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Pharmacokinetic and Hemodynamic Responses to Oral Sildenafil During Invasive Testing in Children With Pulmonary Hypertension

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Objectives The purpose of our study was to characterize the hemodynamic and corresponding pharmacokinetic responses to a single dose of oral sildenafil by children with pulmonary arterial hypertension (PAH) undergoing invasive testing.

Background Although used frequently for the treatment of children with PAH, data regarding the acute responses to sildenafil are limited.

Methods Thirty-six patients (mean age 7.5 ± 5.9 years; 24 females) were studied during cardiac catheterization with general anesthesia. Eight of 36 (22%) had idiopathic PAH; the remainder had associated congenital heart disease. Hemodynamics and serum cyclic-guanosine monophosphate levels (cGMP) were evaluated at baseline and after inhaled nitric oxide (NO) (40 ppm). In addition, cGMP and sildenafil levels were measured 30 min after administration of sildenafil (0.5 mg/kg, suspended in 5 ml sterile water) through a nasogastric tube.

Results For the 36 patients, the pulmonary vasodilating capability of oral sildenafil was lower than that of inhaled NO (2.8% vs. 11.6% reduction in pulmonary vascular resistance indexed to body surface area [PVRI], respectively; $p = 0.01$). However, only 21 of 36 (58%) patients had a detectable sildenafil level. In those with detectable sildenafil levels, the fall in PVRI was greater (−11.6% vs. −19.1%, p = NS). Mean cGMP levels at baseline and after NO were 41.8 ± 20.0 pmol/ml and 83.8 ± 35.5 pmol/ml, respectively ($p < 0.0001$). Surprisingly, there was no significant increase in cGMP in patients with either undetectable (37.5 ± 29.8 pmol/ml) or detectable (44.4 ± 31.7 pmol/ml) sildenafil levels (p = NS compared with baseline) with sildenafil.

Conclusions Our study demonstrates suboptimal absorption of sildenafil in almost half the children undergoing acute hemodynamic testing. When detectable, there was no statistically significant difference between the fall in PVRI associated with sildenafil and NO despite lower circulating cGMP levels in the sildenafil group. These data should be taken into account when designing acute testing protocols, and assessing the acute response to sildenafil in patients with PAH. (J Am Coll Cardiol 2010;55:1456–62) © 2010 by the American College of Cardiology Foundation

Acute administration of a single oral dose of sildenafil to adults with pulmonary hypertension causes a significant decrease in mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) (1,2), and its utility in chronic therapy is now established (3,4).

The effectiveness of sildenafil as a pulmonary vasodilator in children with congenital heart disease (CHD) was first reported in a small case series post-operatively in 1999 (5), and confirmed 4 years later in the first detailed prospective open-label study during cardiac catheterization and post-operatively (6). Using an intravenous preparation in that study, the authors were able to show a similar acute hemodynamic response to that of inhaled nitric oxide (NO), and a direct relationship between cyclic-guanosine monophosphate (cGMP) level and therapeutic response. Although sildenafil is now used frequently for long-term treatment of children with pulmonary arterial hypertension (7), clinical data regarding the acute pharmacokinetic and hemodynamic responses to sildenafil are limited.

Therefore, the purpose of this study was to characterize the responses to fixed dosing of oral sildenafil for children with pulmonary hypertension undergoing invasive hemodynamic testing in the catheterization laboratory.

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Methods

The study design was open label, prospective, and interventional. The study protocol was approved by the research and ethics review board of the Hospital for Sick Children, Toronto, Canada, and informed signed consent was obtained from the study subjects and their parents.

Protocol. All patients undergoing cardiac catheterization to assess pulmonary hypertension, defined as mean pulmonary arterial pressure (mPAP) >25 mm Hg or pulmonary vascular resistance index (PVRI) >5 Wood units (WU), indexed for body surface area (BSA), were eligible for inclusion. These patients routinely undergo pulmonary vascular reactivity drug testing in the cardiac catheterization laboratory before decisions about therapy. We excluded patients with hepatic or renal insufficiency and known retinal disease.

Patients were studied under general anesthesia with mechanical ventilation with a baseline fraction of inspired oxygen (FiO_2) of 0.25 (if not required to be higher for clinical reasons). Anesthesia was induced with sevoflurane, midazolam, and remifentanil. Sevoflurane was discontinued after induction. Rocuronium was used for muscle relaxation. A nasogastric tube was placed, and its position confirmed by fluoroscopy. Measurement of baseline hemodynamics included arterial and venous saturations, blood gases, systemic and pulmonary artery pressures, left atrial (or pulmonary capillary wedge) pressure, and right atrial pressure in the standard manner with fluid-filled catheters. End-tidal carbon dioxide and systemic oxygen consumption were continuously determined using respiratory mass spectrometry. Oxygen saturations were measured by co-oximetry after sampling in the superior vena cava, pulmonary vein, pulmonary artery, and systemic artery. We estimated systemic and pulmonary blood flows from the Fick equation. We calculated systemic and PVRs from standard equations (mean arterial pressure minus mean atrial pressure divided by flow). Blood flow and vascular resistances were indexed to BSA.

Assessment of pulmonary vascular reactivity was undertaken as follows: measurements were made at baseline (at "usual" FiO_2) and with FiO_2 0.7 (if higher than usual requirements). The patients were then returned to baseline FiO_2, and after 10 min, the effect of additional inhaled NO at 40 ppm for 10 min was recorded. The NO was then discontinued, and new baseline hemodynamics were measured after 10 min. Subsequently, a dose of sildenafil (0.5 mg/kg, suspended in 5 ml sterile water) was administered through the nasogastric tube. Measurements were repeated at 30 min.

For the determination of sildenafil and cGMP levels, blood samples of each patient were taken from the pulmonary artery and were then transferred to heparinized polypropylene tubes and centrifuged for 10 min at 4,000 rpm; the supernatant plasma was pipetted into screw-capped polypropylene tubes and stored at −80°C, within 50 min of blood sample collection. Measurements of cGMP levels were recorded at baseline, after 10 min of inhaled NO, and before and 30 min after administration of sildenafil. Plasma samples were analyzed using a commercially available enzyme immunoassay (Amersham cGMP, GE Healthcare UK Ltd., Buckinghamshire, United Kingdom). The sildenafil level was measured 30 min after oral administration of sildenafil. The quantitative analyses for sildenafil and its N-desmethyl metabolite were performed at NMS Labs, Willow Grove, Pennsylvania, using high-performance liquid chromatography with tandem mass spectrometry.

Abbreviations and Acronyms

- **BSA** = body surface area
- **cGMP** = cyclic-guanosine monophosphate
- **CHD** = congenital heart disease
- **FiO_2** = fraction of inspired oxygen
- **mPAP** = mean pulmonary arterial pressure
- **NO** = nitric oxide
- **PAH** = pulmonary arterial hypertension
- **PVR** = pulmonary vascular resistance
- **PVRI** = pulmonary vascular resistance index
- **WU** = Wood units

The primary outcome measure was the PVRI and the mPAP at cardiac catheterization. A significant acute response to NO and/or sildenafil was defined as a fall in mPAP and/or PVRI of at least 20% relative to the baseline value (8). The secondary outcome measure was the cGMP level at baseline, after NO, and after sildenafil, as well as the sildenafil level 30 min after oral administration.

Data analysis. Data are presented as mean and standard deviation. Comparisons were performed by nonparametric Mann-Whitney test if the sample groups were not paired, for example, comparison between patients with idiopathic and PAH associated with CHD, or the comparison between responders and nonresponders. Paired *t* tests were utilized to compare the hemodynamic parameters after each intervention to the corresponding baseline value of each patient and to evaluate differences of the effect on PVR of NO and sildenafil.

We used a linear regression test to examine the correlation between plasma sildenafil concentration and cGMP levels, and fall in PVRI, respectively. Analysis was performed using GraphPad statistical software package (San Diego, California). The null hypothesis was rejected when $p < 0.05$.

Results

Patient population. Thirty-six patients (mean age 7.5 ± 5.9 years; 24 females) fulfilled entry criteria and were enrolled in the study protocol. The clinical characteristics of the patients are outlined in Table 1. The diagnosis was idiopathic pulmonary hypertension in 8 of 36 (22%) patients, and 28 (78%) patients had associated CHD. At baseline, the mPAP was 46.4 ± 18.2 mm Hg, and the PVRI was 16.5 ± 10.8 WU × m^2 BSA.

Hemodynamic parameters. Mean pulmonary artery pressure decreased with hyperoxia from 46.4 ± 18.2 mm Hg to

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