Thus in the context of advanced neoplastic disease immunotherapy carried out by the method described provides a form of palliation for some patients. It does not offer a cure in these patients. Whether this method would improve the survival rate by killing all tumour cells in patients with only a small residual tumour load after surgery remains to be decided. Other aspects require investigation. What are the mechanisms of the tumour rejection observed? Is there an increase in the number of cytotoxic lymphocytes, is blocking factor (Hellström and Hellström, 1970a) reduced, are unblocking factors (Hellström and Hellström, 1970b; Bansal and Sjögren, 1971) produced? With a greater understanding of the mechanisms involved it might prove possible to design a more effective immunotherapeutic regimen by altering the constitution, frequency, and number of doses of vaccine. It might also prove possible to determine which patients are likely to derive most benefit from immunotherapy. It is, however, very unlikely that immunotherapy will ever replace other, conventional forms of therapy but it could become a useful adjunct to surgery, radiotherapy, and chemotherapy.

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References

- Bansal, S. C., and Sjögren, H. O. (1971). *Nature New Biology*, 233, 76.
 Brandes, L. J., Galton, D. A. G., and Wiltshaw, E. (1971). *Lancet*, 2, 293.
 Currie, G. A., Lejeune, F., and Fairley, G. H. (1971). *British Medical Journal*, 2, 305.
 Czajkowski, N. P., Rosenblatt, M., Wolf, P. L., and Vazquez, J. (1967). *Lancet*, 2, 905.
 Finney, J. W., Byers, E. H., and Wilson, R. H. (1960). *Cancer Research*, 20, 351.
 Foley, E. J. (1953). *Cancer Research*, 13, 835.
 Gorer, P. A., and Kaliss, N. (1959). *Cancer Research*, 19, 824.
 Graham, J. B., and Graham, R. M. (1959). *Surgery, Gynecology and Obstetrics*, 109, 131.
 Graham, J. B., and Graham, R. M. (1962). *Surgery, Gynecology and Obstetrics*, 114, 1.
 Guyer, R. J., and Crowther, D. (1969). *British Medical Journal*, 4, 406.
 Hellström, I., Hellström, K. E., Pierce, G. E., and Yang, J. P. S. (1968). *Nature*, 220, 1352.
 Hellström, K. E., and Hellström, I. (1969). *Advances in Cancer Research*, 12, 167.
 Hellström, K. E., and Hellström, I. (1970a). *Annual Review of Microbiology*, 24, 373.
 Hellström, K. E., and Hellström, I. (1970b). *International Journal of Cancer*, 5, 195.
 Ikonopisov, R. L., et al. (1970). *British Medical Journal*, 2, 752.
 Kaliss, N. (1958). *Cancer Research*, 18, 992.
 Kaliss, N., and Molomut, N. (1952). *Cancer Research*, 12, 110.
 Nadler, S. H., Chambers, H., and Russ, A. (1922). *Lancet*, 1, 217.
 Klein, E. (1969). *Cancer Research*, 29, 2351.
 Klein, G., Sjögren, H. O., Klein, E., and Hellström, K. E. (1960). *Cancer Research*, 20, 1561.
 Mathé, G. (1969). *British Medical Journal*, 4, 7.
 Mathé, G. (1970). *British Medical Journal*, 4, 487.
 Murray, G. (1958). *Canadian Medical Association Journal*, 79, 249.
 Nadler, S. H., and Moore, G. E. (1966). *Annals of Surgery*, 164, 482.
 Old, L. J., Benacerraf, B., Clarke, D. A., Carswell, E. A., and Stockert, E. (1961). *Cancer Research*, 21, 1281.
 Pruitt, J. C., Mengoli, H. F., Carpenter, H. M., and Prater, T. (1963). *Proceedings of the American Association for Cancer Research*, 4, 54.
 Sjögren, H. O., Hellström, I., and Klein, G. (1961). *Experimental Cell Research*, 23, 204.
 Southam, C. M., Brunschwig, A., Levin, A. G., and Dizon, Q. S. (1966). *Cancer (Philadelphia)*, 19, 1743.
 Woodruff, M. F. A., and Boak, J. L. (1966). *British Journal of Cancer*, 20, 345.
 Woodruff, M. F. A., and Nolan, B. (1963). *Lancet*, 2, 426.

Oral Prostaglandins in the Induction of Labour

WALLACE BARR, W. C. M. K. NAISMITH

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Summary

Prostaglandins E₂ and F_{2α} were administered by mouth to induce labour in 24 patients at or past term. The drugs were administered at two-hourly intervals in doses ranging from 0.5 to 1.5 mg for prostaglandin E₂ and from 5 to 15 mg for prostaglandin F_{2α}. Of the 10 cases in which prostaglandin E₂ was used, labour was successfully induced in eight and there were no side effects. With prostaglandin F_{2α} labour was induced in 12 of 14 patients nine of whom had gastrointestinal disturbance, mostly of mild degree. With both drugs the infant was apparently unaffected and Apgar scores were satisfactory. Uterine hypertonus was not observed and the postpartum blood loss was within normal limits.

Introduction

Recent clinical trials with prostaglandins E₂ and F_{2α} have established their efficacy in inducing labour when administered by continuous intravenous infusion (Karim *et al.*, 1968, 1970; Beazley *et al.*, 1970; Embrey, 1970; Karim, 1970.) It has also

been reported (Karim, 1971; Karim and Sharma, 1971) that these drugs are effective when given by mouth, but the available evidence is scanty and there is as yet no published work on the subject from the Western hemisphere. The present study is of a preliminary trial of the action of both these prostaglandins in the induction of labour when administered by the oral route and reports the results obtained in 24 patients who were studied in detail.

Patients and Materials

Twenty-four patients were included in the series, of whom 10 were treated with prostaglandin E₂ and 14 with F_{2α}. All were at or past term, and the reasons for induction are listed in Table II (E₂) and Table III (F_{2α}). Ages ranged from 21 to 37 years, and all, with the exception of one primigravida, were healthy parous patients whose membranes were intact at the onset of treatment. In all cases the "inducibility" rating of the patient was assessed by the method of Bishop (1964) (see Table I) and

TABLE I—Inducibility Rating—Bishop's (1964) Method

Factor	Score 0	Score 1	Score 2	Score 3	Factor Score*
Dilatation (cm)	Closed	1-2	3-4	5 or more	0-3
Effacement ..	0-30 %	40-50 %	60-70 %	80 % or more	0-3
Station ..	-3	-2	-1, 0	+1, +2	0-3
Consistency ..	Firm	Medium	Soft	—	0-2
Position ..	Posterior	Mid	Anterior	—	0-2
Total score					0-13

*0-5 = unfavourable, 6-13 = favourable.

Queen Mother's Hospital, Glasgow G3 8SH

WALLACE BARR, F.R.C.S., F.R.C.O.G., Consultant Obstetrician and Gynaecologist

W. C. M. K. NAISMITH, M.B., CH.B., M.R.C.O.G., Senior Registrar in Obstetrics and Gynaecology

uterine activity was monitored by external tocodynametry using either a Devices DC5 unit or a Sonicaid FM2 instrument which also provides continuous fetal heart recording. The external method of uterine recording was chosen since it was thought that the alternative method of introducing a cannula within the uterus might itself have contributed to the initiation of labour and so falsified the results. Spontaneous uterine activity was recorded for at least 30 minutes before the prostaglandins were administered and the recordings were continued in all cases until delivery, or until the drug was discontinued. During induction all cases were subject to normal nursing care, and every 15 minutes observations of maternal and fetal well-being were recorded. Blood biochemistry and haematology were recorded before induction and 12 hours post partum. These are described below.

Prostaglandin E₁

PREPARATION AND DOSAGE

Prostaglandin E₁ was prepared immediately before use as an 0.5-mg/ml solution in ethanol, and the appropriate dose was added at the bedside to a convenient quantity of drinking water (about 100 ml) to provide a clear almost tasteless fluid. A test dose of 0.5 mg was followed 30 minutes later by a further test dose of 1 mg. Thereafter, dependent on uterine response, doses of 1 or 1.5 mg were swallowed at intervals of two hours until the patient was considered to be in active labour, as indicated by dilatation of the cervix and by the activity of the uterine muscle as recorded by tocography. At this stage amniotomy was performed.

RESULTS

The results obtained in the 10 cases investigated are shown in Table II. It will be seen that in Cases 1 to 8 orderly uterine activity was readily established and resulted in normal delivery. Fig. 1 shows a tracing which is typical of the findings obtained.

FIG. 1—Typical tocographic tracing.

The time taken from the onset of induction until delivery ranged from 4 hours 27 minutes to 16 hours 47 minutes, with a mean of 11 hours 36 minutes. No patient received more than seven doses (9 mg) of the drug. In Case 8 the supply of prostaglandin became exhausted when the cervix was 6 cm dilated and

Syntocinon infusion was then begun, with delivery ensuing 68 minutes later.

The remaining two cases must be classed as failures. Case 9 had almost continuous vomiting during the course of the attempted induction and it transpired that this patient had behaved similarly throughout her four previous labours. In retrospect she was not a suitable candidate for any kind of oral treatment, and absorption must have been impaired by repeated vomiting. On the following day amniotomy and escalating dosage of intravenous Syntocinon resulted in normal spontaneous delivery after 5 hours 44 minutes.

Case 10 was the only primigravida in the series. Amniotomy with subsequent intravenous Syntocinon infusion had originally been intended and the former was attempted, but proved to be impossible on account of a high tightly-closed cervix and a high free-presenting head. With 0.5-mg aliquots of prostaglandin E₁, regular contractions were induced, but any increase above this dosage produced excessive and irregular uterine activity with transient bradycardia. This is illustrated in Fig. 2. Although

FIG. 2—Case 10. Effect of 1 mg of prostaglandin E₁.

it would seem that the contraction baseline does not return to the normal resting level between contractions, this is an artefact associated with the method of external tocography which was used; there was no evidence of uterine hypertonus. After five doses (5 mg) of prostaglandin E₁ the cervix had dilated sufficiently to allow amniotomy, and thereafter intravenous Syntocinon infusion was begun. However, within eight minutes there was recurrence of excessive uterine activity similar to that seen with the increased dosage of E₁, and this was coincident with fetal bradycardia, the heart rate dropping to 80 beats per minute (see Fig. 3). After 14 minutes the infusion was discontinued

FIG. 3—Case 10. Effect of Syntocinon infusion.

and lower-segment caesarean section performed, securing an active healthy infant. Postnatal pelvimetry showed a very adverse pelvis of android configuration.

TABLE II—Prostaglandin E₁

Case No.	Age	Parity	Maturity (weeks)	Indication for Induction	Inducibility Rating—Bishop	No of Oral Doses	Induction Delivery Interval Hr Min	Amniotomy Delivery Interval Hr Min	Apgar Score 5 min	Mode of Delivery
1	28	3 + 0	41 +	Past dates	4	3	4 27	0 27	10	S.V.D.
2	21	1 + 0	41 +	" "	5	4	11 8	2 36	10	S.V.D.
3	28	1 + 0	41 +	" "	5	4	9 46	1 31	10	S.V.D.
4	34	3 + 1	40	Age	5	6	12 54	4 24	10	S.V.D.
5	23	1 + 0	43	Past dates	9	6	12 19	3 49	8	S.V.D.
6	26	1 + 0	41 +	" "	8	4	9 14	2 24	9	S.V.D.
7	32	2 + 1	40	Rhesus	5	7	16 28	10 58	10	S.V.D.
8	28	1 + 0	40	" "	4	6 (+ Syntocinon)	16 47	11 17	7	S.V.D.
9	36	4 + 0	40	Age	2	6	Failure	—	10	S.V.D.
10	32	0 + 0	40	" "	0	5	Failure	—	10	L.U.S.C.S.

S.V.D. = Spontaneous vaginal delivery. L.U.S.C.S. = Lower uterine segment caesarean section.

SIDE EFFECTS

Maternal.—Apart from Case 9, whose tendency to vomit in labour should probably have excluded her from the trial, no side effects were recorded. The maternal heart rate and blood pressure were unaffected, and in three cases the following laboratory estimations were recorded before and also after treatment. Blood chemistry: serum creatinine, urea, glucose, bilirubin, alkaline phosphatase, S.G.O.T., and S.G.P.T. Haematology: haemoglobin, packed cell volume, white cell count (total and differential), and platelet count. Urine analysis: albumin, sugar, and acetone. Electrolytes: serum sodium, potassium, chloride, and CO₂ content. In no case was there a significant alteration after prostaglandin E₂ therapy. There was no case of abnormal postpartum loss of blood, and no evidence of uterine hypertonicity in any case.

Fetal.—As shown in Table II the Apgar scores at five minutes were all in the satisfactory range. Routine recording of the fetal heart rate throughout labour showed no significant variation except for that described in Case 10.

Prostaglandin F_{2α}

PREPARATION AND DOSAGE

Initially it was attempted to administer prostaglandin F_{2α} in the same manner as prostaglandin E₂—namely, in the form of a draught of water containing the drug—but in the first three patients this produced rapid onset of vomiting and diarrhoea of such severity that the drug had to be discontinued and alternative methods of induction used. These cases have not been included in the series.

Thereafter the drug was administered in capsule form, each capsule containing 5 mg of prostaglandin F_{2α}. A test dose of 5 mg was followed in half an hour by a further dose of 10 mg, and, dependent on uterine response, subsequent doses of 15 mg were administered every two hours until, as with E₂, labour was established and amniotomy was undertaken.

RESULTS

Fourteen patients were treated and the results are shown in Table III. In 12 cases labour was readily established and in all but one resulted in normal delivery, the time from induction to delivery ranging from 3 hours 45 minutes to 14 hours 53 minutes, with a mean of 11 hours 18 minutes. Fig. 4 shows sample recordings of the uterine contractions from Case 12. The exception was Case 13, who responded well to the drug and in 10 hours 30 minutes had reached full dilatation of the cervix, but fetal bradycardia then developed and the head had failed to engage. Caesarean section produced a healthy male child weighing no less than 4.36 kg. In Case 19 prostaglandin F_{2α} was only partially successful, regular contractions being established, but by 18 hours the active phase had not ensued. Thereafter intravenous

Syntocinon was administered and spontaneous delivery occurred 100 minutes later. The remaining case (No. 20) was a failure and the only response to six doses of F_{2α} was distressing diarrhoea. Syntocinon in escalating dosage was then begun, resulting in spontaneous delivery six hours later.

FIG. 4—Case 12. Sample recording of uterine contractions.

SIDE EFFECTS

Maternal.—Mild gastrointestinal disturbance was noted in 9 of the 14 patients treated. This took the form of nausea with occasional vomiting or loose bowel motions. Only one patient (Case 20) was seriously inconvenienced. The usual time of onset of these symptoms was after three to five doses of prostaglandin F_{2α}. There were no other side effects. Blood pressure and heart rate remained unaffected. In 11 of the 14 patients pretreatment and posttreatment blood chemistry, haematology, urine analysis, and electrolytes were evaluated as detailed for prostaglandin E₂. In no case was there significant alteration. There was no abnormal postpartum blood loss and no evidence of uterine hypertonicity during labour.

Fetal.—Observations on the fetal well-being were conducted throughout labour (Table III). Only in Case 13, described above, was there fetal bradycardia, and the Apgar score at five minutes was 2. In the remaining cases the Apgar scores at five minutes were 10 (9 cases), 9 (2 cases), and 8 (2 cases).

Discussion

To the best of our knowledge there have been only two publications describing the clinical use of oral prostaglandins in the induction of labour. In the first of these Karim (1971) explored the effect of these drugs in a small pilot series of six cases, and in the second paper Karim and Sharma (1971) reported on 100 cases, 80 with prostaglandin E₂, of which 79 were successful, and 20 with F_{2α}, of which 16 were successful. In the present series our dosage regimen with F_{2α} was closely similar to that of Karim and our results were similar, labour being induced successfully in 12 out of 14 cases. However, with E₂, despite a considerable increase in dosage, we were unable to match the

TABLE III—Prostaglandin F_{2α}

Case No.	Age	Parity	Maturity (weeks)	Indication for Induction	Inducibility Rating—Bishop	No. of Doses of PG F _{2α}	Induction Delivery Interval		Amniotomy Delivery Interval		Apgar Score 5 min	Mode of Delivery
							Hr	Min	Hr	Min		
11	26	1 + 1	41 +	Past dates	6	3	5	33	—	28	10	S.V.D.
12	32	4 + 0	41 +	" "	6	4	6	25	—	22	9	S.V.D.
13	30	1 + 0	42	" "	7	6	10	30	3	55	2	L.U.S.C.S.
14	26	1 + 0	41	" "	4	6	10	55	3	35	9	S.V.D.
15	32	1 + 0	41 +	" "	4	6	10	35	2	20	8	S.V.D.
16	29	4 + 0	41 +	" "	6	3	10	43	—	53	10	S.V.D.
17	37	6 + 0	41 +	" "	6	7	14	53	8	03	10	S.V.D.
18	24	1 + 0	40	Pre-eclampsia	8	3	3	45	—	30	10	S.V.D.
19	26	1 + 1	42	Past dates	6	7	19	45	13	30	10	S.V.D.
20	32	1 + 0	40	Pre-eclampsia	3	6	17	13	10	03	10	S.V.D.
21	21	2 + 0	40	" "	7	6	11	52	3	24	8	S.V.D.
22	34	5 + 1	40	Age	5	6	9	59	3	04	10	S.V.D.
23	23	1 + 0	42	Past dates	4	8	14	35	7	35	10	S.V.D.
24	32	4 + 1	41 +	" "	5	4	5	43	No amniot.	10	10	S.V.D.

high success rate of Karim as we had two failures in 10 cases. Moreover, all but one of our patients were parous, whereas two-thirds of Karim's group were primigravidae. It may be that persistence with the drug for a longer time would have ultimately brought success, and Karim described a case in which prostaglandin E₂ was given in repeated doses of 0.5 to 1.5 mg over a period of two days.

We do not feel that it is justifiable to persist with any single method of induction for more than six to eight hours, and if labour has not been established within that time then alternative methods of induction should be sought. However, with further experience of these drugs it is probable that more effective dose schedules will be evolved without loss of safety to mother or infant. Neither drug seemed to have an adverse effect on mother or infant, but with F₂α vomiting and diarrhoea occurred in most cases and this might prove to be a limiting factor in the number of doses administered.

It was also noted that the small number of patients who failed to respond to prostaglandin and were subsequently treated with intravenous infusion of Syntocinon proceeded rapidly to delivery. This supports the theory, at present under investigation, that there may be a synergistic action between these drugs.

In conclusion, there is no doubt that prostaglandins E₂ and F₂α, given by mouth, are often effective in inducing labour. Extensive trials are now in progress and it remains to be seen

what role they will ultimately assume in the search for the ideal induction agent, which must be safe, effective, and convenient to use.

We are indebted to Dr. Margaret Lawson, who gave unstintingly of her time and energy to monitor these patients during labour. We also thank Mrs. Davidson and her staff in the labour suite of the Queen Mother's Hospital, and Mr. Sheerlaw, the hospital pharmacist, and his staff, who prepared the drugs for oral administration. Our thanks are also due to our consultant colleagues for permission to include patients under their care in the trial and to Messrs. Upjohn Ltd., who supplied the prostaglandins.

References

- Beazley, J. M., Dewhurst, C. J., and Gillespie, A. (1970). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 77, 193.
 Bishop, E. H. (1964). *Obstetrics and Gynaecology*, 24, 266.
 Embrey, M. P. (1970). *British Medical Journal*, 2, 256.
 Karim, S. M. M. (1970). Conference on Prostaglandins, New York Academy of Sciences.
 Karim, S. M. M. (1971). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 78, 289.
 Karim, S. M. M., Hillier, K., Trussell, R. R., Patel, R. C., and Tamusange, S. (1970). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 77, 200.
 Karim, S. M. M., and Sharma, S. D. (1971). *British Medical Journal*, 1, 260.
 Karim, S. M. M., Trussell, R. R., Patel, R. C., and Hillier, K. (1968). *British Medical Journal*, 4, 621.

Amniotomy and Oral Prostaglandin E₂ Titration for Induction of Labour

IAN CRAFT

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Summary

The efficacy of oral prostaglandin E₂ used on a titration basis in association with amniotomy for the induction of labour was investigated in a series of 50 patients. Induction was successful in 29 out of 32 primigravid and 17 out of 18 multigravid patients. The mean induction-delivery intervals in successful cases were 10½ and 6 hours respectively. There were no significant effects on the fetuses.

Introduction

The induction of labour by the intravenous infusion of prostaglandins is now well documented (Karim *et al.*, 1968; 1970; Beazley *et al.*, 1970; Embrey, 1970; Karim, 1970). Other studies have compared the effectiveness of using prostaglandin E₂ with oxytocin administered by this route (Beazley and Gillespie, 1971; Craft *et al.*, 1971; Karim, 1971).

Karim and Sharma (1971) reported the induction of labour with oral prostaglandins. This was successful in 79 out of 80 patients treated with prostaglandin E₂ and in 16 out of 20 patients treated with F₂α. There were no serious side effects. Amniotomy was not performed at the outset in this study.

Since current obstetric practice is tending to favour an active approach to induction consisting of membrane rupture and simultaneous oxytocic stimulation, a study was undertaken into

the efficacy of oral prostaglandins used on a titration basis in association with amniotomy. Initially prostaglandin F₂α capsules were used but because of gastrointestinal side effects and limited success experienced with this formulation it was discontinued. This paper reports the results of using prostaglandin E₂ orally in association with amniotomy in a series of 50 patients requiring induction.

Patients and Methods

The patients, who were unselected, were induced at or near term for a variety of reasons. Their inclusion in this study was based solely on their willingness to act in a volunteer capacity and not on other factors known to affect the outcome of induction—for example, favourability of the cervix, descent of the presenting part, maturity, etc. Of the total, 32 patients were primigravid and 18 multigravid. The presentation was cephalic in each instance, including three cases of multiple pregnancy.

A standard method of induction was undertaken by me in each subject. After premedication with intravenous diazepam 10 mg forewater rupture was performed. At the same time a prelabour score (Bishop, 1964), indicating an inducibility rating, was assessed by noting the state of the factors recorded in Table I. No factor was given extra weighting in the calculation of this score. Simultaneously oral prostaglandin E₂ was begun according to the titration schedule described below.

The progress of labour was assessed by noting the strength and frequency of uterine contractions, alteration in the state of the cervix, and descent of the presenting part. Vaginal examinations were performed every four hours as a routine, and at intervals between to confirm full dilatation if suspected, usually by the same observer. Initially uterine contractions and fetal heart recordings were monitored continuously throughout

Department of Obstetrics and Gynaecology, Kingston Hospital, Kingston, Surrey
 IAN CRAFT, F.R.C.S., M.R.C.O.G., Senior Registrar