ARTICLE

Oral Sildenafil in Infants With Persistent Pulmonary Hypertension of the Newborn: A Pilot Randomized Blinded Study

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ABSTRACT

BACKGROUND. Persistent pulmonary hypertension (PPHN) occurs in as many as 6.8 of 1000 live births. Mortality is ~10% to 20% with high-frequency ventilation, surfactant, inhaled nitric oxide, and extracorporeal membrane oxygenation but is much higher when these therapies are not available. Sildenafil is a phosphodiesterase inhibitor type 5 that selectively reduces pulmonary vascular resistance.

OBJECTIVE. Our goal was to evaluate the feasibility of using oral sildenafil and its effect on oxygenation in PPHN.

DESIGN. This study was a proof-of-concept, randomized, masked study in infants >35.5 weeks’ gestation and <3 days old with severe PPHN and oxygenation index (OI) >25 admitted to the NICU (Hospital Niño Jesús, Barranquilla, Colombia). The sildenafil solution was prepared from a 50-mg tablet. The first dose (1 mg/kg) or placebo was given by orogastric tube <30 minutes after randomization and every 6 hours. Preductal saturation and blood pressure were monitored continuously. OI was calculated every 6 hours. The main outcome variable was the effect of oral sildenafil on oxygenation. Sildenafil or placebo was discontinued when OI was <20 or if there was no significant change in OI after 36 hours.

RESULTS. Six infants with an OI of >25 received placebo, and 7 received oral sildenafil at a median age of 25 hours. All infants were severely ill, on fraction of inspired oxygen 1.0, and with similar ventilatory parameters. Intragastric sildenafil and placebo were well tolerated. In the treatment group, OI improved in all infants within 6 to 30 hours, all showed a steady improvement in pulse oxygen saturation over time, and none had noticeable effect on blood pressure; 6 of 7 survived. In the placebo group, 1 of 6 infants survived.

CONCLUSIONS. Oral sildenafil was administered easily and tolerated as well as placebo and improved OI in infants with severe PPHN, which suggests that oral sildenafil may be effective in the treatment of PPHN and underscores the need for a large, controlled trial.

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Key Words
neonatal, pulmonary hypertension

Abbreviations
PDE5 — phosphodiesterase inhibitor type 5
cGMP — cyclic guanosine monophosphate
NO — nitric oxide
PPHN — persistent pulmonary hypertension of the newborn
ECMO — extracorporeal membrane oxygenation
HFV — high-frequency ventilation
iNO — inhaled nitric oxide
OI — oxygenation index
SpO2 — pulse oxygen saturation
BP — blood pressure

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275)
Sildenafil (Viagra) is a phosphodiesterase inhibitor type 5 (PDE5) that has been shown to selectively reduce pulmonary vascular resistance in both animal models and adult humans. Sildenafil produces vasodilation by increasing cyclic guanosine monophosphate (cGMP) through inhibition of the phosphodiesterase involved in the degradation of cGMP to guanosine monophosphate.

A recent study in a neonatal model showed an effect of sildenafil in vasorelaxation of pulmonary arteries. The results suggest that PDE5 is a key regulator of nitric oxide (NO)–induced vasodilation in the postnatal pulmonary arteries. PDE5 inhibition is able to produce pulmonary vasodilation even in the absence of a functional endothelium and potentiates the vasorelaxant response to exogenous NO and nitroprusside. In a different neonatal model, sildenafil was shown to be effective in decreasing pulmonary arterial pressure and pulmonary vascular resistance. Potential beneficial effects in adult humans have been shown also. One of the recent adult randomized crossover studies shows that oral sildenafil significantly improves exercise tolerance, cardiac index, and quality of life in adult patients with primary pulmonary hypertension. In another randomized trial, sildenafil caused preferential pulmonary vasodilation and improved gas exchange in adult patients with severe lung fibrosis and secondary pulmonary hypertension. In newborns and children, only isolated case reports have been published, and in 1 case, it has been considered a promising drug for persistent neonatal pulmonary hypertension.

The incidence of neonatal refractory hypoxemia and/or persistent pulmonary hypertension (PPHN) in term or near-term infants is reported to vary between 0.43 and 6.8 of 1000 live births. The treatment for PPHN has evolved over the past 10 to 15 years but reported mortality remains at 10% to 20% in newborns with PPHN. Extracorporeal membrane oxygenation (ECMO) has been proven of value for this condition, and several “alternative” therapies such as high-frequency ventilation (HFV), surfactant, and inhaled NO (iNO) used in a rescue mode have produced varying degrees of success to decrease ECMO use. With as many as 30% of cases failing to respond, iNO has not proven to be the single magic bullet.

The use of iNO as a treatment option for neonates with refractory hypoxemia has been reviewed recently in detail by Kinsella and Abhman. In addition to these therapies, inhaled prostacyclin has been reported effective also. However, ECMO and iNO are expensive and unavailable in many regions of the world in which mortality resulting from severe PPHN is much higher than in industrialized nations. ECMO is not free of serious adverse effects. Furthermore, in industrialized nations, some of the PPHN survivors have high morbidity in the forms of neurodevelopmental and auditory impairment, cognitive delays, hearing loss, and a high rate of rehospitalization.

Finding an effective and selective pulmonary vasodilator with little or no adverse effects for the treatment of PPHN has been elusive over the past 20 years. Oral sildenafil, a potential such therapy, has not been systematically evaluated in newborns with PPHN. However, reviews have been published recently both for adults and neonates. In addition, published uncontrolled case reports presented a abstract in the Pediatric Society annual meeting, and verbal communication demonstrate that oral sildenafil is being used off-label without any protocol or clinical guideline. According to these reviewed and not reviewed claims, sildenafil may provide some benefit in newborn infants with PPHN and refractory hypoxemia. Our objective for this proof-of-concept, randomized masked study was to systematically obtain preliminary information regarding the feasibility of administration of oral sildenafil and its effect on oxygenation (OI values) in infants with severe PPHN.

METHODS

This proof-of-concept pilot study was randomized, prospective, and masked and performed between 2003 and 2004 in the NICU of Hospital Niño Jesús in Barranquilla, Colombia. This is a regional NICU serving a population of ~10 000 deliveries per year, which is well equipped with modern technology but in which surfactant used is limited for preterm infants with respiratory distress syndrome, and there is no iNO, HFV, or ECMO available.

Eligible infants for the study were term or near-term gestation (>35.5 weeks’ gestation) with severe hypoxemia and pulmonary hypertension confirmed by echocardiogram. Only very sick and critically ill term or near-term newborn infants with PPHN were considered for the study. The infants had to be on mechanical ventilation with an oxygenation index (OI) ≥40, show clinical signs of severe refractory hypoxemia, and have a known high risk for mortality at this center. The echocardiogram (Sonosite 180 plus) performed before entry had to show evidence of right-to-left shunt and estimated pulmonary artery pressures ≥40 mm Hg. Exclusion criteria included congenital abnormalities. Congenital heart disease of any type was excluded, including pulmonic stenosis, atrial septal defect, abnormal pulmonary venous drainage, and ventricular septal defect.

Arterial blood gases were monitored from an umbilical arterial catheter, and OI was calculated 2 hours after each dose of drug or placebo and analyze and report the OI at this time to ensure consistency and accurate comparisons. Pulse oxygen saturation (SpO2) and mean arterial blood pressure (BP) were

1078 BAQUERO, et al
monitored continuously. For consistency and to avoid including a large number of data points at many different times, we chose to report the data on $\mathrm{SpO}_2$ and BP at these preestablished set points of time, 2 hours after each dose, after the predesigned protocol.

Clinical management protocols used in the NICU by attending physicians caring for infants with PPHN were not altered if the infant was a study subject. The clinical approach for all of the infants included: no “hyperventilation” but avoidance of hypercarbia (ie, $\mathrm{Paco}_2$: 35–50 mm Hg), manual ventilation when needed (ie, severe episode of hypoxemia or of low pH with high $\mathrm{Paco}_2$), avoidance of significant acidosis, (ie, maintain pH >7.30), no alkalosis (ie, not aiming to keep pH >7.45), inotropes (dopamine), and volume infusion to try to preserve intravascular volume and maintain mean arterial BP $\geq$50th percentile, and no nitroprusside or tola- zoline were used.

Improvement in OI was defined as a decrease in OI of $\geq$6 from the previous calculated value. Although this is an arbitrary measure, we agreed a priori on the significance of a reduction $>10\%$. For infants with an initial OI value of 40, a decrease of 6 would be a 15% effect.

The preparations and schedule for administration of drug and placebo were as follows. A 50-mg tablet of sildenafil was diluted in Orabase as much as will suffice to 25 mL for a final concentration of 2 mg/mL. (If this compound is refrigerated, it would expire 1 month after preparation.) For placebo, an equal volume of diluent (0.5–1 mL/kg) was used. Both drug and placebo were given by orogastric tube, and the protocol for dosing schedule was (a) first dose of 1 mg/kg (0.5 mL/kg) $<30$ minutes after randomization, (b) dosing every 6 hours, (c) dose could be doubled (2.0 mg/kg or 1.0 mL/kg) if the OI did not improve and the mean BP remained stable after the previous dose, and (d) discontinuation of treatment decided according to 1 of 2 criteria, whichever is earlier: an OI of $<20$ or maximum number of doses of 8 (ie, a maximum period of 42 hours after the first dose).

Randomization was by simple allocation of presealed numbers. Pharmacy prepared the oral preparations in the same containers for placebo and medication and had the sealed code for identification. The administration of drug or placebo was randomly assigned, masked, and bedside clinicians were unaware of group assignment. At the onset of the study it was elected to enter only very sick and critically ill newborn infants with PPHN (OI $\geq$ 40), with a known high mortality rate. The initial sample size calculated to assess feasibility, and OI response was 25 infants in each group. Stopping rules for breaking of the codes and analyzing the data included potential significant adverse effects like hypotension, gastric intolerance or bleeding, renal failure, or death in 6 infants.

The main outcome variable was the feasibility of administration, gastric tolerance, and the effect of oral sildenafil on OI values. Other variables analyzed were $\mathrm{SpO}_2$, $\mathrm{Pao}_2$, BP, and survival. Statistical methods used were analysis of variance for comparison of repeated measurements of OI, BP, and $\mathrm{SpO}_2$ and Newman-Keuls for posthoc analyses. Fisher’s test was used to compare baseline characteristics and survival between study groups. Significance was set at $P < .05$. The research protocol was reviewed by the institutional review board and approved by the ethics commit- tee at Hospital Niño Jesús, with the stopping rules men- tioned above. Eligible infants were entered only after parental informed consent was obtained.

**RESULTS**

There were 42 infants with significant refractory hypoxemia, and 22 met entry criteria with severe PPHN (OI $\geq$ 40). Of the 22 infants, 2 died, for 3 the parents were not approached for consent, and for 4 the parents refused. Thirteen infants with an OI of $\geq$40 had been enrolled in the study when the study was stopped at institutional review board request for detailed analysis because of 6 deaths. The median age of the 13 infants at the time of entry was close to 25 hours (range: 3–72 hours). Six of the infants had received placebo, and 7 had received oral sildenafil.

Table 1 summarizes the characteristics of the infants enrolled, the ventilatory parameters, and the initial blood gases and OI at the time of entry. The gender distribution, gestational age, birth weight, Apgar scores, route of delivery, and condition associated with severe refractory hypoxemia, as well as the ventilatory parameters and blood gases were comparable in both groups (Table 1). The mean OI was 56 in the treatment group and 46 in the placebo group with low $\mathrm{Pao}_2$ at entry; 34.2 (±12.5) mm Hg and 42.7 (±11.3) mm Hg, respectively. All of the infants were critically ill, receiving fraction of inspired oxygen 1.0 and dopamine for inotropic support. All had been treated at least once with manual ventila- tion, sodium bicarbonate, and volume infusion.

In the treatment group, oxygenation improved in all of the infants sometime between 6 and 30 hours after initiation of treatment, and all of the infants showed a steady and significant improvement in $\mathrm{SpO}_2$ over time, different from the placebo group. Figures 1 and 2 show the changes in oxygenation after placebo and sildenafil. The differences were significant ($P < .05$) at different times, as shown in the figures. The first dose induced an improvement in OI compared with baseline and with the placebo group, and the significant differences persisted until the last measurement (Figs 1 and 2). There were also differences in $\mathrm{Pao}_2$ between the groups, and this became significant over time after 4 doses or 36 hours after entry. In addition, Table 2 shows the individual OI values for each infant in relation to the dose of sildenafil or placebo. Figure 3 shows that oral sildenafil produced no noticeable effect on BP during the study period with the doses used. All of the infants in both groups received dopamine (dose range: 6–20 $\mu$/kg per minute). There
was no difference in pressure support or volume infusions between groups. Furthermore, we were unable to identify any adverse effect that could be associated with the treatment. In the treatment group, 6 (85%) of 7 infants survived; the infant who died did so at 72 hours because of a pneumopericardium. In the placebo group, infants survived; the infant who died did so at 72 hours after the sixth dose by 36 hours. In 1 of these infants, all of the doses were of 1.0 mg/kg, and in the other infant, the dose was 1.0 mg/kg for the first dose and 2.0 mg/kg per dose for the next 5 doses (Table 2). The other 5 infants in the sildenafil group received 7 doses before the OI was <20 (Table 2). Four of them received all 7 doses at 0.5 mL/kg per dose (1 mg/kg), and 1 received the first 2 doses of 0.5 mL/kg and the other 5 of 1.0 mL/kg (2 mg/kg; Table 2). Therefore, the total amount of sildenafil per kilogram varied between infants from 6 to 12 mg/kg (median: 7 mg/kg). In the placebo group, the 6 infants received 0.5 mL/kg as the first dose. All but 1 of the infants received all of the other doses at 1.0 mL/kg (Table 2).

No evidence of rebound hypoxemia was found in any of the infants in whom sildenafil was discontinued because of achievement of the prespecified improvement in OI (ie, OI < 20). We cannot comment on the degree of change in pulmonary artery pressure, because we did not perform repeated echocardiograms before and after each dose.

DISCUSSION

In this proof-of-concept study, oral sildenafil in term/near-term infants with severe PPHN and severe hypoxemia improved OI and SpO2 and did not cause systemic hypotension or noticeable adverse effects. We acknowledge that in this study the measurements at the end of the interval of 2 hours may have led to underestimation of beneficial acute effects on oxygenation of sildenafil.

PPHN has a significantly wide spectrum of severity. The initial OI in the infants enrolled reflects, at least in part, the degree of illness severity and the high risk for mortality in these infants, particularly without iNO and ECMO. No infant with mild or moderate PPHN was entered into this study. The findings of this study suggest that oral sildenafil may be associated with increased survival in cases of severe PPHN in areas where resources like HFV, surfactant, iNO, and ECMO are limited or unavailable. However, these data need to be interpreted with caution, because the survival in the placebo group is low (1 of 6 [17%]). This survival rate of 17% is similar to what was initially used as ECMO criteria in the United States more than a decade ago (predicted survival of 20%). In addition, before initiation of the study, the

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**TABLE 1** Infant’s Characteristics, Respiratory Settings, and Blood Gases at the Time of Entry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sildenafil (n = 7)</th>
<th>Control (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female/male</td>
<td>3/4</td>
<td>3/3</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>38.4 (±2.6)</td>
<td>37.2 (±1.9)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>2803 (±617)</td>
<td>2710 (±554)</td>
</tr>
<tr>
<td>Apgar, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>6 (3–8)</td>
<td>6 (2–8)</td>
</tr>
<tr>
<td>5 min</td>
<td>8 (5–9)</td>
<td>8 (5–9)</td>
</tr>
<tr>
<td>Cesarean section, n</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Meconium aspiration, n</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory distress syndrome, n</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Peak inspiratory pressure, cm H2O</td>
<td>33.2 (±5.1)</td>
<td>34.0 (5.7)</td>
</tr>
<tr>
<td>Peak end expiratory pressure, cm H2O</td>
<td>4.2 (±0.75)</td>
<td>4.8 (±0.97)</td>
</tr>
<tr>
<td>Mean airway pressure, cm H2O</td>
<td>19.2 (±4.2)</td>
<td>18.1 (±2.6)</td>
</tr>
<tr>
<td>Rate, beats per min</td>
<td>42.2 (±5.4)</td>
<td>46.1 (±8.0)</td>
</tr>
<tr>
<td>Fraction of inspired oxygen</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>pH</td>
<td>7.32 (±0.39)</td>
<td>7.30 (±0.89)</td>
</tr>
<tr>
<td>PaCO2</td>
<td>54.0 (±8.2)</td>
<td>34.5 (±5.8)</td>
</tr>
<tr>
<td>PaO2</td>
<td>342.2 (±12.5)</td>
<td>427.2 (±11.3)</td>
</tr>
<tr>
<td>HCO3</td>
<td>191.1 (±29.2)</td>
<td>182.2 (±39.2)</td>
</tr>
<tr>
<td>OI</td>
<td>56 (±16.8)</td>
<td>46 (±9.5)</td>
</tr>
</tbody>
</table>

No difference was significant. Values represent mean (±SD).

**FIGURE 1**

Oral sildenafil produced significant changes in OI. *P = .04 versus baseline; †P = .03 versus placebo. † indicates dose of drug or placebo.

**FIGURE 2**

SpO2 improved after oral sildenafil. *P = .03 versus baseline; †P = .03 between groups.
survival rate for the sickest infants with PPHN (comparable very ill infants to the 13 infants studied), varied between 20% and 35% per year in our unit. For the few infants not entered in the study and for the infants treated in our unit since we completed the study, the overall survival has been 29%. Therefore, we consider that we cannot conclude from this study that oral sildenafil improves survival. This needs to be evaluated in trials with larger sample size.

The administration of drug or placebo was randomly assigned, was masked, and bedside clinicians were unaware of group assignment. They treated infants with severe PPHN based on a protocol regardless of participation in the study or group assignment. However, clinical response of each infant (Table 2) could not be masked, and “interpretations” by clinicians could not be forbidden. After clinicians and nurses cared for 4 to 5 infants with “faster” improvements in oxygenation than previously, comments were being made about who may have or not have received treatment or placebo. Soon thereafter, the institutional review board had requested putting the study on hold and perform a detailed analysis because of 1 of the stopping criteria being met (6 deaths). After the results were analyzed, we were asked to stop this proof-of-concept study and started planning for a larger, multicenter international trial.

In this study we did not evaluate any beneficial or detrimental effect of oral sildenafil used in conjunction with iNO. In adults, several investigators have assessed the combination therapy.3,4,19 Whether oral or intravenous sildenafil will be of value in neonatal care when iNO is available remains to be determined. However, a recent animal study shows that the combination of intravenous sildenafil with iNO may produce an unacceptable deterioration in oxygenation and systemic vasodilatation.7

In this proof-of-concept study, it is impossible to assess adverse effects of the treatment. However, evidence exists for the association between sildenafil and various systemic adverse effects, which have included the gastrointestinal, cardiovascular, visual, and central nervous systems. In awake rats, sildenafil (4 mg/kg intramuscularly) has been shown to delay gastric emptying and gastrointestinal transit of a liquid meal and also to transiently decrease mean arterial BP by 25%.23 Concerns have already been expressed about the potential risk of irreversible retinal damage linked to phosphodiesterase inhibitor type 6 inhibition.24–26 This issue is of serious concern in preterm neonates, and severe retinopathy of prematurity has been reported in a premature infant treated with sildenafil acetate for pulmonary hypertension.27

Furthermore, several studies in different adult animal models have shown that sildenafil can affect the central nervous system in various ways. Volke et al28 showed that augmentation of the NO-cGMP cascade induces an anxiogenic-like effect in mice. Many adverse-event reports in adults have considered sildenafil as the primary suspect of central nervous system disturbances, like emotional and psychological disorders, amnesia, loss of consciousness, aggressive behavior, and intracerebral

**TABLE 2** Changes in OI for Each Individual Infant 2 Hours After Each of the Doses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Predose OI</th>
<th>2 h After Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dose 1</td>
</tr>
<tr>
<td>S1</td>
<td>42</td>
<td>34</td>
</tr>
<tr>
<td>S2a</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>S3</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>S4</td>
<td>46</td>
<td>22</td>
</tr>
<tr>
<td>S5</td>
<td>64</td>
<td>43</td>
</tr>
<tr>
<td>S6</td>
<td>76</td>
<td>38</td>
</tr>
<tr>
<td>S7 (+)b</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>C1 (+)a</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>C2 (+)a</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>C3 (+)a</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>C4 (+)a</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>C5 (+)a</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>C6</td>
<td>40</td>
<td>29</td>
</tr>
</tbody>
</table>

(+) indicates that the infant died. Six infants received all doses at 0.5 mL/kg (1 mg/kg).
*a These 6 infants received the first dose at 0.5 mL/kg (1 mg/kg) and all other doses at 1 mL/kg (2 mg/kg).
*b One infant received the first 2 doses at 0.5 mL/kg (1 mg/kg) and all other doses at 1 mL/kg (2 mg/kg).

**FIGURE 3**
Mean arterial BP (MAP) did not change after oral sildenafil.
hemorrhage. Finally, effects of phosphodiesterase inhibition on cortical spreading depression and associated changes in extracellular cGMP have been reported recently. The potential mechanisms of deleterious effects on the central nervous system by sildenafil may include inhibition of PDE5 in the brain, accumulation of cGMP, decrease NO, and/or effects on cell-cell signaling and modulation. Therefore, adult human and animal and basic studies suggest an impact of PDE5 inhibition in the central nervous system and other organs. However, there are no studies of sildenafil on the developing central nervous system, and this requires additional investigation. In this proof-of-concept study, it is not possible to completely assess adverse effects of the treatment, but we are performing detailed neuroimaging and developmental evaluations of the 6 treated infants who survived and will report the findings after their second birthday.

CONCLUSIONS

This pilot study provides preliminary and feasibility information on oral administration of sildenafil for newborn infants with refractory hypoxemia. The study shows that oral sildenafil may be of benefit in improving oxygenation in such infants and, therefore, can serve as the basis for planning the initiation of larger clinical studies of oral sildenafil in neonates with severe neonatal hypoxemic respiratory failure and severe PPHN. In future studies, pharmacokinetics and optimal dosing need to be better characterized. In addition, a controlled, multicenter study with an adequately large sample size is needed to evaluate the safety, efficacy, and long-term outcome after treatment with systemic sildenafil in neonates, both in areas with and without widespread availability of alternative therapies, like iNO and/or ECMO. Until these studies are completed and based on the many potential adverse effects of sildenafil, it is recommended that clinicians wait for definite evidence of effectiveness and safety before prescribing oral sildenafil off-label for severe and refractory neonatal hypoxemic respiratory failure.

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BAN ON WAR ELEPHANTS!

“How is a nuclear bomb like an ancient African battle elephant? On a recent visit to the National Atomic Museum in Albuquerque, NM, I found hidden among the predictable exhibits—metal casings identical to those used in the Little Boy and Fat Man devices dropped on Hiroshima and Nagasaki, films of mushroom clouds expanding over atomic- and hydrogen-bomb test sites, photos of Robert Oppenheimer and the gang at Los Alamos, CA—a reproduction of a 16th-century Flemish tapestry with a placard beside it that tried to answer this riddle. The tapestry depicts elephants striding among Roman legionnaires and their foes. The placard explains, ‘One of the best-known ancient arms control agreements was negotiated between Rome and Carthage following Scipio Africanus’s victory over Hannibal in the Battle of Zama in 202 B.C. This treaty required the Carthaginians to surrender all their war elephants.’”

Williams M. Technology Review. July 2005