Effect of Orally Administered Prostaglandin E_2 and its 15-Methyl Analogues on Gastric Secretion

S. M. M. KARIM, D. C. CARTER, D. BHANA, P. ADAIKAN GANESAN

British Medical Journal, 1973, 1, 143–146

Summary

The effect of orally administered prostaglandin E_2 and its synthetic 15-methyl analogues on gastric secretion in man was studied. The parent E_2 compound did not inhibit basal secretion, whereas both the 15 (S) 15-methyl-E_2 methyl ester and its isomer, 15 (R) 15-methyl-E_2 methyl ester inhibited basal acid secretion. This action is likely to be a direct one on the parietal cell, and it could prove of value in the treatment of peptic ulcer.

Introduction

The inhibition of gastric acid secretion in man by intravenous infusion of prostaglandins E_1 (PGE_1), E_2 (PGE_2), and A_1 (PGA_1) has been reported by several investigators (Classen *et al.*, 1970; Wada and Ishizawa, 1970; Wilson *et al.*, 1971). While PGE_1 in contact with gastric mucosa inhibited acid production in anaesthetized rats (Ramwell and Shaw, 1968) and in isolated bullfrog mucosa preparations (Way and Durbin, 1969) there have been no reports of locally administered prostaglandins having a similar effect in man. On the contrary, Horton *et al.* (1968) found that in man orally administered PGE_1 had no effect on pentagastrin-induced acid secretion.

A possible explanation for the lack of effect of orally administered naturally occurring prostaglandins on acid secretion is their rapid enzymatic inactivation and metabolism. One of the most important points in the metabolism of naturally occurring prostaglandins is dehydrogenation at carbon 15, which is brought about by the enzyme prostaglandin 15-OH dehydrogenase. This metabolism occurs very readily and the resulting compounds possess a greatly reduced biological activity. Prostaglandin analogues modified at carbon 15 have now been synthesized (Bundy *et al.*, 1971; Yankee and Bundy, 1972). Two such compounds are prostaglandin 15 (S) 15-methyl-E_2 methyl ester and its isomer 15 (R) 15-methyl-E_2 methyl ester (fig. 1). These analogues are not substrates for enzyme prostaglandin 15-OH dehydrogenase and consequently enzymic degradation at carbon 15 is prevented. The increase in some of the biological actions of analogues with modification at carbon 15 has been confirmed (Karim and Sharma, 1972; Karim *et al.*, 1972a; Kirton and Forbes, 1972).

The present study was undertaken to assess the effect of PGE_2 and its synthetic analogues 15 (S) 15-methyl-E_2 methyl ester and 15 (R) 15-methyl-E_2 methyl ester on basal human gastric acid secretion when administered orally to normal healthy male volunteers. This screening study represents only one part of a larger survey, but because of the implications of the early results it was considered of value to publish them in this *preliminary* form.

Makerere University Medical School, P.O. Box 7072, Kampala, Uganda

S. M. M. KARIM, PH.D., Professor of Pharmacology
D. C. CARTER, F.R.C.S., Lecturer in Surgery
D. BHANA, F.R.C.S., Senior Lecturer in Surgery
P. ADAIKAN GANESAN, Senior Research Technician in Pharmacology

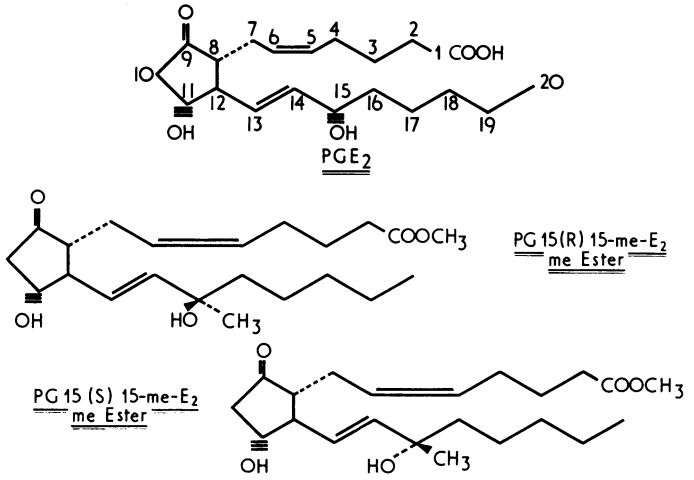

FIG. 1—Chemical structure of prostaglandin E_2 and synthetic analogues 15 (R) 15-methyl-E_2 methyl ester and 15 (S) 15-methyl-E_2 methyl ester.

Materials and Methods

A total of 26 tests were carried out in healthy male volunteers using the above prostaglandins. In 7 tests the parent PGE_2 was given orally, in 15 tests the 15 (R) analogue was given orally, and in the remaining 4 tests the 15 (S) analogue was similarly administered. For 20 of these tests data were available from control studies in the same individuals where the vehicle was given without the prostaglandin.

After a 12-hour overnight fast a nasogastric tube (F.G. 14-16) was passed into the stomach. The fasting residue was discarded and the tube position adjusted to allow the ready recovery of a trial 20 ml instillate of water. Although continuous suction was applied tube patency was also ensured by periodic air insufflation. Specimens of gastric juice were collected every 15 minutes and assessed in terms of volume (ml), pH, acid concentration (mEq/l.), and acid output (mEq). Titrations were performed to end-point pH 7 by using a glass electrode and 0·05N NaOH solution. After a basal period of two 15-minute collections the prostaglandin was given by instillation down the nasogastric tube in 10 ml of water. Aspiration was discontinued for 30 minutes to allow contact with the gastric mucosa. Collection was then restarted for a further three hours. The control studies differed only in that prostaglandins were excluded from the instillate.

Subjects were questioned specifically about untoward gastrointestinal and other side effects during the test and asked to report any alterations in bowel habit in the succeeding 24 hours.

Results

PROSTAGLANDIN E_2

Of the seven tests carried out with the parent compound three were performed using 2·5 mg orally and four with a dose of 4 mg. In view of the recognized side effects of oral PGE_2 it was deemed unwise to use a higher dosage (Karim, 1971). In none of the tests was a consistent or even transient inhibition of acid secretion obvious either in absolute terms or relative to the

Comparison between Acid Output in Control Studies and Output after Locally Administered Prostaglandins

Dose of Prostaglandin	Effect of Prostaglandin on Mean Hourly Acid Output (mEq/hr)*			Effect of Prostaglandin on Mean Three-hour Acid Output†
	1st Hour	2nd Hour	3rd Hour	
		PGE_2		
2·5 mg (1 test):				
Prostaglandin	4·98 (108)	2·98 (51)	2·60 (92)	10·56 (251)
Control	2·41 (126)	3·41 (99)	2·08 (100)	7·90 (325)
4·0 mg (3 tests):				
Prostaglandin	2·99 (128)	2·83 (91)	2·83 (60)	8·66 (279)
Control	2·28 (92)	1·83 (69)	1·57 (70)	5·68 (231)
		15 (R) 15-methyl-E_2 Methyl Ester		
100 µg (3 tests):				
Prostaglandin	2·17 (96)	1·95 (65)	2·48 (53)	6·50 (214)
Control	3·38 (113)	2·02 (62)	3·31 (63)	7·70 (238)
150 µg (2 tests):				
Prostaglandin	0·67 (59)	0·42 (49)	1·02 (67)	2·11 (176)
Control	4·06 (96)	1·99 (77)	1·52 (53)	7·57 (226)
200 µg (5 tests):				
Prostaglandin	0·63 (104)	0·44 (98)	0·65 (81)	1·71 (283)
Control	3·08 (99)	2·24 (85)	2·73 (75)	8·09 (259)
		15 (S) 15-methyl-E_2 Methyl Ester		
25 µg (2 tests):				
Prostaglandin	0·70 (68)	1·63 (86)	1·94 (78)	4·27 (232)
Control	4·06 (96)	1·94 (77)	1·51 (54)	7·57 (226)
50 µg (2 tests):				
Prostaglandin	0·40 (90)	0·01 (66)	1·06 (70)	1·47 (225)
Control	5·32 (95)	1·28 (35)	1·52 (42)	8·12 (172)

*Mean hourly volume of aspirate is given in parentheses.
†Mean total volume of aspirate is given in parentheses.

control data available for four of the subjects (see table). No side effects were reported from the use of this compound at these dose levels.

PROSTAGLANDIN 15 (R) 15-METHYL-E_2 METHYL ESTER

Dose 100 µg (5 tests).—As shown in fig. 2 the acid output in mEq/30 min fell in all cases after instillation of the prostaglandin. In three subjects the reduction was marked and sustained for the duration of the test, whereas in one subject the output rose again to basal levels within one hour of restarting aspiration.

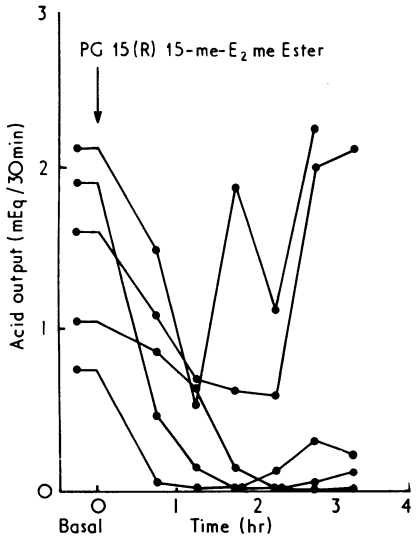

FIG. 2—Effect of oral dose of 100 µg prostaglandin 15 (R) 15-methyl-E_2 methyl ester on basal acid secretion.

A repeat test in this individual showed a similar pattern of secretion. The fall in output in all cases was due primarily to a reduction in the acidity rather than volume of secretion. The comparison of the acid output after prostaglandin with control values is summarized in the table.

Dose 150 µg (3 tests).—In the three individuals tested at this dose level inhibition of acid secretion was noted in all cases (fig. 3). As with the lower dose the effect was mediated primarily by a reduction in acid concentration and was reflected in a sustained rise in pH. In two cases the aspirate remained alkaline for 90 minutes after instillation. In the two subjects where control data were available the three-hour output after prostaglandin was 51·6% and 7·8% respectively of the control values.

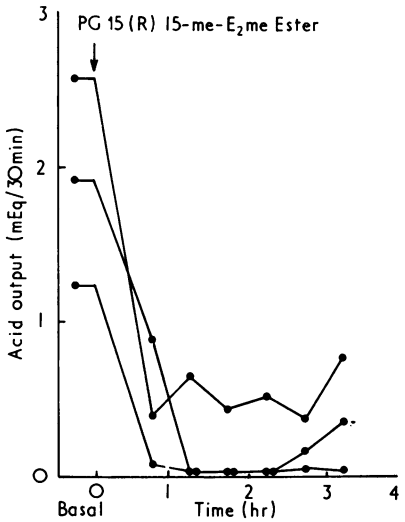

FIG. 3—Effect of oral dose of 150 µg prostaglandin 15 (R) 15-methyl-E_2 methyl ester on basal acid secretion.

Dose 200 µg (7 tests).—Five of the seven tests carried out with 200 µg of the analogue showed a profound and sustained reduction in acid production, the aspirate remaining alkaline for at least 120 minutes (fig. 4). In the other two tests a marked fall in acid secretion was also noted but the pH did not rise above 7 in either case. Control data were available for five of these tests and the comparison with the acid output after prostaglandin is summarized in the table. The reduction in mean three-hour acid output effected by this dose of prostaglandin was again achieved by a fall in acid concentration while the volume of aspirate appeared unaffected.

No untoward side effects were noted during or in the 24 hours after any of the tests using the 15 (R) 15-methyl-E_2 methyl ester.

PROSTAGLANDIN 15 (S) 15-METHYL-E_2 METHYL ESTER

Dose 25 µg (2 tests).—In both tests a transient fall in acid output was observed (fig. 5), and although the aspirate became

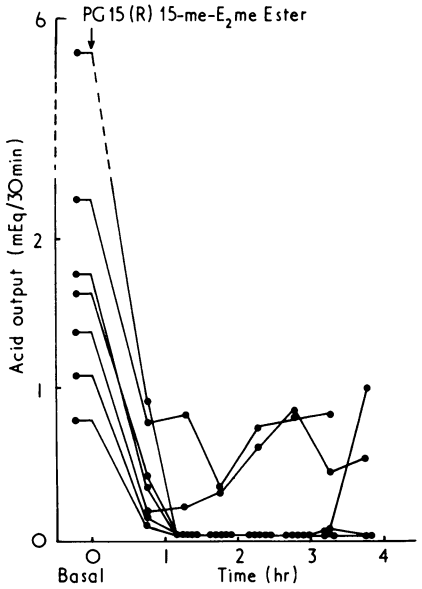

FIG. 4—Effect of oral dose of 200 μg prostaglandin 15 (R) 15-methyl-E_2 methyl ester on basal acid secretion.

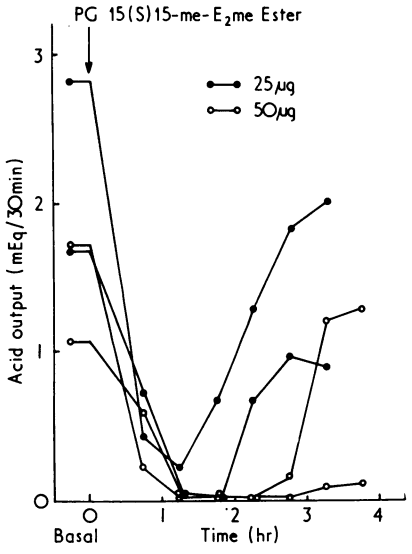

FIG. 5—Effect of 25 and 50 μg of orally administered prostaglandin 15 (S) 15-methyl-E_2 methyl ester on basal acid secretion.

alkaline in one case for 45 minutes the pH in the other subject did not rise above 4. As with the 15 (R) compound the variations in output resulted from a fall in acidity rather than volume.

Dose 50 μg (2 tests).—Complete inhibition of acid secretion occurred in both of these tests and was sustained for 90 minutes (fig. 5). Once more little or no fluctuation in volume was observed and the pH rose in both instances to remain higher than 7 for at least 90 minutes.

Comparative control data were available for all four tests performed with the 15 (S) analogue (see table). No adverse side effects were reported after 25 μg, but after 50 μg one of the subjects complained of nausea, and borborygmi were apparent during the procedure.

Discussion

The inhibition observed in response to oral administration of prostaglandin 15 (R) 15-methyl-E_2 methyl ester was both striking and sustained after 200 μg, although a less marked inhibitory effect was also apparent after 100 and 150 μg of this compound. The reduction in acid secretion was mediated primarily by a fall in acid concentration as no consistent alteration in the volume of the aspirate was noted. It was a subjective impression that viscosity of the gastric mucus was increased after exposure to the analogue, and it is possible that the inhibitory effect on acid production did not extend to the non-parietal component of gastric secretion.

Although the 15 (S) 15-methyl-E_2 methyl ester compound showed a similar effect on basal secretion its use in this context is limited by its recognized excitatory effect on smooth muscle, in particular that of the uterus. Even in the limited dose range explored some unpleasant gastrointestinal symptoms were reported, and for these reasons the compound was not examined further once the broad pattern of response had been established. The 15 (R) analogue, on the other hand, appeared free from side effects and its uterine actions by the oral route are also known to be less marked.

The failure of the parent E_2 compound to inhibit basal acid secretion is probably due to its rapid metabolism and inactivation. The 15-methyl derivatives are some 100 to 500 times more active and their duration of action on the uterus is longer by a factor of 3 to 4 when compared with the parent prostaglandin (Karim and Sharma, 1972; Karim *et al.*, 1972 a). When given in high doses by intravenous infusion PGE_2 has been reported as having an inhibitory effect on acid production but only at the expense of an appreciable incidence of undesirable sequelae (Wada and Ishizawa, 1970). It is therefore highly unlikely that PGE_2 will ever enjoy a therapeutic role in the suppression of acid secretion.

It has been suggested that the inhibition of gastric secretion by prostaglandins is due to a reduction in mucosal blood flow. While it is accepted that both the A and E series of compounds have a peripheral vasodilatory action the doses used in the present study had no effect on the blood pressure recorded by brachial artery cannulation (Karim *et al.*, 1972 b). In addition Jacobson (1970), working with dogs, showed that the inhibitory effect of PGE_1 was not due to a primary action on mucosal blood flow. While inhibition may result from changes in cyclic AMP concentrations it is also possible that there may be a direct action on the parietal cell. This last mechanism is supported by the observations that other prostaglandin fractions are capable of suppressing the secretion induced by histamine, pentagastrin, and vagal excitation (Ramwell and Shaw, 1968; Robert *et al.*, 1968 a; Main, 1969; Wilson *et al.*, 1971). These mechanisms of inducing acid secretion are currently being challenged in our laboratory by the 15 (R) 15-methyl-E_2 methyl ester and the results will be published in detail separately. Our preliminary experience is that the compound is very effective in the reduction of pentagastrin-induced acid secretion.

The main interest in the present report lies in the fact that for the first time an oral preparation of prostaglandin has been shown to inhibit acid production. Of the two synthetic analogues the 15 (R) isomer shows the greater promise in that the effect is apparently free from side effects. The oral route of administration has obvious advantages if the analogue is to have therapeutic application to the problem of peptic ulceration, and we have had similar results after giving the dose in a hard gelatin capsule. The vehicle of 10 ml of water described here was used to ensure adequate contact with the secretory mucosa although it is possible that the contact time of 30 minutes does not allow complete absorption. In this context we have not attempted to measure the amount of prostaglandin returning with the aspirate, and it is possible that the doses used may give an artificially high impression of the amount of prostaglandin producing the observed effect.

In experimental animals Robert *et al.* (1968 b, 1971) showed the ulcer-sparing effect of PGE_1 in experimentally induced gastric and duodenal ulceration in short-term experiments. It is conceivable that the 15 (R) analogue used in our studies could produce a similar beneficial effect in the human peptic ulcer situation. If the compound is to be assessed in this context it is

important to ascertain whether the inhibition extends to pepsin secretion, and this aspect is currently under review.

We wish to thank Professor S. K. Kyalwazi for his support and encouragement, and Mr. E. Zirimabagabo for technical help. The prostaglandins used in this study were either synthesized by Dr. W. P. Schneider in our laboratory or supplied by the Upjohn Company of Canada. We gratefully acknowledge the financial support of the Upjohn Company, Kalamazoo, Michigan, U.S.A.

During the performance of this work D. C. C. was on secondment from the Department of Clinical Surgery, Edinburgh.

References

Bundy, G., Lincoln, F., Nelson, N., Pike, J., and Schneider, W. (1971). *Annals of New York Academy of Sciences*, **180**, 76.
Classen, M., Koch, H., Deyhle, P., Weidenhiller, S., and Demling, L. (1970). *Klinische Wochenschrift*, **48**, 867.
Horton, E. W., Main, I. H. M., Thompson, C. J., and Wright, P. M. (1968). *Gut*, **9**, 655.
Jacobson, E. D. (1970). *Proceedings of the Society for Experimental Biology and Medicine*, **133**, 516.
Karim, S. M. M. (1971). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **78**, 289.
Karim, S. M. M., and Sharma, S. D. (1972). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **79**, 737.
Karim, S. M. M., Sharma, S. D., and Filshie, G. M. (1972 a). *Proceedings of Brook Lodge Symposium on Prostaglandins.*
Karim, S. M. M., Somers, K., and Adaikan, Ganesan P. (1972 b). In preparation.
Kirton, K. T., and Forbes, A. D. (1972). *Prostaglandin*, **1**, 319.
Main, I. H. M. (1969). *British Journal of Pharmacology*, **36**, 214P.
Ramwell, P., and Shaw, J. E. (1968). *Journal of Physiology*, **195**, 34P.
Robert, A., Phillips, J. P., and Nezamis, J. E. (1968 a). *Gastroenterology*, **54**, 1263.
Robert, A., Nezamis, J. E., and Phillips, J. P. (1968 b). *Gastroenterology*, **55**, 481.
Robert, A., Stowe, D. F., and Nezamis, J. E. (1971). *Scandinavian Journal of Gastroenterology*, **6**, 303.
Wada, T., and Ishizawa, M. (1970). *Japanese Journal of Clinical Medicine*, **28**, 2465.
Way, L., and Durbin, R. P. (1969). *Nature*, **221**, 874.
Wilson, D. E., Phillips, C., and Levine, R. A. (1971). *Gastroenterology*, **61**, 201.
Yankee, E. W., and Bundy, G. L. (1972). *Journal of the American Chemical Society*, **94**, 3651.

Multiple Renal Silica Calculi

A. M. JOEKES, G. ALAN ROSE, JUNE SUTOR

British Medical Journal, 1973, **1**, 146–147

Summary

Investigation of a patient with a history of renal colic, who had taken the equivalent of 2 g magnesium trisilicate after every meal for many years, showed that he was forming silica calculi. The nature of the stone was diagnosed only after quantitative analysis.

Introduction

Silica stone was first described by Herman and Goldberg (1960) in the U.S.A. and was attributed to the ingestion of magnesium trisilicate for treatment of oesophagitis. Five more cases, also in the U.S.A., were reported by Lagergren (1962). Few cases have been described since then, and none in this country. Herring (1962) did not report any in his survey of 10,000 urinary calculi analysed by crystallographic and *x*-ray diffraction techniques. It was therefore thought appropriate to report a case of recurrent silica stones in this country.

Case Report

A 68-year-old man was first seen in November 1971 with a history of two episodes of presumed renal colic in 1940 with no precise diagnosis made at the time. After a fall in 1966 he developed a severe left-sided renal colic and radiography showed a large stone in the lower end of the left ureter with a much smaller stone immediately below it. Shortly afterwards a small stone weighing 100 mg was passed. At the beginning of 1969 he started having a series of renal colics affecting both the left and the right side. In June a stone was apparently removed from a diverticulum in the bladder. Some months later a small stone about 4 mm long was passed. This was slightly yellowish and very hard. He was free of any further colic until the beginning of 1971, when he passed two small stones. He again passed a small stone after a renal colic in September 1971. On no occasion was the passage of stones accompanied by macroscopic haematuria.

On examination he was an active, well-preserved man. Blood pressure was 190/90 mm Hg lying and standing. There was a healthy, rather wide, left paramedian scar. No other significant abnormal physical signs were found.

Investigations were: haemoglobin 12·7 g/100 ml, white cell count 7,000/mm^3, packed cell volume 41%, E.S.R. 25 mm in 1 hr, plasma urea 46 mg/100 ml, creatinine 1·1 mg/100 ml, sodium 140 mEq/l., potassium 4·0 mEq/l., bicarbonate 26 mEq/l., total protein 7·6 g/100 ml, calcium 9·6 mg/100 ml, phosphate 2·4 mg/100 ml, uric acid 8·1 mg/100 ml, 24-hour creatinine clearance 75 ml/min, 24-hour calcium excretion 85 and 84 mg, 24-hour urinary uric acid excretion 370 and 360 mg.

An intravenous pyelogram showed that the kidneys concentrated well and that the upper urinary tract was normal. There was a 1-cm low density calculus in the pelvic portion of the left lower ureter. The bladder was slightly trabeculated with a moderate residue after micturition.

A radioactive renogram with 20 μCi of ^{131}I Hippuran and a urine flow rate of 4 ml/min showed a normal curve for the right kidney with no excretory abnormality. The left kidney showed considerably less good function with evidence of an obstructive lesion with a very slow excretory phase.

The day after the intravenous pyeolography the patient had a severe suprapubic pain eventually radiating to the left flank. This continued for two days and he then passed the calculus that we had seen in the pelvic portion of the left ureter.

STONE ANALYSIS

Quantitative stone analysis was carried out by using the system of Westbury and Omenogor (1970), but as extended by Westbury (1972) to include oxalate determination. In addition, the usual qualitative tests were performed (see table). It was also noted that the powdered material was insoluble in dilute HCl but was soluble in dilute NaOH, and could be precipitated from this solution on acidification with HCl, and that the fresh precipitate was soluble in further excess HCl. These reactions are those of silica, the presence of which was therefore suspected. The confirmation of this suspicion was sought by *x*-ray crystallography. Silica occurs in calculi in the opaline state which is non-crystalline, but on heating it can be transformed into various crystalline forms depending on the temperature of ignition. The *x*-ray powder diffraction method was therefore used to determine if any crystalline material was present in the stone. Small samples from

St. Peter's Hospitals and Institute of Urology, University College, London WC2H 9AE
A. M. JOEKES, B.M., F.R.C.P., Nephrologist
G. ALAN ROSE, M.R.C.P., M.R.C.PATH., Consultant Chemical Pathologist
JUNE SUTOR, M.SC., PH.D., Research Fellow