A Survey of Diagnostic Practices and the Use of Epoprostenol In Patients With Primary Pulmonary Hypertension*

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**Study objective:** To obtain information about the diagnosis and management of primary pulmonary hypertension (PPH), especially about the use of epoprostenol (Glaxo-Wellcome; Research Triangle Park, NC) in this patient population.

**Background:** Long-term IV epoprostenol therapy was approved recently for use in patients with PPH who are unresponsive to conventional therapy. Although epoprostenol represents a major advance in the treatment of PPH, there is no published consensus regarding the optimal use of this therapy.

**Methods:** A five-page survey was mailed to 23 investigators at medical centers treating five or more patients with PPH with long-term epoprostenol therapy.

**Results:** Nineteen of 23 investigators responded to the survey. During the initial hemodynamic evaluation, 11 investigators used changes in pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP), and cardiac output, 5 investigators considered PVR and PAP only, and 2 investigators analyzed PVR alone to define a short-term vasodilator response. During long-term therapy, two thirds of the investigators increased the dose at scheduled intervals, while all investigators increased the dose in response to worsening symptoms. Epoprostenol doses were reported to range from 0.5 to 270 ng/kg/min. Nine investigators routinely repeated right heart catheterization an average of 7.5 ± 3.8 months after starting epoprostenol, and the mean decrease in pulmonary artery pressure was between 15 and 25%.

**Conclusion:** This survey indicates that there is wide variation in the evaluation of patients with PPH and in the use of epoprostenol therapy. The lack of consensus suggests the need for multicenter collaborative studies in order to optimize the use of epoprostenol therapy for PPH.

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**Key words:** epoprostenol; primary pulmonary hypertension; vasodilator

**Abbreviations:** CCB = calcium channel blocker; CO = cardiac output; NO = nitric oxide; PAP = pulmonary artery pressure; PPH = primary pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; PWP = pulmonary wedge pressure; TBFC = thermodilution balloon flotation catheter

In the last decade, the standard of care at institutions with expertise in the treatment of patients with primary pulmonary hypertension (PPH) has evolved markedly. Most patients diagnosed with PPH (using the criteria established in the National Institutes of Health National Registry) underwent a diagnostic right heart catheterization with short-term vasodilator testing to determine whether the pulmonary vascular bed is vasoreactive. Patients that are responsive to vasodilating agents usually undergo a therapeutic trial of long-term calcium channel blockers (CCBs). Those patients without significant evidence of pulmonary vasoreactivity may be offered long-term therapy with epoprostenol, an intravenous vasodilator that has been approved recently by the Federal Drug Administration for use in patients with PPH.

There is no published consensus regarding dosing strategies and other important aspects related to the use of epoprostenol, and the mechanism of its

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†A complete list of contributing investigators is located in the Appendix.
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For editorial comment see page 1234
beneficial effects remains uncertain. Because patients receiving epoprostenol are usually those without acute vasoreactivity of the pulmonary vascular bed, it seems likely that epoprostenol does not exert all of its beneficial effects through vasodilation. There is no general agreement on the optimal vasodilator with which to test patients with PPH, on the criteria that signify a meaningful response to vasodilator testing, or on which adjunctive therapy should be used with epoprostenol. Furthermore, while a recent randomized, multicenter trial involving 81 patients with PPH demonstrated statistically significant hemodynamic improvement and increased survival in the group of patients receiving epoprostenol over a 3-month period, there is little published information addressing the benefits and side effects of continuous epoprostenol therapy for longer periods of time.

We surveyed the majority of referral centers in the United States that offer epoprostenol therapy for PPH. Our intention was to obtain and summarize basic information about the evaluation and treatment of PPH, with particular regard to the use of epoprostenol, in order to describe the range of and differences in management strategies. We believe that the information from these centers may serve as a starting point for further dialogue about the best use of epoprostenol.

**Materials and Methods**

A survey was sent to 23 medical centers, each treating five or more patients with PPH with long-term epoprostenol therapy. The list was obtained from Olsten Health Services Corp (Pittsburgh, PA), which is the sole distributor of epoprostenol. Olsten did not provide any information regarding the number of patients followed at each center, and they did not identify any patient receiving epoprostenol. The survey is a semiquantitative instrument that was designed to be completed in < 30 min, to elicit information about practice habits, and to provide estimates of clinical variables. Data were tabulated using Excel (Microsoft; Richmond, WA). Averages are presented as the mean (± SD) and represent unweighted means to the answers of all respondents unless otherwise noted.

**Results**

**General Characteristics**

Nineteen of 23 centers responded to the survey, providing information about more than 500 patients with PPH who were receiving treatment with epoprostenol. A total of more than 800 patients were reported to have received epoprostenol therapy at these institutions; approximately 300 had died or undergone lung or heart-lung transplantation. All 19 institutions were tertiary care, university-affiliated centers. The number of patients at each center varied from 6 to more than 100, with a mean (± SD) of 30 ± 30. Twelve investigators were pulmonologists, and seven investigators were cardiologists. Seventeen centers treated only adults, while two treated adults and children. The majority of patients were reported to be between 18 and 40 years old.

**Pulmonary Hypertension Evaluation and Short-term Vasodilator Testing**

Ten investigators used a thermodilution balloon flotation catheter (TBFC) with internal guidewire for the measurement of pulmonary artery pressure (PAP) and cardiac output (CO), one investigator used a TBFC with continuous measurement of CO, and eight investigators used an unmodified TBFC. Twelve centers used the internal jugular vein as the preferred catheter insertion site, while seven institutions primarily used the femoral vein. The number of baseline hemodynamic measurements, obtained as soon as 10 min and up to 4 h after catheter insertion, ranged from 1 to 5, with a mean (± SD) of 3 ± 1. Levels of blood oxygen saturation were obtained routinely from the pulmonary artery at 84% of the centers responding and from the right atrium at 37% of the centers.

Inhaled nitric oxide (NO) was used by 32% of the investigators as the primary vasodilator, with fewer investigators using CCBs, adenosine, epoprostenol, and prostaglandin E1. Secondary drugs included oxygen, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists. The majority of centers used more than one vasodilator, some employing up to five during the initial testing. Two to three vasodilators was the average number tested during short-term studies. Serious adverse reactions during diagnostic vasodilator testing are infrequent, but five investigators reported transient systemic hypotension in 10 to 50% of patients. Hypoxemia was noted occasionally. Arrhythmias are rare; however, two deaths during short-term vasodilator testing were reported.

The criteria used to determine a positive response to acute vasodilator testing differed substantially among the centers, and the results are summarized in Table 1. Eleven investigators used changes in pulmonary vascular resistance (PVR), PAP, and CO to define an acute vasodilator response, five considered PVR and PAP only, and two analyzed PVR alone. The magnitude of change that represents a significant response is not uniform. Eleven investigators thought that a decrease in PAP of > 20% was meaningful, and six believed that an increase in CO of > 20% was significant, though the range of changes reported was 10 to 30%. Six investigators...
were given nicardipine two most widely used CCBs, nifedipine, diltiazem, amlodipine, or nicardipine in decreasing order of frequency. Of the two most widely used CCBs, nifedipine doses ranged from 30 to 360 mg/d, and diltiazem doses ranged from 60 to 720 mg/d. The combined average number of responders to long-term CCB therapy was 22 ± 9% (range, 5 to 40%), only two thirds of the number demonstrating vasoreactivity during short-term testing. The longest reported response to CCBs was 18 years.

Evaluation of Less Common Subsets of PPH

More than half of the investigators responding to the survey routinely evaluated patients with PPH for pulmonary veno-occlusive disease (PVOD). Increased interstitial markings on a chest radiograph, a history of pulmonary edema with normal pulmonary wedge pressure (PWP), an elevated PWP at catheterization, and an increase in PWP or the development of pulmonary edema during short-term vasodilator testing are all thought to be suggestive of PVOD. In an effort to diagnose PVOD, PWP measurements from multiple sites are performed routinely at five centers and were performed at another three centers if the initial PWP was elevated. Catheter tip PWP, wedge angiograms, high-resolution CT, and lung biopsy were cited as other methods employed to diagnose PVOD. Ten centers reported that they would attempt therapy with epoprostenol in patients with suspected PVOD. Nearly 50 cases of PVOD were reported. Pulmonary capillary hemangiomatosis also has been diagnosed in 9 patients at these 19 institutions.

Initiation of Epoprostenol Therapy

The mean starting dose of epoprostenol in patients receiving long-term therapy was 2 ± 1 ng/kg/min. The average daily increase in dose during the initial hospitalization was between 1 and 2 ng/kg/min, and the maximal daily increase in dose was generally no more than 2 ng/kg/min. The average length of hospitalization was 4 ± 3 days, with a range of 0 to 16 days. The mean dose of epoprostenol at discharge was 6.5 ± 2.5 ng/kg/min, with a range of 2 to 16 ng/kg/min. Nine of the 19 centers placed all appropriate patients on the active waiting list for lung transplantation when epoprostenol therapy was initiated. Table 3 summarizes the use of epoprostenol during the initiation of therapy and during long-term treatment.

Early side effects from epoprostenol were generally mild and are listed in Table 4. Most institutions reported nausea, headache, tachycardia, and diarrhea in 10 to 50% of patients and flushing and jaw pain in > 50% of patients during the initiation of therapy. Hypotension was reported by seven inves-

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### Table 1—Hemodynamic Evaluation

<table>
<thead>
<tr>
<th>Acute Testing</th>
<th>Variables Analyzed</th>
<th>During Acute Vasodilator Testing</th>
<th>% Institutions</th>
<th>Evaluation During Chronic Therapy</th>
<th>% Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of baseline measures</td>
<td>3 ± 1*</td>
<td>PAP decrease</td>
<td>89</td>
<td>Repeat right heart catheterization</td>
<td>58</td>
</tr>
<tr>
<td>No. of vasodilators</td>
<td>3 ± 1*</td>
<td>CO increase</td>
<td>58</td>
<td>Repeat vasodilator testing</td>
<td>32</td>
</tr>
<tr>
<td>No. of centers using CCBs</td>
<td>13</td>
<td>PVR decrease</td>
<td>95</td>
<td>Echocardiographic study</td>
<td>16</td>
</tr>
<tr>
<td>No. of centers measuring SvO₂↓</td>
<td>16</td>
<td>PAP and PVR decrease</td>
<td>84</td>
<td>None or not stated</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all three variables</td>
<td></td>
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*± SD.

SvO₂ = mixed venous saturation.

*Two investigators repeated right heart catheterization only in patients not improving with epoprostenol therapy.

### Table 2—Calcium Channel Blocker Use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Use (Dose Range)</th>
<th>Chronic Use (Dose Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>10–240 mg (20 mg/h maximum)</td>
<td>30–360 mg/d</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>30–260 mg (30 mg/h maximum)</td>
<td>60–720 mg/d</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>2.5–20 mg (2.5 mg/h maximum)</td>
<td>160–240 mg/d</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>*</td>
<td>5–40 mg/d</td>
</tr>
</tbody>
</table>

*No dose range given.
investigators to occur in 10 to 50% of patients, while vomiting, chest pain, and arthralgias were noted infrequently. Side effects, such as headache and nausea, can be delayed and may present 1 to 2 h after a dose increase.

Long-term Epoprostenol Therapy

Two thirds of the respondents increased the dose of epoprostenol on a scheduled basis (Table 3). The mean interval was 3 ± 1 week. All centers increased the dose in response to the recurrence of symptoms, which included increasing dyspnea, fatigue, and chest pain; the median dose increase was 2 ng/kg/min, and the range was 0.5 to 3 ng/kg/min. At the time that the survey results were received, the lowest continuous dose reported was 0.5 ng/kg/min, with a median of 8 ng/kg/min, and the highest continuous dose reported was 270 ng/kg/min, with a median of 115 ng/kg/min. Most institutions reported sustained improvement in > 70% of patients receiving long-term epoprostenol therapy. The longest continuous use of epoprostenol in a single patient was 11 years.

Catheter site infections, bone pain, worsening or new thyroid disease, weight loss, rash, ascites, and relative or absolute thrombocytopenia were the most common long-term complications, with one or more complications reported to occur in over half of the patients at individual centers (Table 4). Less common problems included septicemia, catheter thrombosis/migration/fracture, and myocardial ischemia, which was reported by two centers. Weight loss, rash, thrombocytopenia, and muscle, joint, and leg pain were reported to occur more often with higher doses of epoprostenol.

Hickman catheters (Bard Access Systems; Salt Lake City, UT) were used by most centers for long-term infusion, although pediatric Hickman and Groshong (Bard Access Systems) catheters were used by some centers. Opinion was almost evenly divided as to whether the catheter site needs daily washing. Only three institutions had patients flush the catheter daily with heparin. Double-lumen catheters were used infrequently. Cephalixin and dicloxacillin were used most often as the initial antibiotic for suspected catheter-related infections.

Concurrent Therapy

Fourteen of 19 centers used oral vasodilators in addition to epoprostenol. The average number of patients receiving oral vasodilators at these institutions was 28 ± 24%, ranging from 10 to 90%. CCBs were used in the vast majority of patients, but angiotensin-converting enzyme inhibitors, nitrates, and NO were prescribed for a small number of patients. All centers routinely administered anticoagulation therapy to their patients; > 90% of patients received warfarin sodium. The mean target international normalized ratio was 2 ± 0.5. Digoxin was used by 16 investigators in as few as 20% and in as many as 100% of patients. Supplemental oxygen was used by 10 to 75% of patients. Other frequently used medications were antidepressants and multivitamins.

Evaluation of Efficacy

The results of follow-up evaluations of patients who received epoprostenol therapy are summarized in Table 2. Nine investigators repeated a right heart catheterization within the first year after starting therapy; the mean time before follow-up was 7.5 ± 3.8 months. Six investigators repeated acute vasodilator testing during follow-up right heart catheterization. Two investigators repeated hemodynamic evaluation only in patients not exhibiting a beneficial response to therapy. The mean decrease in PAP during repeat right heart catheterization was reported to be between 15 and 25%, the decrease in PVR was > 25%, and the increase in CO was > 25%. In addition to these 11 institutions, 3 centers evaluated patients with serial echocardiograms at 3- to 4-month intervals. The remaining investigators did not employ routine follow-up evaluations of cardiac function or hemodynamics. At centers with extensive

<table>
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<th>Table 3—Use of Epoprostenol</th>
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<tr>
<td>Initiation of Therapy</td>
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<tr>
<td>Starting dose</td>
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<tr>
<td>Dose increase/d</td>
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<td>Dose a discharge</td>
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<tr>
<td>Length of hospital stay</td>
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<tr>
<td>Chronic therapy</td>
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<tr>
<td>Dose</td>
</tr>
<tr>
<td>Amount of dose increase</td>
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<tr>
<td>Frequency of scheduled increase</td>
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<tr>
<th>Table 4—Commonly Reported Side Effects and Complications of Epoprostenol</th>
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<tr>
<td>Early</td>
</tr>
<tr>
<td>Jaw pain</td>
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<tr>
<td>Flushing</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Tachycardia</td>
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<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Hypotension</td>
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<tr>
<td>Chest pain</td>
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*Absolute or a relative decrease from baseline.
long-term experience with epoprostenol, improvement was reported to persist for > 2 years.

**DISCUSSION**

Patients with PPH receiving treatment with epoprostenol represent an extremely ill group of patients, nearly all of whom are defined as New York Heart Association class III or IV. Despite the fact that more than 500 patients are receiving long-term treatment with epoprostenol, there are few guidelines and no consensus regarding its use; furthermore, its mechanism of action remains unknown. The results of this survey emphasize a number of issues that merit further discussion and study.

Many centers use more than one vasodilator during short-term testing. No correlation can be drawn between the type of vasodilator and the percentage of patients responding. Despite the fact that this is a clinically unstable population, only two deaths were reported to occur during short-term vasodilator testing. This highlights the fact that right heart catheterization is a safe procedure in patients with pulmonary hypertension when undertaken by experienced practitioners.

The lack of standard criteria for determining a clinically meaningful acute vasodilator response makes comparison between institutions difficult. Changes in CO affect PVR, but whether changes in CO and PVR without significant reduction of PAP can be used to accurately predict sustained hemodynamic improvement remains uncertain. A number of studies indicate that reduction of right ventricular afterload is the key determinant of whether patients with pulmonary hypertension will derive benefit from vasodilator therapy. It is not surprising, then, that only about 20% of patients derive long-term benefits from treatment with CCBs even though about one third of patients were reported to respond to short-term vasodilator testing. Studies aimed at the standardization of hemodynamic data interpretation should be encouraged so that meaningful comparisons and predictions of long-term responsiveness can be made.

During long-term therapy, the log differences in doses among patients highlights the lack of knowledge about the mechanism of action of epoprostenol. There are no published data on the metabolism of epoprostenol during long-term infusion, and there is no direct evidence that permanent regression of the pathological process occurs, despite the fact that most patients improve symptomatically. The criteria that are used to determine whether patients require a dose increase are quite subjective, since dose escalation is almost always done without an invasive hemodynamic evaluation. Though this therapy is approved only for patients with New York Heart Association class III or IV heart failure, there is variability among institutions with regard to the degree of impairment required before proceeding to therapy with epoprostenol. It is unknown whether the earlier initiation of therapy or higher doses are more effective in preventing disease progression. Regularly scheduled increases may not be possible, even in patients with clinical deterioration, because of prohibitive side effects such as systemic hypotension, severe jaw pain, or diarrhea.

The association of thyroid disease with pulmonary hypertension has been noted previously by investigators in this field, and a recent abstract describes four patients with PPH who developed new thyroid abnormalities while receiving epoprostenol. This association remains unexplained. Ascites has been noted by a number of the respondents and may result from increased vascular permeability related to epoprostenol rather than from worsening right heart failure. Bone, muscle, and joint pain may be related to the ability of epoprostenol to sensitize pain receptors to other pain-producing stimuli or may be related to the direct stimulation of nociceptors. These and other effects of long-term epoprostenol therapy warrant further study.

Oral vasodilator therapy in addition to epoprostenol is used by a majority of investigators. Though many patients are maintained on oral vasodilators begun prior to the initiation of epoprostenol therapy, no investigator reported adding oral vasodilators once epoprostenol therapy had been started. One investigator used both NO and epoprostenol as long-term therapy. With the increasing use of short-term vasodilator testing during the initial evaluation of patients suspected of having PPH, we would expect a greater percentage of unresponsive patients to proceed directly to epoprostenol therapy. To our knowledge, no patient demonstrating substantial improvement has had epoprostenol therapy discontinued and has been maintained on oral vasodilators alone, though one investigator reported discontinuing epoprostenol because of refractory thrombocytopenia.

**SUMMARY**

In the last 15 years, long-term infusion of epoprostenol has emerged as the most effective therapy for patients with PPH who are unresponsive to treatment with CCBs. The vast majority of patients receiving epoprostenol are started on therapy at institutions that evaluate a large number of patients with pulmonary hypertension and that have expertise
in the treatment of PPH. The evaluation of and therapy for PPH should be directed by centers with expertise in pulmonary vascular disease. However, many patients with PPH are treated by their primary physicians, who may have had little exposure to PPH and may have no familiarity with epoprostenol. None of the published information concerning the use of epoprostenol in patients with PPH addresses management during long-term therapy. This study represents the first attempt to provide general information on the evaluation and management of PPH and on the use of epoprostenol therapy in this population.

There are a number of potential limitations of this study. First, care of the pediatric population is not addressed. Second, 4 of 23 centers did not respond to the survey, and there may be other referral centers that were not contacted, so that the survey may not completely reflect nationwide practices. Third, we did not survey European, Canadian, or other foreign institutions that provide epoprostenol therapy. Fourth, many of the questions in the survey required estimates only, and thus recall bias may affect some of the results.

CONCLUSION

Although continuous IV epoprostenol is a dramatic therapeutic advance in the treatment of PPH, many questions regarding this disease are unanswered. It seems likely, from the results of this survey, that randomized, multicenter studies or collaborative investigations among a number of centers might yield useful information. The evaluation of epoprostenol metabolism in patients with and without significant improvement during long-term therapy might provide valuable information about the mechanism of action of epoprostenol. The comparison of aspirin with warfarin and the objective evaluation of other adjunctive therapies such as digoxin, could be addressed as part of a multicenter study or as part of a PPH network registry. In addition, some type of collaborative, multicenter study to critically evaluate vasodilators used during diagnostic testing and to develop clinical pathways for determining a positive response may allow for more accurate predictions of the long-term response to oral vasodilator therapy. Other areas that need investigation are the association of thyroid disease with epoprostenol use, the mechanism of action of epoprostenol and the etiology of the unique side effects associated with its use, and whether disease regression occurs in conjunction with the clinical improvement observed with epoprostenol therapy. Finally, important insights into the pathogenesis of PPH may be gained by the careful study of the lung after its removal in patients undergoing lung transplantation.

APPENDIX

Contributing Investigators

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