

Pharmacokinetics of sildenafil in children with pulmonary arterial hypertension

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Background: Recently, sildenafil was introduced to treat pulmonary arterial hypertension (PAH); however, there are currently few studies on the pharmacokinetics of sildenafil in children. Therefore, we aimed to carry out a pharmacokinetic study of sildenafil in children with PAH using a single dose.

Methods: Twelve children diagnosed with PAH, consisting of with ten males and two females, were recruited for the study after obtaining written consent from their parents or guardians. Blood samples were obtained pre-dose and at 0.25, 0.5, 1, 2, 4, 8 and 12 hours after the oral administration of 1 mg/kg of sildenafil using an extemporal pediatric formulation developed in our laboratory. The samples were analyzed using a previously validated high performance liquid chromatography method.

Results: A pharmacokinetic analysis using the WinNonlin 3.1 program that considered the Akaike information criterion (AIC) for selecting a more adjustable model was performed. The following pharmacokinetic parameters were obtained: maximal concentration (C_{max}): 366 ± 179 ng/mL, time to maximal concentration: 0.92 ± 0.30 hours, elimination half-life ($t_{1/2}$): 2.41 ± 1.18 hours, total clearance (CL_{tot}/F): 5.85 ± 2.81 L/hour, volume of distribution (Vd/F): 20.13 ± 14.5 L, absorption rate constants (K_a): 0.343 hour⁻¹, elimination rate (K_e): 0.35 hour⁻¹, area under curve from

zero to infinity: 2061 ± 618 ng/mL/hour. The data of all patients adjusted to the model of one compartment were corroborated using AIC.

Conclusions: The parameters K_a , K_e and $t_{1/2}$ were found to be similar to those reported in adults; however, the values of C_{max} and Vd/F were significantly higher. Based on these findings, we propose that treatment regimen of sildenafil be adjusted in children with PAH.

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Introduction

Pulmonary arterial hypertension (PAH) is a disorder with elevated blood flow pressure in the vessels between the lungs and the heart.^[1] To date, the precise causes of arterial pressure elevation and the development of hypertension are unknown; however, it is known with certainty that hypertension is provoked by the narrowing of vessels that irrigate the lung,^[2,3] which could provoke respiratory distress.^[4] In addition, this disease can be confused with congenital cardiopathies, and half of the affected patients, if they are not treated, die within three years of its diagnosis.^[5] PAH can specifically affect infants and children with congenital cardiopathy, who present hypertensive crisis during the postoperative period.^[6] In the latter group, PAH is often a disorder that can be associated with other diseases, some of which may be severe. Thus, in addition to the treatment of PAH, patients need other drugs to control associated diseases.^[7,8]

Sildenafil has been used to treat PAH in children because of its effect on relaxing the pulmonary blood vessels, which permits better blood flow into this zone.^[9,10] It increases the effect of nitric oxide by inhibiting phosphodiesterase type 5, which is responsible for the degradation of cyclic guanosine monophosphate, thereby enhancing the relaxation of smooth muscles and

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favoring better blood flow.^[11] Some studies of sildenafil pharmacokinetics in children have been reported, for example, Apitz et al^[12] reported the pharmacokinetics of sildenafil in children after administration of sildenafil, giving 0.5 mg/kg suspended in 5 mL sterile water; however, no description of pharmacokinetic parameters were shown in their study. Ahsman et al^[13] reported the pharmacokinetics of sildenafil in neonates highlighting that their profile fits to model of one compartment in that population. Studies in adults indicate that sildenafil is rapidly absorbed following its oral administration with an absolute bioavailability of 40% (ranged from 25% to 63%).^[14] In adults, the maximum plasma concentration is reached in 30 to 120 minutes (average: 60 minutes) following the oral administration of sildenafil in the fasting condition.^[14,15] Thus, it is pertinent to have a more precise estimate of the pharmacokinetics of the drug in children with PAH who are also suffering from severe concomitant diseases. Hence, the aim of the present work is to study the pharmacokinetics of sildenafil in a population of children with PAH.

Methods

This study is a single dose pharmacokinetic trial performed in 12 children with PAH in combination with one or more of the following diseases: epilepsy, Down syndrome, gastroesophageal reflux, or psychomotor retardation. The age of the patients ranged from 1.5 to 15 years and weighting 7.5 to 26 kg. Some patients presented decreased developmental data concerning weight and height.

The patients received 1 mg/kg of sildenafil via oral administration using a pediatric extemporal formulation developed in our laboratory test assayed by high performance liquid chromatography-ultra violet (HPLC-UV) method, and the water-diluted powder was orally administered with syringe.^[16] After drug administration, 1 mL of blood sample was obtained pre-dose and at 0.25, 0.5, 1, 2, 4, 8 and 12 hours via peripheral vein using peripheral venous catheter placed in the patient arm and maintained in the open state with an infusion of heparinized saline solution.

Written consents were obtained from their parents or guardians and for safety reasons, the patients were accompanied by their cardiologists during the study. The study was approved by our Institutional Review Board and the Ethics Committee with the approbation code INP-086/2010.

Bioanalytical assay

For the quantification of the concentrations of sildenafil in plasma, a previously developed method validated by HPLC was used.^[17] The concentrations of sildenafil

were quantified by analytic method using a C18 column reversible phase with UV detection. The method is based on a precipitation of proteins with perchloric acid and an extraction with dichloromethane. After evaporation, 100 μ L of the re-suspended liquid was taken and injected into a chromatographic system. The method was reliable and specific for this type of pharmacokinetic study. The validation parameters reported are as follows: linearity range from 0.01 to 2 μ g/mL and a value of $r=0.998$ for sildenafil with a precision of $97.7\%\pm 7\%$. The results of recovery obtained were $98.5\%\pm 3.5\%$. Inter and intraday coefficient of variation was $<5\%$. Detection and quantification limits for sildenafil were 1 and 10 ng/mL, respectively.

Pharmacokinetic analysis

Data concerning the serial concentration vs. time of sildenafil were adjusted to the most appropriate model after applying Akaike information criterion (AIC), with absorption and elimination according to the 1st-order kinetics using the WinNonlin 3.1 program (Pharsight, Mountain View, CA), in which the distribution and elimination pharmacokinetics of the drug were obtained.

Analysis using the AIC was performed according to the following equations: $Re = \sum W \times (C_i - C_{aj})^2$. Where Re =residuals, $\sum$ =the sum, W =weighting factor, C_i =observed concentration, C_{aj} =the adjusted concentration.

In the analysis, a lesser AIC was produced and was chosen according to the following behavioral criterion: $AIC = N \times \ln Re + 2P$. Where N =number of data (samples=7 for every patient), $\ln$ =natural log, Re =residual values, P =number of pharmacokinetic parameters.

Table 1. Demographic data of children with pulmonary arterial hypertension included in the study

Patient	Age (y)	Sex	Weight (kg)	Height (cm)	Additional diseases
1	1.4	M	7.5	60	Anomalous pulmonary venous drainage
2	6.8	M	16.5	115	Psychomotor retardation
3	6.2	M	15.0	100	GER
4	10.4	M	18.0	113	IVC, IAC with triatrium
5	2.7	M	7.9	90	Epilepsy, Down syndrome
6	6.3	M	11.8	98	IVC, thrombosis of portal vein, hepatopulmonary syndrome
7	1.4	M	8.9	74	GER, pulmonary dysplasia, hypothyroidism
8	15	F	26.0	148	Psychomotor retardation
9	12.3	F	14.0	112	GER, IAC, psychomotor retardation
10	3.5	M	12.0	102	Down syndrome
11	6.4	M	16.0	105	GER
12	4.7	M	14.0	119	GER

IAC: interatrial communication; IVC: interventricular communication; GER: gastroesophageal reflux; M: male; F: female.

Results

Demographic data of children included in the study is shown in Table 1. The low weight and size in most of the patients can be noted; however, laboratory values confirm the normal hepatic and renal organ functions. Six patients in addition to sildenafil received either spironolactone or captopril or both, the rest received only sildenafil.

Pharmacokinetic analysis showed the following average parameters for sildenafil (Table 2): maximal concentration ($C_{\max}$): 366 ± 179 ng/mL, time to maximal concentration ($T_{\max}$): 0.92 ± 0.30 hours, elimination half-life ($t_{1/2}$): 2.41 ± 1.18 hours, total clearance (CL_{tot}/F): 5.85 ± 2.81 L/hour, volume of distribution (Vd/F): 20.1 ± 14.5 L, absorption rate constant (K_a): 0.343 hour^{-1} , elimination rate constant (K_e): 0.35 hour^{-1} , area under curve from zero to infinity: 2061 ± 638 ng/mL/hour. The average pharmacokinetic profile of sildenafil in patients with PAH during the study is shown in Fig. 1. It is important to note the rapid process of absorption with a $T_{\max}$ of approximately 1 hour.

Table 2. Pharmacokinetic parameters of sildenafil in children with pulmonary arterial hypertension (PAH) and adults

Pharmacokinetic parameters	Children with PAH ($n=12$)	Adults* ($n=20$)
Absorption rate constant (h^{-1})	0.343	Fast process
Elimination rate constant (h^{-1})	0.35	0.3-0.5
Half-life (h), mean $\pm$ SD	2.41 ± 1.18	3.0-5.0
Volume of distribution (L), mean $\pm$ SD	20.1 ± 14.5	5.0-8.0
Total clearance (L/h), mean $\pm$ SD	5.85 ± 2.81	6.5 ± 3.2
Time to maximal level (h), mean $\pm$ SD	0.92 ± 0.30	1-2
Maximal concentration in plasma (ng/mL), mean $\pm$ SD	366 ± 179	280 ± 185
Area under curve (ng/mL/h), mean $\pm$ SD	2061 ± 638	Variable

SD: standard deviation; *: data from a previous study.^[15]

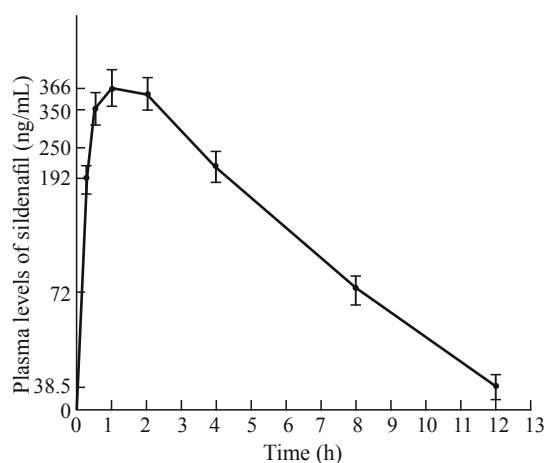


Fig. 1. Pharmacokinetic profile of sildenafil in children with pulmonary arterial hypertension ($n=12$) after being given 1 mg/kg orally. It should be noted that there was a rapid process of absorption with a time to maximal concentration of approximately 1 h.

The AIC for the one compartment model was 198, whereas it was 235 for two compartment model, with the selection criterion being the AIC that had the lowest value and was the best adjusted to the one-compartment open model in all patients studied.^[18] The adverse events, such as headache (2 cases), stomachache (1) and hypotension (1), observed in the present work were of mild to moderate intensity.

Discussion

Sildenafil citrate is a potent vasodilator commonly used for treating erectile dysfunction.^[19] Apitz et al^[12] performed a study in children with idiopathic PAH that did not reflect an integral pharmacokinetic study because they only reported sildenafil concentrations of 69.3 ng/mL. However, the patients were presented at a specific treatment point, where changes in hemodynamic parameters are mentioned. Vachier et al^[20] evaluated the pressure changes on oral and intravenous administration using non-compartmental analysis in adult patients with PAH. A work that seems similar to the present study was carried out by Watt et al,^[21] who studied the use of cardiovascular drugs in critically ill children with extracorporeal membrane oxygenation, which contributed to the management of patients with these conditions.

Hill et al^[22] reported that the pharmacokinetics is altered by the elevated hepatic pressures and the modifications of the hepatic clearance. Despite the absence of pharmacokinetic information, the drug is used in our hospital and other hospitals in a dose-response manner, beginning with 1 mg/kg. Other studies have used doses of 3 mg/kg which has a potential risk of reaching high concentrations with its possible consequences. Thus, it is of great interest to have a more precise estimate of the drug behavior, particularly for those administered in the presence of some processes of retention or slow elimination as reported by Karatza et al,^[23] in children with pulmonary hypertension. Although the parameters of K_a , K_e and $t_{1/2}$ in this study were similar to those reported in adults, the values of $C_{\max}$ and Vd/F obtained with other parameters were very different and significantly higher than those reported in adults (Table 2).^[15] This finding indicates that the distribution of this drug in children with PAH occupies different spaces because of the physiological conditions of the patients who are generally underweight and shorter in stature in addition with their concomitant diseases. All these contribute to the pharmacokinetic behaviors. Although, it is known that the metabolite of sildenafil has a pharmacokinetic activity at 50%, a limitation of our study was that this compound was not measured.

In adults, the maximum concentration of sildenafil is approximately 280 ng/mL.^[24] In this study, the maximum concentration was approximately 366 ng/mL, which indicates a considerable increase in concentrations, even when an equivalent dose to that administered to adults were used. However, the concentrations were consistent with those reported in previous studies in children with levels near to 385 ng/mL.^[25]

The volume of distribution of sildenafil in the state of equilibrium in adults was 0.5 L/kg,^[14] but in children, the value was approximately 0.8 L/kg, thus demonstrating its distribution in deep tissues. The total body clearance was reported as 4 L/hour, with a half life terminal phase of 3-5 hours.^[15] In the present work, the half life was 2.41 hours, similar to that observed in adults.

On the basis of these findings, the treatment regimen should be adjusted to take the population parameters into consideration. Such adjustment would help to prevent the potential toxicity that might result from high levels (more than 500 ng/mL), a level which has been reported to produce flushing and pain engorgement in the penile region.^[26] In adults, adverse effects such as headache, insomnia and dizziness have been reported. However, in clinical studies, sildenafil has been demonstrated to have systemic vasodilatation properties that result in a transient reduction of arterial pressure. Moreover, the adverse events, such as headache, stomachache and hypotension, observed in the present work were of mild to moderate severity. This finding demonstrates that the drug is safe, although it is very premature to take this assertion as a definitive conclusion. In terms of its future use, more studies are needed to better evaluate the benefit/risk balance of sildenafil citrate in pediatric populations.^[27]

The pharmacokinetic study here described is an initial step for the management of children diagnosed with PAH who are additionally suffering from another disease. Such combination of ailments in children alters the pharmacokinetics of sildenafil in this population and so should be followed by clinical studies in which the treatment regimens are adjusted.^[28] Although no severe adverse effects were observed in the present study, it is necessary to carry out additional studies where the mean value of pharmacokinetics parameters as C_{max} , $t_{1/2}$, CL, etc are determined in light of either hemodynamic and side effects. Based on this, a reliable therapeutic range can be established.

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Competing interest: The authors declare that they have no competing interests.

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