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Respiratory Arrest following First Dose of Timolol Ophthalmic Solution

David S. Prince, M.D.; and Nathan H. Carliner, M.D.

Within 30 minutes of the administration of his first dose of timolol ophthalmic solution, a 67-year-old man with stable chronic obstructive pulmonary disease experienced severe dyspnea leading to respiratory arrest. He recovered after endotracheal intubation and mechanical ventilation. Patients with bronchospastic pulmonary disease who are candidates for therapy with timolol ophthalmic solution should receive their first dose under medical supervision and should have continued close medical follow-up for as long as they receive timolol.

Timolol maleate, a nonselective beta-adrenergic blocker, is used as an ophthalmic solution for the treatment of glaucoma. It possesses the therapeutic advantage of lowering the intraocular pressure with a lower incidence of causes causing pupillary size or causing diminution of vision, side effects which are prominent with miotic medications such as pilocarpine. Over half the reports of adverse reactions to timolol ophthalmic solution reflect systemic beta blockade due to absorption from the conjunctiva. Thus, therapeutic doses of timolol ophthalmic solution may cause a significant decrease in airflow in patients with bronchospastic pulmonary disease. The present case is important to note because the patient suffered a potentially fatal respiratory arrest within 30 minutes of his first dose of timolol ophthalmic solution.

Case Report

A 67-year-old man had been receiving outpatient treatment for chronic obstructive pulmonary disease, non-critical calcific aortic stenosis, essential hypertension, and glaucoma. His medications included hydrochlorothiazide, theophylline sustained-action tablets, and metaproterenol sulfate, both orally and by inhalation. Pulmonary function tests, performed seven months prior to admission, demonstrated moderate obstructive disease with air trapping. The forced vital capacity was 3.2 L and the forced expiratory volume in one second was 1.76 L (55 percent). There was no significant change in flow rate following the administration of bronchodilator drugs. He had been clinically stable, except for worsening glaucoma.

On the day of admission, he had been seen in the ophthalmology clinic, and because of progression of glaucoma despite pilocarpine therapy, timolol ophthalmic solution (0.5 percent) was prescribed. That evening, within approximately five minutes of his first dose of one drop in each eye, he noted the acute onset of shortness of breath. His symptoms were not relieved by three of four puffs from his metaproterenol inhaler. Over the next ten minutes, his dyspnea progressed rapidly, and his wife noted that he was markedly cyanotic. She summoned the paramedics; when they arrived, the patient was unresponsive and apneic. Assisted ventilation with an Ambu bag and supplemental oxygen were begun, and he was transferred to a nearby community hospital.

When he arrived in the emergency room, the pulse rate was 120 beats/min and the blood pressure was 250/120 mm Hg. There was no effective spontaneous respiration. The arterial blood gas levels were pH, 6.93; PCO₂, 141 mm Hg and PO₂, 71 mm Hg. Following insertion of an endotracheal tube under morphine sedation, mechanical ventilation was begun. He received intravenously-administered aminophylline and steroids and aerosolized isethionate hydrochloride. Forty minutes after intubation, he was responsive and able to follow commands. His breath sounds were much improved, although bilateral wheezes were present. The arterial blood gas levels were pH, 7.07; PCO₂, 93 mm Hg and PO₂, 197 mm Hg (fractional concentration of oxygen in inspired gas [FIO₂], 0.50). Two hours after intubation, the arterial blood gas levels (FIO₂, 0.40) were: pH, 7.41; PCO₂, 36 mm Hg and PO₂, 191 mm Hg. Although intermittent wheezing persisted, the patient was successfully extubated 15 hours later.

Discussion

We did not rechallenge our patient with timolol in view of the severity of his bronchospasm; however, the temporal relationship between his first dose of timolol and the subsequent respiratory arrest strongly implicated timolol as the inciting agent. Timolol is known to be absorbed from the conjunctiva into the systemic circulation bypassing the liver where it is normally metabolized. The relative potency of timolol is approximately six times that of propranolol so that absorption of even the small doses of timolol used in ophthalmic solutions may cause systemic beta blockade. Patients with obstructive airway disease may be critically dependent upon beta-adrenergic stimulation for the maintenance of airway patency and thus be susceptible to severe and potentially fatal bronchospasm following the administration of timolol solution. In such patients, timolol ophthalmic solution should be considered only as a last resort when other methods of therapy have failed to control glaucoma. When timolol therapy is contemplated in a patient with obstructive airway disease, it may be helpful to perform spirometric evaluation before and after topical administration of timolol to determine if clinically inapparent bronchospasm is provoked. We believe that patients with clinical evidence of increased airway reactivity should receive the initial dose of timolol ophthalmic solution under medical observation and that personnel and facilities should be available to perform resuscitation, if needed. Even if there is no apparent adverse reaction to the first dose, continued close medical follow-up is mandatory throughout the course of timolol therapy.

Respiratory Arrest after Timolol Ophthalmic Solution (Prince, Carliner)
Chest Pain as a Presentation of Reactive Hypoglycemia*

Sudhir Bansal M.D., † Sang H. Toh M.D., ‡ and Kenneth A. LaBresh M.D. †

Reported herein is a patient with multiple hospital admissions for atypical chest pain syndrome who underwent extensive noninvasive and invasive cardiologic testing to exclude ischemic heart disease as an etiology. During one episode of chest pain, the patient was found to have hypoglycemia with a blood sugar level of 46 mg/dl. Two subsequent oral glucose tolerance tests reproduced chest pain during hypoglycemia with values of 47 mg/dl and 27 mg/dl. The patient had previously no significant clinical response to typical antianginal medications. Following evidence of concurrent hypoglycemia, the chest pain syndrome has significantly decreased with the patient on a low-carbohydrate diet.

A typical chest pain syndrome is often present diagnostic and therapeutic dilemmas for clinicians. The noninvasive and invasive evaluation for some patients is time-consuming and expensive. On occasion, no etiology is demonstrated and empiric therapy with antianginal agents or antacids is undertaken. Despite assurance that the chest pain is not ischemic in origin, patients continue to have recurrent episodes of pain and significant disability.1 We report such a patient in whom reactive hypoglycemia, an unusual and treatable etiology of chest pain, was documented and treated with significant symptomatic improvement.

Case Report

A 52-year-old male retired laundry worker with a history of Graves' disease and atrial fibrillation with congestive heart failure secondary to rapid rate, was evaluated for chest pain. The chest pain was first noted in 1978 and described as left-sided precordial tightness associated with dyspnea and occasionally radiating to the right chest. The pain occurred once weekly, and was not associated with exertion. In July, 1980 he sought medical attention for palpitations, chest pain and dyspnea. He was noted to be hyperthyroid with atrial fibrillation and mild congestive heart failure. There was no enzyme or electrocardiographic evidence of infarction or ischemia. He was treated with digitalis, furosemide and propranolol in addition to 6.03 mcg of 131I. He was euthyroid for the subsequent six months, but suffered relapse in March 1981 which was treated with propylthiouracil.

The previous infrequent episodes of chest discomfort increased in frequency to once daily during 1981. The pain continued to be left-sided precordial tightness and occurred predominantly at rest. It typically lasted less than ten minutes and persisted for three to five minutes after nitroglycerin. It was usually associated with diaphoresis and dyspnea and rarely with dizziness. While the episodes were somewhat more common in the evening, there was no clear relationship to eating. The tightness was unrelieved by ingestion of food. Superimposed on the episodic tightness was constant diffuse chest tightness which persisted for several hours or entire days and did not respond to administration of nitroglycerin. On seven occasions, the prolonged chest tightness resulted in admissions to the coronary care unit. Assessment during episodes of diffuse tightness or left-sided precordial exacerbations demonstrated diaphoresis, flushing and agitation. There were elevations in blood pressure without tachycardia, S4, or ECG changes. Therapeutic trials of nitrates and beta blockers as an outpatient had no effect on the frequency or severity of the chest discomfort.

The patient had a 35-pack-year history of smoking and rarely drank alcohol. He has a positive family history for coronary artery disease and two brothers had non-insulin-dependent diabetes mellitus. Endocrine tests confirmed thyrotoxicosis prior to 131I treatment including T3, 23.1 μg/dl (4.5-11.5); T4 uptake, 51 percent (25-35). Vanilmandelic acid in 24 hours urine collection was 7.5 mg and 9.6 mg (1-12 mg/24 hours). Urinary metanephrine level in 24 hours was 0.4 mg (0-1 mg). Unstimulated serum renin was 2.6 mg/ml/hour (1.4-3.8).

His cardiac evaluation included an inconclusive exercise tolerance test in April, 1981 with failure to achieve target heart rate. (The peak heart rate was 145 at 9.5 minutes of exercise in the standard Bruce protocol.) No symptoms, arrhythmias or ST-T wave changes were noted. Exercise testing with thallium 201 demonstrated no perfusion defects or ECG changes with 11 minutes of exercise. Two-dimensional echocardiography showed normal left ventricular wall motion and global function. Radionuclide ventriculograms in November, 1980 and July, 1981 demonstrated low normal left ventricular ejection fractions of 56 percent and 43 percent, respectively. Cardiac catheterization was ultimately performed because of continued chest pain and demonstrated a low normal left ventricular ejection fraction of 56 percent with normal hemodynamics and normal coronary arteries.

During an admission in September, 1981, an episode of the patient's typical chest discomfort occurred late in the afternoon accompanied by symptoms of weakness, profuse diaphoresis, and near syncope. It was relieved after therapy with sublingual nitroglycerin and oxygen. A blood sugar level drawn at the time of the episode was 46 mg/dl. A five-hour oral glucose tolerance test with 100 g of glucose performed the following day (Table 1), produced the typical symptom complex four hours after glucose loading. The blood sugar at the time of symptoms was 47 mg/dl.

**Table 1**—Results of Oral Glucose Tolerance Test and Related Hormonal Measurement

<table>
<thead>
<tr>
<th>Date, Time in min</th>
<th>Fasting</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/81 Glucose</td>
<td>mg/dl</td>
<td>83</td>
<td>242</td>
<td>272</td>
<td>226</td>
<td>89</td>
<td>47</td>
</tr>
<tr>
<td>6/82 Glucose</td>
<td>mg/dl</td>
<td>97</td>
<td>...</td>
<td>186</td>
<td>206</td>
<td>106</td>
<td>27</td>
</tr>
<tr>
<td>Insulin</td>
<td>U/ml</td>
<td>15.3</td>
<td>82.5</td>
<td>143.0</td>
<td>91.0</td>
<td>14.2</td>
<td>20.2</td>
</tr>
<tr>
<td>GH mg/ml</td>
<td>not detected</td>
<td>0.5</td>
<td>0.1</td>
<td>0.9</td>
<td>4.1</td>
<td>15.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Cortisol</td>
<td>μg/ml</td>
<td>20.8</td>
<td>17.3</td>
<td>15.4</td>
<td>10.0</td>
<td>9.2</td>
<td>17.7</td>
</tr>
</tbody>
</table>

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