ANTI-INFLAMMATORY DRUGS IN THE TREATMENT OF MECONIUM ASPIRATION SYNDROME

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Abstract

Meconium aspiration syndrome (MAS) is a major cause of respiratory distress in both the term and post-term neonates. Obstruction of the airways, dysfunction of pulmonary surfactant, inflammation, lung edema, pulmonary vasoconstriction and bronchoconstriction participate in the pathogenesis of this disorder. Since the inflammatory changes associated with meconium aspiration cause a severe impairment of the lung parenchyma including surfactant and influence the reactivity of both vascular and airway smooth muscle, administration of anti-inflammatory drugs may be of benefit also in the management of MAS. This article reviews effects of various anti-inflammatory drugs used in experimental models of MAS as well as in the treatment of newborns with meconium aspiration.

Key words: meconium aspiration syndrome, inflammation, anti-inflammatory drugs, newborn, animal model

Meconium aspiration syndrome (MAS)

MAS is a serious disease in both the term and post-term newborns. Obstruction of the airways by aspirated meconium with subsequent alveolar atelectasis behind the plug and air-trapping, inactivation of pulmonary surfactant, inflammation, edema, pulmonary vasoconstriction are often leading to persistent pulmonary hypertension (PPHN), and bronchoconstriction participate in the pathogenesis of MAS (Figure 1). Because meconium-induced inflammation with its multiple impacts on the lungs plays more important role than was previously thought, various anti-inflammatory drugs have been tested in the treatment of MAS. This article reviews inflammatory changes in MAS as a rationale for anti-inflammatory treatment and introduces anti-inflammatory drugs mostly used in the treatment of MAS.

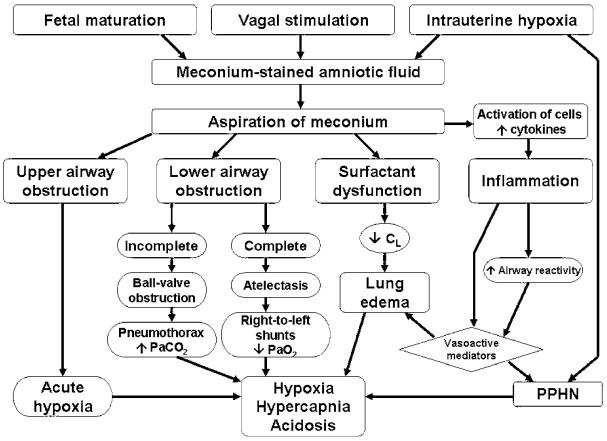

Fig. 1. Scheme of pathomechanisms participating in MAS.

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Inflammation in MAS

Meconium is a source of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)α or interleukines (IL-1β, IL-6, IL-8) (1), which may directly or indirectly through the cytokines produced by neutrophils (2), macrophages (3) and epithelial cells injure the lungs. Neutrophils are activated by macrophages and cytokines, stimulating adhesion of neutrophils on the endothelium. Besides this, meconium itself potentiates chemotactic activity of neutrophils (4). Within several hours, instillation of meconium causes an accumulation of neutrophils in the lungs, while their number in the peripheral blood decreases (5-7).

Activated neutrophils and macrophages may damage the lungs by different ways. Production of pro-inflammatory substances (TNFα, interleukins, prostaglandins, leukotrienes), activation of complement, activation of coagulation cascade, release of platelet activating factor (PAF) and vasoactive substances may finally lead to destruction of capillary endothelium and basement membranes. Injury of alveolocapillary membrane results in leak of liquid, plasma proteins and cells into the interstitium and later also into the alveolar spaces. Closure of capillaries by fibrin and cellular debris participates in the development of pulmonary hypertension, a frequent complication observed in MAS (8).

Together with mediators, proteolytic enzymes are released from the neutrophilic granules. Proteases, e.g. elastase, may destruct the membranes and surfactant proteins, and stimulate the synthesis of bioactive substances and increase endothelial permeability (9). Activated leukocytes produce also reactive nitrogen and oxygen species (RONS) with cytotoxic effect. Peroxidation of unsaturated free fatty acids causes a loss of the functional integrity of membranes and increase of capillary permeability. Oxidation stress finally results in vasoconstriction, bronchoconstriction, platelet aggregation, increased cellular apoptosis (10) and injury of cerebral structures (11).

Activated cells produce high amounts of phospholipase A_2 (PLA_2), too. In addition, meconium itself contains pancreatic PLA_2, which may directly or through the stimulation of arachidonic acid metabolites injure the lung epithelium, endothelium and surfactant and participate in intensified apoptosis (12). Arachidonic acid released from membrane lipids under stimulation of PLA_2 is a precursor for synthesis of both cyclooxygenase (COX) and lipooxygenase products, e.g. for thromboxan A_2 (TXA_2) increasing pulmonary vascular resistance (13), or for leukotrienes causing bronchoconstriction (14), both potentiating microvascular permeability. PLA_2 stimulates also the production of PAF, which participates in pulmonary hypertension, increased capillary permeability and bronchoconstriction, as well as in aggregation and degranulation of neutrophils, macrophages and platelets (15).

In addition, cytokines enhance expression of inducible NO synthase (iNOS) (16, 17) and production of NO (18). Excessive amounts of produced NO via iNOS then lead to increased formation of reactive nitrogen species (e.g. peroxynitrite) and finally increase permeability of alveolocapillary membrane and lung injury (19). Furthermore, cytokines increase production of endothelin-1 (ET-1), a potent vasoconstrictor stimulating proliferation of smooth muscle (20). Inflammation and release of bronchoactive substances (e.g. leukotrienes, PAF etc.) are probably responsible also for increased airway reactivity in MAS (7).

Anti-inflammatory treatment in MAS

Regarding the above mentioned knowledge on the role of inflammation in the pathogenesis of MAS, several anti-inflammatory drugs were administered in experimental models of MAS as well as in the treatment of newborns with meconium aspiration. Their pharmacological action and effects in MAS is reviewed in further subsections.

Glucocorticoids

Potent anti-inflammatory activity of glucocorticoids (GCs) results from reducing the migration and activation of neutrophils, eosinophils, mononuclears, and other cells (endothelial, epithelial etc.) as well as from modulation of chemotaxia and action of mediators released from the activated cells. In addition, by stabilization of cell membranes and by decreased production of pro-inflammatory and vasoactive substances GCs reduce microvascular permeability. Furthermore, directly modulating pulmonary vasomotoric tone GCs diminish pulmonary vasoconstriction and inhibit fibrogenesis (22).

GCs possess both genomic and non-genomic mechanisms of the action. In genomic action, GCs penetrating into the cytoplasm interact with glucocorticoid receptor (GR). The activated complex moves into the nucleus and binds to specific nuclear sequence of DNA (glucocorticoid responsive element, GRE). When GC-GR complex interacts with negative responsive element (GRE^-), inhibition of transcription factors including nuclear factor (NF)-κB and protein activator (AP)-1 inhibits an expression of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF_a etc.), enzymes (PLA_2, COX-2, iNOS etc.) and other biologically active substances such as PAF, ET-1 etc. (22, 23). On the other hand, interaction of GC-GR complex with positive responsive element of DNA (GRE^+) increases transcription of lipocortine-1 in leukocytes, which inhibits activity of PLA_2, and thereby decreases production of arachidonic acid and its metabolites as well as of PAF (23).

Besides genomically mediated mechanisms, GCs act also through nongenomically-mediated ones, which are responsible for rapid GCs action until the effects mediated by genomic mechanisms occure (24). GCs may exert effects on various cells modulating hormone secretion, neuronal excitability, ion cycling, saccharide metabolism, and other processes within seconds or minutes (24, 25). Rapid effects of GCs are presumably responsible for inhibition of airway hyperreactivity (26), as well as for cardiovascular changes (27) or improved respiratory parameters (28, 29) in animals with MAS observed within minutes after GCs administration.

In *in vitro* studies, GCs suppressed meconium-induced expression of COX-2 and iNOS in macrophages, epithelial and endothelial cells (16, 17), as well as production of NO and TXA_2 in epithelial cells (18, 30).

In animals with MAS, GCs inhibited expression of PLA_2 in the lungs (6, 31). Interruption of cytokine cascade and inhibition of chemotaxia by GCs resulted in reduced neutrophil influx into the lungs with simultaneous increase in leukocyte count in the blood (5-7). Although treatment with hydrocortisone in newborn rabbits (32) and in newborns with MAS (33) led to controversial results, higher doses of more potent GCs in later experiments were of benefit. Administration of methylprednisolone (5) or prednisolone (34) effectively improved the lung functions. Similarly, pretreatment and early treatment with dexamethasone reduced pulmonary vasoconstriction and improved oxygenation (6, 35). In rabbits, dexamethasone administered 30 minutes after meconium instillation enhanced gas exchange, reduced ventilatory pressures and decreased number of neutrophils, edema formation, and oxidative lung injury, and alleviated meconium-induced airway hyperresponsiveness to histamine (7, 28). Similarly in newborns with MAS, dexamethasone decreased number of leukocytes in tracheal aspirate and levels of several cytokines, improved lung functions and facilitated weaning from the ventilator (14, 36).

Taken together, neonates with severe MAS could benefit from systemic GCs. However, timing of administration is critical for ideal response, as the changes associated with meconium aspiration become severe very early. Nevertheless, repetitive administration of GCs may increase the effectiveness of the treatment. Administration of dexamethasone in two doses enhanced gas exchange and reduced oxygen requirements in piglets (14) and in rabbits with MAS (28). In newborns with MAS, dexamethasone given for several days in a reducing schedule improved lung functions and facilitated weaning from the ventilator (36). Thus, GCs may be effective also in well-established MAS, but repetitive doses should be used.

On the other hand, systemic administration of GCs may be associated with various adverse effects. In our experiments single-dose, but especially two-dose dexamethasone increased blood pressure, decreased heart rate, increased heart rate variability, and increased incidence of cardiac arrhythmia in meconium-instilled rabbits (27).

Nevertheless, occurence of adverse effects of GCs depends on the properties of individual GCs, duration and dosing, as well as on the route of administration. For example, local administration may eliminate the side effects of GCs. In meconium-instilled rabbits, we have administered budesonide directly into the jet of ventilator during inpulsion regime of high-frequency jet ventilation (inspiration time 20 %). Budesonide improved oxygenation and decreased pulmonary shunting, edema formation, neutrophil count in the lungs and markers of oxidative injury compared to non-treated group (29), with less cardiovascular side effects. In other study, shortened duration of oxygenotherapy and hospitalization, improved x-ray of the lungs without increased incidence of sepsis after both systemic (methylprednisolone) and nebulized (budecort) GCs were observed in newborns with MAS (37, 38).

Adverse effects of GCs may be reduced also by combined administration with drugs with similar or additive effects, e.g. with methylxanthines or antioxidants. In our study, intratracheal budesonide followed by intravenous aminophylline showed more pronounced improvement in lung functions than single aminophylline (39).

Inhibitors of phosphodiesterase

Phosphodiesterases (PDE) are a superfamily of enzymes degrading cAMP and cGMP. From up to now 11 PDE families identified, predominantly PDE3, PDE4, and PDE5 isoforms may be involved in MAS due to their pro-inflammatory and smooth muscle contraction activity (40). Therefore, non-selective (methylxantines) as well as selective inhibitors of PDE could be potentially used in the therapy of MAS.

Non-selective PDE inhibitors (methylxanthines)

Methylxanthines improve respiratory and hemodynamic parameters by their vasodilation, bronchodilation, and anti-inflammatory effects. Decreasing PDE activity, methylxanthines increase intracellular cAMP and cGMP, decrease the concentrations of intracellular calcium, acetylcholine and monoamines, and reduce the releasing and action of various mediators. In addition, methylxanthines via antagonizing adenosine receptors improve the immune activity of mastocytes and basophils, increase surfactant secretion and mucociliary transport, and enhance the up-take of ROS (41, 42). Furthermore, in low plasma concentrations methylxanthines exert anti-inflammatory action resulting from direct activation of histone deacetylase activity leading to reduced transcription of inflammatory genes (42).

In *in vitro* incubation with meconium, pentoxifylline inhibited degranulation of polymorphonuclears and decreased the production of TNF_a (43). In piglets with MAS, pentoxifylline prevented local ventilatory perturbations as well as increase in macrophage count of BAL fluid, TNF_a and protein concentrations in the lungs, but had no significant effect on the lung neutrophil accumulation (44).

Other methylxanthine derivative - aminophylline - improved gas exchange, reduced lung edema and number of neutrophils in the lungs and decreased oxidative lung injury and airway hyperreactivity to histamine in a rabbit model of MAS (45). Comparing two different doses of aminophylline we found that higher-dose aminophylline (2 mg/kg) had stronger effect on pulmonary functions, lung edema and number of neutrophils in the lungs than lower-dose aminophylline. Nevertheless, lower-dose aminophylline more effectively diminished protein oxidation in the lungs and lung tissue reactivity to histamine (45).

Selective PDE inhibitors

As mentioned above, particularly the activity of PDE3, PDE4 and PDE5 may be presumed in meconium-induced inflammation and pulmonary vaso- and bronchoconstric-

tion. In piglets with MAS, PDE5 inhibitor sildenafil reversed an increase in pulmonary vascular resistance within 1 hour of the treatment, without affecting the systemic hemodynamics (46). Milrinone, a selective PDE3 inhibitor, improved oxygenation and survival of neonates with MAS (47). In our experiments, PDE3 inhibitor olprinone enhanced pulmonary functions, reduced lung edema and diminished inflammation and oxidative lung injury in meconium-instilled rabbits (48). While PDE3 and PDE5 inhibitors were already tested in MAS, there are no remarks about the use of PDE4 inhibitors in MAS. As they have been proven as efficient in asthma (49), their possible benefits in MAS need to be evaluated.

Nevertheless, possible side effects of PDE inhibitors on cardiovascular functions should be considered. As previously noticed, cardiovascular side effects may be comparable in both selective and non-selective PDE inhibitors (42). In our recent study, administration of both aminophylline and olprinone caused rapid, but short-term increase in blood pressure and heart rate (unpublished observation).

Interactions with renin-angiotensin-aldosterone (RAA) system

Angiotensin II as a product of angiotensin-converting enzyme (ACE) action is responsible for contraction of vascular smooth muscle. Furthermore, angiotensin II is suggested to regulate locally the apoptosis of alveolar epithelial cells and to affect the neutrophil accumulation in the tissue (50). Pretreatment with ACE inhibitor captopril before meconium instillation in newborn rabbits decreased levels of ET-1 and pro-inflammatory cytokines and reduced apoptosis (50). Similarly, pretreatment with a non-specific angiotensin II receptor blocker saralasin prevented an increase in lung tissue myeloperoxidase activity, endothelial monocyte-activating polypeptide, and lung epithelial apoptosis in rats with MAS (51). Therefore, influencing the action of angiotensin II via inhibition of ACE or blockade of angiotensin receptors seems to be promising in the treatment of MAS.

Antioxidants

Since RONS and products of lipid and protein peroxidation impair the lung tissue in MAS, administration of substances with antioxidant properties may be of benefit. Intratracheal administration of recombinant human superoxide dismutase decreased myeloperoxidase activity, NO and 8-isoprostane levels and lung injury score in meconium-instilled rats (52), as well as increased oxygenation and reduced vasoconstriction and oxidative injury in newborn lambs with persistent pulmonary hypertension (53). In our recent experiments, intravenous N-acetylcysteine enhanced gas exchange and reduced inflammation in meconium-instilled rabbits, with negligible cardiovascular side effects (unpublished observation).

Inhibitors of cyclooxygenase

Inhibitiors of cyclooxygenase are used for their analgesic, antipyretic, and anti-inflammatory effects. According to their selectivity, they are divided to COX-2 selective and COX non-selective non-steroid anti-inflammatory drugs. In MAS, indomethacin inhibited release of TXA_2 from epithelial cells (30), but did not influence an expression of COX-2 or iNOS in the lungs (16). On the other hand, pretreatment with acetylsalicylic acid prevented the initial pulmonary hypertensive response and reduced release of prostanoids in piglets with meconium aspiration (13). However, these results are insufficient to recommend COX inhibitors for MAS treatment at the moment, although their adverse effect profile (especially of COX-2 selective inhibitors) is more convenient compared to that in GCs.

Endothelin antagonists

Considering the role of ET-1 in the meconium-induced pulmonary vasoconstriction (20), administration of endothelin receptor antagonists may improve the status of meconium-injured newborns. In hypoxia-induced pulmonary hypertension in rats, pretreatment with orally given antagonist of ET-1 receptors ET_A and ET_B bosentan attenuated pulmonary hypertension, right heart hypertrophy, and remodelling of small pulmonary arteries (54). Similarly, intravenous administration of other ET_A receptor blockers lowered pulmonary vascular resistance, and enhanced survival in piglets with MAS (55).

Prostacyclin analogues

Prostacyclin as a potent pulmonary vasodilator may be beneficial particularly in the conditions of hypoxia (56). In addition, inhaled PGI_2 may be well combined with other drugs. For example, inhalation of PGI_2 showed a synergistic effect with PDE inhibitors in experimental pulmonary hypertension (57). In a model of MAS, synthetic analogue of PGI_2 iloprost was combined with dual endothelin A and B receptor blocker tezosentan. Since intravenous tezosentan improved gas exchange and hemodynamics, inhaled iloprost enhanced only gas exchange reducing intrapulmonary shunts (58).

Exogenous surfactant

Pulmonary surfactant may protect the lungs also from the inflammation modulating the peroxidation, nitric oxide, PLA_2, arachidonic acid metabolites, and cytokines (59). Similar effects may be theoretically observed also in exogenous surfactants containing surfactant proteins A and/or D (60). Anyway, considering other favourable effects of surfactant, its anti-inflammatory properties seem to be of minor importance in MAS.

Drugs potentially beneficial in MAS

Considering similar pathogenesis, several other drugs being successfully tested or used in the treatment of persistent pulmonary hypertension or acute lung injury may be potentially beneficial also in MAS, e.g. inhibitors of complement, cytokine monoclonal antibodies, inhibitors of proteolytic enzymes, anticoagulants, or calcium-channel blockers.

Conclusion

Advances in our understanding of the pathogenesis of MAS lead to the development of novel approaches focusing on pulmonary inflammation and oxidative injury. Wide variety of anti-inflammatory drugs acting on different levels of inflammatory cascade may alone or in combination with exogenous surfactant and vasodilators potentially improve the clinical status and survival of newborns with MAS. Nevertheless, effects of anti-inflammatory drugs including their side effects in meconium-induced lung injury should be tested thoroughly in experimental and clinical conditions till their use may be recommended.

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