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The effect of fenoterol on fetal metabolism: cord blood studies

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Albumin, total protein, total bilirubin, glucose, cholesterol, triglycerides, blood urea nitrogen, alkaline phosphatase and glutamic oxaloacetic transaminase levels were determined in the serum of cord blood of neonates born to mothers previously treated with the betamimetic drug fenoterol. The results were compared with those of untreated controls. More deviations from the control were found if the interval between termination of treatment and delivery was shorter than 48 hours. A longer drug-free interval seems more favourable for the metabolic balance of the newborns. Newborns whose mother has received beta-sympathomimetic tocolytic treatment need careful supervision.

The side-effects of beta-sympathomimetic treatment of imminent premature delivery on the maternal circulation and metabolism are well-known [13, 14]. Less is known about the effects on the fetus or on the neonate born following such treatment. A few papers have already pointed out that newborn babies born during betamimetic treatment, i.e. after unsuccessful tocolysis or following betamimetic therapy applied during labour are prone to metabolic acidosis and hypoglycaemia [1, 5]. These effects may be secondary to maternal effects but also direct effects of the drugs on the fetus may occur, since their passage through the placenta has been confirmed [2, 9, 10, 17].

Thus, it seemed justified to study the fetal effects of betamimetic drugs. We have attempted to clarify whether changes in cord blood composition indicating drug effects on fetal metabolism can be demonstrated following betamimetic tocolysis. We also compared newborns born immediately after tocolysis and those delivered after an interval following completion of tocolytic treatment. Isolated blood samples taken from the umbilical vein and the arteries have also been compared.

Methods

The following metabolic indicators were determined from cord blood: bilirubin, total protein, albumin, serum GOT, alkaline phosphatase, triglycerides, cholesterol, urea nitrogen and glucose. The blood was

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sampled immediately after cutting the cord, before birth of the placenta. Mixed cord blood was obtained after easing the ligation of the cord, paying attention to avoid admixture of maternal blood to the samples. Isolated venous and arterial blood samples were taken by cannulating the corresponding blood vessel of the ligated cord. The blood was centrifuged immediately after clotting, the serum was kept at $-20°C$ until analysis. All measurements were performed by a Technicon MT II Autoanalyser.

Material

1. *Neonates born immediately after tocolysis.* Fifteen babies were born by delivery taking place during the intravenous period of betamimetic treatment or during the oral period of sustained betamimetic therapy, within 48 hours after termination of treatment. Nineteen newborns born by uncomplicated delivery during the same period and after a gestation similar in duration served as controls. The two groups were comparable on the basis of gestational age, birthweight, Apgar-score, and duration of delivery, as tested by the two-sample *t*-test. The mean duration of tocolysis was 25.29 ± 13.42 days, the mean interval between termination of therapy and birth was 30.07 ± 17.40 hours. In these groups isolated venous and arterial blood samples were also collected.

2. *Neonates born later after completion of tocolytic treatment.* Fourteen newborns born after sustained betamimetic treatment and 26 untreated newborns were examined. The mean duration of tocolysis was 24.14 ± 15.92 days and the mean interval elapsing between termination of therapy and birth was 21.00 ± 8.59 days. The treated and control groups were again comparable in respect to the above obstetrical criteria.

Betamimetic treatment with fenoterol was administered in all cases for imminent premature labour. The treatment was introduced by a saturating dose of 2 μg/min given in intravenous infusion, this was followed by a maintenance dose of 1 μg/min over 12—16 hours. Thereafter oral therapy was given with one 5 mg tablet administered every 6—8 hours. In each case the treatment was supplemented with verapamil in an intravenous dose of 40—80 μg/min during intravenous tocolysis, and one 40 mg tablet for each tablet fenoterol. None of the mothers had received glucocorticoid treatment during pregnancy.

Statistical analysis of the data was carried out by the two-tailed *t*-test (Student and Welch).

Results

It has to be stressed in advance that neither clinical observations nor the examinations revealed any symptom ascribable to deranged fetal metabolism. In the group treated with betamimetics, one newborn died, he was severely malformed and died of peritonitis when three days old. All the other newborns were healthy during their six-day stay in hospital and at discharge.

Results are summarized in Table I. In addition to cord blood results, the maternal venous values obtained in Group 2 are also indicated for information. Evaluation of these values or searching for an eventual relationship between the maternal and fetal values was not intended.

Several parameters obtained in the group born immediately after tocolysis, Group I in Table I, were found to be significantly different from the values measured in the control group. In the treated group serum cholesterol ($p < 0.01$) and blood urea nitrogen ($p < 0.05$) were higher, while total protein ($p < 0.001$) and serum albumin ($p < 0.01$) were lower than in the controls. There was a trend for higher blood glucose and lower SGOT in the treated newborns than in the controls ($p \approx 0.05$).

The values of Group 2, the newborns born later after termination of betamimetic therapy, differed less from the control values. The albumin and triglyceride levels of the treated newborns were slightly but significantly lower and the urea nitrogen

TABLE I

Cord blood values of newborns born to mothers treated with fenoterol resp. to untreated mothers

	Group 1		Group 2		
n	treated 15	controls 19	maternal blood 14	treated 14	controls 26
albumin, g/l	36.3±5.3**	41.1±3.0	40.1±3.2	36.8±2.3*	39.1±3.3
total protein g/l	55.7±4.7***	63.5±5.8	71.3±5.2	55.5±4.4	58.3±5.6
bilirubin, μmol/l	29.4±10.1	28.3±9.6	8.6±3.6	32.8±9.2	29.5±6.5
glucose, mmol/l	4.99±0.83~*	4.35±1.18	5.52±1.20	3.94±1.46	4.91±1.45
cholesterol, mmol/l	2.94±0.64**	2.26±0.51	6.11±1.19	2.27±0.55	2.31±0.37
triglyceride, mmol/l	0.35±0.14	0.37±0.24	3.02±1.02	0.28±0.11*	0.38±0.17
urea nitrogen, mmol/l	3.57±0.69*	3.09±0.70	3.95±1.04	3.23±0.97*	2.44±0.80
alkaline phosphatase U/l	171.2±46.4	201.5±65.1	183.8±73.6	162.0±41.7	186.0±62.2
SGOT, U/l	45.6±15.4~*	57.4±19.3	36.5±17.0	42.8±11.3	47.2±17.7

Group 1: newborns born within 48 hours after discontinuation of tocolysis
Group 2: newborns born beyond 48 hours after discontinuation of tocolysis plus maternal values (venous blood)
The data are means±SD
***: $p < 0.001$
**: $p < 0.01$
*: $p < 0.05$
~+: $0.05 < p < 0.07$
no sign: not significant

TABLE II

Results in venous and arterial blood of newborns of mothers treated with fenoterol and of untreated mothers
Means and standard deviations

	Treated		Controls	
n	Artery 15	Vein 15	Artery 19	Vein 19
albumin, g/l	35.5±5.0	36.8±5.5	40.7±2.9	41.6±3.2
total protein, g/l	56.2±8.3	57.6±6.9	64.5±6.0	64.5±5.7
bilirubin, μmol/l	30.6±10.0	28.4±10.3	26.8±10.0	29.7±9.2
glucose, mmol/l	4.85±0.69	5.08±0.92	4.34±0.84	4.27±1.33
cholesterol, mmol/l	3.26±1.02	2.79±0.77	2.28±0.55	2.23±0.47
triglyceride, mmol/l	0.33±0.11	0.39±0.14	0.36±0.22	0.36±0.22
urea nitrogen, mmol/l	3.71±0.99	3.45±0.86	3.11±0.70	3.06±0.71
alkaline phosphatase, U/l	169.2±48.8	179.2±53.1	204.1±63.5	203.0±68.4
SGOT, U/l	55.2±33.6	44.5±23.2	55.1±22.7	59.1±17.1

For none of the parameters was there a significant difference between venous and arterial values

values slightly but significantly higher than the control values ($p < 0.05$). Blood glucose appeared lower in the treated group but the difference from the control values did not attain the 5% level of significance.

None of the parameters differed between the isolated venous and arterial samples (Table II).

Evaluation of the results was partly hampered by the scarcity of normal cord blood values in the literature. On the basis of several sources, the normal mean value for glucose is 3.8 mmol/1 with a range of 2.36—5.05 mmol/1 [5, 7], for cholesterol 1.75 (1.38—2.49) mmol/1 [1, 8]. We found a single set of normal data for triglycerides [1]: 0.30 (0.24—0.47) mmol/1; for total protein [7]: 61.0 (43.0—73.0) g/1, and for SGOT [7]: 5—120 U/1.

Discussion

Brazy and Pupkin [4] observed a significantly higher incidence of hypotension, hypoglycaemia, hypocalcaemia and intestinal paralysis and an increased mortality rate in newborns born to mothers treated with isoxsuprine as compared to babies of untreated mothers. The betamimetics have been demonstrated in the blood of neonates born after tocolytic therapy by several investigators. Lierde and Thomas [10] administered ritodrine to mothers prior to elective Caesarean section and in the cord blood they found one third of the betamimetic concentration of the maternal blood. Brazy et al [2] found 0—35.6 μg/ml isoxsuprine in the cord blood of newborn babies of mothers treated with the drug in the last 24 hours prior to delivery. There was a negative correlation between the isoxsuprine concentration in the cord blood and the time elapsing between termination of maternal treatment and delivery; values exceeding 10 μg/ml were only encountered if the baby was born within 2 hours after termination of maternal betamimetic therapy. Severe complications in the newborn only occurred if that level had been exceeded. The relationship between time of betamimetic exposition and incidence and severity of complications was more marked in preterm babies. The half-time of isoxsuprine was 1.5—3 hours in term neonates while in preterm babies it was as long as 6—8 hours [2, 3].

In this study we have attempted to clarify the fetal effects of maternal betamimetic treatment by determining some chemical parameters in cord blood. The newborns in both treated groups appeared healthy in clinical terms, none of the complications described in the literature have been encountered in any of them. Blood chemistry, however, revealed clear-cut differences between the treated and the control infants. The alterations were more pronounced in babies born within 48 hours after termination of betamimetic therapy, as for four parameters out of nine the difference was statistically significant and for two other parameters there was a clear trend for a difference. In the babies born a longer time after the cessation of betamimetic therapy

only three parameters differed from the control values and the difference was slight statistically.

Cord blood glucose was higher in the babies born immediately after cessation of betamimetic treatment than in the controls. This finding was in agreement with data in the literature [5, 11, 12] and can easily be explained by the well-known effect of betamimetics on carbohydrate metabolism. Weidinger et al [15] on the other hand found diminished blood glucose levels in cord blood of neonates born immediately after tocolytic therapy, but were unable to explain the unexpected finding. Sustained fetal hyperglycaemia may set off hyperinsulinism, and this and the depletion of hepatic glycogen stores during prolonged glycogenolysis may convert hyperglycaemia to hypoglycaemia soon after birth [5]. In our material, the babies born a long time after maternal betamimetic therapy had lower blood glucose values than the controls; the difference was, however, not significant statistically. It may be speculated that the low blood glucose level encountered at birth was a consequence of forced glycogenolysis elicited by prolonged betamimetic treatment of the mother; restoration of the liver glycogen contents could, however, be expected to occur a few days after discontinuation of betamimetic therapy.

The cholesterol value was elevated in the babies born immediately after tocolysis. We found a single report in the literature on a similar finding observed after simultaneous administration of ritodrine and betamethasone [1]; these authors attributed the hypercholesterolaemia to the corticosteroid treatment and not to the betamimetic therapy. Since in our cases no corticosteroids were given, only the betamimetic therapy could have been the cause of the increased cholesterol level, and we anticipate that the same was the case in the material of Andersen and Friis-Hansen [1]. The triglyceride level, the other indicator of lipid metabolism in this study, exhibited no difference.

An eventual effect of betamimetic drugs of fetal liver function has been put forward by several authors: it may namely be anticipated that the enzymes of the fetal liver play a role in the metabolism of betamimetic drugs. Rosanelli et al [12] found increased bilirubin levels in newborns born after maternal tocolytic treatment while Weidinger et al [16] observed hyperbilirubinaemia in 28% of newborns following betamimetic treatment. Brazy et al [2] could not demonstrate any alteration in the liver function of neonates whose mother had undergone isoxsuprine treatment and supposed that either the betamimetics had no influence on liver enzymes or they may induce those metabolising the drug itself, leaving the bilirubin metabolism unaltered. In our study, fenoterol had no measurable effect on the cord blood bilirubin level. The slight decrease of alkaline phosphatase and SGOT activity encountered in both treated groups might be ascribed to an eventual effect on liver function.

Serum total protein and albumin levels were lower in both treated groups than in the controls. This finding was paradoxical, being at variance with the anabolic effect of betamimetic drugs promoting fetal growth demonstrated in several previous studies. It should also be noted that although the differences were statistically significant, all mean values fell within normal limits.

The informative value of cord blood findings may depend on the fact whether the sample was taken from the umbilical vein or from one of the arteries, e.g. in case of pH measurements. It was thought therefore that the metabolic parameters might also differ depending on the kind of blood vessel from which the sample had been drawn. Anyhow, it has turned out that none of the parameters differed in this respect significantly. Similar studies have only been published on differential values of blood glucose, the venous and arterial values were identical [6]. It can thus be concluded that isolated blood sampling is not necessary for such purposes, mixed cord blood being suitable in similar studies.

In summary, several metabolic indicators in cord blood taken from newborns delivered following betamimetic treatment differed significantly from the control values, and this points to an effect of such treatment on fetal metabolism. The changes were more pronounced in babies born immediately after betamimetic tocolysis. In spite of statistically significant differences, the deviations were of no biological importance since even the differing means fell within normal limits and the treated newborns were free of clinical symptoms.

The following conclusions have been drawn.

— In spite of demonstrable metabolic alterations, tocolysis performed according to accepted standards does not lead to considerable fetal complications;

— newborns delivered following betamimetic tocolysis need intensive observation;

— the indication of betamimetic tocolysis should carefully be weighed in cases with unfavourable prognosis, as unsuccessful treatment is not only superflous but may lead to metabolic effects unfavourably influencing the preterm baby's condition.

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