Glucocorticoids in the treatment of neonatal meconium aspiration syndrome

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Abstract Meconium aspiration syndrome is a serious neonatal disease with complex pathophysiology. With respect to the contribution of meconium-induced lung edema, inflammation and vasoconstriction on the course of the disease, glucocorticoids are increasingly used in the treatment of MAS despite the fact that principal questions on the choice of GCs derivative, mode of delivery and dosing have not been answered yet. To bring a complex insight into the topic, this article reviews the pathomechanisms of MAS, mechanisms of action of GCs, as well as the advantages and disadvantages of GCs administration in experimental models and newborns with MAS.

Keywords Meconium aspiration • Glucocorticoids • Inflammation

Introduction

Meconium aspiration syndrome

Meconium aspiration syndrome (MAS) is a major cause of respiratory morbidity and mortality in the term and post-term newborns. The incidence of MAS in the well-developed countries stands at about one to two per 1,000 live births; however, in the developing countries, this number may be considerably higher [19]. The clinical picture varies from mild tachypnoea to life-threatening respiratory failure associated with pulmonary hypertension [16]. In addition to acute effects, MAS may also have serious long-term consequences on the respiratory system, whereas abnormal bronchial reactivity, wheezing and other respiratory pathology were found in a considerable portion of infants who overcome MAS in the neonatal period [80].

Despite an improved understanding of the pathomechanisms of MAS and widening the available therapeutic approach, MAS is often difficult to treat. Therefore, a number of various adjunctive or alternative approaches have been tested in MAS. Since some of them have been rather well established (e.g. different modes of ventilatory support, surfactant treatment and inhaled nitric oxide), the therapeutic potential of others (particularly of anti-inflammatory drugs and vasodilators) is still under research [48].

Pathogenesis of MAS as a rationale for the treatment by glucocorticoids

The pathogenesis of MAS is complex, with multiple interactions between the individual pathomechanisms [48]. In an acute phase of the disease, aspirated meconium obstructs the airways. Complete airway obstruction may result in alveolar atelectasis behind the plug. Partial airway obstruction may cause a ball valve effect, and air trapping and air leak into the interstitium may occur [16].

With the initiation of ventilation, aspirated meconium reaches the alveoli, where it inactivates the surfactant [56] and triggers inflammation [86]. Meconium changes the viscosity and ultrastructure of the surfactant [2], decreases the levels of surfactant proteins [15] and accelerates the conversion from large, surface active aggregates into small, less active
forms [35]. Both fractions of meconium, water-soluble (containing bilirubin, bile acids, enzymes, etc.) and lipidsoluble (containing free fatty acids, cholesterol, triglycerides, etc.) ones, impair lung functions [56]; however, the lipidsoluble fraction is much more deleterious [76]. The dysfunction of surfactant is further potentiated by plasma proteins leaking through an injured alveolocapillary membrane, as well as by the action of proteolytic enzymes and reactive oxygen and nitrogen species (RONS) released from activated cells during the inflammation.

Meconium itself acts as a potent chemoattractant for neutrophils [87], increasing their number in the lungs within several hours after the aspiration, which is linked with their decrease in the blood [55, 66]. In addition, meconium is a source of pro-inflammatory mediators, such as interleukins (IL) -1, -6 and -8, tumour necrosis factor α (TNFα), etc. [20]; thus, it may induce inflammation directly or indirectly through the stimulation of oxidative burst in neutrophils [69] and alveolar macrophages [17]. The activated macrophages and released cytokines may stimulate the adhesion of neutrophils on the endothelium and the formation of microemboli in the capillary bed, participating in the onset of pulmonary hypertension. This process is facilitated by complement, the activation of which has been proved also in MAS [11]. The activated cells (leukocytes, platelets, epithelial and endothelial cells, etc.) produce a wide spectrum of substances like TNFα, IL, leukotrienes (LT), prostaglandins (PG), platelet-activating factor (PAF), proteolytic enzymes and RONS, injuring the lung parenchyma and surfactant [27, 92]. Inflammatory cytokines induce angiotensin II (ANG II) expression which, after binding to AT1 receptors, cause apoptotic death of the lung cells as well [82]. Subsequently, a leak of proteinaceous fluid and cells into the alveolar spaces through the alveolocapillary membrane further deteriorates the lung function. In addition, meconium contains high concentrations of phospholipase A2 (PLA2), which may directly or via the arachidonic acid metabolism increase the production of lipid mediators and participate in the apoptosis of epithelial cells [29] and surfactant dysfunction [65]. Meconium also enhances the expression of inducible cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in the macrophages and epithelial and endothelial cells [42, 44]. Furthermore, the release of bronchoactive substances like LT and PAF is probably responsible for increased airway reactivity to bronchoconstrictor agents [38, 55].

Meconium aspiration is often associated with pulmonary vasoconstriction from hypoxia and/or from the vasoconstriction effect of meconium and substances released during the inflammation. The presence of meconium in the amniotic fluid may cause ischemic changes of the lungs, umbilical cord and placenta [7]. Postnatal meconium instillation elevates the pulmonary artery pressure and vascular resistance in a concentration-dependent manner [28], which is linked with higher levels of thromboxane A2 (TXA2), LT, PG and endothelin-1 (ET-1) [41, 68, 86].

**Glucocorticoids**

**Mechanisms of action**

Cortisol, a major endogenous glucocorticoid (GC), is secreted by the cortex of adrenal glands. Only a small proportion of GCs (<10%) is free and metabolically active since majority of GCs is bound to proteins during their transport in the blood. The daily production of cortisol in adults may be about 13–20 mg and may increase up to 300 mg/day [75]. In children and adolescents, the daily production of cortisol is about 6.8 mg/m2/day [45]. The plasma concentration of cortisol in adults varies in the range of 50–500 nmol/l, in the term newborns about 140 nmol/l and in premature newborns about 180 nmol/l [75]. The action of GCs contributes to the compensatory mechanisms which help the body to get a stress situation under control. GCs supply energy for these processes by protein catabolism, gluconeogenesis and glucogenesis, finally resulting in hyperglycaemia, hyperlipidaemia and other changes in the blood, bones, muscles and cardiovascular, gastrointestinal, endocrinal and central nervous systems [24, 34].

Free GC molecules penetrate through the cell membrane into the cytoplasm, where they interact with a specific glucocorticoid receptor (GR). Heat-shock protein HSP90, which is normally attached to a free GR and prevents its transport to the nucleus, is released in this process. After binding GCs to a GR receptor, the activated complex moves into the nucleus and binds to a specific nuclear sequence of DNA (glucocorticoid-responsive element, GRE). As a result, it may activate or inhibit the transcription of mRNA and thereby modulate the production of various proteins (Figs. 1 and 2). The newly synthesized substances then mediate physiological or pharmacological responses, including metabolic and anti-inflammatory effects.

In case of their anti-inflammatory action, the activated GR complex interacts with negative-responsive element (GRE−). The subsequent inhibition of transcription factors including nuclear factor (NF)-κB and protein activator (AP)-1 inhibits the expression of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNFα, etc.), enzymes (PLA2, COX-2, iNOS, etc.) and other biologically active substances such as PAF, ET-1, ICAM-1, etc. [24, 34, 57] (Fig. 2).

The anti-inflammatory effect of GCs is supplied also through enhancing the activity of lipocortines. The increased transcription of lipocortine-1 in leukocytes is related to the interaction of GC–GR complex to the positive-responsive element of DNA (GRE+). Lipocortines inhibit the activity of PLA2 and thereby decrease the
production of arachidonic acid and mediators of lipooxygenase and cyclooxygenase pathway as well as of PAF [57]. It is assumed that the activation of the cell by a noxious stimulus causes the inactivation of lipocortines and development of inflammation. On the contrary, the increased production of lipocortines induced by GCs has opposite, anti-inflammatory effects [57].

GCs reduce the penetration of neutrophils into the lungs, decreasing their adherence to the endothelium and thereby increasing secondarily a count of circulating neutrophils [30, 50, 51, 55, 66]. Moreover, GCs decrease the counts of circulating mononuclears, eosinophils and basophils as well as the synthesis of cytokines by macrophages, eosinophils and T lymphocytes. GCs stabilize lysosomes, inhibit the release of lysosomal enzymes, chemotaxia and other functions of neutrophils as well [34]. Furthermore, GCs stimulate the production of secretion leukocyte protease inhibitor, an important antiprotease, which may suppress an inflammation in the airways. GCs facilitate the transcription of β2-receptor gene and reduce the mast cells count and production of mucus in the airways, too. By stabilizing the cell membranes and decreasing the production of pro-inflammatory and vasoactive substances, GCs reduce microvascular permeability. In addition, by direct modulation of the pulmonary vasomotoric tone, GCs diminish pulmonary vasoconstriction and inhibit fibrogenesis [24, 34].
Majority of the above-mentioned action of GCs is mediated by interactions with intracellular cytoplasmic receptors, leading to the production of protein with specific regulatory functions. In these genomic effects, transcription and translation with subsequent proteosynthesis requires at least several hours until some changes may be observed on the systemic level. However, GCs act also through nongenomically mediated mechanisms, which are responsible for rapid GCs action until the effects mediated by genomic mechanisms occur [71]. In literature, three possible nongenomic mechanisms are discussed (Fig. 1): specific interaction with cytosolic GC receptors (cGCR) and successive release of HSP90 and special proteins Src and MAPK, non-specific interactions with cellular membranes and specific interactions with membrane-bound glucocorticoid receptors. GCs may exert rapid effects on various tissues and cells, modulating hormone secretion, neuronal excitability, carbohydrate metabolism, cell morphology, cell behaviour and other processes within seconds or minutes [23, 71]. The GC action may be related to affecting ion cycling [81], cellular energy metabolism [8] or neuronal activity [12], as well as to rapid effects on second messenger systems [8]. In the respiratory system, GCs presumably via nongenomic action modulated Na+/H+ exchange activity in bronchial epithelial cells [81] and inhibited airway smooth muscle contraction within 10 min after GCs inhalation [73, 91]. Similarly, in a rabbit model of MAS, GCs already significantly improved several respiratory parameters within 30 min after the administration [50, 51].

In addition, interactions between genomic and nongenomic mechanisms have been claimed, thereby controlling genomic mechanisms through nongenomic ones [85]. Nongenomic effects occur faster and may be clinically relevant over a limited period, “bridging the gap” until the long-term genomic effects take place [9].

Irrespective of the mechanisms of their action, GCs may effectively suppress polymorphonuclear inflammation, lung edema formation and pulmonary vasoconstriction. However, the effect of the treatment depends on the specific properties, dose and mode of delivery of the individual GCs as well as on the current status of the newborn or experimental animal with MAS.

Glucocorticoids in the treatment of MAS

Despite GCs having been used in various animal models of MAS as well as in several clinical studies, some questions still remain unanswered. Particularly:

1. According to the pharmacological properties, which of the available synthetic GC preparations is the best choice—i.e. most effective with low side effects?

2. What way of GCs administration is better—intravenous or intratracheal?

3. What dosing and timing should be used? When to administer GCs and in what dose per individual GCs preparation? Is it better to use single or repetitive doses of the GC preparative?

4. Is it possible to combine GCs with other drugs emphasizing their favourable effects?

Pharmacological properties of GCs preparations

Individual GCs may exert different pharmacological properties including different mineralocorticoid activity. Although accepted in practice, the clinical potencies of GC preparations have been difficult to assess using classical approaches. For example, the potency of GCs to suppress cortisol production does not sufficiently reflect the ability to suppress inflammation [21]. In addition, it is suggested that different GCs may have different potency per target tissue. The basic characteristics of commonly prescribed GCs preparations are listed in Table 1.

In addition, regarding their nongenomic action, the relative drug potency of individual GCs may differ from the hierarchy for the classic genomic effects. For example, assessing some rapid nongenomic effects, dexamethasone was shown to be the most potent among the tested GCs, thanks probably to the lowest lipophilicity facilitating its interaction directly with the cell membrane [9, 46, 64, 79].

Side effects of GCs

The administration of GCs may be accompanied by mostly unwanted side effects due to their influencing the physiological processes in the body. The occurrence and intensity of adverse effects depend on the type of GCs preparation, dosing, timing and way of administration. While adverse effects are rare in the administration of low (“physiological” or “substitutional”) doses of GCs in substitution therapy, the long-term administration of high (“pharmacological” or “supraphysiological”) doses of GCs may be associated with the side effects of various characters. GC drugs suppress the function of the hypothalamic–pituitary–adrenal axis, decreasing the secretion of corticotropin, which in turn reduces the secretion of cortisol by adrenal glands. Prolonged adrenal suppression may cause reduced responses to stress [3]. In addition, long-term GCs administration may lead to hyperglycaemia, hypokalemia, dyslipidemia, reduced fibrinolysis, hypertension, posterior subcapsular cataract, exacerbation of glaucoma, increased intracranial pressure, peptic ulcers, upper gastrointestinal bleeding, immunosuppression, neuro-psychiatric disturbances, osteoporosis, myopathy, irregularities of the menstruation cycle, etc. [63].
Due to the relatively wide spectrum and high risk of side effects of systemic GCs, the local administration of GCs is generally preferred. However, depending on the system of delivery and dose used, <20% of the nebulized GCs is deposited into the lungs and the rest may be absorbed into the circulation from the gastrointestinal system and subsequently cause systemic effects [61]. In addition, inhalation of GCs may worsen the course of bacterial infections after initial improvement and may increase the risk of oropharyngeal candidiasis, dysphonia, cough, throat irritation and other local side effects [3].

**Use of GCs in perinatal respiratory diseases**

In respirology, GCs (mainly inhalational GCs such as budesonide) are used in asthma and exacerbations of chronic obstructive pulmonary disease [6, 43, 61]. In perinatal period, GCs may be administered antenatally or postnatally. Antenatal GCs (particularly betamethasone and dexamethasone) are used to induce early lung maturation and stimulate the synthesis of pulmonary surfactant in premature infants [5, 60]. Postnatally, GCs (especially dexamethasone) take part in the treatment of chronic lung disease or bronchopulmonary dysplasia after neonatal respiratory distress syndrome [1, 40, 83]. However, long-term GCs administration may exert adverse effects on neuromotor function and the somatic growth of the treated infants [89]. In adult/acute respiratory distress syndrome, GCs (mostly methylprednisolone) may be of benefit in fibroproliferative or late phase of the disease, but use in the early stages of the disease is controversial [24, 34].

**Use of GCs in MAS**

In animal models and in newborns with MAS, hydrocortisone, prednisolone, methylprednisolone, dexamethasone and budesonide have been used, with the subjects having various responses to treatment. Hydrocortisone is a synthetic equivalent of cortisol and used as an immunosuppressive drug in severe allergic reactions such as anaphylaxis and angioedema. Comparing the strength for the anti-inflammatory effect, prednisolone is about four times and dexamethasone is about 30 times stronger than hydrocortisone. Thanks to both glucocorticoid and mineralocorticoid effects, hydrocortisone may be used in substitution therapy; however, expressing mineralocorticoid activity, hydrocortisone may potentiate a dysbalance of liquids and electrolytes in the body.

In the study by Frantz et al. [25] carried out in 1975, the subcutaneous administration of hydrocortisone at a dose of 7.5 mg/kg immediately after meconium instillation and then every 8 h up to 48 h non-significantly improved the histology of the lungs and decreased the frequency of breathing in newborn rabbits. However, a higher mortality of the hydrocortisone-treated animals was observed irrespective if they aspirated meconium or saline, probably due to the infection at the tracheotomy site and sepsis [25]. Two years later, hydrocortisone, at a dose of 20 mg/kg, was

| Agent                        | Activity | Equivalent oral dose (mg) | Forms available |
|------------------------------|----------|---------------------------|----------------|
| Short- to medium-acting GCs   |          |                           |                |
| Hydrocortisone (cortisol)    | 1        | 20                        | p.o., inj., top.|
| Cortisone                    | 0.8      | 25                        | p.o.           |
| Prednisone                   | 4        | 5                         | p.o., inj.     |
| Prednisolone                 | 5        | 5                         | p.o., inj.     |
| Methylprednisolone           | 5        | 4                         | p.o., inj.     |
| Meprednisone                 | 5        | 4                         | p.o., inj.     |
| Intermediate-acting GCs       |          |                           |                |
| Triamcinolone                | 5        | 4                         | p.o., inj., top.|
| Paramethasone                | 10       | 2                         | p.o., inj.     |
| Fluprednisolone              | 15       | 1.5                       | p.o.           |
| Long-acting GCs               |          |                           |                |
| Betamethasone                | 25–40    | 0.6                       | p.o., inj., top.|
| Dexamethasone                | 30       | 0.75                      | p.o., inj., top.|
| Mineralocorticoids           |          |                           |                |
| Fludrocortisone              | 10       | 2                         | p.o.           |
| Hydrocortisone acetate       | 0        | 2                         | p.o., inj.     |

**Table 1** Basic characteristics of commonly used natural and synthetic corticosteroids [36]
administered four times every 12 h via umbilical catheter in 17 neonates with MAS [88]. Blood gases, X-ray, incidence of pneumothorax or pneumomediastinum, requirements for mechanical ventilation and mortality were comparable in the hydrocortisone-treated vs. placebo-administered group. However, longer period to wean to room air and remaining clinical signs of respiratory distress were observed in the treated group than in controls [88]. We may speculate that no benefit of the treatment may be caused by low dose or by late treatment, respectively, since the first dose of hydrocortisone was administered at about 5 h of age [88] when severe respiratory distress and inflammation have already been developed. No effect of hydrocortisone on meconium-induced lung edema in the study by Frantz et al. [25] may be explained by fluid retention in the lungs or delayed reabsorption of the fluid due to mineralocorticoid action of hydrocortisone. In addition, the anti-inflammatory potential of hydrocortisone is several times weaker than that of other GCs.

**Prednisolone** is a GC drug with predominant glucocorticoid and low mineralocorticoid activity. Thanks to its strong anti-inflammatory and immunosuppressive action, it is used for the treatment of a wide range of inflammatory and auto-immune disorders, such as bronchial asthma, rheumatoid arthritis, ulcerative colitis, etc.

In the study by Kirimi et al. [39], the intravenous administration of prednisolone at standard (2 mg/kg) and high (30 mg/kg) doses immediately after meconium instillation improved gas exchange and increased the frequency of breathing in meconium-instilled puppies in comparison with the non-treated group. In addition, high-dose prednisolone showed a more obvious improvement in lung histology compared to the standard dose, without hyperglycaemia or hypertension as side effects. However, high-dose prednisolone significantly increased the plasma levels of malonyldialdehyde, product of lipid peroxidation, compared to standard-dose group and controls at 20 h after meconium aspiration. It may suggest a paradoxically lower effectiveness of high-dose vs. standard-dose prednisolone in the reduction of oxidation stress resulting from inflammation or even the potentiation of oxidation stress by a mega-dose of prednisolone [39]. Nevertheless, the value of this information is limited by the small number of animals included in the treated groups (n=3 each).

**Methylprednisolone**, a methylated derivative of prednisolone, has similar properties and use as prednisolone. Since it may reach higher concentrations in the lungs than prednisolone due to a higher distribution volume, slower elimination and higher accumulation in the alveolar epithelium, it is used also for the short-term treatment of bronchial inflammation or acute bronchitis.

Soukka et al. [66] found that, in 10-week-old pigs with MAS, pretreatment with methylprednisolone (30 mg/kg, i. v.) 30 min before the instillation of meconium tended to prevent an early (0–1 h) increase in pulmonary artery pressure and significantly inhibited the second-phase (1–6 h) progressive rise in pulmonary artery pressure and pulmonary vascular resistance, decreased venous admixture and formation of lung edema and improved oxygenation [66]. In another study by Soukka et al. [67], premedication with methylprednisolone decreased the level of endothelin (ET)-1 and increased the level of atrial natriuretic peptide (ANP). The modulation of the ratio ET-1/ANP for ANP diminished pulmonary hypertension and indicated the protective effect of GCs on the endothelium-mediated regulation of the pulmonary vascular tone [67]. Thus, premedication with GCs before the labour might be beneficial in the case of verified massive meconium staining of the amniotic fluid and prenatal meconium aspiration to reduce remodelling of the pulmonary vascular lining and lung inflammation. However, up to this time, no clinical study was performed to evaluate the possible benefits of prenatal GCs delivery in MAS.

Postnatally, methylprednisolone has been recently used in two trials carried out in India [4, 77, 78]. Methylprednisolone administered for a period of 7 days starting after 24 h of age in 34 newborns with MAS shortened the period of oxygen delivery and duration of hospital stay and improved the radiological clearance of the lungs, while no serious adverse effects including sepsis were observed [4]. In the study by Tripathi and co-workers [77, 78], methylprednisolone was given in 17 newborns with MAS at a dose of 0.5 mg/kg/day, i.v., in two divided doses every 12 h for 7 days. Similarly to the study by Basu et al. [4], methylprednisolone shortened the duration of stay, oxygen dependence and X-ray of the lungs, decreased the levels of TNFα in tracheal aspirate and did not increase the incidence of sepsis.

**Dexamethasone** is a synthetic GC with potent anti-inflammatory and immunosuppressive action. It is >30 times stronger than hydrocortisone and about five times stronger than prednisone. Dexamethasone is also used for diagnostic procedures (to suppress the natural pituitary–adrenal axis) in obstetrics to promote the maturation of foetal lungs as well as in a wide spectrum of endocrine, oncological and other diseases.

The first successful use of dexamethasone in MAS has been referred to in the 1990s, when it improved pulmonary ventilation and facilitated weaning from the ventilator in several newborns with severe MAS [86]. Later, numerous experimental and clinical studies evaluated the efficacy and management of dexamethasone administration in the conditions of MAS. Commonly, dexamethasone at a dose of 0.5 mg/kg body weight has been used.

However, the timing of dexamethasone delivery appears to be critical for the effectiveness of treatment. In
meconium-instilled piglets, pretreatment with dexamethasone (1 h before meconium instillation) reduced pulmonary vascular resistance and lung edema, improved oxygenation and prevented ultrastructural changes of the lungs [30]. Similarly, the early administration of dexamethasone (30 min after meconium instillation) significantly reduced right-to-left pulmonary shunting, improved gas exchange and decreased ventilatory pressures in meconium-instilled rabbits compared to non-treated controls [50]. Furthermore, early dexamethasone decreased the neutrophil count in BAL fluid and reduced lung edema, meconium-induced tracheal hyperreactivity to histamine and concentrations of lipid and protein peroxidation products in the lung homogenate compared to controls [50, 55]. On the other side, the late administration of dexamethasone (1 h after meconium instillation) led to only non-significant improvement of oxygenation and had no effect on lung edema in piglets with MAS [30]. The results have clearly showed a better effect of GCs in early administration occurring before extensive tissue response to the meconium instillation.

Considering time-related inflammatory changes in MAS, limitations of the treatment efficacy in late administration of GCs may be reduced by repetitive administration. It is known that the action of dexamethasone is fast, but of a short term. The half-life of dexamethasone in adults is 110–190 min, with the biological half-life of 36–72 h [14, 74]. In newborns, the plasma half-life of dexamethasone is 150–300 min and the biological half-life is between 36–54 h [47]. Therefore, in acute situations, repetitive administration every 2–4 h is recommended (data given by the producer, Dexam, Medochemie, Cyprus).

In meconium-instilled piglets, two-phase dexamethasone administration at 2 and 8 h after meconium instillation significantly improved gas exchange and lung compliance compared to controls [37]. In a rabbit model of MAS, the repetitive administration of dexamethasone 0.5 and 2.5 h after meconium instillation suppressed inflammation and enhanced gas exchange more effectively than a single dose administered 0.5 h after meconium [50, 52]. Similarly, in newborns with MAS, dexamethasone administered in gradually decreasing doses within maximally 9 days (at a dose of 0.5, 0.25 and 0.125 mg/kg/day, each administered for 3 days) decreased the oxygenation index and facilitated weaning from the ventilator [18].

Nevertheless, high doses of systemic GCs or their repetitive administration may exert various undesirable effects. Although the acute cardiovascular changes may be critical for neonates with meconium-induced lung injury, the side effects of repetitive GCs administration in MAS have not been investigated yet in a clinical study. In a rabbit model of MAS, the slow intravenous administration of one dose, but especially of two doses of dexamethasone, was associated with acute changes of blood pressure, heart rate and heart rate variability within 5 h of treatment [52, 54]. A detailed analysis of cardiovascular changes showed increased blood pressure, decreased heart rate, increased heart rate variability and a higher occurrence of cardiac arrhythmias particularly during and immediately after dexamethasone administration, while decreased heart rate and increased heart rate variability were observed until the end of the observation period (i.e. 5 h after the first dose of dexamethasone) [52, 54].

Budesonide is an inhalational GC used in the treatment of bronchial asthma, non-infectious rhinitis (including hay fever and other allergies) and nasal polyposis. Budesonide has high first-pass metabolism and its administration is associated with a lower incidence of systemic manifestations than with other GCs (fewer bone density losses and little influence on the hypothalamic–pituitary–adrenal axis) [3, 31].

In meconium-instilled rabbits, budesonide (Pulmicort, 0.25 mg/kg) was administered intratracheally 30 min after meconium instillation and then 2 h later using the influsion effect of high-frequency jet ventilation (inspiration time 20%). The treatment effectively alleviated inflammation, decreased lung edema formation and meconium-induced tracheal and lung smooth muscle hyperreactivity to histamine, improved gas exchange and decreased the oxidation injury of the lungs compared to non-treated controls [51]. In addition, intratracheal budesonide administration was associated with negligible acute cardiovascular effects [49] compared to dexamethasone [52, 54].

In 32 newborns with MAS, budesonide administered for a period of 7 days starting after 24 h of age shortened the period of oxygen delivery and duration of hospital stay and improved the radiological clearance of the lungs, while no serious adverse effects were found [4]. In another study [77, 78], budesonide was given in 17 newborns with MAS at a dose of 50 μg/kg/day, i.v., in two divided doses every 12 h for 7 days. Comparably to Basu et al. [4], budesonide shortened the duration of stay, oxygen dependence and X-ray of the lungs, decreased the levels of TNFα in tracheal aspirate and did not increase the incidence of sepsis.

Local administration predisposes the inhalational GCs to be faster and of more potent action at the site of inflammation. Thanks to high lipophilicity, inhalational GCs (budesonide) have rapid direct effects on cells involved in airway inflammation including macrophages, eosinophils, T lymphocytes and airway epithelial cells [3]. In vitro comparison of potency to reduce a release of IL-8 from airway epithelial cells, budesonide has shown ten-times-stronger activity than dexamethasone [59]. It corresponds well with our findings in the rabbit model of MAS, where intratracheal budesonide improved gas exchange and reduced lipid and protein peroxidation in the lung tissue more effectively compared to dexamethasone. In addition, budesonide reduced both tracheal and lung smooth muscle hyperresponsiveness to histamine, while dexamethasone
decreased only tracheal reactivity with no effect on lung tissue [50, 51]. Nevertheless, in the above-mentioned clinical studies [4, 77, 78], no differences between the methylprednisolone- and budesonide-treated groups were found. Similarly, inhaled GCs (beclomethasone) showed no priority to intravenous GCs (dexamethasone) in ventilator-dependent preterm newborns [72].

We may speculate that the absence of superior action of locally administered GCs to systemic GCs may be related to the method of administration used—nebulization. Considering high extrapulmonal losses (>80%) of nebulized material [61], other ways of administration, such as slow administration directly into the trachea, should be considered. In our study, budesonide administered via insufflation effect of HFJV effectively improved the lung functions with minimum losses of the drug and negligible side effects [49, 51]. Intratracheal administration of GCs may be further mitigated by the use of suitable vehicle, e.g. saline or exogenous surfactant [22]. In experimental conditions, an addition of GCs to exogenous surfactant did not alter the surface properties of the surfactant and GCs were well distributed throughout the lungs with 30–60% of the delivered material detected in the lung tissue [58]. In preterm infants, intratracheal instillation of a mixture of budesonide (0.25 mg/kg) and beractant (100 mg/kg) every 8 h decreased the mean airway pressure, oxygenation index and PCO2 and reduced deaths and chronic lung disease at 36th week of postconceptual age compared to the group treated solely by Survanta (100 mg/kg, every 8 h) [90].

**Combinations of GCs with other drugs**

Regarding the results of experimental and clinical studies, GCs may show some benefit in the treatment of MAS. However, due to the complex and multifactorial pathophysiology of the disease, other drugs (e.g. exogenous surfactant) should be included in the therapeutic scheme, too. In newborns with MAS, intravenous dexamethasone at a single dose of 0.5 mg/kg was administered within the first 5 h of life prior to a bronchoalveolar lavage using beractant (5 mg/ml) in a volume of 15 ml/kg in four aliquots [62]. The authors found that the surfactant lung lavage in combination with dexamethasone pretreatment may improve the status of the newborns with MAS more effectively than the surfactant lavage alone [62]. Similarly, in animal models of acute lung injury, the combination of dexamethasone with exogenous surfactant showed an additional improvement to the surfactant treatment alone [13, 26].

By utilization of their synergic or additive effects, GCs may be well combined also with other medicaments, e.g. with methylxanthine derivatives such as theophylline [32], with antioxidants such as N-acetylcysteine [33] or with β2-agonists such as terbutaline [84]. In the experimental model of MAS, intratracheal budesonide followed by the intravenous administration of aminophylline improved the lung functions more effectively than aminophylline alone [53].

**Concluding remarks**

Despite the increasing number of trials with GCs in experimental models and newborns with MAS, their administration is still missing in the generally accepted therapeutic protocol of MAS. However, favourable results from the studies indicate that GCs may be beneficial, particularly in severe forms of MAS with apparent lung edema, pulmonary vasoconstriction and inflammation.

Summarizing all mentioned data, in the future, the research activities should be focused on an appropriate dosing, timing and ways of administration of GCs considering their individual properties and possible acute and long-term side effects. Since the causal treatment of MAS should consist of several agents, it is necessary to also verify the promising combinations of GCs with other drugs, particularly with exogenous surfactant, anti-inflammatory drugs and pulmonary vasodilators.

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