Combination of low-dose budesonide and low-dose aminophylline may improve lung function in reduced adverse effects compared with high-dose monotherapy. Adult rabbits intratracheally received 4 ml/kg of saline or meconium (25 mg/ml). Meconium-injured rabbits were treated at 0.5 and 2.5 h after meconium instillation by intravenous aminophylline (1.0 mg/kg), by intratracheal budesonide (0.125 mg/kg) followed by intravenous aminophylline (1.0 mg/kg), or were untreated. Although aminophylline improved some respiratory parameters, budesonide+aminophylline more effectively reduced intrapulmonary shunts and improved gas exchange, without significant cardiovascular effects. Combined treatment reduced lung edema and number of lung neutrophils to a higher extent than aminophylline alone. Both treatments reduced lung peroxidation and in vitro airway reactivity to histamine, with a better effect after aminophylline alone. Combination of budesonide and aminophylline enhanced respiratory parameters more effectively, having fewer side effects than aminophylline alone. However, no additive effect of budesonide was observed on lung peroxidation and in vitro airway reactivity.

Key words: aminophylline, budesonide, inflammation, meconium aspiration

INTRODUCTION

Meconium aspiration syndrome (MAS) is a frequent cause of respiratory failure in the mature neonates. Aspirated meconium is responsible for airway obstruction,
dysfunction of pulmonary surfactant, inflammation, lung edema, and pulmonary vasoconstriction and bronchoconstriction. Recent studies have shown that administration of anti-inflammatory drugs, e.g., glucocorticoids (GCs) (1-3) and methylxanthine (MX) derivatives (4, 5) may diminish the symptoms of MAS and thereby improve lung function in MAS (6). Nevertheless, both GCs (7) and MX (8) at high doses may adversely influence other functions. Side effects of the mentioned drugs may be diminished by their local administration and/or by their suitable therapeutic combinations with other drugs. Combined administration of inhaled GCs and MX is well established in the treatment of asthma or chronic obstructive pulmonary disease (8, 9). Since there is no information on such treatment in MAS, the present study evaluated the effects of combined treatment with intratracheal budesonide and intravenous aminophylline on respiratory and cardiovascular parameters and several inflammatory markers in a rabbit model of MAS.

MATERIAL AND METHODS

The design of the experiments was approved by a local Ethics Committee of the Jessenius Faculty of Medicine in Martin, Slovakia. Meconium was collected from 20 healthy term neonates, lyophilized, and stored at -20°C. Before use, meconium was suspended in 0.9% NaCl at a concentration of 25 mg/ml.

Adult rabbits of 2.6 ±0.3 kg were anesthetized with intramuscular ketamine (20 mg/kg; Narkamon, Spofa, Czech Republic) and xylazine (5 mg/kg; Rometar, Spofa, Czech Republic) followed by infusion of ketamine (20 mg/kg/h). Tracheotomy was performed and catheters were inserted into a femoral artery and right atrium for sampling the blood, and into a femoral vein to administer anesthetics. Animals were paralyzed with pipecuronium bromide (0.3 mg/kg/30 min; Arduan, Gedeon Richter, Hungary) and subjected to a pressure-controlled ventilator (Beat-2, Chirana, Slovakia). All animals were ventilated with a frequency of 30/min, fraction of inspired oxygen (FiO₂) of 0.21, peak inspiratory pressure (PIP) to keep a tidal volume (Vₜ) between 7-9 ml/kg and no positive end-expiratory pressure (PEEP) at this stage of experiment. After stabilization, ventilatory parameters were recorded and samples of arterial and mixed venous blood were taken for blood gas analysis and estimation of hemoglobin (Rapidlab™348, Bayer Diagnostics, Germany). Then, 4 ml/kg of saline (Sal group, n=7) or meconium suspension (25 mg/ml) was instilled into the tracheal tube. From this moment on, all animals were ventilated with 100% oxygen. Within 30 min after meconium instillation, respiratory failure developed, defined as >30% decrease in dynamic lung-thorax compliance (Cdyn) and PaO₂<10 kPa at FiO₂ 1.0. Blood samples were taken and parameters recorded again. Meconium-instilled animals were treated by intravenous aminophylline (1.0 mg/kg, Syntophyllin, Hoechst-Biotika; Mec+A group, n=7), by intratracheal budesonide (0.1 mg/kg, Pulmicort susp. inh., AstraZeneca) administered within 2 min by means of infusion effect of high-frequency jet ventilation (i.e., asymmetric HFJV (10); f. 300/min, inspiration time Ti=20%) followed 5 min later by intravenous aminophylline (1.0 mg/kg, Syntophyllin, Hoechst-Biotika; Mec+BA group, n=8); both treatments administered at 0.5 and 2.5 h after meconium instillation, or animals were untreated (Mec group, n=7). All animals were oxygen-ventilated for additional 5 h, with blood gas analysis and recording of parameters at 0.5, 1, 2, 3, 4, and 5 h of the treatment.

Tracheal airflow and Vₜ were measured by a Fleisch head connected to a pneumotachograph. Airway pressure was registered via a pneumatic catheter placed below the tracheal tube and
connected to an electromanometer. $C_{dyn}$ was calculated as a ratio between $V_t$ (adjusted per kg) and airway pressure gradient (PIP-PEEP). Mean airway pressure (MAP) was calculated as MAP=(PIP+PEEP)/2 and oxygenation index (OI) as OI=MAP x FiO$_2$/PaO$_2$. Right-to-left pulmonary shunts were calculated by a computer program using the Fick equation (10). Central venous pressure (CVP) was registered through the catheter inserted into the right atrium, connected to an electromanometer. Systolic (SBP) and diastolic (DBP) blood pressures were measured via the catheter in a femoral artery connected to an electromanometer, and the mean arterial blood pressure (MABP) was calculated as MABP=DBP + 1/3 (SBP - DBP). Heart rate (HR) was calculated from the ECG recorded by subcutaneous electrodes. Samples of arterial blood were taken before meconium instillation and at 1, 3, and 5 h of the treatment and a total WBC count was determined in Bürker's chamber after staining by Türck. Differential WBC count was estimated microscopically after staining by Pappenheim. At the end of experiments, animals were killed by an overdose of anesthetics and the lungs and trachea were excised. The left lung was lavaged by saline (0.9% NaCl, 37°C) 3 x 10 ml/kg, bronchoalveolar lavage (BAL) fluid was centrifuged at 1500 rpm for 10 min, and differential WBC count in the sediment was evaluated microscopically after staining by Pappenheim. The right lung was cut, strips of the tissue were weighed and dried at 60°C for 24 h to determine the wet/dry weight ratio, were used for estimation of lung tissue reactivity, or were homogenized for biochemical analyses.

The concentration of theophylline was determined in blood plasma taken at the end of experiments and was measured by EMIT immunoassay (TDM Theophylline assay, Siemens HealthCare, Germany) on biochemical analyzer ADVIA 1240 (Siemens HealthCare, Germany). Products of lipid and protein oxidation were determined in the homogenate of the right lung. Concentrations of lipid peroxidation (LPO) products (thiobarbituric acid-reactive substances, TBARS) was determined from the absorbance at 532 nm and expressed in nmol/mg protein (5). Oxidative modification of proteins demonstrated as the accumulation of dityrosine and lysine-LPO products was determined by fluorescence method and expressed in arbitrary units (5). Tracheal and lung smooth muscle reactivity to cumulative doses of histamine ($10^{-8}$-$10^{-3}$ mol/l, Sigma-Aldrich, Germany) was estimated by an in vitro method (5) and shown in grams (g) of smooth muscle tension.

Data were expressed as means ±SE. Between-group differences were evaluated by ANOVA with a post-hoc LSD test, within-group differences were evaluated by Wilcoxon's test. A P<0.05 was considered statistically significant.

RESULTS

Intratracheal instillation of meconium caused severe impairment of lung function within 30 min. A significant decrease of lung compliance and an increase of the right-to-left pulmonary shunts resulted in worsened gas exchange and increased requirements for artificial ventilation compared with the values before meconium instillation and with saline-instilled animals (all P<0.05). Aminophylline reduced shunting and improved oxygenation compared with the non-treated group, but budesonide combined with aminophylline more effectively enhanced lung function than aminophylline alone (Table 1, Fig. 1, Fig. 2).

Meconium instillation increased the accumulation of liquid in the lungs compared with saline-instilled animals. Budesonide and aminophylline reduced lung edema, while a decrease in wet/dry weight ratio in aminophylline-treated group was insignificant (Fig. 3).
Instillation of meconium potentiated a leak of neutrophils into the airspaces. The combined treatment diminished the number of neutrophils in the BAL fluid, which was associated with their increase in the blood, to a higher extent than after aminophylline alone (Fig. 4). Changes in the relative number of neutrophils were

Table 1. Mean airway pressure, central venous pressure, mean arterial blood pressure, and heart rate in saline-instilled (Sal), meconium-instilled non-treated (Mec), meconium-instilled aminophylline-treated (Mec+A) and meconium-instilled budesonide+aminophylline-treated (Mec+BA) animals.

<table>
<thead>
<tr>
<th></th>
<th>Before S/M</th>
<th>After S/M</th>
<th>0.5 h</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
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<td>0.3±0.0</td>
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<td>0.6±0.0</td>
<td>0.6±0.0</td>
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<td>207±9</td>
<td>212±7</td>
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<td>221±11</td>
<td>231±12</td>
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Before, After S/M: before and after saline/meconium instillation, MAP: mean airway pressure (kPa), CVP: central venous pressure (kPa), MABP: mean arterial blood pressure (in kPa), HR: heart rate (beats per minute). Data are expressed as means ±SEM. For Sal vs. Mec, Mec+A and Mec+BA: *P<0.05, **P<0.01, ***P<0.001; Mec+A vs. Mec: †P<0.05, ‡P<0.01; Mec+BA vs. Mec: §P<0.05, ¶P<0.01.

Fig. 1. Right-to-left pulmonary shunts (RLS) in saline-instilled (Sal) group and meconium-instilled un-treated (Mec), aminophylline-treated (Mec+A), and budesonide and aminophylline-treated (Mec+BA) animals. For Sal vs. Mec, Mec+A, and Mec+BA: *P<0.01, **P<0.001; for Mec+A vs. Mec: †P<0.05, ‡P<0.01; for Mec+BA vs. Mec: §P<0.05, ¶P<0.01.
linked with changes in the total WBC count in the peripheral blood. The highest WBC count was observed in the Sal group compared with all meconium-instilled groups during the whole course of the experiment. At the end of experiments, the total WBC count was slightly higher in the aminophylline-treated group (P>0.05) and significantly higher in the combined treatment group (P<0.05) compared with the non-treated group (Fig. 5).

Plasma concentrations of theophylline were comparable in both treated groups (4.9 ±0.7 in Mec+A vs. 4.8 ±0.4 in Mec+BA; P>0.05). Meconium instillation caused massive peroxidation of lipids and proteins in the lungs compared with the Sal group. Both treatments significantly reduced lung peroxidation, with no differences found between the treated groups (Fig. 6).
In vitro airway reactivity to histamine increased with cumulative doses of histamine in all groups. Meconium instillation increased the contractile response of the trachea compared with the Sal group at histamine concentrations of $10^{-8}$-$10^{-3}$ mol/l (all $P<0.05$). Aminophylline alone decreased reactivity of tracheal strips at histamine concentrations of $10^{-8}$-$10^{-4}$ mol/l and the combined treatment at concentrations of $10^{-7}$ and $10^{-6}$ mol/l compared with the Mec group (all $P<0.05$). Instillation of meconium increased also reactivity of the lung tissue strips at

**Fig. 4.** Percentage of neutrophils in arterial blood and in BAL fluid at the end of experiments in saline-instilled (Sal) group and meconium-instilled untreated (Mec), aminophylline-treated (Mec+A), and budesonide and aminophylline-treated (Mec+BA) animals. For between-group comparisons: ***$P<0.001$.

**Fig. 5.** Total number of white blood cells (WBC) in arterial blood before saline/meconium (S/M) instillation and at 1, 3, and 5 h of the treatment in saline-instilled (Sal) group and meconium-instilled untreated (Mec), aminophylline-treated (Mec+A), and budesonide and aminophylline-treated (Mec+BA) animals. For Sal vs. Mec: $aP<0.01$, $bP<0.001$; for Sal vs. Mec+A: $cP<0.01$, $dP<0.001$; for Sal vs. Mec+BA: $eP<0.05$, $fP<0.001$; for Mec+BA vs. Mec: $gP<0.05$. 

histamine concentrations of $10^{-7}$ and $10^{-6}$ mol/l (both $P<0.01$) and $10^{-5}$-$10^{-3}$ mol/l (all $P<0.05$). Aminophylline alone reduced lung reactivity at concentrations of $10^{-7}$ and $10^{-6}$ mol/l (both $P<0.01$), while the combined treatment reduced lung reactivity at concentrations of $10^{-8}$ and $10^{-4}$ mol/l (both $P<0.05$). Aminophylline alone decreased lung reactivity at histamine concentration of $10^{-7}$ mol/l more effectively also when compared with the combined treatment ($P<0.05$; data not shown).

A tendency to increase both blood pressure and heart rate was observed after aminophylline treatment, while the combined treatment had no cardiovascular effects (all $P>0.05$; Table I).

DISCUSSION

The rationale for the combined use of GCs and MX in respiratory diseases is based on their properties and mechanisms of action. Synergistic effects of GCs and MX administered at low doses may give results comparable with a high-dose monotherapy, but with lower side effects (9). The addition of theophylline to inhaled GCs was more effective in the control of asthma than a doubling the dose of GCs (11). According to these findings, in the present study we investigated the possibility that a combination of low doses of intratracheal budesonide and intravenous aminophylline may keep their favorable effects on lung function and have reduced adverse effects. We found that low-dose aminophylline improved some respiratory parameters, but budesonide combined with aminophylline reduced intrapulmonary shunts and improved gas exchange more effectively, with no cardiovascular effects. In addition, the combined treatment reduced lung edema and the number of lung neutrophils more than aminophylline alone. Both

Fig. 6. Markers of lipid oxidation (TBARS; in nmol/mg protein) and protein oxidation (dityrosine and lysine-LPO products; in arbitrary units, A.U.) in the lung homogenate in saline-instilled (Sal) group and meconium-instilled un-treated (Mec), aminophylline-treated (Mec+A), and budesonide and aminophylline-treated (Mec+BA) animals. For between-group comparisons: ***$P<0.001$. 

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**DISCUSSION**

The rationale for the combined use of GCs and MX in respiratory diseases is based on their properties and mechanisms of action. Synergistic effects of GCs and MX administered at low doses may give results comparable with a high-dose monotherapy, but with lower side effects (9). The addition of theophylline to inhaled GCs was more effective in the control of asthma than a doubling the dose of GCs (11). According to these findings, in the present study we investigated the possibility that a combination of low doses of intratracheal budesonide and intravenous aminophylline may keep their favorable effects on lung function and have reduced adverse effects. We found that low-dose aminophylline improved some respiratory parameters, but budesonide combined with aminophylline reduced intrapulmonary shunts and improved gas exchange more effectively, with no cardiovascular effects. In addition, the combined treatment reduced lung edema and the number of lung neutrophils more than aminophylline alone. Both
treatments reduced lung peroxidation and \textit{in vitro} airway reactivity to histamine, but these effects were slightly more pronounced after aminophylline alone. The discrepancy in our results suggests the existence of different mechanisms influencing the evaluated parameters. Respiratory and cardiovascular parameters, tracheal reactivity, leak of neutrophils, and lung edema formation seem to be predominantly influenced by rapid (non-genomic) mechanisms, while peroxidation processes and lung tissue reactivity may be more influenced by slow (genomically) mediated mechanisms.

A rapid action of GCs may be mediated \textit{via} nongenomic interaction with cytoplasmic GR receptors and/or via direct interaction with the cell membrane (12, 13). Thereby, GCs may influence intracellular signaling and many biological functions such as vasoregulation, ion cycling, cellular metabolism, \textit{etc.}, which may be observed within 5-10 min after GCs administration (14). Rapid effects of GCs were demonstrated also in meconium-instilled animals, where dexamethasone and budesonide reduced shunting and improved gas exchange within 30 min after the administration (3, 15). The analysis of cardiovascular changes showed decreased heart rate and increased blood pressure and parameters of heart rate variability already during and immediately after administration of dexamethasone (16).

Similarly to the rapid action of GCs, aminophylline (a mixture of theophylline and ethylenediamine) is able to influence bronchial and vascular tone in very short time. Rapid improvement in lung functions after aminophylline was observed also in meconium-instilled rabbits (5). Our finding is consistent with the observations in patients with asthma or COPD, where the therapeutic levels of theophylline may be obtained within several minutes, with maximum plasma concentration at 20 min following intravenous administration (17).

Contrary to a rapid action, genomically mediated action of GCs and MX derivatives needs more time to be clinically relevant. For example, changes in the level of GCs regulator proteins may be detected up to 30 min, while changes at the systemic level may occur within hours or days (12). Classic genomic action of GCs goes through a binding to cytoplasmic GR receptor, which then translocates to the nucleus. The activated complex may enhance transcription of anti-inflammatory genes or suppress that of pro-inflammatory genes. Effects of theophylline are strongly dose-dependent. At high doses, theophylline leads to bronchodilation, vasodilation, diminished edema formation, and to some anti-inflammatory and anti-oxidative action mediated by phosphodiesterase (PDE) inhibition and adenosine receptor antagonism (8). Low-dose theophylline shows anti-inflammatory action, which is not mediated by either PDE inhibition or adenosine receptor antagonism, but by direct activation of histone deacetylase activity leading to reduced transcription of inflammatory genes (18).

GCs and MX derivatives closely cooperate in the transcription process of inflammatory genes. In the cell nucleus, gene expression is regulated by acetylation of histones which open up the chromatin structure to allow
transcription factors and RNA polymerase, thus initiating transcription. Inflammatory stimuli (IL-8, TNF-α, etc.) activate pro-inflammatory transcription factors (like nuclear factor-κB and activator protein-1), which bind to coactivator molecules and activate histone acetyltransferase. That results in increased transcription of inflammatory genes and expression of inflammatory proteins, like IL-8 and GM-CSF. Histone acetylation is reversed by histone deacetylase (HDAC). Theophylline directly activates HDAC, which leads to suppression of inflammatory genes. GCs also activate HDAC, but through a different mechanism, resulting in the recruitment of HDAC to the activated transcriptional complex via activation of GR which functions as a molecular bridge (8, 18).

Activity of HDAC may be reduced in oxidative/nitrative stress and/or in active cytokine-mediated inflammatory process. Oxidative/nitrative stress leads to the formation of peroxynitrite which nitrates tyrosine residues on certain proteins including HDAC. Increased tyrosine nitration impairs the HDAC function, which results in increased expression of inflammatory genes and reduced GCs responsiveness (18). Contrary, action of low-dose theophylline on HDAC activity appears to be potentiated under the conditions of oxidative stress, and theophylline is then able to restore GCs responsiveness (8). The fact that the effect of low-dose aminophylline is much stronger in the condition of oxidative stress and acute inflammation (i.e., both situations observed also in MAS) may explain its high efficacy in reduction of lipid, but particularly of protein, peroxidation in the lungs and in reduction of meconium-induced airway hyperreactivity to histamine.

We can only hypothesize why no additive effects of budesonide and aminophylline, compared with aminophylline alone, were found in reduction of lung peroxidation and airway hyperreactivity. Reduced responsiveness of budesonide due to oxidative stress, inappropriate dosing, or too short a time of observation to detect changes at the level of genomically mediated mechanisms may be responsible for the lack of expected additive responses. No differences between the high- and low-dose inhaled GCs and low-dose inhaled GCs plus low dose theophylline were observed in patients with chronic asthma either (19).

Together with lung function and inflammatory parameters, we monitored basic cardiovascular variables. In the evaluated time intervals, no significant differences were found between the groups. Nevertheless, aminophylline alone showed the tendency to increase both heart rate and blood pressure. These cardiovascular effects are probably mediated through the antagonism with adenosine receptors (8). On the other side, combined treatment with budesonide and aminophylline caused no obvious cardiovascular changes. Since GCs have the tendency to decrease heart rate (7), we suppose that administration of budesonide before aminophylline 'counteracted' the side effects of aminophylline by unknown mechanisms.

In conclusion, a combination of budesonide and aminophylline reduced shunting, improved gas exchange, decreased lung edema, and the number of
neutrophils in the lungs of meconium-instilled rabbits more effectively and with fewer side effects than aminophylline alone. However, no additive effects were observed on lung peroxidation and airway reactivity to histamine.

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