Sildenafil, Nitric Oxide, and Acute Lung Injury: Pathophysiology Beats Pharmacotherapy?

Commentary on the article by Shekerbemian et al. on page 413

INGRAM SCHULZE-NEICK AND ANDREW N. REDINGTON

Clinic of Congenital Heart Disease/Pediatric Cardiology, Deutsches Herzzentrum Berlin, Berlin, Germany [I.S.-N.]; and Division of Cardiology [A.N.R.], Hospital for Sick Children, Toronto, Ontario M5G 1X8, Canada

The discovery of nitric oxide (NO) as the endothelial-derived relaxing factor has revolutionized the concept of many diseases and their treatment. NO is formed in endothelial cells by oxidation of the amino acid L-arginine in the presence of a NO synthase. It is highly soluble and rapidly enters the smooth muscle cell and activates soluble guanylate cyclase, resulting in increased levels of cGMP, which is responsible for most of the vasodilatory effects of NO (1). Its biologic half-life is short, as it is rapidly degraded by a family of phosphodiesterases (PDEs) (2). The pulmonary circulation is uniquely accessible to direct supplementation of gaseous NO by inhalation. It is used in the treatment of acute pulmonary disorders associated with pulmonary hypertension (PHT) such as acute respiratory distress syndrome (3), persistent pulmonary hypertension of the newborn (4), and postoperative pulmonary hypertension (5). There are potential disadvantages to its use, however; the danger of pulmonary hypertensive rebound upon discontinuation, concerns about toxicity at high dosage, enhancement of inflammation and alteration of coagulation, and, recently, its costs (6) all have been highlighted. Nonetheless, for many, it has become established as the treatment of choice for selective pulmonary vasodilation. With newer agents, such as sildenafil, arriving on the scene, it is timely to reevaluate the role of both NO and these novel substances.

Sildenafil has been touted as a candidate to inherit the role of NO in the treatment of pulmonary hypertensive disorders. Originally synthesized as compound UK 92480 by Pfizer, its action as a PDE5 inhibitor was 100-fold (IC_{50} 3.5 nM) that of its source compound zaprinast. PDE5 is particularly richly expressed in lung tissue (7), and although sildenafil is administered systemically, because of this it provides a selective pulmonary vasodilating effect. A significant therapeutic effect has been described in primary PHT (8), PHT associated with the lupus syndrome (9), chronic thromboembolism (10), thalassemia (11), HIV (12), lung fibrosis (13), and congenital heart disease (14). Oral sildenafil markedly augments and prolongs the pulmonary vasodilating effect of inhaled prostanoids (8),

and it shows an additive effect when combined with inhaled NO (15) in patients with primary PHT.

However, in PHT associated with acute parenchymal lung injury, such as the adult respiratory distress syndrome or the neonatal meconium aspiration syndrome, pulmonary vasodilation is a double-edged sword. Whereas sildenafil is relatively selective for the pulmonary circulation, it is not selective in terms of its effects within that circulation. Unlike inhaled NO, where its site of action is restricted to ventilated areas of lung, sildenafil will potentially reverse hypoxic vasoconstriction (the Euler-Liljestrand reflex) secondary to alveolar hypoxia, resulting in increasing VQ mismatch and systemic hypoxemia. Thus, PHT may be relieved at the cost of arterial desaturation, in an already compromised patient, in terms of systemic oxygenation. Indeed, our own data obtained in children after cardiopulmonary bypass surgery (16) showed a fall in arterial PO_2 of an average of 75 mm Hg even under the circumstances of relatively mild parenchymal disease associated with the effects of cardiac surgery. This effect may be even more profound when more marked parenchymal disease is present and begs the question as to whether a combination of sildenafil and inhaled NO may be advantageous under these circumstances.

In this journal, Shekerdemian *et al.* examine this question in a porcine model of neonatal PHT secondary to meconium aspiration. This work is a counterpart of a previous publication examining the effects of both NO and sildenafil, which were administered separately in an identical model (17). In that study, i.v. sildenafil reversed PHT in a selective manner without affecting systemic vascular resistance or oxygenation. In the present study, the effects of coadministered i.v. sildenafil and inhaled NO are examined. Although the combined therapy augments pulmonary vasodilation, there were serious adverse side effects of systemic vasodilation and deterioration of oxygenation. The authors must be commended for their systematic approach and clear and efficient study design, dissecting out a very important finding that is intriguing from both its pharmacologic and its pathophysiologic aspects. It clearly may also have important clinical implications.

It is unclear whether these unwanted effects may be caused, at least in part, by an inappropriately high dose of sildenafil. Although the optimal dose is not yet known, *in vitro* studies show 50%, 75%, and 90% inhibition of the PDE5 achieved at plasma levels of 40, 120, and 360 ng/mL (18). In our clinical

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Correspondence: Andrew N. Redington, Ph.D., Division of Cardiology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; e-mail: Andrew.redington@sickkids.ca

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study using i.v. sildenafil in children soon after return from congenital heart surgery, levels of 200–300 ng/mL were achieved with an infusion of 0.25 mg/kg. Shekerdemian *et al.* do not give us plasma levels, but an implicit dose-response relationship of i.v. sildenafil can be seen from their figures: 30 min of sildenafil infusion corresponded to an infused dose of 0.5 mg/kg. Although speculative, when combined with inhaled NO, a much lower dose may be sufficient to selectively decrease pulmonary vascular resistance while minimizing unwanted effects. Perhaps more interesting, however, is why the concomitant inhalation of NO with i.v. sildenafil seems to amplify the adverse effects of sildenafil on VQ mismatching.

Shekerdemian *et al.* suggest that this may be due to a redirection of blood flow away from ventilated areas toward inappropriately vasodilated but unventilated areas of the lung. However, this is difficult to reconcile with the lack of such an effect when i.v. sildenafil is used alone. Comparing data from their previous study, the current experiment can be seen as demonstrating the effects of inhaled NO superimposed on the effects of sildenafil. Consequently, the adverse effects of NO are counterintuitive. Although we can offer no better explanation, our own study in children after heart surgery are at variance with the current finding. We found a marked increase in VQ mismatch in these patients with sildenafil alone, in keeping with previous studies of i.v. administered pulmonary vasodilators (19), which was not amplified by the subsequent addition of inhaled NO. Thus, in this particular clinical situation, it is sildenafil and not inhaled NO that is the culprit in terms of increased VQ mismatch when PHT coexists with parenchymal lung disease.

Whatever the mechanism, Shekerdemian *et al.* are to be congratulated for highlighting the potential adverse effects of an increasingly widely used new therapy. Although sildenafil clearly has enormous potential as a therapeutic agent in PHT, there may be significant adverse effects under certain circumstances. It behooves us all to examine the effects of new therapeutic agents in both clinical and experimental models of disease.

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