Van Goïdenhoven et al (1963), is supported by our data. Another possibility, which cannot be excluded, is that the pancreas and/or biliary tree is abnormally sensitive to exogenous secretin in cirrhosis.

The delayed response to C/P noted in the cirrhotic patients may be due to a gallbladder ‘inertia’ in the face of stimulation (Turnberg and Grahame, 1970).

The duodenal juice collected presumably arose from the pancreas, biliary tree and, to a lesser extent, the duodenal mucosa, and the experimental constraints of these studies do not allow a conclusion to be drawn regarding the particular source for the increased volume and altered anionic constitution of the aspirated secretions.

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References


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