Valvular Heart Disease in Hyperprolactinemic Patients Treated With Low Doses of Cabergoline

Afección valvular cardiaca por dosis bajas de cabergolina en pacientes hiperprolactinémicos

To the Editor,

Between 1992 and 1997,1 a valvular heart disease similar to that produced by carcinoid tumors associated with fibrosis, leaflet retraction, and calcification was reported in patients treated with ergotamine derivatives (fenfluramine-phentermine). The activation of 5-hydroxytryptamine (serotonin) 2B (5-HT2B) receptors, which are highly abundant in the valvular endocardium, through signaling pathways mediated by Src kinases, stimulates fibroblast mitogenesis, with increased extracellular matrix production. It also causes the histological changes typical of this restrictive valvular heart disease, referred to as fen-phen since it was first described.2 In recent years, the development of this type of valvular heart disease has also been reported in patients with Parkinson’s disease treated with dopamine agonists3 and, more recently,
comparison was not significant.

Our aim was to evaluate the prevalence of valvular heart disease in a group of patients with hyperprolactinemia and compare it with the incidence in a control group of healthy volunteers who worked in our center. Patients from the neuroendocrinology unit who had been undergoing active treatment with cabergoline for at least 6 months prior to inclusion in the study were consecutively enrolled. Both the cumulative dose received and the duration of treatment were evaluated in these patients. The study of valvular heart disease was carried out by means of echocardiography to rate the presence of regurgitation and stenosis as insignificant, mild, moderate, or severe in accordance with the recommendations of the European Society of Cardiology guidelines. In the morphological examination, the mitral valve tenting area was considered to be an indicator of restricted valve closure (cm²), a thickening greater than 5 mm in leaflets or annulus was considered to be indicative of disease, and the presence of calcifications anywhere in the valve or subvalvular apparatus was evaluated qualitatively. For the statistical analysis, we used the Student t test for the comparison of means or the chi-square test for the comparison of proportions, and logistic regression analysis was performed to correlate the presence of valvular heart disease with the duration of treatment and the cumulative dose. Patients with previously diagnosed valve or heart disease were excluded from both groups.

In all, 32 patients with hyperprolactinemia of any origin were compared with 32 healthy controls. Seventy-five percent of the patients and 65% of the controls were women, with a more advanced mean age in the control group (38.78 [10.4] years vs 46.68 [12.5] years; P=.008) and a similar distribution of cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking habit) in both groups. The majority of the patients had hyperprolactinemia due to microprolactinoma (42%). With respect to the doses of cabergoline administered, the median cumulative dose was 158 mg [interquartile range: 69-363 mg] and the median dose received at the time of enrollment was 0.5 mg/week [0.25-1.25 mg/week], with a median treatment duration of 46 months [30-96 months]. Severe valvular disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with valvular regurgitation (n=5)</th>
<th>Patients without valvular regurgitation (n=27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration, months</td>
<td>43 [27-93]</td>
<td>72 [48-111]</td>
<td>ns</td>
</tr>
<tr>
<td>Cumulative dose, mg</td>
<td>150.7 [67.4-347]</td>
<td>272 [148-423]</td>
<td>ns</td>
</tr>
<tr>
<td>Current dose, mg/week</td>
<td>0.5 [0.25-1.37]</td>
<td>1 [0.38-1.25]</td>
<td>ns</td>
</tr>
<tr>
<td>MVTA, cm²</td>
<td>1.63 (0.39)</td>
<td>1.16 (0.32)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

MVTA, mitral valve tenting area; ns, not significant.
Data are expressed as median [interquartile range] or mean (standard deviation).

Table 2
Comparison of the Prevalence of Valvular Heart Disease in Patients and Controls.

<table>
<thead>
<tr>
<th>Valvular regurgitation</th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR (Yes/No)</td>
<td>7 (22)/25</td>
<td>19 (59)/13</td>
<td>.044</td>
</tr>
<tr>
<td>Insignificant</td>
<td>5 (15)</td>
<td>11 (34)</td>
<td>.034</td>
</tr>
<tr>
<td>Mild</td>
<td>2 (6.25)</td>
<td>7 (21)</td>
<td>ns</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>1 (3)</td>
<td>ns</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>AR (Yes/No)</td>
<td>1 (3)/31</td>
<td>1 (9)/29</td>
<td>ns</td>
</tr>
<tr>
<td>Insignificant</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Mild</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>ns</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>TR (Yes/No)</td>
<td>20 (62.5)/12</td>
<td>16 (50)/16</td>
<td>ns</td>
</tr>
<tr>
<td>Insignificant</td>
<td>17 (53)</td>
<td>12 (37.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Mild</td>
<td>2 (6.25)</td>
<td>4 (12.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (3)</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>PR (Yes/No)</td>
<td>3 (9)/29</td>
<td>4 (9)/28</td>
<td>ns</td>
</tr>
<tr>
<td>Insignificant</td>
<td>3 (9)</td>
<td>3 (6)</td>
<td>ns</td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Vascular</td>
<td>0</td>
<td>1 (3)</td>
<td>ns</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>MVTA, cm²</td>
<td>1.63±0.39</td>
<td>1.30±0.27</td>
<td>ns</td>
</tr>
</tbody>
</table>

AR, aortic regurgitation; MR, mitral regurgitation; MVTA, mitral valve tenting area; ns, not significant; PR, pulmonary regurgitation; TR, tricuspid regurgitation.
Data are expressed as No. (%) or mean±standard deviation.
Diabetes Mellitus and Risks of Dual Blockade of the Renin-angiotensin-aldosterone System

**Diabetes mellitus y riesgos del bloqueo dual del sistema renina-angiotensina-aldosterona**

To the Editor,

In recent years, clinical research aimed at determining the effects of antihypertensive strategies—beyond simply reducing and controlling blood pressure—has intensified substantially. In fact, dual renin-angiotensin-aldosterone system (RAAS) blockade that simultaneously interferes with angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists or direct renin inhibitors (aldikiren) has focused these strategies on patients at high cardiometabolic risk.

The possibility that dual RAAS blockade might yield better results than the use of each drug on its own is an attractive hypothesis. However, the ONTARGET (The ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study found that dual blockade with angiotensin II receptor antagonists (telmisartan) and an angiotensin converting enzyme inhibitor (ramipril) offered no additional benefit (vs monotherapy) in reducing cardiovascular morbidity and mortality in patients at high cardiovascular risk and did, in fact, increase the incidence of adverse effects. More recently, the ALTITUDE (Alikiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) study was interrupted prematurely because dual therapy was not showing clinical benefits in patients with diabetes being treated with aliskiren and angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, whereas renal complications, hyperkalemia, hypotension and stroke, among other adverse effects, increased.

The present study evaluated the risks of dual RAAS blockade in patients with diabetes mellitus through a meta-analysis of randomized, controlled clinical trials. For this purpose, we reviewed PubMed up to November 2012 and consulted the Spanish agency for medicines and healthcare products (Agencia Española de Medicamentos y Productos Sanitarios) (www.aemps.gob.es), the European Medicines Agency (www.ema.europa.eu) and the US Food and Drug Administration (www.fda.gov) online. The following search terms were used: renin inhibitor, aliskiren, angiotensin receptor block*, losartan, irbesartan, valsartan, olmesartan, candesartan, eprosartan, telmisartan, angiotensin-converting enzyme inhibit*, captopril, enalapril, lisinopril, perindopril, ramipril, fosinopril, trandolapril, temocapril, imidapril combined with diabetes, diabetic*, and randomized controlled trial [publication type]. We included studies of patients with diabetes using the (dual) combination of RAAS blockers in the intervention group vs any RAAS blocker in

Juan G. Córdoba-Soriano, a,b Cristina Lamas-Olivera,b Víctor M. Hidalgo-Olivares,a Antonia Tercero-Martínez,a Moisés Barambio-Ruíz,a and Jesús Salas-Nietoa

aServicio de Cardiología, Hospital General Universitario de Albacete, Albacete, Spain
bServicio de Endocrinología, Hospital General Universitario de Albacete, Albacete, Spain

*Corresponding author:
E-mail address: jgcordobas@hotmail.com (J.G. Córdoba-Soriano).
Available online 19 January 2013

**REFERENCES**