concept spironolactone, an aldosterone antagonist, has been recommended as a therapeutic agent since any potassium-sparing effect, in combination with its known hypotensive properties (Grieble and Johnston, 1962; Hollander, 1963) would theoretically be of especial value in the management of hypertensive patients. Hollander (1963) noted a rise in K_p in thiazide-treated subjects when spironolactone was added. In a different context Talso *et al.* (1963) showed a suggestive increase in K_E with spironolactone therapy in five subjects with periodic paralysis. Our results show that while some K_E reduction does occur in subjects given spironolactone with chlorthalidone, the magnitude of this loss does not appear to be as great as in subjects treated with chlorthalidone alone.

Prescription of potassium chloride as a prophylactic measure to subjects on long-term diuretic therapy is not universally accepted. There is evidence that combined thiazide and enteric-coated potassium preparations may cause small-bowel ulceration and stricture formation (Lindholmer *et al.*, 1964; Lawrason *et al.*, 1965; Morgenstern *et al.*, 1965). Myers *et al.* (1967) studied the effects of high intraluminal K^+ concentration in loops of small intestine at operation and found evidence of cellular injury throughout the bowel wall.

Slow-K, a non-enteric-coated preparation, is stated by the manufacturers (Ciba) to cause a gradual release of potassium from its resin core. It contains potassium as the chloride salt, since coincident chloride deficiency has been shown to prevent full K repletion (Gulyassy *et al.*, 1962). The results show that the addition of Slow-K to subjects on continued chlorthalidone therapy effectively repletes body stores of K without reversal of the hypotensive effects.

These results are not strictly comparable with the C. + T. and C. + S. groups in that the potassium-sparing agent was not added until K_E depletion had been established by previous diuretic administration for 8-15 weeks. They nevertheless provide a useful index of the response to be expected in subjects already on therapy who are found to be hypokalaemic. It should be noted, however, that subsequent effective replacement of body K content is not reflected in restoration to normal of the lowered plasma concentration (Table IV). This provides an interesting, though frustrating, further indication of the lack of correspondence of these two indices as previously noted (Moore *et al.*, 1963; Healy *et al.*, 1970).

No subject in this study developed significant symptoms that could be ascribed to K deficiency. In our previous study also (Healy *et al.*, 1970) urinary concentration and acidification as well as glucose tolerance and plasma insulin levels remained unaltered. While there is therefore no compelling evidence that potassium should be added as a routine prophylactic measure in this type of subject, the avoidance of K depletion may be important in other situations such as hepatic cirrhosis, diabetes mellitus (Wolff and Parmley, 1964), or subjects receiving digitalis preparations (Friedberg, 1966). Either spironolactone or Slow-K would seem to be effective agents. The absence of side-effects and smaller cost of Slow-K therapy appear to make it the treatment of choice.

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In-vivo Response of the Human Uterus to Orciprenaline in Early Labour

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Summary

The effect of orciprenaline on uterine activity in 10 women in early induced labour at term with intact membranes was studied. Nine had uterine contractions in response to intravenous oxytocin and one to prostaglandin E₁. The inhibition of uterine contractility was

dose-dependent. The effective dose varied between 10 and 20 µg/minute. Tachyphylaxis was not observed. The only significant effects noted in the mother were tachycardia and increased pulse pressure and in the fetus a smaller increase in heart rate.

Introduction

Orciprenaline, a resorcylic ethanolamine and beta-adrenergic stimulant, has been shown to stop uterine contractions and possibly to be effective in the treatment of premature labour (Baillie *et al.*, 1970). In that study clinical considerations required that therapeutic levels be attained rapidly. The uterine response to varying doses of orciprenaline and, more especially, to the presence or absence of tachyphylaxis was not

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established. This communication reports further in-vivo studies of these aspects.

Patients and Methods

Ten patients with clinically normal cardiovascular systems in whom labour was being induced were studied. They agreed to take part in the study after the experimental procedure had been explained fully. The cervixes in all patients were effaced and less than 2 cm dilated and membranes were intact. The relevant clinical details are shown in Table I. Intrauterine pressure was recorded by transabdominal intra-amniotic catheter inserted after the possibility of an anteriorly situated placenta had been excluded clinically and ultrasonically. Blood pressure was recorded every 15 minutes by sphygmomanometer. Maternal and fetal heart rates were recorded phonocardiographically.

TABLE I—Clinical Details of Patients

Case No.	Age	Parity	Gestation (weeks)	Indication for Induction	Maternal Weight at Induction (kg)	Fetal Weight at Birth (g)
1	28	1	38	Small for dates	61	2,977
2	30	2	40	Large fetus	105	3,630
3	20	1	41½	Postmaturity	73	3,147
4	39	2	40	Hypertension	60	3,657
5	23	1	39	Hypertension	75	3,926
6	20	0	41	Static weight	67	2,863
7	29	0	40	Hypertension	76	3,979
8	18	0	41½	Postmaturity	95	4,791
9	23	0	40	Settled pre-eclampsia	75	3,232
10	21	0	40	Settled pre-eclampsia	72	3,742

Oxytocin was administered intravenously at a rate sufficient to produce uterine contractions compatible with early established labour—that is, contractions causing a rise of intrauterine pressure of 40–70 mm Hg above resting pressure about every two to three minutes with a uterine activity of a least 150 Alexandria units (El-Sahwi *et al.*, 1967). In one patient prostaglandin E₂ was used.

starting at 5 µg/min and increased until uterine contractions had been abolished for at least 20 minutes. No study exceeded four hours and at the end of this time orciprenaline infusion was stopped, amniotomy performed and oxytocin continued. In each instance maternal and fetal welfare was very closely monitored, both during the course of the study and subsequently until delivery was completed. This supervision included continuous fetal heart rate monitoring. The usual facilities for fetal electrocardiographic analysis and fetal scalp blood biochemical studies were available, but in the event were not

TABLE II—Uterine Activity (Alexandria Units*) at Varying Doses of Orciprenaline

Case No.	Pre- orciprenaline Activity	Orciprenaline (µg/min)					
		5	7.5	10	12.5	15	20
1	315	283	116	60	25	—	—
2	230	102	150	137.5	27.6	—	—
3	312	116	—	21.5	—	—	—
5	293	—	—	22	—	—	—
6	231	105	—	39	—	17.5	—
9	170	128	—	80	—	37.5	26
10	349	142	105	66	70	20	—

*Alexandria units = Number of contractions every 10 minutes × peak above resting intrauterine pressure (mm of mercury) × duration of contraction (minutes).

TABLE III—Relationship of Effective Dose Orciprenaline to Stimulating Dose Exogenous Oxytocin, Pre-orciprenaline Uterine Activity, and Maternal and Fetal Heart Rates at the Effective Dose

Case No.	Effective Dose Orciprenaline (µg/min)	Stimulating Dose Exogenous Oxytocin (mU/min)	Pre- orciprenaline Uterine Activity (Alexandria units)	Heart Rate (beats/min)	
				Maternal	Fetal
1	12.5	2.5	315	160 (50*)	160 (10*)
2	12.5	2.0	230	150 (35*)	150 (5*)
3	10.0	1.25	312	100 (30*)	140 (0*)
5	10.0	Prostaglandin E ₂	293	110 (20*)	140 (0*)
6	15.0	5.0	231	140 (70*)	140 (10*)
9	20.0	4.0	170	130 (40*)	150 (30*)
10	15.0	2.0	349	130 (60*)	155 (15*)
Mean	13.57	2.78	271	131 (43.5*)	148 (10*)

*Increase above pre-orciprenaline rate.

FIG. 1—Effect of orciprenaline on uterine activity and on maternal and fetal heart rates.

Thirty minutes after uterine contractions of this amplitude had been achieved and sustained orciprenaline was infused intravenously into two groups of patients to reduce uterine activity to less than 30 Alexandria units while maintaining the previously effective dose of oxytocin or prostaglandin. In the first group (three patients) uterine activity was rapidly reduced to this level and the requisite dose of orciprenaline was continued to establish whether or not tachyphylaxis occurred. In the second group (seven patients) orciprenaline was given

required. All patients were delivered within 10 hours of amniotomy, the average being 6 hours 45 minutes. No maternal or perinatal problem was encountered.

Results

The effect of increasing doses of orciprenaline on a term uterus contracting in response to oxytocin is shown in Fig. 1. The

uterine activity (Alexandria units) at varying doses of orciprenaline in seven patients studied for this effect is given in Table II. Tachyphylaxis was not observed in the three patients studied for 25, 70, and 90 minutes at orciprenaline doses of 18, 20, and 20 $\mu\text{g}/\text{min}$. Uterine activity was reduced to less than 30 Alexandria units. The average steady state uterine activity before orciprenaline was 213 Alexandria units.

The orciprenaline effect on uterine contractility is clearly dose-dependent. Quiescent uterine activity, arbitrarily defined as activity of less than 30 Alexandria units, was achieved at doses of from 10 to 20 $\mu\text{g}/\text{min}$, with a mean of 13.7 $\mu\text{g}/\text{min}$. No difference in orciprenaline effect was observed in the patient contracting in response to prostaglandin E_2 . The significant effects on mother and fetus at the effective dose are shown in Table III.

Discussion

These results confirm that orciprenaline reduces uterine activity and show that this reduction is dose-dependent. Tachyphylaxis was not observed in the three patients studied specifically for this effect. This suggests that the previously recommended 20-minute periods of infusion (Baillie *et al.*, 1970), though clinically convenient, could be extended. The effective dose varied from 10 to 20 $\mu\text{g}/\text{min}$, with a mean of 13.6 $\mu\text{g}/\text{min}$. This dose was not related to the initial uterine activity, oxytocin dose, maternal or fetal weight, gestational age, or indication for induction. This effective dose differed markedly from the mean of 30 $\mu\text{g}/\text{min}$ found effective in premature labour (Baillie *et al.*, 1970). Possibly an excessive dose was administered in that study. Alternatively, premature labour on account of the progressive nature of the labour process (Friedman, 1967) may be less easily stopped. The "hormonal setting" of the myometrium may differ in the two circumstances (Pauerstein and Zauder, 1970).

The difference in effective dose in these two situations illustrates the difficulty in attempting to relate results from the study of one clinical situation to another which is apparently closely analogous. Even more fallacious is the attempt to relate to clinical work findings derived from either in-vitro human

studies or any animal studies whether in vivo or in vitro. This lack of correlation is well established and reviewed (Pauerstein and Zauder, 1970; Pulkkinen, 1970).

Alexandria units were preferred to Montivedeo units as the duration of contraction is taken into account, thus giving a more accurate measure of uterine activity.

Maternal tachycardia and increase in pulse pressure were noted in all patients but presented no problems. The most unpleasant side effect was nausea and vomiting which occurred in three patients at the effective dose after 9, 20, and 22 minutes respectively. This may well limit the period of administration. Further clinical experience has shown that diazepam reduces this distressing symptom.

Some difficulty was encountered in recording the fetal heart rate phonocardiographically at higher infusion rates. This was due to the transmission of abdominal aortic sounds when the maternal pulse pressure was markedly increased. The maternal aortic sounds then obscured the fetal heart sounds so that the maternal pulse rate was recorded instead. In these circumstances the fetal heart rate was auscultated in the usual manner without difficulty.

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Aplastic Anaemia, Acute Myeloblastic Leukaemia, and Oxymetholone

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Summary

Four patients developed acute myeloblastic leukaemia after treatment of aplastic anaemia with oxymetholone. Two had previously shown an excellent clinical response to the drug and a third some improvement. Though no definite causal relationship between therapy and the onset of leukaemia has been established, the number of cases

is greater than might have been expected by chance. The association of the two diseases is discussed.

Introduction

Acute leukaemia arising in patients thought to be suffering from aplastic anaemia has been reported on several occasions (Adams *et al.*, 1951; Block *et al.* 1953; Mohler and Leavell, 1958; Wetherley-Mein, 1960), but it is a rare occurrence, and in the 102 cases of aplastic anaemia reported by Bernard and Najean (1965), the 60 reported by Lewis (1965), and the 45 reported by Israëls and Wilkinson (1961) none developed leukaemia. During the past 10 years only five such patients have been seen in the department of clinical haematology at Manchester Royal Infirmary and four of these occurred in the past 18

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