The coefficient of variation for the partial body activation technique used in the present study was assessed by repeated measurements of anatomical specimens and for clinical studies is between 4% and 5% (Catto *et al.*, 1973 a). The technique may be a more sensitive indicator of the rate of progression or of improvement in renal bone disease than either skeletal radiography or photon absorption by a radius (Catto *et al.*, 1973 b). Thus it was thought that this method of activation analysis might be of value in assessing the efficacy of 1α -OHCC in promoting the remineralization of diseased bone.

The three patients in this study were selected from a group of patients on maintenance haemodialysis currently being investigated by activation analysis; selection was based on both the histological features of osteomalacia observed in the bone biopsy samples and the rapid rate of skeletal demineralization quantified by the activation technique during the 18 months before treatment started (see fig.). Treatment with 1α -OHCC has now been evaluated for three months; the reversal of the demineralizing process in all three patients studied is a significant result (table III).

The patients, who all received oral calcium supplements, ingested only relatively small quantities of calcium in their usual diets. This has been noted previously in patients with chronic renal failure (Coburn *et al.*, 1973). Brickman *et al.* (1972) reported that 2.5 μ g synthetic 1,25-dihydroxycholecalciferol given parenterally to four patients with renal insufficiency increased calcium absorption from the gastrointestinal tract. Similar results were obtained when 1α -OHCC was administered intravenously in a daily dose of 10 to 30 μ g (Chalmers *et al.*, 1973) and by mouth in a dose of 25 μ g a day (Peacock *et al.*, 1974). We have shown that 1α -OHCC in a dose of only 1 to 2 μ g daily is effective in promoting both calcium absorption from the gastrointestinal tract and deposition of calcium in bone.

In case 3, in which the largest increase in calcium absorption on treatment with 1α -OHCC was recorded, symptomatic hypercalcaemia developed. The rapid reduction in plasma calcium concentration to normal levels when therapy was temporarily stopped is of clinical importance as it may indicate that the toxic effects of inadvertent overdosage are of short duration. If confirmed this would represent a substantial advantage over conventional vitamin D therapy.

Neutron activation analysis is the only non-destructive method which measures specifically calcium in vivo. Assessed

by this technique 1α -OHCC administered by mouth in a dose of 1 to 2 μ g daily produced an increase in the calcium content of bone in three patients on maintenance haemodialysis. This suggests that 1α -OHCC may be an effective treatment for the metabolic bone disease associated with chronic renal failure.

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References

- Anderson, J., *et al.* (1964). *Lancet*, 2, 1201.
 Boyle, I. T., *et al.* (1972). *Endocrinology*, 90, 605.
 Brickman, A. S., Coburn, J. W., and Norman, A. W. (1972). *New England Journal of Medicine*, 287, 891.
 Brickman, A. S., and Norman, A. W. (1973). *Kidney International*, 4, 161.
 Catto, G. R. D., McIntosh, J. A. R., and MacLeod, M. (1973 a). *Physics in Medicine and Biology*, 18, 508.
 Catto, G. R. D., *et al.* (1973 b). *Lancet*, 1, 1150.
 Chalmers, T. M., *et al.* (1973). *Lancet*, 2, 696.
 Coburn, J. W., Hartenbower, D. L., and Massry, S. G. (1973). *Kidney International*, 4, 96.
 Cohn, S. H., *et al.* (1972). *Journal of Laboratory and Clinical Medicine*, 79, 978.
 Davies, J. L., *et al.* (1973). *Clinical Chemistry*, 19, 411.
 DeLuca, H. F. (1973 a). *New England Journal of Medicine*, 289, 359.
 DeLuca, H. F. (1973 b). *Kidney International*, 4, 80.
 Dent, C. E., Harper, C. M., and Philpot, G. R. (1961). *Quarterly Journal of Medicine*, 30, 1.
 Fletcher, R. F., Jones, J. H., and Morgan, D. B. (1963). *Quarterly Journal of Medicine*, 32, 321.
 Fraser, D. R., and Kodicek, E. (1970). *Nature*, 228, 764.
 Fremlin, J. H. (1972). *Seminars in Nuclear Medicine*, 2, 86.
 Harrison, R. G., Lythgoe, B., and Wright, P. W. (1973). *Tetrahedron Letters*, 37, 3649.
 Henderson, R. G., *et al.* (1974). *Lancet*, 1, 379.
 Holick, M. F., *et al.* (1973). *Science*, 180, 190.
 Lucas, R. C. (1883). *Lancet*, 1, 993.
 Mawer, E. B., *et al.* (1973). *Lancet*, 1, 626.
 Nelp, W. B., *et al.* (1970). *Journal of Laboratory and Clinical Medicine*, 76, 151.
 Ogg, C. S. (1973). *Kidney International*, 4, 168.
 Pak, C. Y. C., *et al.* (1972). *Endocrinology*, 35, 261.
 Peacock, M., Gallagher, J. C., and Nordin, B. E. C. (1974). *Lancet*, 1, 385.
 Stanbury, S. W. (1957). *British Medical Bulletin*, 13, 57.
 Tripp, E. J., and MacKay, E. H. (1972). *Stain Technology*, 47, 129.
 Virchow, L. (1855). *Virchow's Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*, 8, 103.
 Williams, J. A., and Nicholson, G. I. (1963). *Lancet*, 1, 1408.

Prostaglandin E₂ Tablets Compared with Intravenous Oxytocin in Induction of Labour

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Summary

Stimulation of uterine activity after amniotomy has been carried out with prostaglandin E₂ (PGE₂) tablets in two dosage regimens and with intravenous oxytocin. Oxytocin stimulation was the most successful. The difference in success rate was most marked in nulliparous patients and those with a low Bishop score.

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Introduction

The active management of labour with the use of oxytocics to shorten the first stage is rapidly becoming an accepted obstetric practice (Studd, 1973). Prostaglandins E₂ and F₂α have been used as an alternative to oxytocin by the intravenous and, recently, oral routes (Craft, 1972; Kelly *et al.*, 1973). Oral agents are easier to administer than intravenous preparations, do not require pump equipment, and allow the midwife more time for nursing and for monitoring both mother and fetus.

With the introduction of a stable tablet preparation of prostaglandin E₂ (PGE₂; Prostin E₂ dinoprostone) a prospective study was designed to determine its place in the active management of labour.

Materials and Methods

All patients undergoing induction of labour who consented

TABLE I—Results of Induction

	All Cases			Nulliparous			Multiparous			Bishop Score 5 or Under			Bishop Score 6 or Over		
	No. of Patients	Successes		No. of Patients	Successes		No. of Patients	Successes		No. of Patients	Successes		No. of Patients	Successes	
		No.	%		No.	%		No.	%		No.	%		No.	%
Constant dose of PGE ₂	57	46	80.7	30	22	73.3	27	24	88.9	32	23	71.9	25	23	92.0
Escalating dose of PGE ₂	43	37	86.0	16	10	62.5	27	27	100.0	21	16	76.2	22	21	95.5
Oxytocin	51	49	96.0	22	21	95.5	29	28	96.6	25	23	92.0	26	26	100.0

were entered into the trial provided that the following criteria were met: the fetal membranes were intact, the fetus was alive, and the patient was not in labour.

The treatment groups were allotted on a fortnightly basis, the inductions one week being accelerated with PGE₂ tablets and in the other week with intravenous oxytocin. The first week's treatment was chosen at random.

Induction was performed by low amniotomy followed by PGE₂ or oxytocin.

PGE₂ was administered in either constant dosage or incremental dosage. With the first of these the patient received 0.5 mg (1 tablet) PGE₂ at amniotomy and hourly thereafter throughout labour. With the incremental dosage the patient was given 0.5 mg PGE₂ at amniotomy and a further 0.5 mg one hour later; two hours after amniotomy she was given 1 mg (2 tablets), and this was repeated at three hours. In this manner the dosage was increased by 0.5 mg every second hourly dose until a maximum of 2 mg (4 tablets) was reached six hours after amniotomy, and this dosage was continued hourly throughout labour.

Oxytocin was given intravenously either with a Cardiff pump or by conventional gravity-feed infusion starting at 2 mU/min and doubling the dose every quarter of an hour.

With both incremental regimens enough drug was given to produce adequate uterine contractions and the dosage then continued at that level.

The following observations were made: the Bishop score of the cervix at amniotomy (Bishop, 1964), the time interval between amniotomy and regular contractions, the time interval between amniotomy and full dilatation of the cervix, the Apgar score at one and three minutes, any third-stage complications, and any side effects of the uterine stimulants.

Patients were withdrawn from the trial if they suffered from nausea which failed to respond to metoclopramide 10 mg intramuscularly, if vomiting occurred twice in any half-hour, or if they developed diarrhoea.

Induction was deemed to have failed when the cervix did not reach 6 cm of dilatation within 24 hours of amniotomy.

Results

EFFECT ON UTERINE ACTIVITY

Of the 151 patients studied 132 reached 6 cm or more of cervical dilatation within 24 hours of amniotomy. The overall success rate was highest in the oxytocin group and lowest in patients on the constant dosage PGE₂. The difference in success rate was most marked in primigravid patients and those with a low

Bishop score ("the unfavourable cervix"). In each case both prostaglandin regimens were inferior to oxytocin (table I).

Details of the failures are set out in table II. Neither of the failed cases in which oxytocin was used could be attributed to the method of uterine stimulation. The caesarean section rate in the series was 5.3%.

Those patients in whom labour was successfully stimulated did equally well whether the escalating PGE₂ dosage regimen or oxytocin was used, and there was a statistically significant difference ($P < 0.001$) between these two groups and the patients on the constant PGE₂ dosage. Parous patients and those with a Bishop score of 6 or over fared significantly better ($P < 0.001$ and $P < 0.001$ respectively) than the primigravid patients and those with a low Bishop score respectively whatever method of stimulation was tested (table III).

TABLE II—Patients in Whom Induction Failed

Case No.	Parity	Bishop Score	Result
<i>Prostaglandin: Constant Dose</i>			
1	0	3	Dilated 5 cm at 24 h. Then oxytocin. No further progress. L.S.C.S.
2	0	3	Fetal distress. L.S.C.S.
3	1	11	Fetal distress. (S.F.D.) L.S.C.S.
4	4	N.R. (less than 5)	Dilated 3 cm at 24 h. Then oxytocin and vaginal delivery
5	1	7	Dilated 4–5 cm at 24 h. Then oxytocin and vaginal delivery
6	0	3	Dilated 2–3 cm at 24 h. Then oxytocin and vaginal delivery
7	0	3	Dilated 4 cm at 24 h. Then oxytocin and vaginal delivery
8	0	4	No cervical dilatation on PGE ₂ or oxytocin. L.S.C.S.
9	0	5	Dilated 4 cm at 24 h. Then oxytocin and vaginal delivery
10	0	3	Dilated 2 cm at 24 h. Oxytocin and vaginal delivery
11	0	3	Dilated 4 cm at 24 h. Then oxytocin and vaginal delivery
<i>Prostaglandin: Incremental Dose</i>			
12	0	4	No progress (elderly primipara). L.S.C.S. at 6 h
13	0	5	No contractions after 6 h on PGE ₂ . Then oxytocin and vaginal delivery
14	0	9	Oxytocin at 10½ h because of vomiting. Vaginal delivery
15	0	2	Dilated at 4 cm 24 h. Oxytocin and vaginal delivery
16	0	4	Dilated 3 cm at 23 h. Brow. L.S.C.S.
17	0	1	Dilated 3–4 cm at 24 h. Then oxytocin and vaginal delivery
<i>Oxytocin</i>			
18	3	4	Previous L.S.C.S. Breech presentation and Rh-negative with antibodies. Dilated 5 cm at 16 h. L.S.C.S.
19	0	2	L.S.C.S. at 5 h of fetal distress

N.R. = Not recorded.
L.S.C.S. = Lower segment caesarean section.
S.F.D. = Small for dates

TABLE III—Mean Times to Full Dilatation in Successful Cases

	Constant Dose PGE ₂		Incremental Dose PGE ₂		Oxytocin	
	No. of Patients	Mean Time (Hours) ± S.E.	No. of Patients	Mean Time (Hours) ± S.E.	No. of Patients	Mean Time (Hours) ± S.E.
Total group	46	10.5 ± 0.89	37	6.6 ± 0.59	49	8.1 ± 0.65
Nulliparous	22	12.3 ± 1.45	10	8.9 ± 1.41	21	9.4 ± 1.01
Multiparous	24	8.8 ± 0.98	27	5.8 ± 0.55	28	7.1 ± 0.82
Bishop score 5 and under	23	10.9 ± 0.91	16	7.5 ± 1.01	23	10.9 ± 1.02
Bishop score 6 and over	23	10.0 ± 1.54	21	5.9 ± 0.68	26	5.6 ± 0.46

TABLE IV—Mean Times to Regular Contractions

	Constant Dose PGE ₂		Incremental Dose PGE ₂		Oxytocin	
	No. of Patients	Mean Time (Hours) ± S.E.	No. of Patients	Mean Time (Hours) ± S.E.	No. of Patients	Mean Time (Hours) ± S.E.
Total group	56	2.9 ± 0.34	42	1.7 ± 0.21	50	2.0 ± 0.19
Nulliparous	29	3.5 ± 0.61	15	2.2 ± 0.41	21	1.9 ± 0.33
Multiparous	27	2.2 ± 0.23	27	1.5 ± 0.23	29	2.0 ± 0.24
Bishop score 5 and under	31	3.1 ± 0.51	20	1.5 ± 0.33	24	2.1 ± 0.31
Bishop score 6 and over	25	2.5 ± 0.44	22	1.9 ± 0.28	26	1.8 ± 0.24

The interval between amniotomy and the onset of regular contractions showed a similar pattern, with little difference between the escalating PGE₂ dosage regimen and oxytocin; patients in both these groups exhibited a more favourable trend than that in patients on the constant PGE₂ dosage (table IV).

FETAL STATE

There was no difference in the Apgar scores of the infants at one and three minutes. There was one unexplained intrapartum fetal death in the incremental PGE₂ group but no association with the method of uterine stimulation could be shown. Induction was performed at 41 weeks because of a previous twin stillbirth. The first stage of labour lasted nine hours. The second stage lasted 15 minutes, during which the fetal heart was not heard, and a 4150-g infant was delivered which could not be resuscitated. The necropsy report was: "Intrapartum death, no cause found."

SIDE EFFECTS

On the constant dose regimen of PGE₂ five patients (8.8%) were nauseated but none vomited, whereas during the administration of the escalating regimen one patient was nauseated and four vomited (11.6%). Two patients (3.9%) were nauseated with oxytocin. No patient had diarrhoea. There was no difference in the rate of third stage of labour complications between the three groups.

REACTIONS OF NURSING STAFF

The midwifery staff generally commented favourably on the escalating PGE₂ dosage and appreciated the ease of administration of the tablets and the simplicity of the regimen.

Discussion

It is now generally accepted that artificial rupture of the membranes followed by intravenous oxytocin in rapidly escalating dosage is an efficient and rapid method of inducing labour and ensuring the delivery of a healthy infant. (Anderson *et al.*, 1968; Turnbull and Anderson, 1968 a, b). The advent of oral prostaglandin tablets with their greater ease of administration

has raised the question whether oxytocin is the optimal agent for uterine stimulation.

Oral prostaglandins E₂ and F_{2α} have been used to induce labour (Karim, 1971; Karim and Sharma, 1971; Barr and Naismith, 1972; Craft, 1972) but only as a fluid preparation, which needs to be freshly mixed and diluted using scrupulously cleaned glassware and syringes. In this study the more stable tablets of PGE₂ were compared with intravenous oxytocin for uterine stimulation. The constant dose regimen of PGE₂ had no advantage over intravenous oxytocin. The escalating regimen, however, though its success rate was not as high overall, had a similar performance to that of intravenous oxytocin in parous patients and those with a favourable Bishop score. It has the advantage of oral administration and the disadvantage of higher cost. The increased efficacy of the escalating dosage regimen of PGE₂ confirms the findings of Friedman and Sachtleben (1974).

We recommend the use of intravenous oxytocin as the method of choice in primigravid patients and those with an unfavourable cervix. In other patients the escalating dosage regimen of PGE₂ and intravenous oxytocin have a similar efficacy. Ease of administration, availability of Cardiff pumps, patients' attitude, and relative cost are factors which may influence the clinician's choice of uterine stimulant after low amniotomy.

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References

- Anderson, A. B. M., Turnbull, A. C., and Baird, D. (1968). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 75, 800.
- Barr, W., and Naismith, W. C. M. K. (1972). *British Medical Journal*, 2, 188.
- Bishop, E. H. (1964). *Obstetrics and Gynaecology*, 24, 266.
- Craft, I. L. (1972). *British Medical Journal*, 2, 171.
- Friedman, E. A., and Sachtleben, M. R. (1974). *Obstetrics and Gynaecology*, 43, 178.
- Karim, S. M. M. (1971). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 78, 289.
- Karim, S. M. M., and Sharma, S. D. (1971). *British Medical Journal*, 1, 260.
- Kelly, J., Flynn, A. M., and Bertrand, P. G. (1973). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 80, 923.
- Studd, J. (1973). *British Medical Journal*, 4, 451.
- Turnbull, A. C., and Anderson, A. B. M. (1968 a). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 75, 24.
- Turnbull, A. C., and Anderson, A. B. M. (1968 b). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 75, 32.