Antenatal ambroxol usage in the prevention of infant respiratory distress syndrome

Beneficial and adverse effects

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Summary: A bromhexine metabolite ambroxol, is a relatively new promoter of fetal lung maturation. The data on its efficacy and side effects in humans are not yet as many as those of corticosteroids. We found that in 24 premature labor patients ambroxol reduced the incidence of respiratory distress syndrome when compared with the control group, consisting of 58 patients. There was no concomitant disorder in any patient that would have contributed to the fetal lung maturation. We also observed septic morbidity to be less frequent in the ambroxol group. Thyroid hormone levels were within normal range both in maternal and fetal circulation.

There were no side effects attributable to the drug. Maternal liver and renal function test results did not differ significantly throughout the treatment.

Key words: Ambroxol; Respiratory distress syndrome.

INTRODUCTION

Insufficient surfactant production in newborns, the so called the respiratory distress syndrome (RDS), is an important cause of mortality among preterm infants. Even if the victims recover will probably have late sequelae, most commonly those of the central nervous and cardiopulmonary systems. Though it is inversely correlated with gestational age, its incidence among all newborns is almost 1.5% ([1]).

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Various agents have been used up to now to accelerate the fetal lung maturation and hence alveolar surfactant production during intrauterine life.

Corticosteroids, being the most popular were demonstrated to be beneficial in this aim ([2]), but when treatment to delivery time is more than one week, or gestational age is less than 30 and more than 34 weeks, or if the infant is male, the efficacy of the steroids is only slight ([3]). Furthermore, there is a potential risk for maternal and fetal infection, which is extremely life-threatening for the preterm newborn.

A bromhexine metabolite, ambroxol, is a promising agent in the prevention of RDS. Systemic availabilities of tablet and drop formulations of ambroxol are 73 and 81% ([4]). Ambroxol readily crosses the placenta and accumulates in the fetal lung and liver. In the fetal lung it stimulates the intracellular organelles involved in the

surfactant secretion and hence increases surfactant phospholipids in the amniotic and fetal tracheal fluids ([5-9]). Here we present our data on ambroxol usage in RDS prevention in our clinics.

MATERIALS AND METHODS

Eighty-two pregnant women, who were admitted to the Uludag University Medical Faculty, Department of Obstetrics and Gynecology and fulfilled the criteria below, were included in the study:

i) gestational age between 28 and 35 weeks;
ii) presence of threatened or planned premature labor;
iii) no more than two weeks disagreement between the gestational age according to Naegele's formula and the ultrasound data;
iv) no history or existence of chronic hypertension, preeclampsia, eclampsia, hyperprolactinemia, Rh immunization, class B - R diabetes, hyperthyroidism;
v) no evidence of any drug addiction, cigarette smoking or concomitant medical therapy of any type that may accelerate fetal lung maturation;
vi) singleton gestation.

Informed consent of the patients and their husbands were obtained. Tocolysis was allowed, when indicated during the follow-up.

The patients who were admitted to the study by their own wishes were given ambroxol (ambroxol group; n = 24) orally 1300 mg/day until delivery and the rest (control group; n = 58), neither were given anything for fetal lung maturation nor were suitable for tocolysis. None of the mothers took any prophylactic antibiotic for the vaginal delivery, but for the cesarean section.

Maternal blood sample for liver and renal function tests, thyroid stimulating hormone (TSH), total and free T_3 (TT_3, FT_3, TT_4, FT_4) hormone measurements, were taken at the admission and at the end of the ambroxol therapy, but before delivery. Following delivery umbilical cord blood samples for hormone measurements were taken.

Deliveries were performed under the supervision of a neonatalogist, who was responsible for the follow-up of the patients in the neonatology clinic in a blind study.

The diagnosis of RDS was based on the criteria shown in Table 1. The diagnosis of maternal and neonatal infection depended on the clinical picture and the laboratory and the radiological investigations of the patient and confirmed by a positive culture result.

Results were analyzed by student-t test.

Table 1. – *Criteria for the diagnosis of respiratory distress syndrome.*

i) Onset within the first 4 hours of life;
ii) Duration more than 24 hours;
iii) Tachypnea more than 50 per minute;
iv) Intercostal retractions and flaring of the alae nasi;
v) Grunting on expiration;
vi) Cyanosis and PO_2 less than 60 mmHg;
vii) Reticulogranular pattern and/or bronchograms on chest x-rays.

RESULTS

The mean maternal ages, the mean gestational ages at delivery, the mean 10th minute apgar scores and the mean birth weight in both groups did not show any significant differences (Table 2; $p > 0.05$). Tocolist was applied in 17 patients in the ambroxol group (Table 3).

One (6%) of the males and 1 (12%) of the females in the ambroxol group, 5 (18%) of the males and 1 (3%) of the females in the control group developed RDS, and only the male patient in the ambroxol group survived (Tables 2, 3, 4). There was 1 case of sepsis with Escherichia coli in the blood culture in the ambroxol group, whereas Pseudomonas aeroginosa in 2, Escherichia coli in 3 and Klebsiella pneumonia in 3 sepsis cases were cultivated in the control group. During the follow-up, no sign or symptom of maternal infection was detected before the delivery or in the puerperium.

There was no statistically significant difference between the pre- and post-treatment liver and renal function test results and neither did they differ significantly from those of the control group (Tables 6, 7; $p > 0.05$). When the hormonal status were considered, the mean TSH, TT_3, FT_3, TT_4, and FT_4 levels did not change significantly during therapy ($p > 0.05$) and were found within normal ranges in the newborns (Table 8).

Table 2. – *Characteristics of the groups.*

	Ambroxol Group (n = 24)	Control Group (n = 58)
Age (Mean ± SD)	28.29 ± 0.94	27.43 ± 0.72
Gestational age at delivery (days; Mean ± SD)	243.00 ± 21.99	226.53 ± 46.55
ROM to delivery time (minutes; Mean ± SD)	1334.00 ± 1107.92 (n = 5)	3453.24 ± 4587.27 (n = 17)
Cesarean section	13 (1)	11 (2)
10th minute APGAR score (Mean ± SD)	9.17 ± 1.24	9.24 ± 1.44
Sex (Male / Female)	16 (1) / 8 (1)	27 (5) / 31 (1)
Birth weight (grams; Mean ± SD)	2466.67 ± 808.06	2208.10 ± 494.79
Duration of ambroxol usage (days; Mean ± SD)	12.21 ± 9.22 (range 3 - 33 days)	–

ROM: Rupture of membranes. (*) Number of the respiratory distress cases are shown in brackets.

DISCUSSION

The most important strategy in the management of RDS, is its prevention. The risk group for RDS includes preterm, male and caucasian infants of poorly controlled diabetic mothers, who gave birth with cesarean section. Though many agents such as corticosteroids, beta-mimetics, aminophylline and thyroid hormones have been used for the acceleration of fetal lung maturation, they only have either minor beneficial or major side effects [10–15].

More recently, a new, promising brombexine metabolite, ambroxol, is being used for fetal lung maturation. It was first reported as an agent, increasing tracheo-

Table 3. – *Tocolytic agents used in the patients.*

	Ritodrine	$MgSO_4$	Nifedipine
Ambroxol grounp (n = 24) Number of the patients	8	2	7
Total dose (Mean ± SD)	1882.90 + 2369.45 mg	484.50 + 271.53 gr	591.43 + 524.70 mg
Duration of the treatment (Mean ± SD)	9.18 + 7.29	10.00 + 5.66	9.86 + 8.74

Table 4. – *Course of the infants during neonatal period.*

	Ambroxol Group (n = 24)			Control Group (n = 58)		
	Death [%]	Survival [%]	Total [%]	Death [%]	Survival [%]	Total [%]
RDS	1 [4]	1 [4]	2 [8]	6 [10]	–	6 [10]
NEC	–	–	–	4 [7]	–	4 [7]
Sepsis	–	–	1 [4]	5 [8]	3 [5]	8 [13]

RDS: Respiratory distress syndrome; NEC: Necrotizing enterocolitis.

Table 5. – *Characteristics of the respiratory distress syndrome cases in the ambroxol group.*

Route of delivery	GAD (days)	Sex	Weight (gr)	10th minute APGAR score	PROM (hr)	DAU (days)	Tocolysis	Course
SVD	202	Male	1500	7	72	10	Nifedipine total 420 mg	Recovered
SVD	219	Female	2050	8	–	5	Ritodrine total 150 mg	Lived for 24 hours

GAD: Gestational age at delivery; PROM: Premature rupture of the membranes; DAU: Duration of ambroxol usage; SVD: Spontaneous vaginal delivery.

bronchial secretions in animal studies, and hence used as an expectorant for respiratory disorders ([16]). Later on, in vivo and in vitro studies showed that, ambroxol increased surfactant production by type II pneumocytes ([5–8]). Intravenously administered ambroxol, during pregnancy, increased the amniotic fluid phospholipid concentration ([17, 18]). In a multicenter controlled prospective study, antenatally administered ambroxol was found to be as effective as betamethasone in the prevention of RDS ([19]). Wauer has reported that, when compared with untreated groups, antenatal usage of ambroxol significantly decreases the incidence of RDS in neonates ([17]). However, in another multicenter study from Italy, the incidence of RDS was found to be significantly lower in the ambroxol group (13%) than in the betamethasone group (31%), though 100% of the betamethasone patients (but only 18% of the ambroxol patients) completed one course of treatment ([4]).

In our study, 2 newborns in the ambroxol group and 6 newborns in the control group developed RDS. Only 1 case, which had been given ambroxol, recovered from the situation.

Though the RDS rates in males were 6% in the ambroxol group and 18% in the control group, the rates in the female population were 22% and 3%, respectively. In the control group RDS was seen

Table 6. – *The liver function test results of the groups (Mean ± SD).*

	Ambroxol Group (n = 24)		Control Group (n = 58)
	Pretreatment	Post-treatment	
SGOT (IU/ml)	21.13 ± 14.02	21.19 ± 9.13	20.82 ± 7.42
SGPT (IU/ml)	15.02 ± 7.48	16.12 ± 4.21	15.17 ± 3.51
GGT (IU/ml)	12.00 ± 3.48	8.75 ± 3.40	10.24 ± 2.21
Glucose (mg/dl)	96.43 ± 14.93	97.43 ± 18.42	94.21 ± 9.80
Total bilirubin (mg/dl)	0.32 ± 0.16	0.40 ± 0.16	0.31 ± 0.09
Direct bilirubin (mg/dl)	0.14 ± 0.08	0.20 ± 0.09	0.14 ± 0.05
Total protein (gr/dl)	6.25 ± 0.64	6.06 ± 0.92	6.19 ± 0.41
Albumin (gr/dl)	3.21 ± 0.36	3.09 ± 0.37	3.47 ± 0.17
Alkaline phosphatase (IU/ml)	234.47 ± 85.88	262.64 ± 104.26	242.94 ± 67.82

SGOT: Serum glutamate oxaloacetate transferase; SGPT: Serum glutamate pyruvate transferase; GGT: Gamma glutamyl transferase.

Table 7. – *The renal function test results and the serum electrolyte levels of the groups (Mean ± SD).*

	Ambroxol Group (n = 24)		Control Group (n = 58)
	Pretreatment	Post-treatment	
Urea (mg/dl)	20.96 ± 10.87	22.72 ± 12.15	21.77 ± 8.56
Uric acid (mg/dl)	3.54 ± 1.39	4.97 ± 1.63	3.72 ± 0.97
Creatinine (mg/dl)	0.53 ± 0.15	0.62 ± 0.22	0.57 ± 0.11
Sodium (mEq/L)	137.50 ± 4.27	130.08 ± 3.93	132.00 ± 2.97
Potassium (mEq/L)	3.98 ± 0.40	3.93 ± 0.44	3.72 ± 0.28
Chloride (mEq/L)	104.56 ± 6.13	102.14 ± 6.67	100.91 ± 4.53
Phosphorus (mEq/L)	5.75 ± 0.44	3.74 ± 0.86	4.22 ± 0.42
Calcium (mEq/L)	8.81 ± 0.98	9.09 ± 0.83	8.72 ± 0.61
Magnesium (mEq/L)	2.16 ± 0.39	2.18 ± 0.13	2.08 ± 0.12

to arise predominantly in males, as this is mentioned in the literature ([20]). The influence of gender may be explained by the inhibitory action of androgens on fibroblast-pneumocyte factor secretion by fetal lung fibroblasts ([21]). Since one of the hypothesized mechanisms in corticosteroid-induced fetal lung maturation is the agent's action on fibroblasts to secrete this substance ([22]), the efficacy in male fetuses at risk for RDS is not as high as in females ([3]). In animal experiments, it was shown that testosterone treatment delayed lung maturation in female fetuses, while a potent testosterone inhibitor, flutamide, accelerates the surfactant synthesis in male fetuses during the intrauterine period. However, there is no reported evidence yet of such a preponderance in ambroxol usage. This is problably because the ambroxol exerts its action directly on type II pneumocytes, but not indirectly through the fibroblasts.

Though ambroxol was shown to reduce the incidence of RDS in preterm newborn, the mechanism of action is not yet fully obvious. Van Golde ([23]) and Post *et al.* ([5]) have suggested an increased rate of phospholipid synthesis, whereas in an in vitro study by type II pneumocytes, Disse *et al.* ([24]) have reported both an increase in phosphatidylcholine synthesis and a reduction in phosphatidylglycerol catabolism. Probably choline phosphatidyltran-

Table 8. – *Maternal and fetal thyroid hormones in the ambroxol group (Mean ± SD).*

	Normal limits	Maternal Pretreatment	Post-treatment	Fetal	
				Normal limits	Cord blood
TSH (mIU/ml)	0 - 6.5	1.42 ± 1.28	2.38 ± 1.66	< 17.4	8.27 ± 4.04
TT_4 (mcg/dl)	4.5 - 12.5	9.34 ± 2.75	8.13 ± 1.45	4.3 - 9.1	6.92 ± 1.08
FT_4 (ng/dl)	0.6 - 1.7	0.74 ± 0.16	0.70 ± 0.17	0.5 - 1.4	1.02 ± 0.08
TT_3 (ng/dl)	85 - 185	154.39 ± 64.27	142.33 ± 34.51	15 - 75	31.08 ± 27.07
FT_3 (pg/dl)	1.4 - 4.1	2.02 ± 0.82	1.92 ± 0.93	< 1.3	0.65 ± 0.25

TSH: Thyroid stimulating hormone; TT_4, FT_4: Total and free T_4; TT_3, FT_3: Total and free T_3.

sferase is a key enzyme in the mechanism of action ([25]).

Another factor that may influence fetal lung maturation is the thyroid gland. Thyroid hormones may enhance pulmonary surfactant synthesis via the thyroid receptors found on the fetal lung type II cells and thyroidectomy delays lung maturation ([11]). Ballard *et al.* ([12]) have reported an increase in phosphatidylcholine and a reduction in glycogen contents in the fetal rabbit lung, following the antenatal administration of a thyroid hormone analogue that crosses the placenta. Human studies by Klein *et al.* ([13]) and Mashiach *et al.* ([14]) have shown that the intraamniotic administration of thyroxine gives encouraging results. In one of their comparative studies, Luerti M. *et al.* ([26]) found a significantly high level of T_3 in the ambroxol group, in comparison with the betamethasone and control groups.

However, they failed to show any significant difference between the groups in relation of the other thyroid hormones. In our study, we could not see any significant change in the mean thyroid stimulating hormone, total and free T_3 and T_4 levels between the pre- and post-treatment measurements in the ambroxol group. The mean umbilical cord blood hormone levels immediately after parturition were also within the normal range. Hence, it was assumed that the fetal lung accelerating action of ambroxol through thyroid hormones is not so significant, if it ever exists.

Infection is a life threatening condition in premature newborns. The most widely used agents, corticosteroids, though reducing the incidence of RDS, increase the morbidity and mortality of neonatal sepsis ([27]). Puerperal endometritis also arises more frequently in such cases. On the other hand, in controlled multicenter comparative studies, ambroxol was shown to reduce the incidence of neonatal infectious complications in contrast to betamethasone ([19]), which reduces the number of T-helper cells ([28]) and the functions of polymorphonuclear cells ([29]) in the newborn. On the contrary, ambroxol does not cause functional abnormality in immune competent cells and even increases the chemotaxis ([30]). Another contributory factor of ambroxol in infection prevention, especially that of the respiratory system, is that the agent increases mucociliary transport, probably by stimulation of ciliary motility ([31–34]). Hence the attachment of the pathogenic organisms to the target organ is prevented.

Perhaps, one of the most advantageous features of ambroxol, is its direct antimicrobial activity, which has been proved by in vitro and in vivo studies on Pneumococci, Staphylococci, Streptococci, Haemophilus, Proteus, Klebsiella and Escherichia Coli ([35]). In our study, there was 1 sepsis case in the ambroxol group and 8 sepsis cases in the control group, but no puerperal infection in either group. It is obvious that a drug with antimicrobial properties in addition to its RDS-prevention effect is preferable.

In order to be effective, a drug should be consumed without any discomfort to the patient. During follow up, there was only 1 case with a complaint of nausea and hence the medication was discontinued on the 3rd day. There has been no reported adverse drug reaction, except nausea and headache, in the literature up to now ([36–39]). We were unable to detect any sign or symptom of organ dysfunction during antenatal follow-up, and post-treatment liver and renal function test results did not differ significant from either the pretreatment or control group values.

Our results indicate that the ambroxol has no significant maternal, fetal and neonatal side effects. However, its intrauterine surfactant stimulation property may be life-saving in preterm deliveries and its direct and indirect antimicrobial actions may contribute to the survival of the

neonate. Hence, ambroxol may be a valuable alternative to steroids for the prevention of RDS, after the results of larger study groups have become available and the efficacy has been tested in groups with hypertension, diabetes and multiple gestations.

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