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Sildenafil in Use for Treatment of Pulmonary Hypertension in Congenital Diaphragmatic Hernia: Short Literature Review

Andreas Fette*

Lybian German Hospital, Benghazi, Weissach im Tal/FRG, Germany

***Corresponding author**: Andreas Fette, University of Pecs, Hungary-Lybian German Hospital, Benghazi, Lybia, Drosselstr 4; 71554 Weissach im Tal/FRG, Germany, Tel: 49719153306; Fax: 497191493947; E-mail: andreas.fette@gmx.de

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Abstract

Congenital Diaphragmatic Hernia (CDH) is a complex malformation in the newborn baby. The management, either surgical or non-surgical is an ongoing challenge. Especially in regard to the question how to treat the concomitant pulmonary hypertension best.

Here sildenafil, more commonly known in the public as Viagra® and for the treatment of erectile dysfunction seems to have beneficial effects in pulmonary hypertension treatment of CDH patients as well.

Thus, this short review aims to evaluate the actual literature for current evidence and practical application.

Keywords: Congenital diaphragmatic hernia; Pulmonary hypertension; Sildenafil

Introduction

Congenital Diaphragmatic Hernia (CDH) is defined as a defect of the diaphragm that allows the abdominal content to ascend into the thoracic cavity and to compromise the lung growth in utero. CDH occurs in 1:2000 to 3700 live births [1,2]. In the majority of cases the defect is localized on the left side (80%), in 15% on the right side, and in less than 5% bilateral. The size of the defect can vary from small (2 or 3 cm) to very large, where most of the hemidiaphragm is involved [2].

Many years the outcome after this malformation was thought to be solely related to the diaphragmatic defect and potentially curable by "simple" surgical closure of the defect after birth. However, it is nowadays clear, that the degree of lung hypoplasia and the severity of the pulmonary vascular abnormalities, which leads to the persistent Pulmonary Hypertension (PH) in the newborn, are the two main factors that finally limit the outcome [1,2]. New evidence suggested that the CDH malformation includes failure of both alveolar and pulmonary vascular development; also, that the pulmonary hypertension in CDH is characterized by Pulmonary Artery (PA) remodeling with excessive muscularisation of preacinar arteries, reduced external diameter of pre- and intra-alveolar arteries and increased Medial Wall Thickness (MWT) [1].

To date, Extracorporeal Membrane Oxygenation (ECMO), Nitric Oxide (NO) and mechanical ventilation have been used in perinatal medicine to treat CDH. As well as prostacyclins an endothelin receptor antagonist and Fetoscopic Tracheal Occlusion (FETO) an antenatal procedure [1-5]. The pulmonary vasodilator, inhaled NO, which mediates pulmonary vasodilatation at birth via cyclic Guanine Monophosphate (cGMP) production, has long been regarded as the convential intervention [1-5]. FETO and the Ex Utero Intrapartum Treatment (EXIT) procedure, indeed, have been utilized in institutions eligible to perform fetal surgery interventions [4]. However, these treatment options are invasive, expensive, need a complex administration, and are restricted in their practical use. Last but not least, their usefulness remains controversial [1-5].

Despite improvements in perinatal care, both the mortality (initially ~50-70%) and morbidity rate in patients with CDH remain high. Furthermore, in contrast to other cases of neonatal respiratory failure, infants with CDH most often present with a refractory PH that is resistant to NO and does not respond well to ECMO [1-3]. Thus, even among survivors, the prognosis is guarded and chronic PH beyond the neonatal period is increasingly recognized in this patient population [1,2]. As already mentioned in the previous paragraphs, the precise mechanism underlying this refractory PH in CDH patients remains unknown. In summary, it may relate to some combination of (1) altered vasoreactivity (lack of vasodilatation or increased vasoconstriction), (2) vascular remodeling (smooth muscle cell (SMC) proliferation), and (3) a hypoplastic pulmonary vascular bed. Although there are 11 cyclic GMP-specific phosphodiesterase gene families expressed in mammalian SMCs, phosphodiesterase type 5 (PDE 5) is the most vasoactive cGMP-hydrolizing PDE that is active under low-calcium basal conditions. PDE 5 inhibition is expressed in all visceral and vascular SMCs, and has only a modest effect on systemic blood pressure [1].

Sildenafil, a widely used PDE 5 inhibitor, is able to dilate the pulmonary vasculature and has antiproliferative effects on human Pulmonary Artery (PA) SMCs; it also acts as an inducer of apoptosis. These properties have already been harnessed for the treatment of PH in adult patients [1,6].

Sildenafil inhibits PDE 5 resulting in an increase in cGMP and vasodilatation. It has been shown to selectively dilate the pulmonary vasculature in animal models and various types of PH in adult and pediatric patients. Including persistent PH in newborns, where PH is a consequence of cardiac surgery, and where it is associated with congestive heart failure in adults [3,5]. PDE 5 inhibitors may also

augment the pulmonary vasodilator response further to inhaled NO [3]. Sildenafil, actually is therefore increasingly used in the management of PH associated with CDH [1,3,5,6].

Objectives

Unlike other therapies that are based on large randomized trials, the postnatal management of severe CDH presents an on-going challenge. Because, only by a few robust evidence-based interventions are found for support. However, sildenafil is an easy to use, commercially available medication for the treatment of PH in CDH patients.

The ultimate therapeutic goal to improve survival of CDH infants would be to promote their lung growth even before birth. Meaning to develop an efficient strategy that directly treats postnatal refractory PH even in advance. Since CDH in humans can be accurately diagnosed during routine ultrasound examination at approximately 22 weeks of gestational age, CDH might be amenable to such a direct antenatal therapy [1]. Consequently, it has been hypothesized that antenatal PDE 5 inhibitions with sildenafil might be able to attenuate pulmonary vascular abnormalities in experimental CDH and could ultimately become a first- choice treatment in the future [1].

That's why nowadays sildenafil and its oral preparation, the "mysthic" Viagra® is top on the list.

Search Strategy

The primary keywords "congenital diaphragmatic hernia [AND] sildenafil", with no restrictions regarding date of publication, but limited to English and German publications formed the base of the search strategy.

"PubMed", one of the most common database used for this type of medical information and standard professional pediatric surgical textbooks on CDH were used for reference and background reading.

Using the keywords "congenital diaphragmatic hernia [AND] sildenafil", finally a total of 15 records were found. In front of the background reading, it was indicated, that the main focus of attention should be exclusively on pulmonary hypertension (PH) in CDH patients. Thus, other diseases (like the heart) and conditions (notably combination therapies, either applied or diagnosed individually or in combination), were explicitly excluded right from the beginning to avoid bias. Evaluation of the published literature confirmed that choosing these inclusion and exclusion criteria were appropriate and well justified.

The publication of Luong and co-workers [1] a large experimental study - matched all three search terms ("congenital diaphragmatic hernia" [AND] "sildenafil" [AND] "pulmonary hypertension") [1].

The case report of Keller et al. [7] also matched all three terms, but there was clearly a significant comorbidity within their sample of patients [7].

The paper authored by Hunter et al. matched only the terms "congenital diaphragmatic hernia" [AND] "sildenafil", while they made no reference to pulmonary hypertension [6].

However, these authors citied a publication by Carroll and Dhillon [8], which contained the two keywords "sildenafil" [AND] "pulmonary hypertension", but did not include the term "congenital diaphragmatic hernia" [8].

Consequently, all three of these articles were excluded from the final literature review.

The publication of Stultz and co-workers [5], instead, could be selected for inclusion in this review, because it matched the terms "sildenafil" [AND] "pulmonary hypertension" and two (out of the three) patients in their study have been treated for congenital diaphragmatic hernia in a clinical setting, too [5].

The reference lists of all these publications were searched manually for any further potential informative and appropriate articles, but, despite repeated cross-checking of the sources, no further substantial records could be found.

Our search strategy was limited to only a single medical and scientific database, however the risk of missing important information was considered negligible, since PubMed is recognized worldwide as one of the leading medical data sources. The possibility of a publication bias should be considered as well, since publications reporting successful outcomes are in general more likely to be accepted for journal publication in favour of those conveying only negative results. This may especially occur when favorable clinical results extracted from case reports are presented, because screening for a potential publication bias is usually out of scope in their methodology section. Finally, there is potential for selection bias, resulting from the use of a single source of data, and because the search and selection was performed exclusively by a single researcher.

Literature Review

In their animal study, Luong et al. [1] proposed the concept of the antenatal use of sildenafil for regression of PH in CDH, which parallels the use of antenatal glucocorticoid treatment for women with threatened preterm labour in order to mature the fetal lung and to prevent postnatal complications in their preterm infants [1]. As demonstrated in other previous studies when using this type of animal model, prenatal glucocorticoids plus inhaled NO enhances the survival rate of rat pubs with CDH [1]. The authors therefore reasoned that if antenatal sildenafil -an approved and safe medication in adults - were given from embryonic day E 11.5-20.5, it should reduce PH, increase vessel density and might have a beneficial effect on lung vascular development in CDH rats. Furthermore, they speculated whether antenatal sildenafil might also be able to restore depressed lung endothelial Nitric Oxide Synthase (eNOS) and vascular endothelial growth factor (VEGF) protein expression in nitrofen-induced CDH [1].

A common animal model, using Sprague-Dawley rats, was utilized for their study, and CDH and lung hypoplasia in offspring were induced by administration of the herbicide nitrofen [1]. Nitrofen administration at E 9.5 to the pregnant mother typically resulted in a 60 % incidence of CDH in their offspring. A total of 408 cases of CDH were included for analysis and randomized into the following four groups: control, nitrofen treatment, nitrofen + sildenafil treatment and sildenafil treatment alone [1].

Unfortunately, the authors provided no information to indicate whether the sample size was appropriate for a statistical analysis and other data were unreported - for example, the side and grade of the diaphragmatic defect, the degree of lung hypoplasia, growth restrictions or survival data are not specified. Only the CDH cases in the nitrofen and nitrofen + sildenafil group were analyzed, and the overall percentage of CDH that finally resulted in this cohort is not

given. The results may therefore have been prone to preselection bias, since the incidence of nitrofen-induced CDH may have been higher at a different time of administration, or non nitrofen-induced CDHs might have presented in a different way.

The sildenafil dose chosen for the pregnant rats was based on previous studies examining the pharmacokinetics of sildenafil in rodents and was reported as 100 mg/kg/d [1]. In long-term in vivo studies in rats, this dose has yielded mean free plasma concentrations comparable to levels obtained in humans at doses of 1 mg/kg/d - a difference reflecting the near 100-fold higher rate of metabolism of sildenafil in rats [1]. However, due to the small size of the animal in this model and the lack of physiological data, such results are not directly transferable to humans, and many researchers in the field of fetal surgery and perinatal medicine consider the sheep model far more appropriate [2].

In studies, where three or more groups are being compared, the Analysis of Variance (ANOVA) test for normal unpaired data will be an appropriate statistical instrument to use. The null hypothesis therefore will be formulated in such a way to test that no differences exist between the compared groups, which all belong to the same population. The possibility of a Type I error must be considered, if the null hypothesis is rejected, when it is actually true. Thus, significance testing represents a "safety mechanism", that guards against wrongful rejection of the null hypothesis (namely, a Type I error) in a study. By totally arbitrary convention $p<0.05$ is the recognized threshold that indicates statistical significance [9], and this level was applied in this study.

A Type II error will occur if the null hypothesis is accepted, when it is actually false. Therefore, the power of a study is defined as the probability that a Type II error will not be made in this study. By arbitrary convention, a power of 0.8 is generally accepted as being adequate in most research studies [9]. However, in this study, no power calculation was provided by the authors.

The Standard Error of a Mean (SEM) expresses the likelihood of difference between a sample mean and a true mean value of a parameter in the population [9]. SEM values were provided by the authors, but with no associated confidence interval (CI) calculations.

Luong et al. [1] concluded, that maternal-administered sildenafil was able to cross the placental barrier and inhibit PDE 5 activity in fetal rat lungs, after pooled fetal plasma samples tested positive for sildenafil and its metabolite [1]. However, the sample size taken at 6 and 12 h was considerably smaller (n=3-5) than the regular one taken (n=10-12), such that the quantity range for both analytes (2-1000 ng/ml) was extreme, and the associated overall sample size was also quite small [1]. Furthermore, no further information was provided about the selection methodology used when pooling the samples. The results did not reach statistical significance, but are nevertheless interesting.

From the analyses of the effects of antenatal sildenafil on body weight (BW), incidence of CDH and lung hypoplasia, sildenafil alone appeared to have no effect on the incidence of CDH. Nitrofen significantly decreased fetal BW, which loss could be restored by antenatal treatment with sildenafil (ANOVA $p<0.0001$). Lung weight to body weight ratio (LW/BW) was reported to be significantly decreased in the nitrofen-CDH group, but sildenafil had no effect on LW/BW ratio in the nitrofen-CDH group (ANOVA $p<0.0001$) [1].

These analyses focused on the individual effects of nitrofen and sildenafil in relation to CDH- associated morbidities, and excluded any investigation of the specific adverse effects of each individual drug in these morbidities, which might otherwise have produced different results.

Fetal lung concentrations of cGMP were reported to be significantly decreased in nitrofen-CDH, in comparison to controls. These concentrations were restored in CDH animals, following treatment with antenatal sildenafil (ANOVA $p<0.02$). Significant attenuation in active phosphodiesterase A (PDESA) expression was also reported (ANOVA $p<0.0001$) [1], which supports the central concept of the study. Despite the statistical significance of these findings, lung cGMP levels were measured only in a small number (4-5) of samples and no further data about the selection process or the confidence interval (CI) associated with the sample probes were provided [1].

Sildenafil alone was reported to have no effect on lung architecture in the control pups (ANOVA $p<0.001$). The mean linear intercept was significantly higher in animals with nitrofen-induced CDH than in controls. Furthermore, the fetal rats in the nitrofen-induced CDH group treated with sildenafil achieved mean linear intercept values that were similar to those of controls. The proposed positive effect of antenatal sildenafil on lung architecture was therefore confirmed, on the basis of these statistically significant findings [1].

It should be noted that, for the investigation of the lung morphology, all serial sections were taken exclusively from the medial right lung lobe and that no differentiation was made between right- or left-sided CDH or other regions of the lung. This might be a potential source for a systematic error.

The nitrofen-CDH animals in this study showed a significantly lower pulmonary vessel count, in comparison to their controls. Sildenafil significantly increased the pulmonary vessel count in this group of nitrofen-CDH animals, but decreased the pulmonary vessel density in the control group, which was associated with an increased lung eNOS and VGEF protein expression levels (ANOVA $p<0.0001$) [1]. This finding highlights the positive effect of sildenafil in CDH cases, but also the potential negative effects on healthy pulmonal vessels. Antenatal sildenafil enhanced pulmonal artery responsiveness to the NO donor 2-(N,N-diethylamino)-diazenolate-2-oxide (DEANO) also, as the PAs of nitrofen-CDH rats showed significantly less relaxation than controls ($p<0.05$), while antenatal treatment with sildenafil significantly enhanced the relaxation of nitrofen-CDH-PA ($p<0.01$) [1].

However, all the arteriograms and arterial density count data (which appear to have been determined from manual counts) were derived from only five animals per group. The level of intra- and interobserver reliability was not stated, and may be questionable. Pulmonal artery remodeling assessment was performed on "small" (30-100 μm) stained lung sections [1], but the sample size was not reported, though it appears be considerably small, too.

For the assessment of the "PA relaxation to NO" response, pulmonary arteries of the same length were used -now termed "intrapulmonary arteries"- and comparisons were made between the 4 age-matched groups [1]. However, it is possible that NO affected extra pulmonary arteries as well. Furthermore, initially all the results and dosages were based on body weight, until age-matching was subsequently used in parts of this study without any further explanation.

Focusing on Pulmonary Hypertension (PH), antenatal sildenafil has only attenuated the features in CDH, because, despite using the appropriate linear mixed model, taking litter and rat effect into account, the differences has not been statistically significant. Medial Wall Thickness (MWT) was increased in rats with nitrofen-induced CDH, and antenatal sildenafil decreased MWT in the CDH group in comparison to controls. But these differences did not reach statistical significance [1]. This negative result might be explained by the large variance in the number of vessels counted (n=44-156), or by the selective limiting of the vessel- bearing tissue, in regard to localization (exclusively right median lobe) and area (exclusively intrapulmonary vessels). A measurable medial wall thickening in these animals would have required time to develop, too.

The incidence of right ventricular hypertrophy (RVH), as a secondary indicator of PH, was significantly greater in the nitrofen-induced CDH animal group, compared with their controls. Antenatal sildenafil treatment attenuated RVH in the animals with nitrofen-induced CDH, but sildenafil had no effect on RVH in controls. RV weight was significantly reduced in the control group of sildenafil-treated animals. LV weight was significantly reduced, both in the nitrofen-induced CDH group and in the nitrofen-induced CDH + sildenafil treated animals, indicating that sildenafil does not affect the weight of the left ventricle in CDH rats [1].

In their study, ventricular hypertrophy was used as an indirect measurement to quantify the grade of pulmonary hypertrophy. But, measurements of the septum weight were not considered correctly in the calculation formula, or mixed up with the LV weight, and only a very small sample size was analyzed.

In two of their three reported human cases, Stultz et al. [5] administered intravenous sildenafil intermittently for the management of pulmonary hypertension in neonates and infants with CDH. The purpose of their study was to show, that intermittent intravenous sildenafil doses can provide a well-tolerated, practical and potentially effective treatment for PH in a realistic clinical setting [5].

The first case reported was a full term, male neonate, weighing 3025 g at birth. Immediately after birth, he was intubated and required inhaled NO, High Frequency Oscillatory Ventilation (HFOV) and neuromuscular blockade to improve oxygenation. In addition, hemodynamic support by vasopressor infusion and corticosteroids were required. The echocardiography results on day 1 of life confirmed the diagnosis of severe PH. Due to the worsening clinical status and the echocardiography results on day 5, the patient received 5 days of venoarterial ECMO to improve oxygenation. This enabled for discontinuation of inhaled NO and the CDH repair on day 9 with the placement of a prosthetic patch. After surgery, inhaled NO was restarted (at 20 ppm (parts per million)), and a chylothorax, a postsurgical complication, had to be treated by thoracocentesis together with 27 days of octreotide therapy. Since there was no improvement in PH, despite the inhaled NO treatment, IV sildenafil treatment was deemed necessary, and started with a dose of 0.4 mg/kg of body weight on day 16. The sildenafil dose was tapered until an infusion time of 1 h had been attained, in regard to mean arterial pressure and consistent daily fraction of inspired oxygen (FiO_2) requirements. On day 4 of sildenafil treatment, the patient could be weaned from inhaled NO, but, because of ongoing severe PH the treatment had to be restarted on day 7. The newborn was also started on nebulized iloprost (1.25 µg over 10-15mins every 2 h) and NO had to be increased to 40 ppm on day 13. Transient irritability and shifts in mean systemic blood pressure (>30 mmHg) led to a tapered dose and discontinuation by day 20, with reversion of inhaled NO back to a dose of 20 ppm. The resultant moderate PH allowed weaning of NO. On day 36, echocardiography showed only mild PH, so a sildenafil wean could be started again on day 37. However, this has to be slowed down twice due to bradycardia, desaturation events and patient extubation. Finally, sildenafil was discontinued on day 51, and echography on day 80 did not show any evidence of PH. The patient could be successfully weaned from hydrocortisone by day 8, and stabilization in mean systematic blood pressure ensued after 27 days of treatment. Packed red blood cells, albumin and 0.9% sodium chloride injections were also given intermittently. Mean daily FiO_2 requirements fluctuated minimally and the patient could be transitioned to oxygen via nasal continuous positive airway pressure (nCPAP) on day 42 of treatment. The patient became stable on room air at 100 days of life and was discharged home on day 123 [5].

The second case reported by Stultz et al. [5] was a female neonate of 39 weeks of gestational age with a left-sided CDH. Her CDH was managed with inhaled NO for two days, followed by CDH repair with a prosthetic patch on day 2 of life. She remained on inhaled NO (20 ppm) and required HFOV. On day 8 of life an echocardiography revealed severe PH, and, due to its severity and the life threatening respiratory compromise, despite treatment with inhaled NO, IV sildenafil treatment was deemed necessary. Consequently, sildenafil 0.5 mg/kg was administered iv every 6h intermittently on day 9 of life and infusion duration was tapered, as described for the other case. Initially, the mean arterial pressure (MAP) decreased, and the patient's FiO_2 requirements remained stable throughout the dosing intervals. On day 3 of treatment the patient was unable for transition to conventional ventilation due to a tension pneumothorax, requiring a thoracotomy, which resulted in increased FiO_2 requirements over the next 5-6 days. After an echocardiogram revealed severe PH increase, the sildenafil dose was increased to 1 mg/kg every 6 h on day 5, finally allowing the transition to mechanical ventilation on day 10. An echo control on day 12 revealed mild PH, but since the infant`s FiO2 requirements were still unchanged, sildenafil was increased from 1.5 mg/kg to 2 mg/kg every 6 h, until a decline in FiO_2 requirements was noted, and echo control on day 19 confirmed mild PH. On day 20 weaning of inhaled NO was initiated, with discontinuation by day 22. The patient was extubated to nCPAP on day 25 and treatment of oral sildenafil was started. On day 96 of treatment sildenafil could be weaned over 11 days. On day 107 no signs of PH were detected, and the infant was discharged on day 121 of life, requiring nCPAP with 100% FiO_2 at a flow rate of 0.5 l/min [5].

Both patients have been similar in a way, that they both have had CDH repair and received IV sildenafil. However, in one case the authors did not specify the side of the CDH involved. Despite its importance, in terms of the anticipated course and prognosis, since either the liver or the spleen will be involved. Furthermore, no detailed information about the extension of the defect, or the surgical approach (abdominal or thoracic) was provided. In addition, in due course in each patient further thoracotomies and concomitant specific therapies were necessary. Although these interventions are not uncommon in CDH patients, they would clearly have an influence on the results and final outcome. But the authors did not consider this in their paper. IV sildenafil therapy was initiated at different times after CDH repair and the duration of sildenafil treatment also differed widely (50 and 33 days respectively). In both patients, sildenafil was initiated as an "ultimate ratio" indication, when even minimal oxygen saturation and respiration/ventilation requirements could not be achieved by conventional therapies such as NO, ECMO, or HFOV, or even after

using quite high doses of NO (20-40 ppm). None of the potential influences of such therapies, either alone or in combination, were taken into consideration in this publication.

It should also be noted, that the purpose of NO-, ECMO and HFOV therapies is usually to improve oxygenation saturation and not to treat PH, as with sildenafil. Quite contrary, in one of the two patients sildenafil dosage has to be increased to counterbalance the elevated FiO_2 requirements. One patient received a short treatment course with iloprat, which may has helped manage the PH, but may also have interfered with the patient´s respiratory function (i.e. bronchoconstriction) and hemodynamic stability. Consequently, the results attributable exclusively to sildenafil cannot be clearly differentiated. This is also true for the other hemodynamic support medications administered.

From a review of the literature, it is evident that the dosage and administration of iv sildenafil as a treatment for PH has been established mainly for use in adults and not for infants or newborns. The authors of the study considered that daily doses of 1.6-8 mg/kg of BW could be considered equivalent to a loading dose previously reported, and that the use of sildenafil as an infusion could be expected to cause fewer adverse hemodynamically effects. Furthermore, the higher initial doses were shown to produce significant short term improvements in oxygenation. Unfortunately, however, no further details or evidence-based data were provided in support of these sildenafil effects exclusively on pulmonary hypertension in CDH patients.

In general, the pulmonary hypertension in both of these patient cases was classified only semi quantitatively by echocardiography and not additionally by other measurable parameters. Since the data were most probably obtained by a single observer, the potentially critical reliability of the measurements, in terms of variability, has also to be considered.

Discussion

The authors of the animal study showed that maternal sildenafil treatment enhances pulmonary vessel density, reverses RVH and improves the pulmonary vasodilatory response to NO in the nitrofen-induced CDH rat model. This appears to be achievable without significant adverse effects on retinal structures and function or on brain development in the offspring. Nevertheless, some of the results are either not statistically significant or questionable and, since they are derived from an experimental setting in a rodent model, are not directly transferable to the clinical setting.

Case reports or small case series provide only anecdotal or lowest-level evidence, because of their retrospective nature and restricted methodology, in which no randomization or detailed statistical analysis is used [9]. The treatment of patients with CDH is nevertheless always critical and challenging, with many complications. The two patients in this clinical report were severely ill and therefore required additional treatment for their PH. Ultimately, both showed some improvements that were related to the administration of sildenafil. Thus, the use of sildenafil may be warranted in neonates and infants in such cases, but the precise efficacy and safety of the drug in this population needs to be further evaluated.

Conclusion

On the basis of this literature review, the administration of sildenafil in the treatment of CDH seems to be promising but if conclusions are to be based on sound evidence, further large- scale clinical trials and evaluations are necessary.

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