PRELIMINARY COMMUNICATIONS

Prostaglandin 15 (R) 15-methyl-E₂ Methyl Ester for Suppression of Gastric Acidity in Gravida at Term

J. J. AMY, D. M. JACKSON, P. ADAIKAN GANESAN, S. M. M. KARIM

British Medical Journal, 1973, 4, 208-211

Summary

During the second hour after giving 100 µg of orally administered prostaglandin 15 (R) 15-methyl-E₂ methyl ester in the pregnant patient at term a noticeable reduction in basal gastric acid secretion took place. At this dose no excessive uterine stimulation was observed. Prostaglandin 15 (R) 15-methyl-E₂ methyl ester could prove of value in the preoperative preparation of the pregnant patient before anaesthesia for reducing the incidence of acid regurgitation.

Introduction

The inhibitory action of several of the naturally occurring prostaglandins on gastric acid secretion has previously been reported. Prostaglandin E₁ (PGE₁) infused intravenously into unanaesthetized dogs appreciably reduced the gastric secretory response to either food, histamine, pentagastrin, or deoxyglucose stimulation. Complete inhibition was attained at an infusion rate of 1 µg PGE₁/kg/min; 60% inhibition at 0.45 µg/kg/min. For any dose maximum inhibition was reached 30 to 45 minutes after the start and was then maintained throughout the infusion (Robert *et al.*, 1967). In rats both subcutaneous administration (Robert *et al.*, 1968) and perfusion of the gastric lumen with PGE₁ (Shaw and Ramwell, 1968) markedly reduced gastric acid secretion.

Classen *et al.* (1970) were able to inhibit gastric acid secretion in man by intravenous infusion of PGE₁ at the rate of 4 to 5 µg/kg/30 min. Nevertheless, oral administration of this compound in doses up to 40 µg/kg (Horton *et al.*, 1968) or of a single dose of 4 mg of PGE₂ (Karim *et al.*, 1973 a) produced no such inhibition. Karim *et al.* (1973 a) suggested that this lack of effect of orally administered naturally occurring prostaglandins on acid secretion could be due to their rapid enzymatic inactivation and metabolism. These authors undertook to study the effect of oral administration of the 15-methyl analogues of PGE₂ on

gastric secretion in male volunteers. The latter compounds, synthesized by incorporation of an additional methyl group in the 15 position of the parent prostaglandin E₂ (Bundy *et al.*, 1971; Yankee and Bundy, 1972), are not substrates for the enzyme prostaglandin 15-OH dehydrogenase. Both prostaglandin 15 (R) 15-methyl-E₂ methyl ester (fig. 1) and prostaglandin 15 (S) 15-methyl-E₂ methyl ester caused a noticeable reduction in basal gastric acid production. The inhibition observed in response to oral administration of a single dose of 200 µg of prostaglandin 15 (R) 15-methyl-E₂ methyl ester was profound and sustained. A similar though less striking effect was observed after 100 or 150 µg of this compound. No side effects were reported (Karim *et al.*, 1973 a, b).

FIG. 1—Chemical structure of prostaglandin 15 (R) 15-methyl-E₂ methyl ester.

Prostaglandins are now increasingly used for induction of labour at term and for termination of second trimester pregnancy (Karim, 1972). Because of the longer gastric emptying time and the higher intra-abdominal pressure, the pregnant patient is at particular risk when receiving anaesthesia for delivery. The present study was undertaken with a view to establishing an oral regimen of prostaglandin 15 (R) 15-methyl-E₂ methyl ester that would inhibit gastric acid secretion in the gravida at term without causing unphysiological myometrial stimulation.

Patients and Methods

A total of 16 pregnant patients in the Department of Obstetrics and Gynaecology, Mulago Hospital, Kampala, were investigated. Except for one case of mild pre-eclamptic toxæmia and another one of relative cephalopelvic disproportion, there were no complications of pregnancy. Gestational age had been determined in all patients by radiographic identification of fetal ossification centres (two cases) or by amniotic fluid exfoliative cytology (14 cases) in order to exclude prematurity (Amy, 1972). None of the patients were clinically in labour before prostaglandin administration. The fetal membranes were intact in all cases.

A preliminary study was carried out on the first six patients to test myometrial sensitivity to prostaglandin 15 (R) 15-methyl-E₂ methyl ester administered via a nasogastric tube. Myometrial activity was monitored and doses up to 100 µg of the compound were given without excessive uterine stimulation being observed. These patients are not discussed further in this report.

On the basis of this preliminary study, a prospective investigation was then carried out on 10 patients at term. Eight had been fasting for over 12 hours, the other two had had a meal of porridge an hour and a half before testing. After emptying her bladder each patient was examined to determine fetal lie,

Makerere University Medical School and Mulago Hospital, Kampala, Uganda

J. J. AMY, M.D., D.T.M., Lecturer in Obstetrics and Gynaecology (Present address: Kerselaarslaan, 22, B 9800 Deinze, Belgium)

D. M. JACKSON, B.M., F.F.A.R.C.S., Senior Registrar in Anaesthesiology (Present address: Department of Anaesthesia, Queen Mary's Hospital for Children, Carshalton, Surrey)

P. ADAIKAN GANESAN, Senior Research Technician in Pharmacology (Present address: Department of Obstetrics and Gynaecology, University of Singapore, Kandang Kerbau Hospital, Singapore 8)

S. M. M. KARIM, PH.D., Professor of Pharmacology (Present address: Department of Obstetrics and Gynaecology, University of Singapore, Kandang Kerbau Hospital, Singapore 8)

presentation, and position. A pelvic examination was then performed and the station of the presenting part, the integrity of the membranes, and the length, firmness, effacement, and dilatation of the cervix were noted.

Time: - 60 min (= 60 min before PG administration).—An open-ended polyethylene catheter was inserted transcervically into the extra-amniotic space (two patients) or transabdominally into the amniotic cavity (eight patients). It was then connected to a Devices monitoring unit via a Statham transducer for continuous recording of intrauterine pressure.

Time: - 30 min (= 30 min before PG administration).—A nasogastric tube (F.G. 14-16) was passed into the stomach and the gastric contents were aspirated. This was repeated at 30-minute intervals until completion of the test, the last specimen being withdrawn at time + 300 min. Each sample of gastric juice was assessed in terms of volume (ml), pH, acid concentration (mEq/l.), and (except for the first sample) acid output (mEq/30 min). Titrations were performed to end-point pH 7 using a glass electrode and 0.05N NaOH solution.

Time: 0 (PG administered).—After collecting the second sample of gastric juice, the first dose of 100 µg of prostaglandin 15 (R) 15-methyl- E_2 methyl ester, diluted in 10 ml of 0.9% NaCl in water, was administered by instillation down the nasogastric tube. The tube was then flushed by insufflation of 10 ml of air. The second and third doses of prostaglandin were given 120 and 240 minutes respectively after the first one.

Time: + 300 min (= 300 min after administration of 1st dose PG).—The last sample of gastric juice was withdrawn, and the nasogastric tube and the intrauterine catheter were removed. Pelvic examination was then repeated in order to assess progress of labour. The patient was encouraged to take glucose solution by mouth. Induction of labour was continued by oral administration of PGE₂ (2 mg, 2-hourly). Amniotomy was performed as soon as practicable.

Results

OXYTOCIC ACTIVITY

Prostaglandin 15 (R) 15-methyl- E_2 methyl ester, given by nasogastric tube at the dose of 100 µg two-hourly, was moderately oxytocic (fig. 2). In no case were hypertonus or unphysiological contractions observed. None of the patients required analgesia during the period of observation. The data concerning uterine activity are summarized in table I. Progress of labour in terms of cervical dilatation is summarized in table II.

It appears that oral doses of 100 µg of prostaglandin 15 (R) 15-methyl- E_2 methyl ester can be given two-hourly to pregnant

FIG. 2—Continuous record of uterine activity in one case: effect of three oral doses of 100 µg prostaglandin 15 (R) 15-methyl- E_2 methyl ester.

TABLE I—Uterine Activity (Montevideo Units)

	Stimulation		
	Mean (10 Patients)	Minimum (1 Patient)	Maximum (1 Patient)
Basal activity:			
After insertion intrauterine catheter	83	118	100
After insertion nasogastric tube ..	87	83	75
1 hr after 1st dose of PG	184	98	160
1 hr after 2nd dose of PG	246	120	375
1 hr after 3rd dose of PG	275	173	356

TABLE II—Progress of Labour (Cervical Dilatation in cm)

	Mean Dilatation (10 Patients)	Minimum Progress	Maximum Progress
At start of test	1.75		
1 hr after 3rd dose of PG	3.25		
Progress made	1.5	0.5	4.0

patients at term without causing unphysiological uterine activity. Further course of labour was uneventful except for one patient in whom prolapse of the umbilical cord was diagnosed at 7 cm cervical dilatation, requiring immediate caesarean section. The Apgar score one minute after birth was 7 or higher in all babies.

EFFECT ON GASTRIC SECRETION

The pH of the gastric secretion rose after administration of the first dose of 100 µg of prostaglandin 15 (R) 15-methyl- E_2 methyl ester, reaching a peak at 90 minutes ($P < 0.0005$). Thereafter, the pH fluctuated within a wide range of values, but remained higher than the basal pH (fig. 3).

FIG. 3—Effect of three oral doses of 100 µg prostaglandin 15 (R) 15-methyl- E_2 methyl ester on pH of gastric secretion in gravidae at term (mean values and standard deviations).

There was a noticeable reduction in the gastric acid output between 60 and 120 minutes after administration of the first dose of the compound ($P < 0.005$). Thereafter, despite administration of a second and third dose of prostaglandin, a slow rise took place (fig. 4). Gastric acid output during the fifth hour was significantly higher ($P < 0.05$) than that during the second hour.

The reduction of gastric acid secretion was mainly achieved by a fall in acid concentration. Though it parallels the decrease in acid concentration (fig. 5) the reduction in the volume of aspirate (except at 120 min) is not statistically significant.

TABLE III—Effect of Prostaglandin 15 (R) 15-methyl- E_2 methyl ester on Gastric Secretion of Gravida at Term (Mean values, 10 Patients)

Time	Administration of	pH	Acid Concentration (mEq/l.)	Volume (ml)	Acid Output* (mEq/hr)
0	100 μ g	2.87	25.6	23	1.03
0:30		2.59 (P<0.3)	23.2 (P<0.4)	27 (P<0.35)	
1:00		3.93 (P<0.1)	14.2 (P<0.05)	19 (P<0.35)	0.94 (P<0.45)
1:30		5.26 (P<0.0005)	5.4 (P<0.0005)	13 (P<0.1)	
2:00	100 μ g	4.97 (P<0.0025)	8.3 (P<0.01)	10 (P<0.05)	0.12 (P<0.005)
2:30		4.27 (P<0.05)	14.6 (P<0.1)	12 (P<0.1)	
3:00		5.17 (P<0.01)	11.5 (P<0.025)	12 (P<0.1)	0.23 (P<0.01)
3:30		5.49 (P<0.0025)	12.3 (P<0.025)	13 (P<0.15)	
4:00		5.51 (P<0.005)	12.2 (P<0.025)	10 (P<0.1)	0.25 (P<0.0125)
4:30	100 μ g	4.03 (P<0.1)	15.9 (P<0.1)	18 (P<0.3)	
5:00		4.28 (P<0.05)	12.8 (P<0.025)	11 (P<0.1)	0.46 (P<0.05)

*Means of hourly acid outputs for patients taken individually.

FIG. 4—Effect of three oral doses of 100 μ g prostaglandin 15 (R) 15-methyl- E_2 methyl ester on basal acid secretion in gravidae at term (mean values and standard deviations).

FIG. 5—Effect of three oral doses of 100 μ g prostaglandin 15 (R) 15-methyl- E_2 methyl ester on volume and acid concentration of gastric secretion in gravidae at term (mean values).

All data concerning the effect of two-hourly oral administration of 100 μ g prostaglandin 15 (R) 15-methyl- E_2 methyl ester on the gastric secretion of the gravida at term are summarized in table III.

SIDE EFFECTS

One patient had two liquid stools. No other side effects were noted.

Discussion

Karim *et al.* (1973 a, b) found that a single oral dose of 100-200 μ g prostaglandin 15 (R) 15-methyl- E_2 methyl ester was effective in markedly reducing the gastric acid output of male volunteers. The inhibition was maximal 1 hr 15 min after administration of the compound. At 200 μ g the effect was most striking and was sustained throughout the period of observation (3 hr 45 min) in four patients out of seven. At 100 μ g a similar though less striking effect was noted, gastric acid output having returned to basal levels after two hours in two patients out of five. The present investigation is an extension of that carried out by Karim *et al.* (1973 a, b).

The data presented here agree with the generally held belief that gastric secretion is reduced during pregnancy (Hyttén and Leitch, 1971). Basal gastric acid output was lower (mean 1.03 mEq/hr) in pregnant Ugandan women than it was in men (mean 2.37 mEq/hr; Karim *et al.*, 1973 c). No data are available concerning non-gravid Ugandan women.

Prostaglandin 15 (R) 15-methyl- E_2 methyl ester was effective in reducing gastric acid secretion in pregnant women. Gastric acid output decreased to 11.6% (0.12 mEq/hr, S.D. 0.13) of its initial value (1.03 mEq/hr, S.D. 0.94) during the second hour after oral administration of the first dose of 100 μ g of the compound. However, a significant rise (P < 0.05) occurred during the fifth hour despite administration of two additional doses. This lack of sustained inhibition might be due to tachyphylaxis, in which case the chronic administration of prostaglandin 15 (R) 15-methyl- E_2 methyl ester would not be of much value in the treatment of peptic ulcer, as suggested by Karim *et al.* (1973 a, b). Further long-term experiments should easily clarify this point.

The pregnant patient is at particular risk when receiving inhalation anaesthesia for delivery, because of her increased susceptibility to regurgitation and aspiration of stomach contents, resulting from delayed gastric emptying and raised intra-abdominal pressure (Flowers, 1967). A recent survey (Department of Health and Social Security, 1972) showed that over half of maternal deaths associated with general anaesthesia were due to inhalation of regurgitated gastric contents. Furthermore, as emphasized by Crawford (1972), there has been no decrease in the incidence of such anaesthetic disasters compared with the previous triennium (1964-6). Damage to the lungs by aspiration of as little liquid vomit as 1-2 ml is mainly due to the hydrochloric acid (Keating, 1956), and it is generally thought that if the pH of the gastric contents is higher than pH 2.5 the severe progressive pneumonitis described by Mendelson (1946) after inhalation thereof can be avoided.

Howard and Sharp (1973) found a significant acceleration of gastric emptying after intramuscular administration of 10 mg metoclopramide to pregnant women in labour. They suggested routine administration of this drug before emergency anaesthesia. The effectiveness of a single oral dose of 100 μ g of prostaglandin 15 (R) 15-methyl- E_2 methyl ester in reducing gastric acid output, and the lack of undesirable side effects, in particular in terms of excessive myometrial stimulation, should make it—either alone or in combination with metoclopramide—a valuable preoperative medication before obstetric inhalation anaesthesia.

More recently the antisecretory activity of other prostaglandin analogues has been reported (Robert and Magerlein, 1973; Karim *et al.*, 1973 c). Absence of uterine stimulant activity among these compounds would be an additional advantage. They could never, however, remove the need for scrupulous anaesthetic technique.

Oral administration of prostaglandin 15 (R) 15-methyl-E₂ methyl ester (100-200 µg, 2-hourly) would probably constitute a safe means of inducing labour, especially in high anaesthetic risk patients (Crawford, 1970).

The prostaglandin used in this study was supplied by the Upjohn Company of Canada. We are grateful to Sister C. Flory, Sister F. Kibuka, and Nurse M. Kanakulya for technical and nursing help. We are indebted to Dr. J. A. Salmon for statistical analysis of the data. The financial assistance of the Upjohn Co., Kalamazoo, U.S.A., is gratefully acknowledged.

References

- Amy, J. J. (1972). *Uganda Medical Journal*, 1, 74.
 Bundy, G., Lincoln, F., Nelson, N., Pike, J., and Schneider, W. (1971). *Annals of the New York Academy of Sciences*, 180, 76.
 Classen, M., Koch, H., Deyhle, P., Weidenhiller, S., and Demling, L. (1970). *Klinische Wochenschrift*, 48, 876.
 Crawford, J. S. (1970). *British Journal of Anaesthesia*, 42, 70.

- Crawford, J. S. (1972). *Lancet*, 2, 918.
 Department of Health and Social Security (1972). *Confidential Enquiries into Maternal Deaths in England and Wales, 1967-1969*. London, H.M.S.O.
 Flowers, C. E., jun. (1967). *Obstetric Analgesia and Anesthesia*, p. 3. New York, Hoeber Medical Division, Harper and Row.
 Horton, E. W., Main, I. H. M., Thompson, C. J., and Wright, P. M. (1968). *Gut*, 9, 655.
 Howard, F. A., and Sharp, D. S. (1973). *British Medical Journal*, 1, 446.
 Hytten, F. E., and Leitch, I. (1971). *Physiology of Human Pregnancy*, p. 169. Oxford, Blackwell Scientific.
 Karim, S. M. M. (1972). In *Prostaglandins, Progress in Research*, ed. S. M. M. Karim, p. 71. Oxford, Medical and Technical Publishing Co.
 Karim, S. M. M., Carter, D. C., Bhana, D., and Adaikan Ganesan, P. (1973 a). *British Medical Journal*, 1, 143.
 Karim, S. M. M., Carter, D. C., Bhana, D., and Adaikan Ganesan, P. (1973 b). In *Advances in Biosciences*, 9, *International Conference on Prostaglandins*, ed. S. Bergström and S. Bernhard, p. 255. Oxford, Pergamon Press.
 Karim, S. M. M., Carter, D. C., Bhana, D., and Ganesan, P. A. (1973 c). *International Research Communications Systems* March 1973.
 Keating, V. (1956). *Anaesthetic Accidents*, p. 119. London, Lloyd-Luke.
 Mendelson, C. L. (1946). *American Journal of Obstetrics and Gynecology*, 52, 191.
 Robert, A., and Magerlein, B. J. (1973). In *Advances in Biosciences*, 9, *International Conference on Prostaglandins*, ed. S. Bergström and S. Bernhard, p. 247. Oxford, Pergamon Press.
 Robert, A., Nezamis, J. E., and Phillips, J. P. (1967). *American Journal of Digestive Diseases*, 12, 1073.
 Robert, A., Nezamis, J. E., and Phillips, J. P. (1968). *Gastroenterology*, 55, 481.
 Shaw, J. E., and Ramwell, P. W. (1968). In *Prostaglandin Symposium of the Worcester Foundation for Experimental Biology*, ed. P. W. Ramwell and J. E. Shaw, p. 55. New York, Interscience.
 Yankee, E. W., and Bundy, G. L. (1972). *Journal of the American Chemical Society*, 94, 3651.

MEDICAL MEMORANDA

Norwegian Scabies During Immunosuppressive Therapy

W. D. PATERSON, B. R. ALLEN,
G. W. BEVERIDGE

British Medical Journal, 1973, 4, 211-212

Norwegian scabies, first described by Danielssen and Boeck (1848), is caused by an overwhelming infestation by the human scabies mite. The factors summarized in the table are thought to be important in its development. The widespread gross hyperkeratosis, with little or no pruritus, which occurs may give a diagnostic problem solved only when epidemics of the more usual form of scabies occur in contacts. We describe here the first case attributable to therapy with immunosuppressive drugs.

Case Report

A 27-year-old unmarried janitor was admitted to hospital in December 1971 with renal failure (blood urea 530 mg/100 ml) and malignant hypertension due to long-standing hydronephrosis. Intermittent haemodialysis was followed in May 1972 by renal transplantation and immunosuppressive therapy in the form of azathioprine 150 mg and prednisolone 50 mg daily. Satisfactory renal function was achieved (blood urea 72 mg/100 ml) and the patient was allowed home, requiring no antihypertensive therapy.

Aetiological Factors in Norwegian Scabies

Factors	Reference
Mental defect	
Imbecility (esp. Down's syndrome)	Calnan, 1950
Senile dementia	Zoon and Mali, 1949
Gross debility:	
Leukaemia	Dostrovsky <i>et al.</i> , 1956
Beri beri	Backhouse, 1929
Tuberculosis	Backhouse, 1929
Bacillary dysentery	Backhouse, 1929
Rheumatoid arthritis	Wells, 1952
Lack of cutaneous sensation:	
Leprosy	Danielssen and Boeck, 1848
Syringomyelia	Prakken and van Vloten, 1949
Tables dorsalis	Zoon and Mali, 1949
Lack of hypersensitivity:	
Failure of sensitization	Anderson, 1952
Acquisition of tolerance	Burks and Jung, 1956
Corticosteroid and other immunosuppressant drugs	present case

When readmitted in November 1972 for repair of a massive inguinal hernia he had a widespread skin eruption which had developed during the previous few weeks. He was known to be of rather low intelligence but also appeared miserable and withdrawn. Though he scratched occasionally, itching was not a complaint.

Examination showed an exfoliative dermatitis, with yellowish discoloration and thickening of the nails. The palms and soles were grossly hyperkeratotic with large scales and some exudation. There was widespread scaling over the trunk and limbs but his face was less affected. No definite diagnosis was made at first. After a few days of cleansing and the application of a diluted steroid ointment, much of the crusting on his neck and the midline of his back and chest had cleared leaving multiple papules (fig. 1). Norwegian scabies was suspected at this time, and microscopical examination of scrapings from the chest and palms showed large numbers of mites. It was then noticed that there were burrows on his face extending up to his hair line (fig. 2), from which further acari were isolated.

One application of 1% gamma-benzene hexachloride produced a striking reduction of scaling and an improvement in his general well-being. After this treatment no further live acari were found but another application was given a week later.

Within two or three weeks cases of scabies arose in the patients and staff of the surgical ward where he was nursed. It was diagnosed, or

Department of Dermatology, The Royal Infirmary, Edinburgh EH3 9YW

W. D. PATERSON, M.B., M.R.C.P., Registrar
 B. R. ALLEN, M.B., M.R.C.P., Senior Registrar
 G. W. BEVERIDGE, M.B., F.R.C.P., Consultant