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REVIEW ARTICLE

A critical overview of clinical and experimental studies on pulmonary vasodilators in newborns

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ABSTRACT

Pulmonary vasodilators represent a viable alternative in the reduction of neonatal mortality and improvement of postnatal performance. The high rate of babies born with respiratory problems facilitates a prompt evaluation of pharmacological alternatives. This review describes the assessment of pulmonary vasodilators in animal models as well as in some clinical trials. The studies reviewed suggest that the use of experimental animal models is critical for examining, in depth, current alternatives of pulmonary vasodilators intended to be used in human neonates as well as for developing new therapeutic options. However, interspecies differences should be considered when evaluating the mechanisms involved in perinatal asphyxia, its consequences, and treatment. Regarding drug therapy, the administration of tocolytic agents for increasing gestational age has not shown to improve neonatal conditions. Instead, time needs to be optimized by prenatally administering corticosteroids and transferring the mother to a tertiary-care centre with proper neonatal facilities. Currently, the pulmonary vasodilator of choice in neonates with pulmonary hypertension is inhaled nitric oxide (iNO). However, sildenafil has shown to be a good alternative both as a single drug or associated with iNO.

Key words

Animal Experimentation; Persistent pulmonary hypertension of newborn; Vasodilator agents

RÉSUMÉ

Les vasodilatateurs pulmonaires sont une alternative valable pour réduire la mortalité néonatale et améliorer les performances postnatales. Le taux élevé de bébés naissant avec des problèmes respiratoires permet une évaluation rapide d'alternatives pharmacologiques. Cette revue décrit l'évaluation des vasodilatateurs pulmonaires dans des modèles animaux et dans quelques essais cliniques. Les études suggèrent que l'utilisation des modèles animaux est critique pour l'examen en profondeur des alternatives destinées à être utilisées chez le nouveau-né et le développement de nouvelles options thérapeutiques. Les différences inter-espèces doivent toutefois être considérées lors de l'évaluation des mécanismes impliqués dans l'asphyxié périnatale, ses conséquences et son traitement. L'administration de tocolytiques pour augmenter l'âge gestationnel n'améliore pas les conditions néonatales. Sa durée doit par contre être optimalisée pour assurer une corticothérapie prénatale et transférer la mère vers un centre disposant d'un équipement néonatal ap-

proprié. Actuellement le vasodilatateur pulmonaire de choix chez les nouveau-nés souffrant d'hypertension pulmonaire est d'oxyde nitreux en inhalation (iNO). Le sildénafil seul ou associé à l'iNO constitue une bonne alternative.

Mots clés

Expérimentation animale; Hypertension pulmonaire persistante du nouveau-né; Agents vasodilatateurs

RESUMEN

Los vasodilatadores pulmonares representan una alternative viable en la reducción de la mortalidad neonatal y en un mejor desarrollo neonatal. La elevada frecuencia de bebés nacidos con problemas respiratorios facilita una pronta evaluación de alternativas terapéuticas. Sin embargo, los modelos experimentales contíuan siendo una fuente valosa de información. En este trabajo, nosotros revisamos la evaluación de vasodilatadores pulmonares tanto en modelos animales como en algunos estudios clínicos. Los estudios revisados sugieren que el uso de modelos experimentales es un aspecto crítico para examinar a profundidad las actuales alternativas de vasodilatadores pulmonares que se pretenden usar en neonatos humanos así como también para el desarrollo de nuevas alternativas terapéuticas. Sin embargo, algunas diferencias entre especies deberán ser considerads cuando se evalúan los mecanismos de asfixia perinatal, sus consecuencias y su tratamiento. Respecto al manejo farmacológico, la administración de tocolíticos para incrementar la edad gestacional no ha demonstrado mejorar las condiciones neonatales. En cambio, el tiempo necesita ser optimizada para adminsitrar corticosteroides prenatales y transferir a la madre a un centro de tercer nivel que cuente con la infraestructura adecuada para atender neonatos. El vasodilatador pulmonar de elección en neonatos con hipertensión pulmonar es, actualmente, el óxido nítrico inhalado. Sin embargo, el sildenafil ha probado ser una buena alternativa tanto como tratamiento único como asociado al óxido nítrico inhalado.

Palabras clave

Experimentación en animales; Hipertensión pulmonar persistente del recién nacido; Vasodilatadores

INTRODUCTION

Although the most common etiology of neonatal respiratory distress is transient tachypnea that usually resolves spontaneously, other etiologies may lead to persistent or severe respiratory distress. Pulmonary circulation in the newborn depends on fast hemodynamic changes and vasoactive responses at birth [1]. Persistent pulmonary hypertension of the neonate (PPHN) significantly contributes to an increase of neonatal morbidity and mortality, including asphyxia during delivery, meconium aspiration, and respiratory distress syndrome (RDS) [2]. A better knowledge of the physiology of transitory neonatal circulation and pulmonary blood flow are the basis for the treatment of PPHN.

The high rate of babies born with respiratory problems facilitates a prompt evaluation of pharmacological alternatives. In this regard, experimental animal models are a valuable source of information. Some interspecies differences, however, should be considered. In this manuscript, we reviewed clinical and experimental studies on pulmonary vasodilators in neonates, emphasizing the contribution of experimental models to the field. Some well-known, basic concepts were omitted for the sake of simplicity.

REGULATION OF VASCULAR TONE

Vasodilator and vasoconstrictor endogenous compounds are produced by some arterial beds; however, the influence of those dilatators produced by endothelium dominates over the constrictors produced in the smooth muscle [3]. Endothelin is a potent vasoconstrictor working on some vascular beds and promoting muscular proliferation. An increase in circulating endothelin has been associated with pulmonary vascular disorders. The effects of endothelin are excerted via activation of its receptors ET_A and ET_B (ET_{B1} and ET_{B2}) located in the smooth muscular cells; ET_A predominates in damaged vessels. During hypoxia, the muscular response to endothelin blockers is lost, predisposing to contractile responses. Bosental, an endothelin receptor blocker, has non-selective vasodilatation effects and reduces pulmonary pressure in patients with pulmonary hypertension [4].

Altered production of both vasodilator and vasoconstrictor arachidonic acid metabolites has been implicated in the pathogenesis of pulmonary hypertension in both newborns and adults [5] [6]. In newborn piglets, thromboxane, a vasoconstrictor COX metabolite, was found to be involved in the pulmonary hypertension resultant from short hypoxia [3]. Besides its vasoconstrictor effect, thromboxane is a cellular mitogen of the smooth muscle [7]. Intervening with thromboxane at an early time point may not only diminish the early elevation in pulmonary arterial pressure, but may also inhibit progressive smooth muscle hypertrophy and thereby ameli-

orate the progression of hypoxia-induced pulmonary hypertension [3].

COX inhibition reduced arachidonic acid-induced dilation in endothelium-intact pulmonary arteries from control piglets but did not have an effect on arachidonic acid responses in endothelium-intact arteries from hypoxic piglets [8]. A differential regulation of COX-1 and COX-2 by physiological stimuli has been previously described [9]. In addition, the effect on COX metabolite production has been shown to vary with both the degree and duration of hypoxic exposure [10]. However, COX inhibition does not completely abolish arachidonic acid-induced responses in either control or hypoxic arteries [8]. It is probable that other arachidonic acid pathways, such as hydroxyeicosatetraenoic acids [11], could contribute to regulate the pulmonary vascular tone in the newborn.

Shift in production of arachidonic acid metabolites, away from dilators toward constrictors, occurs during exposure to short hypoxia [8]. In addition, differences amongst species must be considered when evaluating mechanisms underlying pulmonary hypertension. For example, porcine pulmonary arteries may be more prone to production of constrictor prostaglandins than other species [12]. Dilatation provoked by Ach (acetylcholine), is weak in the lungs of newborn piglets exposed to hypoxia [13] [14].

EFFECTS OF TOCOLYTIC DRUGS

The tocolytics used in clinical practice can be grouped into five classes: betamimetics, calcium channel blockers, magnesium sulfate, nonsteroidal anti-inflammatory agents, and oxytocin receptor antagonists (atosiban). Ideally, the use of tocolytics should significantly decrease the rates of perinatal death, RDS, intraventricular hemorrhage, and necrotizing enterocolitis in the offspring [15]. Betamimetic drugs, however, are associated with an increased risk of pulmonary edema, cardiac arrhythmias, and hypokalemia in newborns.

Babies born prematurely show a high incidence and severity of intracranial hemorrhage [11]; those born with respiratory complications have an independent relation with a high risk of intracranial hemorrhage [16] [17]. Beta-sympathomimetic tocolytic agents augment aortic blood flow and fetal cardiac output, which could be restricted to the left ventricle, favoring flow redistribution to the upper part of the body. Additionally, the systolic blood pressure may rise, increasing cerebral blood flow in the fetus and favoring the incidence of intracranial hemorrhages in immature fetus encephalon [18]. However, this increased risk of cerebral hemorrhages was not confirmed by another study [16].

Calcium-channel antagonists have been used as tocolytic agents. These agents inhibit calcium ion influx across the cell membrane, thereby decreasing the tone in the smooth muscle vasculature. The tocolytic efficacy of nifedipine is associated with a decrease in the neonatal morbidity, RDS, intracranial hemorrhage and neonatal jaundice [19]. Its safety was also confirmed in experimental animal models [20]. Papatsonis et al., [21] showed that the total incidence of intracranial hemorrhages and bleeding was significantly reduced in the fetus born to women treated with nifedipine for premature labor.

In human adults, calcium channel blockers improved five-year survival rates in patients with primary pulmonary hypertension [22]. This led to the theory that neonatal RDS may also be reduced by a direct effect of nifedipine on improving neonatal pulmonary perfusion [19] [21]. Although nifedipine has been shown to have a more favorable neonatal outcome and better prolongation of gestation, there are still some concerns about a theoretical risk to fetal and placental circulations with its use [23]. In addition, there is no consensus about the dosage, route, and formulation that should be used in a tocolytic regimen of nifedipine [15].

Verapamil has a vasodilatory effect in fetuses, favoring oxygen distribution to the brain when administered to the dam [24] [25]. Administration of verapamil in pregnant females during four weeks caused a decrease in lactate levels, which was possibly related to an increase in blood flow through the brain due to the vasodilatory action of this calcium antagonist [26]. This effect may minimize the blood flow redistribution to the heart, liver, adrenals and other organs observed during perinatal asphyxia. The return to a normal blood flow may increase oxygen concentration in the brain and return to an aerobic cascade of glucose oxidation minimizing lactate production in the fetus encephalum.

Magnesium sulfate can decrease uterine activity, probably by competing with calcium influx in the myometrial cells through voltage-gated channels. Magnesium sulfate is a potent vasodi-

lator and therefore has the potential to reduce the high pulmonary arterial pressures associated with PPHN. However, a recent systematic review found no eligible trials comparing magnesium sulfate versus placebo to support its use in the treatment of PPHN [27].

Vetrabutin chlorhydrate (VC) is a derivative of papaverine that acts as a vasodilator, with direct action on the smooth muscle fibers of the uterine body and cervix [28]. It does not have neurotropic activity, and acts on the myometrial cells, sealing off the membrane against potassium ion flux, thereby increasing membrane potential [29]. A study in farrowing sows showed that animals treated with VC had a shorter interval expulsion between piglets and a shorter parturition compared with the control group [30]. In addition, they found that uterine contractions and frequencies were lower, and piglets had a higher incidence of ruptured and hemorrhagic umbilical cords with the use of VC in the parturient sow [31].

Beta-agonists such as atosiban and calcium channel blockers are more popular tocolytic agents. A tocolytic agent that improves neonatal outcome without maternal or neonatal side effects has not yet surfaced [15].

NON-SELECTIVE PULMONARY VASODILATORS

A non-selective vasodilator may cause pulmonary and systemic vasodilatation. Commonly used non-selective vasodilators include tolazoline, nitroprusside, PGI_2 (epoprostenol, iloprost), fentanyl, isoproterenol and chlorpromazine; these have been administered intravenously and intratracheally in neonates with PPHN [32]. However, these agents are frequently associated with systemic hypotension and other undesirable vascular responses [33] [34], or are still under evaluation [35] [36].

Intravenous vasodilators with systemic effects have limitations, as they cause systemic hypotension and induce reflex sympatic stimulation at the lung level causing pulmonary vasoconstriction and exacerbating the pulmonary arterial hypertension. Systemic hypotension diminishes the right ventricular contractibility secondary to coronary perfusion pressure [37].

Some drugs have negative inotropic effects blocking calcium channels. Therefore, whenever selective pulmonary dilators are available, tolazoline, hidralazin, isoproterenol and nifedipine should preferably be avoided [38] [39].

SELECTIVE PULMONARY VASODILATORS

In 1991, Frostell et al. reported that inhaling low concentrations of nitric oxide (NO) decreased pulmonary artery pressure in lambs with experimental pulmonary hypertension [40]. Since then, inhaled nitric oxide (iNO) has revolutionized the treatment of acute pulmonary hypertension [41] [42] [43] [44] [45] [46] [47]. However, close monitoring of NO toxic metabolites is advisable [48].

Sildenafil is an unspecific inhibitor of type-5 phosphodiesterases (5-PDE) that enhances the vasodilatory effects of nitric oxide by decreasing the biodegradation of a second-messenger GMPc [49] [50] [51]. Sildenafil is an effective pulmonary vasodilator in patients suffering arterial pulmonary hypertension, thromboembolic pulmonary hypertension and severe pulmonary hypertension due to a decrement on RVP [52] [53]. Its administration counteracts the deleterious effects of induced hypoxia in animal models of chronic pulmonary hypertension [41].

Recently, we showed that sildenafil 500 μg kg^{-1} administered from day 35 to the end of gestation in guinea pigs resulted in enhanced fetal growth and better tolerability to induced intrapartum asphyxia than sildenafil 50 μg kg^{-1} [54]; both treatments resulted in better fetal outcomes, compared with controls, and there was no evidence of gross malformations in the piglets born to treated mothers. Sildenafil is gaining popularity for treating adults and babies with pulmonary hypertension [52] [53] [55] [56] [57] [58].

A recently proposed alternative is the combination of oral sildenafil and iNO, as they have shown to act synergistically in patients with pulmonary hypertension and thromboembolic pulmonary hypertension [52]. In patients with pulmonary hypertension, the oral administration of 12.5 mg or 50 mg of sildenafil lowered arterial pulmonary pressure showing a dependent doses-effect [51].

Sildenafil produced important systemic side-effects in humans and animals when administered in combination with nitrates. In patients who previously received iNO, administration of sildenafil was associated with hypotension [59]. On the other hand, an experiment with animals previously treated with iNO and 1 mg kg^{-1} of sildenafil, showed a decrease in the systemic vascular resistances resulting in arterial hypotension [41].

Evaluation of physiological and metabolic responses in experimental animal models may help to further characterize the role of sildenafil in neonate tolerance to asphyxia [60]. Due to the lack of large clinical trials supporting the safety and effectiveness of sildenafil for pulmonary hypertension in neonates, its use is recommended to be restricted to randomized clinical trials [61].

CONCLUSIONS

Experimental animal models are critical for examining, in depth, current pharmacological alternatives for treating human babies as well as for developing new therapeutic options. However, interspecies differences should be considered when evaluating the mechanisms involved in perinatal asphyxia, its consequences and treatment.

Regarding drug therapy, the evidence reviewed herein points to two major conclusions. First, the administration of tocolytic agents for increasing gestational age has not shown to improve neonatal conditions. Instead, time needs to be optimized by prenatally administering corticosteroids and transferring the mother to a tertiary-care centre with proper neonatal facilities. Second, the pulmonary vasodilator of choice in neonates with pulmonary hypertension is currently iNO. However, sildenafil has shown to be a good alternative both as a single drug or associated with iNO.

AUTHORS' PARTICIPATION

M G-L and D M-R conceived the idea; all the authors participated drafting the manuscript and discussing the findings.

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CONFLICT OF INTERESTS/DISCLAIMERS

AA N-O, M A-S, and D M-R are members of the Editorial Board.

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