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Systemic Effects of Sildenafil Citrate on Pregnancy and Perinatal Periods

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Abstract: Sildenafil citrate is an orally administered effective treatment for erectile dysfunction; nevertheless administrated in high concentrations produces relaxation of myometrium in pregnant women, thus sildenafil or related molecules may have future potential tocolytic application. In the present review sildenafil mechanism of action, pharmakocinetics and therapeutic use are discussed. Sildenafil is also considered a potent pulmonary vasodilator in pharmacology representing an alternative to neonates during the last month of in utero development. We conclude that studies in animals including metabolic and physiological traits in the fetus and neonates from treated dams with sildenafil in their last third of pregnancy may help to characterize neonate tolerance to asphyxia with posterior application in human perinatology.

Key words: Sildenafil, phosphodiesterase inhibitors, pregnancy, perinatal, posterior application, erectile dys function

INTRODUCTION

A research program that started in 1985 led to the approval of Sildenafil in 1998, as the first oral treatment for male Erectile Dysfunction (ED). The initial project objective was the design and synthesis of novel inhibitors of Phosphodiesterase (PDE) that would increase tissue levels of Guanosine 3',5'-cyclic Monophosphate (cGMP) and that could be beneficial for the treatment of cardiovascular conditions. The research programme that led to the discovery of sildenafil originated from the interest in factor Atrial Natriuretic Factor (ANF), an endogenous peptide with vasodilator and natriuretic properties. One of the 2 major synthetic pathways for cGMP generation from Guanosine 5'-Triphosphate (GTP) is directed by natriuretic peptides, consisting of Atrial (ANP), B-type (BNP) and C-type (CNP) Natriuretic Peptides, which act via the membrane receptor guanylate cyclases GC-A (highest affinity for ANP, BNP) and GC-B (highest affinity for CNP). ANP and BNP, released from the heart by mechanical stretch in response to increased Atrial pressure/volume and CNP, released from the endothelium, can all cause smooth muscle relaxation and vasodilation. ANF exerts its physiological roles by stimulating guanylate cyclase to increase tissue levels of cGMP, although this second messenger will degrade rapidly by a specific phosphodiesterases (Campbell, 2000; Münzel *et al*., 2003).

The mammalian Phosphodiesterases (PDEs) are composed of 11 families of enzymes that catalyze the termination of second messenger activity in cells by breaking the phosphodiester bond of either cyclic Adenosine Monophosphate (cAMP) or cGMP. Eleven

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distinct families have been identified (PDE-1 to PDE-11) that are known or implicated in a broad range of cellular functions. PDE-5 is cGMP-specific and is present in relatively high concentrations in the smooth muscle of corpora cavernosum of the penis. PDE-5 inhibitors enhance erectile function during sexual stimulation by penetrating into smooth muscle cells and inhibiting PDE-5. This results in decreased degradation of cGMP, which maintains sufficient cellular levels of cGMP in both corpus cavernosum and the vessels supplying it. This increases relaxation of the smooth muscle, which dilates the corporeal sinusoids resulting in increased blood flow, allowing an erection to occur. Sildenafil or one of the other PDE-5 inhibitors foster accumulation of the cell cGMP by competitively inhibiting PDE-5, which triggers penile erection. PDE-5 inhibitors do not increase the nitric oxide level, but they potentiate the nitric oxide effect to stimulate erection. Without sexual arousal, this effect activates the nerve-nitric oxide pathway, these inhibitors are ineffective (Corbin and Francis, 2003). However, with the exception of platelets (a homogenous cell population) the isoforms hydrolyzing cGMP in cells stimulated by NO are uncertain: Most studies have been conducted on tissue homogenates in which PDEs normally located in different cell types or cell compartments are mixed together. Knowledge of the participating isoforms is important for understanding the dynamics of the signal transduction pathways and for providing pharmacological tools to probe those pathways (Bellamy and Garthwaite 2001).

Sildenafil citrate (1-{[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazine) (Gobry *et al*., 2000) is an orally administered effective treatment for Erectile Dysfunction (ED) (Campbell, 2000; Ardeschir *et al.,* 2002; Michelakis *et al.,* 2002; Muirhead *et al.,* 2002), sildenafil has been used with great success in the treatment of male ED, but so far studies in women are scarce (Sher and Fisch, 2000). Moreover, although sildenafil citrate is a well-established drug for treatment of ED, its therapeutic effectiveness in postmenopausal women with diminished sexual response remains to be determined (Zoma *et al.,* 2004).

The citrate of sildenafil not only exerts a relaxant effect directly on the corpus cavernosum, it appears to be such a potent and highly selective inhibitor specific of phosphodiesterase type 5 that augments the vasodilatory effects of Nitric Oxide (NO) by preventing the degradation of the second messenger cGMP (Gobry *et al*., 2000; Sher and Fisch, 2000; Ardeschir *et al*., 2002; Michelakis *et al*., 2002; Sher, 2002; Khan *et al*., 2004). Thus, sildenafil citrate promotes smooth muscle relaxation, however the calcium-activated by potassium channels (BKca) have been implicated directly or indirectly in the actions of sildenafil, NO and cGMP (Khan *et al*., 2004).

In the present review sildenafil mechanism of action and therapeutic use are discussed.

Sildenafil citrate may be recovered from the urine or feces so metabolism is the major mechanism for clearance of sildenafil (Muirhead *et al*., 2002). Sildenafil metabolites are excreted mainly in the feces (80%), whereas urine rate of excretion is lower (13%). The pharmacokinetics of sildenafil may be influenced by its physicochemical characteristics (Gobry *et al*., 2000).

THERAPEUTIC APPLICATIONS OF SILDENAFIL

Pregnancy: Sildenafil citrate used as a therapeutic agent in women´s pregnancies, may improve myometrial perfusion in FGR pregnancies by promoting myometrial small artery vasodilatation, decreasing peripheral resistance and increasing flow within the utero-placental bed (Wareing *et al.,* 2005). Fetal and neonatal asphyxia has been amply studied in human medicine (Lievaart and Tong 1984; da Silva *et al*., 2000; Low *et al*., 2001). Mammal neonates have similar physiological mechanisms during asphyxia (Arbay *et al*., 1996; Singer, 1999), in veterinary medicine the asphyxia process has been studied using as a model the pig (Alward *et al.,* 1978; Randall, 1979; Orozco *et al*., 2006).

Several alternative potential therapeutic applications of sildenafil have brought new lines of investigation (Khan *et al*., 2004). For example, successful pregnancies in previously failed attempts of in vitro fertilization have been attributed to the improved vasodilation that is caused by sildenafil citrate (Sher and Fisch, 2000). In addition, sildenafil may play a role in the treatment of female sexual dysfunction (Khan *et al*., 2004). Sildenafil has been used to improve uterine artery blood flow and sonographic endometrial appearance in four patients (women) with prior failed assisted reproductive cycles due to poor endometrial response (Sher and Fisch, 2000). These authors found that vaginal application of Viagra increases endometrial thickness favoring blood flow of the uterine artery in certain women with thin endometrium undergoing in vitro fertilization. They suggest it is necessary to evaluate a random number of patients in order to validate this sort of treatments. With the popularity of Viagra soaring worldwide, it is not surprising that studies are underway to determine the therapeutic efficacy of Viagra in women with diminished sexual response (Zoma *et al*., 2004). Studies done in women with

pregnancy problems and fetal growth restriction, justifies the use of citrate of sildenafil administered in vivo, since it improves the uterine-placenta blood flow (Wareing *et al.*, 2005).

Perinatal asphyxia: Hypoxia in utero or during labor is produced by various causes, including early rupture or compresión of the umbilical cord, which represents an important cause of weak piglets with poor growing rates (Mota *et al.*, 2005). Asphyxia during labor is an important etiology in intra-partum deaths in pigs a high stillbirth rate is associated with anoxia (Mota *et al.*, 2002, 2006ab; Alonso-Spilsbury *et al.*, 2005). Similarly, in human medicine labor complications play an important role causing hypoxia and fetal suffering, which is a complex metabolic perturbation due to a decrease in maternal-fetal exchange, it evolves quickly and leads to a failure in fetal homeostasis with subsequent tisular alterations or fetal death (Schwarcz *et al.*, 1995). After ductus arteriosus compression, changes in the pulmonary circulation cause progressive increase in pulmonary vascular resistance, altering pulmonary vasoreactivity and inducing vascular and cardiac remodeling, these changes in lung circulation can be prevented by selective PDE-5 inhibition (Larrue *et al.*, 2005). The compression of the ductus arteriosus and the prevention of pre-term labor remains one of the primary goals of obstetric research. Nevertheless, neonatal death most important cause is premature babies prematurity (Norman *et al.*, 1999).

CARDIOPROTECTIVE EFFECTS AFTER ISCHEMIA/REPERFUSION INJURY

Sildenafil inhibits PDE V, the enzyme that specifically hydrolyzes cGMP. By a complex mechanism, increased intracellular cGMP leads to the hyperpolarization of smooth-muscle membranes and subsequent vascular relaxation. Moreover, cGMP is involved in the regulation of myocardial L-type Ca^{2+} channel current (ICa): In guinea pig, frog and human cardiomyocytes, cGMP can also stimulate ICa via inhibition of cGMP-inhibited cyclic Adenosine Monophosphate (cAMP) PDE (PDE III), thus augmenting cardiac output. PDE isozyme types I, III, IV and V are present in the human pulmonary artery. Sildenafil inhibits PDE V, the enzyme that specifically hydrolyzes cGMP. By a complex mechanism, increased intracellular cGMP leads to the hyperpolarization of smooth-muscle membranes and subsequent vascular relaxation. Moreover, cGMP is involved in the regulation of myocardial L-type Ca2+ channel current (ICa): In guinea pig, frog and human cardiomyocytes, cGMP can also stimulate ICa via inhibition of cGMP-inhibited cyclic Adenosine Monophosphate (cAMP) PDE (PDE III), thus augmenting cardiac output. PDE isozyme types I, III, IV and V are present in the human pulmonary artery (Kleinsasser *et al.*, 2001).

Each year, more than 25,000 children undergo corrective surgery for congenital heart disease. Early surgical intervention is important to promote more normal development. Infants undergoing surgery for congenital heart disease are at risk for myocardial ischemia during cardiopulmonary bypass, circulatory arrest, or low-flow states. Brief episodes of ischemia protect the myocardium from more prolonged periods of ischemia, a phenomenon called ischemic preconditioning. A variety of other stimuli, such as hypoxia, thermal stress, pharmacologic agents and endogenous triggers of preconditioning such as nitric oxide and adenosine have also been shown to induce cardioprotective effects in several animal species. Also, recent studies from Ockaili *et al.* (2002) have shown that sildenafil citrate, a selective PDE-5 inhibitor, induces powerful preconditioning-like protective effects in the ischemic heart. Sildenafil induced delayed cardioprotective effect in the mouse heart through up-regulation of inducible Nitric Oxide Synthase (iNOS) and endothelial Nitric Oxide Synthase (eNOS) (Salloum *et al.*, 2003). The hypothesis behind these studies was that the vasodilatory action of sildenafil could potentially release endogenous mediators of preconditioning such as adenosine, bradykinin, or nitric oxide. One or more of these mediators may trigger a signaling cascade leading to activation of protein kinase C and opening of the mito KATP channel resulting in acute and delayed cardioprotective effects. It is possible that sildenafil citrate may be clinically important in protection of the heart in the setting of cardiac surgery using cardiopulmonary bypass, circulatory arrest, or low-flow states in infants with congenital heart disease (Das *et al.*, 2004).

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

The fetal growth restriction is responsible for considerable perinatal mortality and morbidity; infants have increased risk of perinatal complications such as fetal distress, asphyxia, neonatal encephalopathy, hypothermia, hypoglycaemia and poor feeding, as well as risks of long term neurological and developmental disorders (Wareing *et al.*, 2005). The Persistent Pulmonary Hypertension of the Newborn (PPHN) contributes to increase dramatically neonatal morbidity and mortality. It is a clinical syndrome that is associated with diverse neonatal cardiopulmonary diseases, including

birth asphyxia, sepsis, meconium aspiration and respiratory distress syndrome it can be idiopathic too (Larrue *et al*., 2005).

Sildenafil may significantly increase plasma cGMP levels. This increase in cGMP raises the possibility of modulation of cGMP-regulated phosphodiesterases in tissues in which phosphodiesterase 5 is not present (e.g., the myocardium), (Schalcher *et al*, 2002). In lung tissue it is a rich source of phosphodiesterases, Phosphodiesterase-3 (PDE3) and Phosphodiesterase-4 (PDE4) (Ardeschir *et al*., 2002).

MORTALITY

In the United States, sildenafil has already been prescribed more than 6 million times (representing 50 million tablets) and 130 deaths of patients who had been prescribed sildenafil were reported to the U.S. Food and Drug Administration by November 1998.

CONCLUSION

In summary, due to sildenafil citrate´s important use as a potent vasodilator in pharmacology and its different uses in research, we consider that it may represent a viable alternative in models of neonate animals from mothers treated in the last third of pregnancy. Ongoing research evaluating physiological and metabolic traits in animal neonates may help to characterize neonate tolerance to asphyxia with posterior application in human perinatology.

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