SALBUTAMOL, A BETA$_2$ SYMPATHOMIMETIC DRUG, IN PRETERM GESTATION

by

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SUMMARY

Clinical treas of Salbutomol was tried in 36 cases in gestations of 36 weeks or less. Its effectiveness is limited to a cervical dilatation of 3 less than 3 cms. The lung maturing effect of Salbutamol affers for improved perinatal survival.

Preterm parturition and the associated respiratory distress syndrome (RDS) are the leading causes of neonatal morbidity and mortality. Various tocolytic agents such as the beta$_2$ sympathomimetic drugs have been shown to reduce preterm and term uterine contractions and thus inhibit premature labour (Das, 1969, Csapo, and Herczeg, 1977, Bergman and Hedner, 1978; Epstein et al, 1979; Merkatz et al 1980). Clinical trials of salbutamol, a beta$_2$ sympathomimetic agent, have suggested that it is safe and effective in delaying preterm births (Ryden, 1977; Thomas et al, 1977; Lipshitz et al, 1976; Rajan et al, 1983; and Sreedevi and Rajan, 1983).

Whereas labour inhibition and prolongation of pregnancy by salbutamol treatment is instrumental for a substantial reduction in perinatal morbidity and mortality, it has been observed that incidence of RDS is greatly reduced in premature infants born of mothers treated with this agent (Ryden, 1977). This observation is quite encouraging, since even if labour inhibition is not effected by beta$_2$ stimulants in all subjects, their administration for less than 24 hours promote adequate lung maturity and prevent the development of RDS in the premature infants (Hedner, 1978). The mechanism by which beta-agonists prevent RDS is unknown. That lung maturity is achieved within 24 hours of initiation of treatment implies that a mechanism other than stimulation of surfactant synthesis is responsible for this beneficial role. It has been observed that beta-agonists significantly increase the air volume at equivalent low transpulmonary pressures, an effect consistent with increased surfactant activity (Bergman and Hedner, 1978). Walters and Olver (1978) have shown that both epinephrine and isoproterenol by virtue of their beta-adrenergic

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activity inhibit lung liquid secretion and initiate lung liquid absorption and thus promote lung maturity.

Just as in the myometrium, $beta_2$ adrenergic receptors are prevalent in the blood vessels, bronchioles and diaphragm. While the smooth muscle relaxation effect on the uterus is responsible for effective inhibition of preterm labour, the incidental vasodilatation results in certain cardiovascular adjustments. The reduced uterine contractions improve the uterine blood flow. In addition, the decrease in peripheral resistance by vasodilatation that would result in an increased stroke volume of the heart, a widened pulse pressure and tachycardia with an increase in cardiac output would also increase the uteroplacental blood flow. In effect the $beta_2$ mimetic drugs promote improved uteroplacental blood flow and allow for foetal growth and prevents tendency for foetal acidosis and foetal distress, and hence these agents could be employed for the management of acute intrapartum foetal distress (Ariss, 1978; and Lipshitz, 1977).

Moreover, maternal hyperglycaemia (probably from stimulation of hapatic glycogenolysis) and hyperinsulinaemia induced by administration of beta agonists facilitate an increased transfer of glucose to the foetus. This foetal hyperglycaemia induced by salbutamol is also found to be beneficial for the foetus in preventing acidosis and promoting foetal growth.

In effect, administration of salbutamol in preterm gestation has various beneficial effects recommending wider use of the drug, namely (i) inhibition of preterm labour contractions; (ii) promoting pulmonary maturity and reducing the incidence of RDS in premature infants; (iii) improved utero-placental blood flow due to vasodilatation and thus prevent foetal distress and promote foetal growth; and (iv) foetal hyperglycaemia which also promote foetal growth and prevent acidosis.

Materials and Methods

Since December 1981 salbutamol has been included in the therapeutic armamentarium of our obstetric service. Impressed by the effective labour inhibition in preterm gestation and safety of administration in pregnant mothers, we have employed salbutamol for inhibition of preterm labour and also for less defined indications in preterm gestations. In all, 64 patients have been treated with salbuatmol till date for the following preterm gestational problems:

1. *Preterm labours* In gestations of 36 weeks or less where uterin contractions were recorded in 10 minutes or less apart with progressive cervical dilatation and effacement over an observation interval. All patients had intact foetal membranes, and maternal diseases such as taxaemia, heart disease and diabetes were ruled out. There were 18 patients in this group. Duration of pregnancy ranged from 28 to 36 weeks.

2. *Increased uterine contractility in preterm gestation:* Increased uterine contractility must be considered at high-risk for preterm labour until more accurate diagnostic tests for detection of preterm labour can be found (Diakoku and Burnhill, 1980). Cervical dilatation has been shown to occur when uterine contraction pressures exceed 24 mm of HG and at a contraction frequency greater than 11 per hour, (Lindgren, 1973). Hence if painful uterine contractions at a frequency of more than 11 per hour were recorded in preterm gestation we presumed that cervical dilatation will follow

resulting in preterm delivery. This happened to be the indication for employing salbutamol in 26 preterm pregnancies with painful uterine contractions but no cervical effacement or dilatation.

3. *Premature rupture of memranes (PROM)* is considered to be a relative contraindication for labour inhibition with tocolytic agents (Niebel and Johnson, 1980), and premature onset of labour in subjects with intact foetal membrnaes has been considered a prerequisite for considering for labour inhibition employing salbutamol or other beta-2-agonists. However, encouraging results have been reported by employing labour inhibition between 28 to 32 weeks of gestation, with a single foetus, cervical dilatation of 4 cms or less, absent foetal membranes and absence of signs of uterine infection (Christensen *et al*, 1980). Rupture of membranes appears to decrease the incidence of RDS, and if labour can be delayed in premature rupture of membranes by 6 hours in gestations beyond 34 weeks and by 72 hours in gestations less than 34 weeks many premature infants can be saved from development of RDS, (Hobel and Oakes, 1980). Moreover, salbutamol, the tocolytic agent employed to delay labour, by itself promotes lung maturity as indicated earlier. Thus a dual benefit is obtained by administering salbutamol for patients with premature rupture of membranes. Based on these observations we have treated 6 patients with salbutamol, in whom premature rupture of membranes occurred between 28 and 36 weeks of gestation.

.4. *Premature labour in multiple pregnancy*: Eventhough multiple gestation was considered to be acontraindication for labour inhibition (Zlatnik, 1972) it appears safer to treat a false premature labour in multiple pregnancy unnecessarily than to overlook an asymptomatic progress of labour, with the risk of early prematurity and its high perinatal mortality rates (Beiniarz *et al*, 1978). In our series, labour inhibition was attempted in 2 subjects with twin gestation at 34 weeks and 38 weeks.

5. *A.P.H. (suspected placenta praevia)*: When abruptio placenta is excluded, in suspected cases of placenta praevia it is always advantageous to have the pregnancy prolonged to reasonable maturity. If the patient is not exposed to the risk of profuse bleeding and hypotension, inhibition of increased uterine activity by salbutamol is a meaningful therapeutic approach. We had 6 patients admitted for APH and treated with salbutamol, of whom 4 turned out to be placenta praevia.

6. *Preterm labour after 36 weeks of gestation*: Since we found salbutanol to be extremely safe in healthy gravidae, eventhough labour inhibition is not essential after 36 weeks of gestation, we considered labour inhibition and prolongation of pregnancy by few more days will add to the maturity of the foetus with no risk to the mother or foetus. In this group there were 6 subjects who were in labour at 37 and 38 weeks of gestation.

8. *Dose Schedule of Salbutamol*: Salbutamol was diluted in 5% dextrose in water, with 2 mg (4 ampoules) in 500 ml, and was administered in the form of a slow intravenous infusion at a rate of 2.5 micrograms per minute (10 drops per minute). The infusion rate was increased by 2.5 microgram per minute (10 drops per minute) every 10 minutes until contractions were abolished, a maximum rate of 25 micrograms per minute (100 drops per minute) was attained or unacceptable side effects ni the form of maternal tachycardia (pulse rate above 140 per minute) occurred. The infusion

was then maintained at the lowest rate to stop contractions, and if contractions were effectively abolished the treatment was continued for 12 hours, if not effective the treatment was continued for 24 hours. If labour progressed inspite of salbutamol, the infusion was discontinued at the earliest opportunity.

The patients receiving salbutamol were carefully monitored for uterine contractions maternal heart rate, blood pressure and foetal heart rate. Eventhough subjects with medical disorders were not included for this study, the patients were carefully monitored for evidence of hypotension, severe tachycardia tremour and pulmonary oedema.

Oral Salbutamol Maintenance: After successful inhibition of preterm labour by beta agonists, oral maintenance therapy is advocated to prevent recurrence of uterine activity and thus prolong gestation (Creasy *et al*, 1980, and Brown and Tejani, 1981). Oral medication with salbutamol was started immediately after completion of the intravenous infusion. The drug was administered in a dose of 4 mgms twice a day and was continued until the 38th week of gestation or the onset of labour. The risk of neonatal hypoglycaemia has to be considered especially if the foetus is born within 48 hours of drug administration or when there is already an increased risk of hypoglycaemia (Epstein *et al*, 1979, and Brazy and Pupkin, 1979). And hence we have discontinued salbutamol therapy after 38 weeks of gestation. However, in many occasions salbutamol was administered till the onset of labour, especially when lalbour had set in prematurily.

Inspite of oral salbutamol maintenance if premature labour recurred the intravenous regime was restarted followed by oral maintenance.

Results and Discussion

1. *Preterm Labours* (Table I) In 18 patients treated for preterm labour between 28 to 36 weeks of gestation, with cervix effected to 50 per cent or more and dilated 1 to 3 cms, all except 3 achieved labour inhibition and prolongation of pregnancy by 2 days or more. Pregnancy could be prolonged by 7 days or more in 11 patients (61.11%). If cervix was dilated more than 2 cms the treatment was unsuccessful, if cervix was 2 cms the treatment was successful (gestation prolonged atleast one week) in 50 per cent, and if cervix was 1 cm the treatment was successful in 77.77% of patients. Two patients had labour recurrence treated by repeat salbutamol infusion, and 5 patients delivered when they were on oral salbutamol

TABLE I

Effect of Salbutamol in Preterm Labour

Cervix effacement	Cervix dilatation	Total patients	Pregnancy prolongation in days						
			nil	2	4	7	10	15	45
50%	1 cm	8	1	7	7	6	3	3	1
50%	2 cms	5	1	4	4	3	2	—	—
100%	1 cm	1	—	1	1	1	1	1	—
100%	2 cms	3	—	3	1	1	1	1	—
100%	3 cms	1	1	—	—	—	—	—	—
Total patients:		18	3	15	13	11	7	5	1
Percentage:			16.7			61.1		27.8	

maintenance. The birth weight of infants ranged from 2 to 3.5 kg, with a mean of 2.7 kg. There was 1 neonatal death in this series, in a primigravid subject treated at 36 weeks gestation and achieved 5 days prolongation where the infant was weighing 2.5 kgs. She was not on oral salbutamol maintenance at the time of delivery.

Interval between drug administration and abolishion of uterine activity ranged from 30 minutes to 12 hours, with a mean of 2.13 hours, and in more than 50% of subjects the contractions were abolished within 1 hour of treatment.

2. *Increased uterine contractility in preterm gestation*: In this group of 26 subjects admitted between 28 and 36 weeks of gestation with painful uterine contractions in a frequency of more than 11 per huor but not associated with cervical effacement or dilatation, increased uterine activity could be inhibited in all except 2 subjects. The treatment was successful, with a prolongation of pregnancy by atleast one week, in 65.38% (Table II). The fact that, inspite of salbutamol, the remaining 34.62% (9 subjects) delivered within 7 days of treatment suggest that all these patients were at high-risk or preterm labour (even though the cervix was not dilated) and in a good percentage (65.38%) pregnancy could be successfully prolonged by salbutamol therapy.

The labour contractions were abolished within 30 minutes to 6 hours of starting the infusion, with a mean of 2.25 hours. Birth weight of infants ranged from 1.25 to 3 kg, with a mean of 2.65 kg. There was one neonatal death in a patient treated unsuccessfully at 28th week of gestation, with the infant weighing 1.25 kg.

The effect of salbutamol in preterm labour in the two groups, one with cervical dilatation and one with no cervical dilatation, appear to be comparable. Labour contractions are abolished in majority of patients, and this effect is obtained within 2 hours of treatment. Pregnancy could be successfully prolonged in about 61 to 65 per cent of patients. The perinatal mortality is low with minimal risk for RDS in the premature neonates.

3. *Premature rupture of membranes*: (Table III) Six patients with premature rupture of membranes were treated with salbutamol. Delivery could be delayed by 24 hours in all subjects, by 48 hours in 4 subjects, and by 4 days or more in 3 subjects. The birth weight of the infants ranged from 1.9 to 3.25 kg, with a mean of 2.44 kg. There were no perinatal deaths in this series. Since all infants could be saved, particularly the premature infant weighing 1.9 kg, it appears that tocolysis by salbutamol has a definite place in the management of premature rupture of membranes.

4. *Multiple pregnancy*. In multiple

TABLE II

Effect of Salbutamol in Increased Uterine Contractility (No Cervical Dilatation)

Patients	Pregnancy prolongation in number of days						
Total: 26	Nil	2	4	7	10	15	45
No. of patients	2	24	20	17	16	13	1
Percentage	7.70	92.30	76.90	65.40	61.50	50.00	3.80

TABLE III
Salbutamol in Premature Rupture of Membranes

Age	Parity	Pregnancy weeks	Labour inhibition (in hrs.)	Labour postponed	Cervix	Remarks
27	nulli parous	34	1	4 days	100% effaced 2 cms dilated	3.25 kg Alive
32	Para I	36	1	4 days	50% effaced 1 cm dilated	2.25 kg Alive
23	Para 4	34	1	8 days	undilated	2.25 kg breech, alive
19	nulli parous	28	nil	2 days	undilated	1.9 kg alive
25	nulli parous	36	1	1 day	50% effaced 1 cm dilated	2.5 kg L.S.C.S. alive
34	nulli parous	38	1	1 day	undilated	2.5 kg L.S.C.S. alive

pregnancy there is an inherent risk of early prematurity and its high perinatal mortality and morbidity rates. Hence, after excluding maternal diseases, it is always safer to treat multiple pregnancies with salbutamol even if it amounts to unnecessary treatment in some with a false premature labour. We have treated 2 subjects with twin pregnancy, 1 at 34 weeks and 1 at 38 weeks of gestation. The former patient had a fully effaced cervix with 1 cm dilatation, and she did not respond to salbutamol and she delivered 9 hours after initiating the treatment. Both babies were born alive and had no problems of RDS. Pregnancy could be prolonged by 15 days in the second patient who delivered the babies (2.25 kg and 2.3 kg) at term with no problem of RDS (Table IV).

TABLE IV
Salbutamol in Multiple Pregnancy

Age	Parity	Pregnancy	Cervical dilatation	Labour inhibition (hrs.)	Labour postponed	Remarks
24	1	34 wks	100% effaced 1 cm dilated	nil	9 hours	both babies alive
28	1	38 wks	nil	1 hr 30 mts.	15 days	both babies alive

5. *A.P.H. (suspected placenta praevia)*: Patients with placenta praevia, if develop increased uterine activity prematurely, stand exposed to the problem of recurrent bleeding episodes and delivery of a premature infant. Both these risks could be minimised by employing tocolysis with salbutamol when increased uterine contractility is observed in these patients. Before considering salbutamol therapy abruptio placenta, severe anaemia and hypovolaemia should be excluded. In the present study 5 of the 6 patients with APH could be successfully treated with salbutamol, and among them placenta praevia was diagnosed in 4 subjects who were delivered by caesarean section. There was no perinatal loss in this group (Table V).

6. *Preterm labour after 36 weeks of gestation*: Eventhough adequate lung maturity for the foetus is attained by 36 weeks of gestation it is always preferable to deliver a foetus as near term as possible, so that it attains maximum maturity. In a healthy gravida if labour could be inhibited and pregnancy prolonged by a drug, the administration of which provides a good margin of safety and other benefits such as improved foetal growth and reduced risk of foetal distress, such a treatment could be recommended even if pregnancy is past 36 weeks. We have treated 6 patients after 36 weeks, and in the successful cases the improved foetal growth was spectacular (Table VI).

Complications of Salbutamol Therapy: Beta-agonists employed for labour inhibition induce maternal hyperglycaemia, hyperinsulinaemia and hypokalameia. These metabolic effects could conceivably have clinical significance in diseased states such as diabetes, hypertension, cardiac problems and bronchial asthma. Tachycardia, tremor, hypotension, myocardial ischaemia and pulmonary oedema are the other potential complications in patients with some cardiovascular predisposition or patients on steroid therapy. Nonetheless, these pharmacological agents are found to be absolutely safe in healthy gravidae, and the only 2 clinically acceptable complications we have encountered in salbutamol treatment were tachycardia and tremor. The drug dose is adjusted so that the heart rate is always

TABLE V

Salbutamol in A.P.H. (Suspected Placenta Praevia)

Age	Parity	Pregnancy weeks	Labour inhibition (hrs.)	Labour post-poned	Remarks
33	nulli parous	36 wks	1 hr. 30 mts.	28 days	Placenta previa L.S.C.S. 3.5 Kg. Alive
22	nulli parous	32 wks	2 hrs.	42 days	Normal 2.5 Kg. Alive
21	nulli parous	36 wks	1 hr.	1 day	Placenta previa 3 Kg. Alive
25	nulli parous	36 wks	30 mts.	30 days	Placenta Previa 3 Kg. Alive
20	Para I	34 wks	1 hr.	47 days	Normal 2.5 Kg. Alive
30	Para I	34 wks	1 hr.	40 days	Placenta Previa 3.25 Kg. Alive

TABLE VI
Salbutamol for Inhibition of Preterm Labour After 36 Weeks

Age	Parity	Pregnancy weeks	Cervical dilatation	Labour inhibition	Labour postponed	Remarks
28	Para 1	37 wks	50% effaced 2 cms dilated	2 hrs	22 hrs	3.6 Kg Alive
22	Para 0	37 wks	5% effaced 2 cms dilated	4 hrs	19 days	3 Kg Alive
25	Para 1	37 wks	100% effaced 2 cm dilated	2 hrs	7 days	3.2 Kg Alive
26	Para 1	38 wks	100% effaced 2 cm dilated	2 hrs	4 days	2.8 Kg Alive
27	Para 0	37 wks	50% effaced 1 cm dilated	1 hr 30 mts	22 hrs	2.75 Kg Alive
23	Para 2	38 wks	nil	1 hr 30 mts	5 days	2.5 Kg Alive L.S.C.S.

below 140 per minute. Frequent monitoring of the patient for the cardiovascular and respiratory status will forestall any complications.

Foetal hyperglycameia may result in neonatal hypoglycaemia and hypokalaemia and hypocalcaemia are the other neonatal complications reported more with isoxsuprine than with the newer beta-agonists (Brazy and Pupkin, 1979). Hypoglyacemia has been particularly reported where the drug was administered till the time of delivery. However, we had only one case of neonatal hypoglycaemia (treated with I.V. glucose) in our series of salbutamol therapy eventhough 15 patients were on salbutamol treatment (I.V. or oral) at the time of delivery. As a precaution, wherever possible, we stop the salbutamol maintenance at the 38th week of gestation.

Conclusion

Salbutamol is an effective tocolytic agent which promptly inhibits preterm labour and allows for prolongation of pregnancy in 60 to 65%. Its effectiveness is limited to a cervical dilatation of less than 3 cms. Preterm increased uterine

contractility with no cervical dilatation carry the potential risk of preterm labour and hence they are also treated with salbutamol with distinct advantages. The lung maturing effect of salbutamol offers for improved perinatal survival in premature infants even if pregnancy prolongation is unsuccessful. Similarly the mild foetal hyperglycemia and improved uteroplacental blood supply promote better foetal growth and reduce the rirsk of foetal acidosis or distress. In general the neonates of the mother who had received a good dose of salbutamol show an improved foetal growth and increased birth weight. Maternal complications in healthy gravidae are clinically acceptable and are limited to tachycardia and tremor. Exxcept one case of neonatal hypoglyeamia (treated successfully) there were no neonatal complications due to salbutamol therapy. Incidence of RDS was low in this series with 2 neonatal deaths (1.25 kg and 2.5 kg) for the total 64 patients treated. Role of salbutamol in premature rupture of membranes, mutiple pregnancy and suspected palcenta praevia is discussed, and in general the results are quite rewarding.

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