Gastrointestinal hormones in alcoholic patients with and without liver disease

W W Dinsmore, M E Callender, A H G Love, K D Buchanan

Accepted 12 August 1986.

SUMMARY

To assess the effects of both alcoholism and liver disease on gastroenteropancreatic hormones, fasting and post-prandial concentrations were analysed in the following four groups: (1) Alcoholic subjects with liver disease; (2) Alcoholic subjects without liver disease; (3) Control subjects with liver disease; (4) Control subjects without liver disease.

Liver disease was associated with increased fasting serum glucose, plasma insulin, pancreatic polypeptide, gastrin and vasoactive intestinal polypeptide. Alcoholism in the absence of liver disease did not influence either the fasting or post-prandial concentrations of serum glucose, plasma gastrin, insulin, pancreatic polypeptide, gastric inhibitory polypeptide, N- and C-terminal glucagon or vasoactive intestinal polypeptide. Alcoholism with liver disease depressed plasma gastric inhibitory polypeptide concentrations. The results suggest that the abnormalities in gastroenteropancreatic hormone in alcoholics are likely to be related to liver disease which is often concurrent.

INTRODUCTION

Alcohol is known to have widespread effects on the small intestine and chronic alcohol abuse is often associated with liver disease. While there are a few studies available which examine the effect of either alcoholism or liver disease on gastroenteropancreatic hormones, there are none which attempt to separate the effects of alcoholism from the effects of the frequently concurrent liver disease which in itself will distort the results due to decreased liver metabolism, blood flow and porto-systemic shunting.

Accordingly, the aim of the present study was to assess fasting and post-prandial concentrations of gastroenteropancreatic hormones in alcoholics and control groups, both with and without liver disease. The four groups studied were: (1) Alcoholics with liver disease (2) Alcoholics without liver disease (3) Patients with non-alcoholic liver disease (4) Normal volunteers. From these four groups it was hoped to draw conclusions regarding the effects of both alcoholism and liver disease.

Department of Medicine, Institute of Clinical Science, The Queen's University of Belfast, Grosvenor Road, Belfast BT12 6BJ.

W W Dinsmore, MD, MRCP, Registrar.

A H G Love, BSc, MD, FRCP, FRCPI, Professor of Medicine.

K D Buchanan, PhD, MD, FRCP, Professor of Metabolic Medicine.

Royal Victoria Hospital, Belfast BT12 6BA.

M E Callender, MRCP, Consultant Physician.

Correspondence to: Dr W W Dinsmore, Royal Victoria Hospital, Belfast BT12 6BA.

© The Ulster Medical Society, 1986.
disease on fasting and post-prandial glucose, and release of the gastroenteropancreatic hormones studied, which were gastrin, insulin, pancreatic polypeptide (PP), gastric inhibitory polypeptide (GIP), glucagon N, glucagon C and vasoactive intestinal polypeptide (VIP).

MATERIALS AND METHODS
Thirty-two alcoholic subjects (all less than 70 years), with alcohol consumption of greater than 150g/day for five or more years, were divided into a group of 13 patients (12 male and one female) with liver disease, and a group of 19 patients (18 male and one female) without liver disease. Of the 13 patients with liver disease eight had a liver biopsy and the remaining five were diagnosed as having liver disease on the basis of five to seven liver function tests which were greater than three standard deviations from the mean, (increased serum gamma glutamyl transferase, aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, or a reduction in the prothrombin time and serum pseudocholinesterase). The 19 patients without liver disease had all liver function tests (including gamma glutamyl transferase) and were within normal limits, (two standard deviations from the mean). Patients with intermediate liver function tests were excluded from the study. The study had approval of the Research Ethical Committee of the Faculty of Medicine, The Queen's University of Belfast. Liver biopsy was not performed on the 19 patients without evidence of liver disease. All alcoholic patients had an alcohol intake estimated from their history of alcohol consumption during the previous five years and particularly during the preceding week.

Two control groups were used in the study. A group of 17 normal volunteers (14 male and three female) from the staff and students of the hospital, all less than 70 years old, were studied. They did not have any systemic illness, were on no medication and their individual alcohol consumption was less than 10g/day. A further control group of 10 patients (six male and four female) with non-alcoholic liver disease were studied. These patients, all of whom had a liver biopsy, included three with primary biliary cirrhosis, three with chronic active hepatitis, three with idiopathic cirrhosis and one with methotrexate-induced cirrhosis.

Alcoholic patients were studied within 48 hours of admission to hospital. All subjects were fasted overnight from 10 pm prior to study. At 9 pm on the day of study each subject had an intravenous cannula secured in a forearm vein, and an initial blood sample was taken for glucose and gastroenteropancreatic hormone analysis. After 15 minutes a second fasting sample was taken from all subjects, before a standardised meal was given. The meal used in this study consisted of 60g ham, 60g white bread, 15g butter, 100ml orange juice and one cup of tea. This contained 50g carbohydrate, 18g protein and 20g fat and had an energy value of 450 kcalories. This meal was given at time 0 minutes and blood samples were taken at times, 15, 30, 45, 60, 90 and 120 minutes. The cannula was flushed out after each sample with physiological saline (0.9% NaCl). The first 3ml of each sample was discarded to prevent contamination with saline. All hormone samples were immediately transferred to cooled heparinised tubes and kept on ice before centrifugation at the end of the study. All blood samples were analysed for glucose insulin, gastrin, gastric inhibitory polypeptide (GIP), and pancreatic polypeptide (PP). In addition the fasting samples were analysed for N-terminal glucagon, C-terminal glucagon and vasoactive intestinal polypeptide (VIP). All hormones were analysed by radioimmunoassay using methods.
previously established in the Department of Medicine, The Queen's University of Belfast.\textsuperscript{17-20} The results were analysed non-parametrically using the Wilcoxon rank sum test.

**RESULTS**

The mean age of the patients with alcoholic liver disease was 46 years (range 28-65 years); that of the patients without alcoholic liver disease 43 years (range 21-69 years); of those with non-alcoholic liver disease 57 years (range 21-69 years), and of the normal volunteers 45 years (range 19-69 years). There were no significant differences between any of these groups.

The mean estimated daily alcohol consumption of the alcoholics with liver disease was 235g/day (range 150-400g/day) and that of the alcoholics without liver disease was 300g/day (range 150-750g/day) (N.S.). Only one patient with non-alcoholic cirrhosis drank alcohol (10g/day). The mean alcohol consumption in the normal volunteers was 5g/day (range 0-10g/day). The alcoholics with liver disease had been drinking for a mean of 19 years (range 5-34 years) and the alcoholics without liver disease had been drinking for a mean of 18 years (range 5-42 years).

**Fasting gastroenteropancreatic hormone and glucose analysis**

The results of fasting gastroenteropancreatic hormone and glucose analysis are presented in the Table. These fasting results are the average of the two fasting samples taken for each subject.

The fasting serum glucose concentrations were higher both in the alcoholics with liver disease and in the patients with non-alcoholic liver disease when compared with the normal volunteers (p<0.01). The patients with non-alcoholic liver disease had higher mean fasting gastrin concentrations than either the alcoholics with liver disease (p<0.005) or the normal controls (p<0.05). The patients with non-alcoholic liver disease had higher fasting plasma insulin concentrations than either the normal volunteers (p<0.05) or the alcoholics with or without liver disease (p<0.05).

The patients with alcoholic liver disease had higher fasting plasma PP concentrations than either the subjects with non-alcoholic liver disease (p<0.05) or the normal volunteers (p<0.05). The alcoholics with liver disease had lower fasting plasma GIP concentrations than the normal volunteers (p<0.05).

There were no significant differences noted in fasting plasma N-terminal glucagon or C-terminal concentrations in any of the groups. The patients with non-alcoholic liver disease had higher fasting plasma VIP concentrations than either the alcoholics with liver disease (p<0.05) or normal controls (p<0.005).

**Post-prandial changes in gastroenteropancreatic hormones and glucose**

There were significantly higher post-prandial serum glucose concentrations at 120 minutes in the alcoholics with liver disease (6.6 SE ± 0.8 mmol/l) than in the alcoholics without liver disease (4.9 ± 0.4 mmol/l), the patients with non-alcoholic liver disease (5.4 ± 0.8 mmol/l), or the normal controls (4.3 ± 0.2 mmol/l).

There were significantly lower post-prandial insulin concentrations in the alcoholics with liver disease (40 ± 8mU/l) than in either the alcoholics without liver disease at 45 minutes (69 ± 7mU/l), the patients with non-alcoholic liver
### Table

The fasting plasma gastrin, insulin, pancreatic polypeptide (PP), gastric inhibitory polypeptide (GIP), N-terminal glucagon, C-terminal glucagon, vasoactive intestinal polypeptide (VIP), and fasting serum glucose concentrations in 13 alcoholic patients with liver disease, 19 alcoholic patients without liver disease, 10 patients with non-alcoholic liver disease and 17 normal controls.

(mean ± standard error)

|                     | Gastrin ng/l | Insulin mU/l | PP ng/l | GIP ng/l | Glucagon N ng/l | Glucagon C ng/l | VIP ng/l | Glucose mmol/l |
|---------------------|-------------|--------------|---------|----------|----------------|----------------|----------|---------------|
| Alcoholics with liver disease |             |              |         |          |                |                |          |               |
| n = 13              | 51 ± 18     | 13 ± 1       | 125 ± 23| 37 ± 6   | 177 ± 23       | 123 ± 14       | 90 ± 24  | 4.7 ± 0.4     |
| Alcoholics without liver disease |         |              |         |          |                |                |          |               |
| n = 19              | 72 ± 11     | 10 ± 1       | 95 ± 18 | 63 ± 16  | 185 ± 15       | 113 ± 8        | 99 ± 15  | 4.3 ± 0.2     |
| Patients with non-alcoholic liver disease |       |              |         |          |                |                |          |               |
| n = 10              | 110 ± 22    | 21 ± 6       | 139 ± 40| 79 ± 26  | 260 ± 42       | 157 ± 16       | 153 ± 17 | 4.8 ± 0.3     |
| Normal volunteers   |             |              |         |          |                |                |          |               |
| n = 17              | 73 ± 12     | 11 ± 1       | 70 ± 14 | 59 ± 6   | 204 ± 11       | 125 ± 9        | 87 ± 11  | 4.0 ± 0.1     |
The Ulster Medical Journal

144

disease at 60 minutes (42±9mU/l and 87±19mU/l) or the normal volunteers at 30 minutes (32±6mU/l and 68±8mU/l).

There were lower plasma gastrin concentrations in the alcoholics with liver disease than in the patients with non-alcoholic liver disease at 45 minutes (49±20ng/l and 160±60ng/l, respectively) and at 60 minutes (54±22ng/l and 140±61ng/l). There was no significant difference in post-prandial plasma gastrin at the recorded times between the alcoholics with and without liver disease and the normal volunteers. There were no significant differences in post-prandial plasma concentrations of PP or GIP, between any of the groups.

DISCUSSION

In this paper alcoholics were defined as patients who have consumed more than 150g alcohol per day (approximately 15 measures or two bottles of wine) for five or more years before inclusion in the study. While this definition is arbitrary, most authorities would agree that the patients included were likely to have dependence or harm as a result of their alcohol consumption. The slightly higher mean alcohol consumption in the alcoholics without liver disease than the group with liver disease was not significant, and may be related to a decreased ability in the latter group to metabolise alcohol.

There was evidence of post-prandial glucose intolerance in both groups with liver disease in keeping with previous studies. This may be due to a combination of hepatic resistance to the action of insulin and the porto-systemic shunting of both the carbohydrate load and insulin. As there was no elevation of the fasting serum glucose concentration in the alcoholics without liver disease, the present data suggests that liver disease was responsible for glucose intolerance noted in alcoholism. Although the patients with non-alcoholic liver disease had fasting hyperinsulinism, plasma insulin concentrations in either alcoholic group were similar to that recorded in the normal volunteers and these findings are in agreement with previous work. There is a suggestion in the present study that the elevation of fasting plasma insulin concentration is associated with the presence of liver disease (in the subjects with non-alcoholic liver disease) rather than the presence of alcoholism itself as has previously been reported. There was a lower post-prandial insulin response in patients with alcoholic liver disease compared with normal controls, which contrasts with the post-prandial hyperinsulinism associated with alcoholic liver disease in previous studies. These differences could possibly be related to the severity of the liver disease, patients with more severe liver disease having decreased hepatic metabolism of insulin and increased porto-systemic shunting of insulin.

The fasting and post-prandial plasma gastrin concentrations were elevated in the patients with non-alcoholic liver disease, confirming previous work in patients with cirrhosis. Alcoholism, either with or without liver disease, did not affect plasma gastrin concentration.

The fasting plasma PP concentration in both groups with liver disease was higher than in the normal controls, in agreement with previous reports in both alcoholics and subjects with liver failure. PP is known to be a strong inhibitor of pancreatic secretion. Because up to 40% of alcoholics may have pancreatic exocrine insufficiency, even in the absence of clinical evidence of chronic pancreatitis, some authors have suggested that pancreatic insufficiency may be a result of elevation of PP concentrations. However, there was no elevation in PP in the

© The Ulster Medical Society, 1986.
alcoholic subjects without liver disease, and therefore liver disease rather than the presence of alcoholism may be the predominant influence in increasing the fasting plasma concentrations of PP.

The reduction in fasting plasma GIP in alcoholics with liver disease when compared with the normal volunteers was not observed in the subjects with non-alcoholic liver disease, suggesting that alcoholism in combination with liver disease reduces GIP concentrations. While the significance of this in unclear, GIP is known to inhibit gastric acid production in animal experiments and therefore the present reduction in GIP may play a role in the hyperacidity associated with alcohol ingestion.

N-terminal glucagon release is thought to be a measure of both enteroglucagon and pancreatic glucagon, and C-terminal glucagon is thought to be a measure of pancreatic glucagon. There were no differences noted in either N- or C-terminal glucagon concentrations as a consequence of either alcoholism or liver disease which is in agreement with previous studies.

An elevation of fasting plasma VIP concentrations in patients with non-alcoholic liver disease compared with controls has been shown previously. Alcoholism without liver disease, however, had no apparent effect on fasting plasma VIP concentrations. It has been suggested that the elevation of VIP in subjects with liver disease is due to porto-systemic shunting, and this elevation in VIP, while small, may nevertheless be related to some of the features of liver disease including diarrhoea and cutaneous vascular changes.

The purpose of this study was to clarify the changes in gastroenteropancreatic hormones related either to chronic alcohol ingestion or to liver disease. There was no difference in fasting or post-prandial hormone release in the alcoholic group without liver disease compared with that found in the normal volunteers, indicating that alcoholism without hepatic complications does not influence gastroenteropancreatic hormone release.

This work was supported by a grant from the DHSS (NI). We would like to thank Mrs Marie Loughran for typing the manuscript and all the volunteers who have taken part in this study.

REFERENCES

1. Wilson FA, Hoyumpa AM. Ethanol and small intestinal transport. Gastroenterology 1979; 76: 388-403.
2. Lelbach WK. Epidemiology of alcoholic liver disease. Progr Liver Dis 1976; 5: 494-515.
3. Wright J. Endocrine disease in the alcoholic. In: Clark PMS, Kricka LJ, eds. Medical consequences of alcohol abuse. Chichester: Ellis Horwood, 1980: 157-70.
4. Megyesi C, Samols E, Marks V. Glucose tolerance and diabetes in chronic liver disease. Lancet 1967; 2: 1051-5.
5. Fink RS, Adrian TE, Margot DH, et al. Increased plasma pancreatic polypeptide in chronic alcohol abuse. Clin Endocrinol 1983; 18: 417-21.
6. Stewart A, Johnston DG, Alberti KGMM, et al. Hormone and metabolic profiles in alcoholic liver disease. Eur J Clin Invest 1983; 13: 397-403.
7. Mazzacca G, Budillon G, De Marco F, et al. Serum gastrin in patients with cirrhosis of the liver. Digestion 1974; 11: 232-9.
8. Sullivan SN, Chase RA, Christofides ND, et al. The gut hormone profile of fulminant hepatic failure. Am J Gastroenterol 1981; 76: 338-41.

© The Ulster Medical Society, 1986.
9. Greenberg GR, McCloy RF, Adrian TE, et al. Inhibition of pancreas and gall bladder by pancreatic polypeptide. *Lancet* 1978; 2: 1280-2.

10. Mezey E, Jow E, Slavin RE, et al. Pancreatic function and intestinal absorption in chronic alcoholism. *Gastroenterology* 1970; 59: 657-64.

11. Pedersen RA, Brown JC. Inhibition of histamine, pentagastrin and insulin-stimulated canine gastric secretion by pure “gastric inhibitory polypeptide”. *Gastroenterology* 1972; 62: 393-400.

12. Woodward ER, Robertson C, Ruttenberg HD, et al. Alcohol as a gastric secretory stimulant. *Gastroenterology* 1957; 32: 727-37.

13. Irvine WT, Watkin DB, Williams EJ. The mechanism by which alcohol stimulates acid secretion. *Gastroenterology* 1960; 39: 41-7.

14. Said SI, Faloona GR, Deon M, et al. Vasoactive intestinal polypeptide: elevated levels in patients with hepatic cirrhosis. *Clin Res* 1974; 22: 367A.

15. Hunt S, Vaamonde CA, Rattassi T, et al. Circulating levels of vasoactive intestinal polypeptide in liver disease. *Arch Intern Med* 1979; 139: 994-6.

16. Henriksen JM, Staun-Olsen P, Fahrenkrug J, et al. Vasoactive intestinal polypeptide (VIP) in cirrhosis: arteriovenous extraction in different vascular beds. *Scand J Gastroenterol* 1980; 15: 787-92.

17. O’Hare MMT, Daly JG, Buchanan KD. Radioimmunoassay for pancreatic polypeptide, and its age-related changes in concentration. *Clin Chem* 1983; 29: 1923-7.

18. Buchanan KD, McCarroll AM. Comparison of methods of separation of free from bound hormone in the radioimmunoassay of insulin. In: Kirkham KE, Hunter WM, eds. Radioimmunoassay methods. Edinburgh: Livingstone, 1971: 136.

19. Buchanan KD, Teale JD, Harper G. Antibodies to unconjugated synthetic and natural secretins. *Horm Metab Res* 1972; 4: 507.

20. Dinsmore WW. Studies on alcohol and liver disease. Belfast: The Queen's University of Belfast, 1984. MD thesis.