Sildenafil as a Substitute for Subcutaneous Prostacyclin in Pulmonary Hypertension


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Introduction

The treatment of pulmonary arterial hypertension (PHT) with prostacyclin in its different forms (intravenous, subcutaneous, inhaled, and oral) is effective from a clinical and functional point of view, although only intravenous prostacyclin (epoprostenol) has been shown to improve survival. Treprostinil is a stable form of prostacyclin administered in continuous subcutaneous infusion. The most common adverse effect of this drug is pain in the injection area. Although this pain is usually controllable, sometimes it means that treatment must be suspended.

Sildenafil is a selective inhibitor of phosphodiesterase-5 (PDE-5) with pulmonary vasodilating effects. We describe the use of sildenafil as a substitute for treprostinil in a patient with pulmonary hypertension associated with lupus erythematosus. Treatment with treprostinil was discontinued due to uncontrollable abdominal pain.

Key words: Pulmonary hypertension. Treprostinil. Sildenafil.

Sildenafil como sustituto de prostaciclina subcutánea en la hipertensión pulmonar

La prostaciclina subcutánea (treprostinil) es efectiva a corto plazo para el tratamiento de la hipertensión pulmonar. El efecto adverso descrito con más frecuencia es el dolor sobre la zona de infusión, que en raras ocasiones obliga a suspender el tratamiento. El sildenafil es un inhibidor selectivo de la fosfodiesterasa-5 con efecto vasodilatador pulmonar. Describimos el cambio de treprostinil por sildenafil en una paciente con hipertensión pulmonar asociada a lupus eritematoso, a quien se le retiró el treprostinil debido a dolor abdominal incontrolable.

Palabras clave: Hipertensión pulmonar. Treprostinil. Sildenafil.

Clinical Observations

A 25-year old woman with SLE was diagnosed with PHT with no response to a vasoreactivity test with epoprostenol. The patient suffered repeated effort-related syncopes once treatment with inhaled prostacyclin began. For this reason treatment with subcutaneous prostacyclin, at a dose of up to 15 ng/kg/min in continuous infusion, was started in January 2002. Until then she had been clinically stable (New York Heart Association [NYHA] type 2, 460 m on foot, 6-minute walking test). The patient reported intense abdominal pain near the injection site, however, as the dose increased. The pain could not be controlled with topical or oral medication (an antiinflammatory drug and gabapentin).

Treatment with sildenafil was started on compassionate grounds with consent from the patient and from the health authorities. The starting dose was 25 mg every 12 hours. Initially the same dose of subcutaneous prostacyclin was maintained. Every 4 days the subcutaneous prostacyclin dose was reduced and the dose of sildenafil was increased until a stable dose of 25 mg every 6 hours was reached (Table). The abdominal pain remitted as soon as treatment with subcutaneous prostacyclin was discontinued. The patient from severe PHT associated with systemic lupus erythematosus (SLE). Treatment with sildenafil was substituted for treprostinil due to incapacitating pain in the area of injection.
In a double-blind trial). Anti-inflammatory drugs, gabapentin, or corticosteroids), controllable by topical or oral medication (paracetamol, adverse side effect (85%) and although it is often clinical use. Injection site pain is the most common reason for its efficacy in treating erectile dysfunction and dilation mainly in the aforementioned regions. This is the reason for its potential beneficial effect in PTH.

Table 1: Substitution of Treprostinil by Sildenafil

<table>
<thead>
<tr>
<th>Day</th>
<th>Treprostinil dose (ng/kg/min)</th>
<th>Sildenafil dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>11.25</td>
<td>25 mg/6h</td>
</tr>
<tr>
<td>7</td>
<td>7.5</td>
<td>25 mg/6h</td>
</tr>
<tr>
<td>12</td>
<td>3.75</td>
<td>25 mg/6h</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>25 mg/6h</td>
</tr>
</tbody>
</table>

The table shows the modifications in doses of both drugs during the treatment conversion until administration of subcutaneous prostacyclin (treprostinil) was terminated.

Discussion

Subcutaneous prostacyclin is effective in treating PHT in terms of short-term (3 months) clinical improvement and has recently received approval for clinical use. Injection site pain is the most common adverse side effect (85%) and although it is often controllable by topical or oral medication (paracetamol, anti-inflammatory drugs, gabapentin, or corticosteroids), treatment must sometimes be suspended (in 8% of cases in a double-blind trial).

Sildenafil is a selective inhibitor of PDE-5. The decrease in the nitric oxide production rate and in guanosine 3’5’-monophosphate (cGMP) activity contributes to the development of PHT in the pulmonary bed. Nitric oxide, produced in the vascular endothelium, has a very short half-life and is a very strong pulmonary vasodilator by guanylate cyclase activation, through which cGMP is produced. cGMP is degraded by phosphodiesterases, of which there are 11 known types. PDE-5 selectively deactivates cGMP and is widely present in the cavernous bodies of the penis and in the vascular pulmonary bed. Selective inhibition of PDE-5 with sildenafil induces nitric oxide dependent vasodilation mainly in the aforementioned regions. This is the reason for its efficacy in treating erectile dysfunction and for its potential beneficial effect in PTH.

That oral sildenafil alone, combined with nitric oxide or with inhaled prostacyclin causes vasodilation and a decrease in pulmonary pressure has been established experimentally. Although clinical experience is scarce, cases have been reported in which sildenafil was used to treat PHT, with clinically favorable outcome at a 3-month follow up. Empirically established doses have varied greatly.

In our patient, the uncontrollable pain caused by the treprostinil injection required suspension of that drug. Treatment with sildenafil alone was not only effective in preventing possible deterioration due to withdrawal of treprostinil, but also led to improved short- and midterm outcome at 9 months. To our knowledge, no other cases of substitution of prostacyclin by sildenafil in monotherapy have been reported.

Although there is little experience with sildenafil, it may be useful in treating PHT. The efficacy of this drug alone and combined with prostacyclin and the determination of the optimal dose are being studied in multicenter trials.

REFERENCES