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REVIEW

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Phosphodiesterase inhibitors: Potential role in the respiratory distress of neonates

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Abstract

Phosphodiesterases (PDEs) are a superfamily of enzymes that catalyze the hydrolysis of phosphodiester bonds of 3′,5′ cyclic adenosine and guanosine monophosphate (cAMP and cGMP). PDEs control hydrolysis of cyclic nucleotides in many cells and tissues. Inhibition of PDEs by selective or nonselective PDE inhibitors represents an effective targeted strategy for the treatment of various diseases including respiratory disorders. Recent data have demonstrated that PDE inhibitors can also be of benefit in respiratory distress in neonates. This article outlines the pharmacological properties of nonselective and selective PDE inhibitors and provides up-to-date information regarding their use in experimental models of neonatal respiratory distress as well as in clinical studies.

KEYWORDS
neonate, phosphodiesterase inhibitors, respiratory distress

1 | INTRODUCTION

Phosphodiesterases (PDEs) include 11 superfamilies of enzymes that catalyze hydrolysis of phosphodiester bonds of 3′,5′ cyclic adenosine and guanosine monophosphate (cAMP and cGMP). Each type of cell generates several different PDE subtypes. Their origins and localizations are part of the primary regulatory mechanism of the concentration of cyclic nucleotides (cAMP and/or cGMP) in their respective tissues or cells. Control of hydrolysis of cyclic nucleotides by PDE inhibitors represents a potential therapeutic strategy in various diseases, including respiratory distress in neonates.[1]

1.1 | Nonselective PDE inhibitors

The best known nonselective PDE inhibitors are methylxanthines. The representative methylxanthine, caffeine, is used because of its stimulatory effects on respiration, cognitive function, and attention. Two other methylxanthines, theophylline, and theobromine, are used in the therapy of bronchial asthma and chronic obstructive

pulmonary disease[2,3] because of their bronchorelaxation, vaso relaxation, and cardiostimulation effects.

The mechanisms of methylxanthine action are complex and not yet completely understood. They increase intracellular levels of cAMP and cGMP, and this causes bronchodilation and vasodilation. Furthermore, methylxanthines lower levels of calcium, acetylcholine, and monoamines in cells and suppress the release and action of a variety of pro-inflammatory substances.[2,4] Due to the similarity in their chemical structures, methylxanthines compete with other purines for receptor binding sites on adenosine receptors. As adenosine is an endogenous purine that participates in many processes including bronchoconstriction and chronic inflammation in the airways,[5] competitive inhibitors of adenosine receptors such as methylxanthines cause bronchodilation. Moreover, methylxanthines stimulate production of surfactant, enhance mucociliary clearance, and scavenging of reactive oxygen species (ROS).[4] Methylxanthines exert positive inotropic and chronotropic cardiac effects, increase blood pressure and renal blood flow, and stimulate breathing through the medullary respiratory center. However, characteristics of individual methylxanthines differ according to their ability to influence the particular families of PDEs and/or the extent of interaction with adenosine receptors.

Theophylline influences bronchial and vascular tone rapidly—therapeutic plasma levels are reached within several minutes, reaching maximum plasma concentration 20 min after intravenous delivery.[6] The action of theophylline strongly depends on the dose, with a narrow therapeutic window. Therapeutic doses of theophylline with plasma concentrations between 10-20 μg/mL produce bronchodilation and vasorelaxation, diminish capillary permeability and provide some anti-inflammatory actions, such as enhanced production of anti-inflammatory interleukin (IL)-10, suppression of nuclear factor (NF)-κB, and scavenging of ROS. These effects are mediated primarily by PDE inhibition and adenosine antagonism.[2] Supra-therapeutic doses of theophylline at plasma concentrations >20 μg/mL may be accompanied by adverse effects on the gastrointestinal system (mediated via PDE inhibition) and the cardiovascular system (mediated predominantly via adenosine A_1 receptor antagonism).[4] Conversely, anti-inflammatory and immunomodulatory effects of theophylline at low plasma concentrations (5-10 μg/mL) are thought to be mediated neither by PDE inhibition nor by adenosine receptor antagonism, but by direct activation of histone deacetylase.[2]

Aminophylline is a mixture of theophylline and ethylenediamine, the latter of which enhances its water-solubility and absorption. Due to similarities between aminophylline and theophylline, the former is also used as a bronchodilator, an antioxidant, an anti-inflammatory agent, and a stimulator of respiration.[2]

Another representative methylxanthine is *pentoxifylline* (or dimethylxanthine). Pentoxifylline has potent anti-inflammatory effects and excellent hemorheologic properties, reducing aggregation of platelets, and creation of thrombi, thereby improving peripheral blood flow.[7,8]

Caffeine (or trimethylxanthine) acts as a stimulant of the central nervous system (CNS) via reversible blocking of adenosine at the receptor level,[9] as well as activating various parts of the autonomic nervous system.[10]

1.2 | Selective PDE inhibitors

PDE isoforms are expressed in various cells and tissues in variable amounts. Because the distribution and activity of individual PDEs may be higher or lower in various types of cells (eg, immune cells, endothelial cells, smooth muscle cells), selective inhibition of individual PDEs can influence the function of these cells.[11] Therefore, selective PDE inhibitors reduce activation of immune cells, produce vasodilation or bronchodilation, etc.

With respect to the changes involved in the pathophysiology of respiratory distress, selective inhibitors of PDE3, PDE4, and PDE5 may be of benefit.[11–13] PDE3, particularly the isoform PDE3A, is present in the myocardium, vascular and airway smooth muscle, fat tissue, and platelets. Thus, ***PDE3 inhibition*** enhances myocardial contraction, leads to vasodilation, and suppresses platelet aggregation. PDE3 inhibitors such as olprinone and milrinone probably act through inhibition of a PDE3B isoform in T-lymphocytes and macrophages, demonstrating anti-inflammatory effects as well.[12] Because PDE4 isoforms are widely expressed in immune cells, ***PDE4 inhibitors*** (eg, roflumilast or rolipram) exert potent anti-inflammatory activities. However, PDE4 is also present in high concentrations in the vascular endothelium and brain.[12,13] The isoforms PDE5A1 and PDE5A2 are expressed in platelets, vascular smooth muscle, brain, lung, heart, kidney, and skeletal muscle, whereas PDE5A3 is specific to vascular smooth muscle. The topical distribution of PDE5 isoforms determines the use of selective ***PDE5 inhibitors***, such as sildenafil and dipyridamol, to act as effective vasodilators.[13,14]

1.3 | Side effects of PDE inhibitors

The administration of PDE inhibitors can be accompanied with serious side effects, such as tachycardia, gastroesophageal reflux, and increased diuresis.[1,2] However, the side effects of PDE inhibitors can be pronounced in preterm neonates because of the immaturity of hepatic enzymes.[15] To evaluate the acute cardiovascular effects of PDE inhibitors, changes in blood pressure, heart rate, and heart rate variability were analyzed during administration and within 5 h after administration of intravenous aminophylline and the selective PDE3 inhibitor olprinone in a rabbit model of meconium aspiration syndrome (MAS). Both agents acutely increased blood pressure and heart rate, whereas heart rate variability remained higher until the end of experiment, correlating well with biochemical markers of cardiovascular injury.[16,17]

2 | RESPIRATORY DISTRESS IN THE NEONATES

2.1 | Respiratory distress syndrome (RDS)

RDS is a life-threatening condition that occurs particularly in preterm neonates. Signs of respiratory distress develop soon after birth, resulting from immaturity of the lung and insufficient synthesis of pulmonary surfactant.[18,19] For prevention of RDS, antenatal steroids

are given to the mother to enhance fetal lung maturation and to promote surfactant production. Mild forms of RDS respond to supplemental oxygen and the application of continuous positive airway pressure (CPAP) ventilation. More severe cases require endotracheal intubation and administration of exogenous surfactant with or without the need for mechanical ventilation.[19,20]

Although the pathophysiology of RDS is related primarily to the insufficient production of functional surfactant that can be resolved by surfactant supplementation, it is worth considering strategies such as the use of PDE inhibitors that can reduce lung inflammation in ventilated preterm babies during the acute stages of RDS and may potentially reduce the time on mechanical ventilation.[21]

2.1.1 | In vitro studies

In an in vitro study, pentoxifylline down-regulated the expression of CD14, CD11b, CD64, CD71, and CD80 in blood monocytes in a concentration-dependent manner, with the greatest effect on CD14 and CD11b in samples from preterm infants. Pentoxifylline suppressed production of TNFα, IL-1β, and IL-6 in samples from all age groups (adults, term, and preterm neonates), reduced early production of IL-10 in monocytes of the preterm and term neonates, downregulated TLR4 expression on the cellular and mRNA level and suppressed phagocytosis.[22]

2.1.2 | Experimental studies

Favorable effects of PDE inhibitors were also observed in animal models of RDS, in which surfactant depletion (resembling the changes in RDS) was produced by repetitive saline lung lavage. In surfactant-depleted rats, intratracheally delivered PDE4 inhibitor roflumilast prevented hyaline membrane formation and lung infiltration by neutrophils but did not influence oxygenation. However, additional improvement was observed when roflumilast was added to rSP-C surfactant.[23] In saline-lavaged rabbits, roflumilast reduced neutrophil leak into the lung associated with a decrease of blood neutrophils. Roflumilast decreased lung edema formation expressed as the wet/dry lung weight ratio, improved oxygenation, decreased right-to-left pulmonary shunts, reduced pro-inflammatory cytokines, lowered markers of tissue injury, and markers of oxidative stress and diminished apoptosis of lung epithelial cells.[24]

2.1.3 | Clinical studies

Early caffeine administration (initial dose on the 1st day of life) in very preterm neonates improved outcomes, reduced the need for invasive ventilation and total duration of mechanical ventilation and decreased future complications, such as intraventricular hemorrhage, patent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD).[15,25] These effects may be attributed to broad anti-inflammatory properties, the ability to stimulate breathing and increase sensitivity to CO_2, improvement in hemodynamics and in cerebral blood flow, as well as to antagonism of several prostaglandins.[25]

2.2 | Apnea of prematurity (AOP)

AOP is a common complication of preterm birth that occurs as a result of immature respiratory control. An apneic spell is usually defined as cessation of breathing for 20 s or longer, or a shorter pause accompanied by bradycardia (<100 beats per minute), cyanosis, or pallor.[26] The incidence of apneic episodes corresponds inversely to gestational age and birth weight.[27] Methylxanthines, mainly caffeine and theophylline, have been used for prevention and treatment of AOP for years. Methylxanthines generally act as stimulants of CNS and as stimulators of respiratory drive, lowering the threshold of sensitivity to hypercapnia, increasing the contractility of the diaphragm, and facilitating weaning off mechanical ventilation.[27] As the pioneering "Caffeine for Apnea of Prematurity (CAP)" trial,[27,28] the effects of caffeine on the incidence of AOP, BPD, retinopathy of prematurity, and PDA have been confirmed in many studies.[25,30–33] The standard dosing regimes of caffeine citrate include an intravenous loading dose of 20 mg/kg followed by a maintenance dose of 5 mg/kg/day.[15] Higher doses of caffeine (a loading dose of 40 mg/kg and a maintenance dose of 20 mg/kg/day) were also well-tolerated and significantly decreased the frequency of apnea, though with a higher risk of episodes of tachycardia.[34]

Caffeine demonstrated better enteral absorption, higher therapeutic ratio and longer half-life; this allowed once-daily administration with fewer plasma concentration fluctuations, greater penetration into the CNS without producing fluctuations in cerebral blood flow and fewer adverse effects than theophylline.[15,27] Although several studies suggested aminophylline was a comparable, more easily available and cheaper alternative to caffeine,[35,36] caffeine has become the drug of choice for AOP.[21]

2.3 | Bronchopulmonary dysplasia (BPD)

BPD remains a major complication of prematurity. The etiology includes exposure to mechanical ventilation, oxygen toxicity, infection, and inflammation. These factors contribute to arrested alveolar development and associated abnormal vascular growth and damage to the distal airways.[37] BPD is defined as supplemental oxygen dependency for at least 28 days from birth, and at 36 weeks corrected gestational age.[18,19] When RDS in extreme prematurity progresses to BPD, in addition to supportive treatment, protective ventilation strategies, and supplemental oxygen are used. Inflammation with complex interactions among inflammatory cells, chemokines, adhesion molecules, ROS, proteases, and growth factors are major contributors to the pathogenesis of BPD.[38] Therefore, anti-inflammatory drugs such as corticosteroids and antioxidants may be useful.[37] However, PDE inhibitors also appeared to be of benefit.[15,37]

2.3.1 | In vitro studies

In lung epithelial cells, the nonselective PDE inhibitor caffeine and the PDE4 inhibitor rolipram inhibited important signaling pathways for cell development and growth, including those involved in airway remodeling, suggesting the potential for PDE4 inhibitors in BPD.[39]

2.3.2 | Experimental studies

Caffeine was also effective in animal models of hyperoxia-induced lung injury that served as models of BPD. In a hyperoxia-induced model of BPD in rat pups, early caffeine treatment increased cAMP levels in the lungs and improved alveolar structure and angiogenesis.[40] Teng et al[41] found that caffeine treatment attenuated hyperoxia-impaired alveolar formation and suppressed the hyperoxia-induced activation of cyclooxygenase-2 and markers of apoptosis. In another study, caffeine attenuated chemokine and cytokine upregulation as well as the influx of leukocytes, suggesting that the protective effects of caffeine in the neonatal lung were partially mediated by reduction of pulmonary inflammation.[42] In preterm rat pups exposed to hyperoxia, treatment with the PDE4 inhibitors rolipram and piclamilast prolonged median survival and reduced alveolar fibrin deposition, lung inflammation and vascular leakage by decreasing influx of monocytes and macrophages and protein efflux, as measured in bronchoalveolar lavage (BAL) fluid. Analysis of mRNA expression demonstrated significant improvement in key genes involved in inflammation, fibrin deposition and alveolarization.[43] In addition, neuroprotection in the developing brain was recently demonstrated in hyperoxia-exposed neonatal rats where caffeine reduced oxidative stress, promoted antioxidative responses and down-regulated pro-inflammatory transcription factors, cytokines and pro-apoptotic effectors.[44]

2.3.3 | Clinical studies

Complex antioxidant, anti-inflammatory, antiapoptotic properties, and potential neuroprotective effects of caffeine on the developing brain were also confirmed in preterm infants with BPD.[21,45] In the CAP trial, infants who received caffeine had a lower incidence of BPD.[28,29] At 18-month follow-up, treated infants had a lower incidence of cerebral palsy and cognitive delay.[29] By 5 years of age, the reduction in rates of cerebral palsy with caffeine treatment were no longer statistically significant, but gross motor function was improved and the incidence of developmental coordination disorder was decreased.[30,32] Early caffeine therapy initiated within 3 days[31] or 2 days of life[33] Led to lower incidence of BPD. The protective effects of caffeine on the lungs could be attributed to reduced lung inflammation, improved pulmonary mechanics, reduced airway and total lung resistances, enhanced lung compliance, improved ventilation efficiency index, and increased respiratory muscle contractility.[15]

Pentoxifylline is another nonselective PDE inhibitor that can be potentially beneficial in BPD.[46] In addition to anti-inflammatory properties, it lowered blood viscosity and improved microcirculation and tissue perfusion, with rare adverse effects.[47] In a pilot study, nebulized pentoxifylline administered to very low birth weight infants at a dose of 20 mg/kg every 6 h on three consecutive days reduced the risk of BPD.[48]

2.4 | Meconium aspiration syndrome (MAS)

MAS usually occurs in full term neonates. The aspiration of meconium (or the first feces of the newborn) into the lung causes airway obstruction, surfactant dysfunction, neutrophil-mediated lung inflammation, lung edema formation, and pulmonary vasoconstriction, resulting in persistent pulmonary hypertension of the newborn (PPHN).[49] Treatment approaches were historically based on oro- and nasopharyngeal suctioning after delivery of the head but before delivery of the shoulders; however, routine suctioning on the perineum is no longer recommended as it did not reduce the incidence of MAS.[50] Current guidelines from 2017 postulate that if the infant is vigorous with good respiratory effort and muscle tone, the infant can remain with the mother to receive the initial steps of newborn care. If an infant born through meconium-stained amniotic fluid presents with poor muscle tone and inadequate breathing efforts, the initial steps of resuscitation should be completed under a radiant warmer. Appropriate intervention to support ventilation and oxygenation should be initiated as indicated for each infant. Infants with meconium-stained amniotic fluid should no longer routinely receive intrapartum suctioning, whether they are vigorous or not.[51]

Further improvement in severe cases of MAS could be seen with the use of exogenous surfactant and inhaled nitric oxide (NO), or anti-inflammatory drugs, for example, corticosteroids.[49,52] Nevertheless, the results of the following in vitro and in vivo experimental studies indicated that PDE inhibitors may be beneficial in MAS as well.

2.4.1 | In vitro studies

In an in vitro study, pentoxifylline decreased meconium-induced degranulation of elastase and lactoferrin from azurophilic and specific granules of polymorphonuclears (PMNs).[53]

2.4.2 | Experimental studies

In a piglet model of MAS, pentoxifylline prevented an increase in TNFα and protein content and the counts of alveolar macrophages in BAL fluid but had no significant effect on pulmonary neutrophil accumulation.[54] In rats with meconium-induced injury, pentoxifylline pretreatment showed a tendency to prevent an increase in TNFα and protein content in BAL fluid and to improve the oxygenation index (OI).[55]

In meconium-instilled rabbits, intravenous aminophylline improved gas exchange, decreased right-to-left pulmonary shunts, and ventilatory pressures, reduced formation of lung edema, airway hyperreactivity to histamine, neutrophil counts in the BAL fluid, and diminished oxidative modifications of proteins and lipids in the lung.[56] A comparison of two doses showed that aminophylline delivered at a higher dose (2 mg/kg) was superior to aminophylline at a lower dose (1 mg/kg) in terms of improvement in lung function, as well as in reduction of lung edema, lipid oxidation, tracheal reactivity to histamine, and migration of neutrophils into the lung. However, low-dose aminophylline suppressed protein oxidation and meconium-induced lung tissue hyperreactivity to histamine, suggesting that low-dose methylxanthines exerted some anti-inflammatory properties.[57] In another study, olprinone in meconium-instilled rabbits significantly reduced the number of PMNs in BAL fluid, decreased the formation of oxidation markers in the lung, reduced lung edema, and prevented a

decrease in total antioxidant status in the lung and plasma.[58] In a neonatal rat model of MAS, sildenafil at a dose of 25 mg/kg attenuated histopathological changes and lung injury scores, reduced myeloperoxidase activity in the lungs and levels of TNFα in serum, suppressed oxidative stress in the lungs as assessed by levels of NO, superoxide dismutase activity and malondialdehyde levels, attenuated apoptosis in the lungs and increased levels of cAMP and cGMP in serum.[59]

2.4.3 | Clinical studies

Clinical studies carried out on the neonates with MAS addressed the use of PDE inhibitors in association with PPHN; therefore, they are mentioned in the following section.

2.5 | Persistent pulmonary hypertension of the newborn (PPHN)

Failure of the pulmonary vasculature to adapt to the ex-utero environment after birth results in persistence of high pulmonary vascular resistance (PVR), right-to-left shunting, including shunts via the PDA and the foramen ovale, leading to pulmonary hypoperfusion, hypoxia, and acidosis. PPHN can be primary (idiopathic) or secondary to parenchymal lung disease, such as MAS, pneumonia, asphyxia, RDS or BPD, or to lung hypoplasia (with congenital diaphragmatic hernia or oligohydramnios).[60] In an effort to reduce PVR, oxygen and pulmonary vasodilators (eg, inhaled NO) were used in the treatment of PPHN.[19,20] However, in PPHN or in abnormally constricted pulmonary vasculature, selective PDE3 and PDE4 inhibitors, particularly PDE5 inhibitors, may be useful.[13,61] PDE5 inhibitors (eg, sildenafil and tadalafil) caused larger reductions in pulmonary vascular resistance than in systemic resistance, therefore they represent a promising pulmonary vasodilator in patients with PPHN, particularly in medical facilities with no available iNO or ECMO.[13,61,62] PDE3 inhibitors (eg, milrinone) are known for their inotropic, vasodilator, and myocardial relaxation actions as well as for their ability to improve ventricular function.[63] These effects could be particularly important in preterm neonates with BPD in whom left ventricular diastolic dysfunction contributes to clinical abnormalities, including pulmonary hypertension, and recurrent pulmonary edema.[64,65]

2.5.1 | Experimental studies

In a hypoxia-induced piglet model of PPHN, oral tadalafil (1 mg/kg) decreased pulmonary arterial pressure, elevated cardiac output, and increased PaO_2.[66] Intravenous delivery of another PDE5 inhibitor, sildenafil (infusion of 2 mg/kg over 2 h), in a piglet model of PPHN induced by intratracheal instillation of meconium completely reversed increases in pulmonary vascular resistance within 1 h after commencing the infusion, and improved cardiac output that was not accompanied by deterioration in oxygenation.[67] In another study, the effects of increasing doses of intravenous sildenafil (0.4, 1, and 3 mg/kg) on hemodynamics and oxygenation were evaluated in piglets with meconium-induced pulmonary hypertension. Sildenafil reduced mean pulmonary artery pressure and pulmonary vascular resistance by 30%, whereas, this effect was achieved at the lowest dose, without subsequent changes at the higher doses. Nevertheless, sildenafil produced a dose-related increase in OI.[68]

In an ovine model of PPHN, milrinone relaxed pulmonary arterial rings in a dose dependent-manner, enhancing the vasodilator effects of prostacyclin and iloprost.[69]

2.5.2 | Clinical studies

There are several clinical studies in which sildenafil was administered orally or intravenously. In a randomized, blinded study of infants >35.5 weeks' gestation and <3 days old with severe PPHN and OI >25, sildenafil (1 mg/kg) was given by orogastric tube every 6 h. In the treated group, OI and pulse oxygen saturation improved in all infants over time, and none had noticeable effects in terms of blood pressure; six of seven survived. In the placebo group, one of six infants survived.[70] In a double-blind randomized clinical trial in full-term infants with PPHN, 31 infants received 3 mg/kg of oral sildenafil every 6 h, improving oxygenation parameters and reducing mortality.[71] Oral sildenafil (1-2 mg/kg every 6 h) was efficacious in 21/27 newborns ≥36 weeks gestational age with significant reductions of OI and FiO_2, an increase of PaO_2 and no significant short-term complications.[72]

Sildenafil can also be delivered intravenously[73,74] with a loading dose of 0.42 mg/kg over 3 h (0.14 mg/kg/h) followed by 1.6 mg/kg/day continuous maintenance infusion (0.07 mg/kg/h).[73] Although there has been no evidence of serious adverse events in infants exposed to sildenafil,[75] the intravenous route should be restricted to the most severe and refractory cases.[17,74]

Based on available data, recent meta-analyses confirmed that sildenafil had the potential to reduce mortality and to improve oxygenation in neonates with PPHN, especially in resource-limited settings where iNO was not available.[76,77] However, large-scale randomized trials comparing sildenafil with active controls (other pulmonary vasodilators) providing follow-up for survivors are needed to assess the comparative effectiveness and long-term safety of sildenafil versus other pulmonary vasodilators.[76,77]

Sildenafil could also be effective in some cases of PPHN associated with BPD.[78,79] Mourani et al[78] conducted a retrospective review of 25 patients <2 years of age with BPD in whom sildenafil was given for treatment of pulmonary hypertension. Chronic sildenafil therapy (dose range, 1.5-8.0 mg/kg/d) was initiated at a median of 171 days of age for a median duration of 241 days. Twenty-two patients achieved hemodynamic improvement and eleven of the 13 patients showed clinically significant reductions in pulmonary hypertension. A retrospective review showed that treatment with sildenafil citrate in 21 preterm infants with BPD-associated pulmonary hypertension led to significant reduction in estimated right ventricular peak systolic pressure, but the majority of infants showed no improvement in gas exchange at 48 h of treatment.[79]

The PDE3 inhibitor milrinone appeared to be another alternative for the treatment of PPHN.[13,61,63,80] Bassler et al[81] reported

substantial improvement in OI after milrinone treatment in four patients with severe PPHN unresponsive to therapy including iNO. In other study, intravenous milrinone produced early improvements in oxygenation and heart rate without compromising systemic blood pressure in nine full-term neonates.

In a retrospective case review conducted on infants <32 weeks gestation with pulmonary hypertension and right ventricular dysfunction, milrinone administration was associated with a decrease in OI and iNO dose. Following an initial decline in blood pressure over the first 6 h, there was an increase in blood pressure over the subsequent 72 h and an increase in indicators of myocardial performance.[82] Similarly, in term neonates with PPHN, milrinone increased both left and right ventricular outputs and reduced NO dose and oxygen requirement over the subsequent 72 h.[83]

3 | CONCLUDING REMARKS

Both non-selective PDE inhibitors and selective PDE3, PDE4, or PDE5 inhibitors represent valuable classes of medications that are useful in the treatment of various respiratory disorders and that appear to be potentially beneficial also in the treatment of respiratory distress in neonates. However, their broader clinical application in the future requires intensive testing in preclinical conditions as well as detailed and critical evaluation in clinical studies.

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