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The Effect of Metformin Treatment on Gastric Acid Secretion and Gastrointestinal Hormone Levels in Normal Subjects

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Summary. Gastric acid secretion and gastrointestinal hormone levels were measured in healthy non-diabetic subjects after metformin treatment (1.5 g/day). The maximum acid output was increased from 15.7 ± 3.9 mmol/h (mean ± SEM) to 30.0 ± 7.1 mmol/h ($p < 0.05$) and the peak acid output was increased from 16.4 ± 4.1 mmol/h to 31.7 ± 7.2 mmol/h ($p < 0.05$) after two weeks treatment. Serum insulin, gastric inhibitory polypeptide and secretin levels were normal. After treatment for one week, however, there was a significant increase in fasting vasoactive intestinal peptide (VIP) from 83 ± 6 ng/l to 102 ± 9 ng/l ($p < 0.02$) and in stimulated VIP from 58 ± 5 ng/l to 79 ± 5 ng/l ($p < 0.05$). Stimulated glucagon-like immunoreactivity (GLI) was also increased from 82 ± 10 ng/l to 174 ± 24 ng/l ($p < 0.01$) after one week's treatment. It is suggested that metformin acts as a weak histamine agonist.

Key words: Metformin, biguanides, gastric acid secretion, histamine, gastrin, insulin, vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide (GIP), secretin, glucagon-like immunoreactivity (GLI).

Biguanides act through a variety of effects including inhibition of intestinal active transport systems [1]. Delayed gastric emptying and decreased intestinal motility have also been demonstrated following biguanide therapy. There is some evidence to suggest that these changes may result in the proliferation of microflora in the small bowel [1]. Although achlorhydria is frequently associated with increased intestinal microflora, no studies have been carried out on the effect of metformin on gastric acid secretion. Therefore, it is not known whether biguanides inhibit the gastric acid active transport system sufficiently to cause hypochlorhydria and help establish an environment for small intestinal microflora. Furthermore, gastric acid secretion, gastric emptying and intestinal motility appear to be controlled both neurologically and by the gut endocrine system [2]. In this study we have examined gastric acid secretion and gastrointestinal hormone levels in non-diabetic volunteers following metformin treatment.

Subjects

Twelve healthy non-diabetic adults agreed to participate in the study. They were fully informed of the procedure and possible risks of the study before giving their voluntary consent. Six of these volunteers took part in the gastric acid secretion study (5 males and 1 female). The mean age of the group was 24 years with a range of 19 to 40. The mean % ideal bodyweight was 102 with a range of 98 to 107. The other six volunteers took part in the hormone study (4 males and 2 females). The mean age of this group was 25 years with a range of 21 to 39 and the mean % ideal bodyweight was 102 with a range of 98 to 106. None of the subjects were taking drugs of any description at the time of the study.

Procedure and Methods

(a) Gastric Acid Secretion Study

Following an overnight fast, the subjects were given a standard pentagastrin test meal containing 6 μg pentagastrin per kg bodyweight [3] to assess their normal gastric acid outputs. They were then asked to take 0.5 g of metformin three times a day before meals for two weeks. During this period one subject experienced considerable nausea, vomiting and diarrhoea and could not complete the study. At the end of the two week period a further pentagastrin test was carried out on the remaining five subjects. They had again fasted overnight and the test was carried out two hours after the morning dose of metformin (0.5 g). The volume

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Table 1. Sensitivities, coefficients of variation and normal ranges for the hormone assays

Hormone	Sensitivity	Coefficient of variation %	Normal range (fasting)
Insulin	0.5mU/l	13.2	0–15 mU/l
Gastrin	6ng/l	9.8	0–100 ng/l
Secretin	6ng/l	12.7	0–50 ng/l
GIP	8ng/l	13.2	0–150 ng/l
VIP	4ng/l	12.4	0–150 ng/l
Glucagon C-terminal	6ng/l	17.4	0–150 ng/l
Glucagon N-terminal	8ng/l	19.2	0–250 ng/l

Table 2. Gastric acid secretion data for the five subjects before and after two weeks treatment with metformin (1.5 g/day). The post treatment test was performed 2 hours after the morning dose of metformin (0.5 g). Paired analyses were performed on before and after treatment levels using Student's paired t-test

	Before treatment Mean ± SEM	After treatment Mean ± SEM	P
Maximum acid output mmol/h	15.7 ± 3.9	30.0 ± 7.1	< 0.05
Peak acid output mmol/h	16.4 ± 4.1	31.7 ± 7.2	< 0.05
Peak volume (ml)	87 ± 24	124 ± 20	NS
Peak $[H^+]$ concentration mmol/l	82 ± 19	91 ± 12	NS

and pH of the gastric aspirates were measured and the hydrogen ion $[H^+]$ concentration was assessed as titratable acidity to pH 3.5 using 0.1 mol/l NaOH. Acid output was calculated as the product of volume and $[H^+]$ concentration in each 15 min sample. The maximum acid output was estimated as the sum of the two highest consecutive 15 min output × 2, expressed as mmol HCl secreted per hour. The peak acid output was estimated as the mean of the two highest outputs also expressed as mmol HCl/h. A Schilling test was carried out on all subjects after the treatment period to assess vitamin B12 absorption.

(b) Hormone Study

In this study, blood samples were taken fasting and 30 min after a standard stimulatory meal which contained 18 g protein, 50 g carbohydrate and 20 g fat and had an energy value of 450 calories. The subjects then took 0.5 g of metformin three times a day before meals for one week. At the end of this period blood samples were again taken both fasting and after the test meal. In this study also, the subjects had taken their morning dose of metformin (0.5 g) two hours before the test. Insulin, gastrin, gastric inhibitory polypeptide (GIP), secretin and vasoactive intestinal peptide (VIP) levels were measured using established radioimmunoassay techniques. Glucagon-like immunoreactivity (GLI) was measured by two antibodies, one reactive with the N-terminal, and the other reactive with the C-terminal. The product, measured by these two antibodies, was referred to as N-terminal glucagon-like immunoreactivity (N-GLI) and C-terminal glucagon-like immunoreactivity (C-GLI). N-GLI probably represents all known species including pancreatic and gut glucagon. C-GLI is more representative of pancreatic glucagon alone. The sensitivities, coefficients of variation and normal ranges for all the hormone assays are given on Table 1.

Table 3. Fasting and 30 min post meal hormone levels before and after 1 week treatment with metformin (1.5 g/day). Paired analyses were carried out to estimate the response to a meal and the response to treatment using Student's paired t-test

	Fasting (mean±SEM)	Post meal (mean±SEM)	Response to meal p
Insulin (mU/l) (n = 6)			
before treatment	4.1 ± 0.8	29.7 ± 5.4	< 0.01
after treatment	3.3 ± 0.7	28.1 ± 8.3	< 0.05
Response to treatment (p)	NS	NS	
Gastrin (ng/l) (n = 6)			
before treatment	34 ± 4	78 ± 9	< 0.01
after treatment	32 ± 8	65 ± 11	NS
Response to treatment (p)	NS	NS	
GIP (ng/l) (n = 4)			
before treatment	68 ± 20	525 ± 97	< 0.02
after treatment	59 ± 38	462 ± 84	< 0.02
Response to treatment (p)	NS	NS	
Secretin (ng/l) (n = 6)			
before treatment	24 ± 2	22 ± 2	NS
after treatment	26 ± 1	27 ± 2	NS
Response to treatment (p)	NS	NS	
VIP (ng/l) (n = 6)			
before treatment	83 ± 6	58 ± 5	< 0.002
after treatment	102 ± 9	79 ± 5	NS
Response to treatment (p)	< 0.02	< 0.05	
N-terminal GLI (ng/l) (n = 6)			
before treatment	57 ± 4	82 ± 10	< 0.05
after treatment	72 ± 11	174 ± 24	< 0.01
Response to treatment (p)	NS	< 0.01	
C-terminal GLI (ng/l) (n = 6)			
before treatment	36 ± 3	36 ± 3	
after treatment	42 ± 4	52 ± 7	NS
Response to treatment (p)	NS	< 0.02	

n = number of subjects NS = not significant

Statistical Analysis of Results

In both studies, Student's paired t-test was used to estimate significance. In the hormone study paired analyses were carried out to determine significant responses to (i) the stimulatory meal and (ii) treatment with metformin.

Results

(a) Gastric Acid Secretion Study

The maximum acid output was increased in all subjects after the treatment period (Table 2). The increase was statistically significant ($p < 0.05$). The peak acid output was also significantly increased ($p < 0.05$) after metformin treatment. There were no statistical differences between the pre and post treatment levels of peak $[H^+]$ concentration or peak volume (Table 2).

Two of the five subjects had borderline low Schilling tests at the end of the treatment period (normal range > 10.0%). However, the maximum acid output of both subjects had increased during the treatment period excluding achlorhydria.

(b) Hormone Study

The results are shown in Table 3.

(i) Response to a Meal. There were significant postprandial rises in the levels of insulin, gastrin, GIP and N-GLI before treatment. This response was also significant after the treatment period in the case of insulin, GIP and N-GLI but not for gastrin. Initially, VIP levels dropped significantly after the meal. However, after the treatment period, the decrease in post meal VIP levels from 102 ± 9 to 79 ± 5 ng/l was not significant. Secretin and C-GLI levels were not significantly altered by the test meal either before or after metformin treatment.

(ii) Response to Metformin Treatment. Insulin, gastrin, GIP and secretin levels were not significantly changed by treatment with metformin either fasting or after a test meal. VIP levels were increased significantly by metformin, both fasting and post-prandially. Post meal N-GLI levels increased dramatically after metformin treatment although both before and after treatment fasting levels were similar. The post meal rise in N-GLI levels was accompanied by a smaller but significant rise in C-GLI.

Discussion

Treatment with metformin resulted in a significant rise in gastric acid secretion. The gastrin response to a meal was smaller in four out of six subjects than before treatment. VIP levels were increased both fasting and after the meal and post prandial N-GLI levels were also increased, partially because of a small rise in C-GLI and principally because of a dramatic rise in intestinal GLI levels. These results indicate that if there is any inhibitory effect of metformin on the active transport system of the gastric mucosa it is counteracted by a stimulatory effect.

All five subjects who completed the pentagastrin study had an increased stimulated gastric acid output after the treatment period. Abnormal Schilling tests have frequently been reported in patients on biguanide therapy [4]. Although two of these five volunteers had borderline low Schilling tests, their maximum acid outputs had increased dramatically after metformin. It is unlikely therefore that the development of a contaminated small bowel syndrome in patients on metformin treatment is provoked by altered conditions in the stomach.

Biguanides have not been found to accumulate in the gastric mucosa [5] so a significant inhibition of the active transport systems in this region would not be expected. However, a significantly increased gastric acid output after the treatment period presumably involves stimulation of the parietal cell. Histamine, gastrin and acetyl choline are the major naturally occurring substances which stimulate gastric acid secretion. Metformin, histamine, and acetyl choline have an important feature in common. They are all strongly basic and at physiological pH are predominantly in the cationic form. The guanidine analogue of histamine (N-α-guanyl histamine) has been shown to be a partial agonist of histamine [6]. Although presence of the imidazole ring is important for histamine like activity [7], it is possible that metformin in small amounts enhances the gastric acid response to pentagastrin because of its similarity to histamine and acetyl choline. This would not necessarily contradict the findings of Diniz [8] who showed that gastric acid secretion was inhibited in rats following phenformin treatment, since the concentration of phenformin used in their study was considerably higher than the normal therapeutic dose for humans and other weak histamine agonists have antagonistic properties at higher doses [6].

Gastric acid secretion is controlled by complex neural and hormonal mechanisms. Patients with duodenal ulcers have been shown to have significantly higher levels of gastrin after a meal than normal subjects [9]. An increase in intestinal GLI levels has previously been reported following phenformin treatment in diabetics [10] and in patients with the dumping syndrome [11]. The physiological effect of intestinal GLI is as yet unclear. However, the increased levels found after metformin treatment are another manifestation of the major effect of biguanide drugs on the intestinal mucosa. The physiological relevance of VIP has also not been fully described but there is evidence to show that its action includes stimulation of adenylate cyclase and secre-

tion in the colon, ileum and jejunum [12]. It also may participate in the regulation of gastrointestinal motor tone, and motility. The high levels found after metformin treatment may thus be connected with alterations in both intestinal motility and active transport systems.

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