Preliminary Communications

Treatment of Premature Labour with Orciprenaline

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Summary: The use of orciprenaline, a β -adrenergic agent, in 30 patients with probable premature labour proved to be effective and safe to both mother and fetus under the conditions employed.

INTRODUCTION

Prematurity is the chief cause of perinatal loss in Great Britain (Gruenwald, 1969) and is becoming increasingly important (Baillie *et al.*, to be published). It is also a major cause of neonatal morbidity, and any measure found effective in combating premature labour could have an appreciable beneficial effect. This communication discusses the use in premature labour of orciprenaline (Alupent), a β -adrenergic agent.

PATIENTS AND METHODS

The first 30 patients presenting before the 35th week of pregnancy at the United Oxford Hospitals with painful contractions at least every 10 minutes and a cervical dilatation of less than 3 cm. were treated (Table I). Every primigravida in the series had an effaced cervix. Diazepam 20mg. was administered and if contractions continued orciprenaline was infused in 5% dextrose water at a rate of 2.5 μ g. a minute for five minutes to test for acute sensitivity.

The maternal blood pressure was measured at least every five minutes. Uterine contractions were monitored by an external tocograph and the maternal heart rate was recorded phonocardiographically. For the first few cases the fetal heart rate was also recorded but the only change observed was a tachycardia with higher infusion rates. As the maternal tachycardia produced by the drug limited the rate of infusion, we thought it more relevant to record this rather than the fetal heart rate since only one phonocardiograph was available.

The rate of infusion was rapidly increased to a level sufficient to maintain the maternal heart rate at 130 to 140 beats per minute. This dosage ranged between 12 and 80 μ g. per

stress caused by the uterine contractions produced a maternal tachycardia which did not settle after diazepam, caudal epidural analgesia was carried out before starting orciprenaline.

RESULTS

The treatment was thought to have failed if the patient delivered before 36 weeks' gestation (Table II). Failure was associated with continuing accidental haemorrhage in five cases (four perinatal deaths) and with premature rupture of membranes in three (one neonatal death). In only one case was failure not associated with premature rupture of membranes or accidental haemorrhage. This failure occurred early in the series and in addition to delay in starting treatment inadequate dosage was administered.

DISCUSSION

Orciprenaline undoubtedly stops uterine contractions (see Chart), and was chosen rather than other β -adrenergic agents

Effect of orciprenaline (2 mg. in 350 ml. of dextrose) at 80 and 150 drops per minute on maternal pulse rate and uterine contractions.

TABLE I

Gestational Age	Age			Parity			Aetiology			
	20	20-30	30	0	1-4	5	Accidental Haemorrhage	Premature Rupture of Membranes	Idiopathic	Other
< 28 weeks	1	5	—	5	1	—	3	2	1	2*†
28-31 "	2	12	2	8	5	3	5	2	7	
32-35 "	2	5	1	5	2	1	2	0	6	
Total	5	22	3	18	8	4	10	4	14	2

*Placenta praevia. †Amniocentesis.

TABLE II

Gestational Age	No.	Delivery < 36 weeks	Perinatal Deaths
< 28 weeks	6	2	3
28-31 "	16	12	3
32-35 "	8	7	0
Total	30	21	6

minute, with an average of 30 μ g., and was maintained for 20 minutes. The contractions usually stopped immediately. If they recurred the infusion was restarted for a further course. The maximum number of courses in 24 hours was three. If dis-

because of the good therapeutic index (Brugger *et al.*, 1966) and lack of rebound effect. More effective agents will probably be developed (Brugger *et al.*, 1968). The toxic effects of sympathomimetic agents appear to be related to the degree of peripheral vasospasm produced (Lands and Brown, 1967). Hypertension was not encountered among our patients, the only alteration of blood pressure being a widening of pulse pressure without an appreciable effect on the systolic pressure. The maximum decrease in diastolic pressure was 30 mm. Hg. The possibility of maternal tachycardia proceeding to ventricular fibrillation is academic in the case of β -adrenergic agents, as they are used in the management of this condition when associated with hypotension (Corday *et al.*, 1965). They are probably effective by virtue of the increase in coronary artery flow. Two patients complained of palpitations and one of a choking sensation—symptoms which were rapidly abolished by decreasing the dosage. One patient developed a migrainous type of headache.

Maternal distress producing tachycardia limits the dosage of orciprenaline. In two cases with severe maternal distress caudal analgesia was effective in reducing the maternal pulse rate and therefore enabled us to increase the dosage of orciprenaline to therapeutic levels. We feel it important to emphasize that a therapeutic dosage of orciprenaline should be attained within two minutes of excluding idiosyncrasy.

The importance of this factor became more apparent as the series progressed, as lower doses were ineffective. Experience showed that after 20 minutes of administration a bradycardia, possibly a vagal reflex, commonly supervened.

Furthermore, tachyphylaxis, a widespread phenomenon among sympathomimetic agents (Goodman and Gilman, 1965), may well have manifested itself. This was difficult to prove in our cases because of the lack of a steady state. Tachyphylaxis may account for the success of intravenously administered isoxsuprine as compared with other routes of administration; the former route would tend to be used for a much shorter period. Orciprenaline is, however, a far more effective drug.

Fetal tachycardia occurred with higher infusion rates. The overall effect of orciprenaline may well be to improve the fetal condition, either by increasing the fetal cardiac output (Rudolph, 1969) or by decreasing the stress of contractions (Caldeyro Barcia *et al.*, 1969). Other workers have noticed no alteration of the fetal heart rates with β -adrenergic agents (Wansbrough *et al.*, 1968). Caesarean section became necessary in one case for an increasingly severe accidental haemorrhage at 31 weeks of gestation. No difficulty was encountered with either anaesthesia or haemostasis. The infant was delivered in good condition and has thrived.

With one exception the treatment failed because of either increasing accidental haemorrhage or premature rupture of membranes. Labour is unlikely to be arrested under these circumstances. This has been noted in the case of alcohol (Fuchs *et al.*, 1967).

Caution is necessary in interpreting the results of this preliminary series. The evidence suggests that orciprenaline can stop uterine contractions and may arrest the progress of premature labour. A controlled trial is indicated, but the ethics of depriving the "controls" of what appears to be an effective form of therapy will have to be carefully considered.

The major difficulty of such a trial would be the definition of the onset of labour.

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Medical Memoranda

Metabolic Findings in a Patient with Hyperosmolar Non-ketoacidotic Diabetic Stupor

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Diabetic hyperosmolar non-ketotic coma has been recognized with increasing frequency since it was first described over a decade ago (de Graeff and Lips, 1957; Sament and Schwartz, 1957). In the case described below we had the opportunity of measuring a wide range of biochemical and hormonal values during the acute stage before treatment. We feel that our findings may warrant a reconsideration of currently held views on the development of this disorder.

CASE REPORT

The patient, a 50-year-old man, was admitted to hospital with symptoms of dyspnoea, lethargy, and weakness. He confessed to a heavy consumption of alcohol for several years before presentation but gave no previous or family history of diabetes. On examination he was in mild congestive cardiac failure with atrial fibrillation; blood pressure was 150/100. He had Dupuytren's contracture of both hands and the liver was palpable 8 cm. below the costal

margin. Glycosuria was not detected at this stage. He was given digoxin, frusemide, and potassium supplements, with good initial clinical response.

Two weeks later, during a morning ward round, he had become drowsy and confused, and frequent twitching of the extremities was seen. The tongue was dry but the skin texture was normal, as was his respiration. A random blood sugar test was reported to show greater than 1,000 mg./100 ml., and the urine contained sugar 2 g./100 ml. but no ketones. Therapy with intravenous hypotonic saline and insulin was now started.

Laboratory findings on the blood samples were as follows: haemoglobin 17.6 g./100 ml.; haematocrit 57%; white cell count 6,900/mm.³; blood sugar 1,075 mg./100 ml.; urea 100 mg./100 ml.; serum sodium 135 mEq/l.; potassium 5.8 mEq/l.; chloride 97 mEq/l.; CO₂ content 20 mEq/l.; osmolarity 373 m-osmole/l.; amylase 1.9 i.u. Plasma ketones absent, plasma immunoreactive insulin 0 μ -u./ml. (mean value in this laboratory for fasting immunoreactive plasma insulin is 9 μ -u./ml. in normal adults). Plasma growth hormone (radioimmunoassay) 4.4 ng./ml., cortisol 37.5 μ g./100 ml., plasma free fatty acid (Duncombe method) 610 μ Eq/l.

During the first 18 hours he received 2 litres of hypotonic saline intravenously and about 2 litres of water by mouth; also 140 units of insulin intravenously. The blood sugar fell to 170 mg./100 ml. and the serum osmolarity to 320 m-osmole. This was accompanied by noticeable improvement in his general condition. Insulin requirements declined gradually over the next few weeks and he was finally discharged on an oral hypoglycaemic agent. This has resulted in satisfactory control to date. Before his