Continuous Intravenous Epoprostenol for Pulmonary Arterial Hypertension: Highlighting Practical Issues, Special Considerations

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Continuous intravenous epoprostenol sodium (Flolan®) is a long-term, complex, and expensive therapy. Its pivotal role in the management of pulmonary arterial hypertension (PAH) is based on randomized studies that clearly established clinical efficacy. Subsequent studies have confirmed its benefits with regard to symptomatic and functional improvement, sustained hemodynamic effect, and enhanced survival. Initial studies demonstrated both acute (**Figure 1A**) and short-term (**Figure 1B**) hemodynamic improvement.[1,2] Exercise capacity in epoprostenol-treated patients, as measured by 6-minute walk test distance, improved during 12 weeks of follow-up compared with conventionally treated patients (**Figure 2**).[2] Improved exercise capacity, as assessed by improvement in peak oxygen consumption, has also been documented (**Figure 3**).[3] Importantly, increased survival has recently been reported in two large case series of patients with PAH (**Figure 4**).[4,5] Although the US Food and Drug Administration (FDA) has recently approved alternative subcutaneous and oral drugs, intravenous epoprostenol remains the most effective agent in the therapeutic armamentarium for PAH patients with World Health Organization (WHO) Class III or IV symptoms.

Despite its proved efficacy and cumulative experience since the commercial availability of epoprostenol in 1996, intravenous epoprostenol remains a complicated and potentially dangerous therapy. With the approval of additional therapies for advanced PAH, the selection of appropriate candidates for epoprostenol treatment has become particularly challenging. Health care providers must assess the potential risks and benefits of epoprostenol therapy compared with alternative treatment for each patient. This assessment should consider the patient's medical diagnosis, comorbidities, psychosocial status, support structure, financial resources, and stability.

Providers should also consider the available resources in their own facility to provide the comprehensive and intensive management that these patients require. Importantly, although epoprostenol therapy can be life-saving when used appropriately, it can potentially complicate, and in some cases worsen, symptoms with catastrophic results if it is incorrectly initiated, administered, or managed over the long term. Careful attention to four aspects of treatment is required when considering long-term use of epoprostenol: (1) patient eligibility, (2) patient education, (3) drug initiation, and (4) treatment maintenance and follow-up.

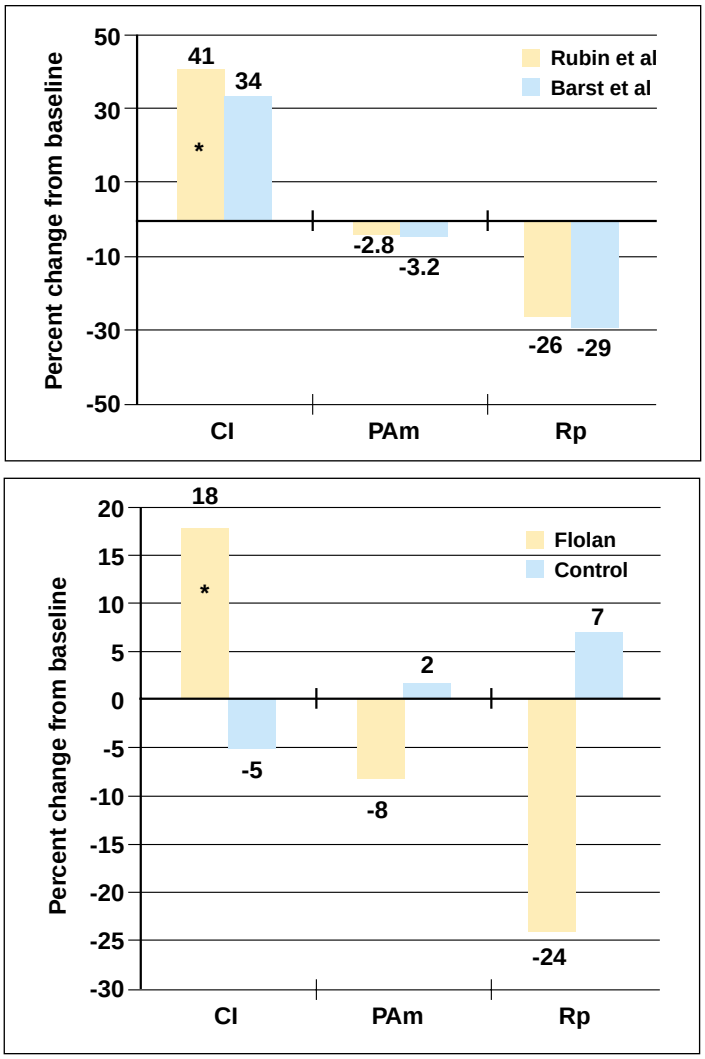

Fig. 1—(A, top). Acute hemodynamic response to intravenous epoprostenol in 23 patients[1] and in 81 patients[2] with PPH studied in the two original randomized efficacy studies. Although the change in mean pulmonary arterial pressure (PAm) was minimal, cardiac index (CI) increased and pulmonary vascular resistance (Rp) decreased (*$P < .0003$). (B, bottom). After 8 to 12 weeks of follow-up, hemodynamic benefit was maintained in patients treated with epoprostenol and was significantly better than in patients receiving conventional therapy (*$P < .03$ compared with baseline).

Patient Eligibility

The decision about whether a patient should be treated with epoprostenol requires consideration of a number of issues:

- Does the patient have appropriate clinical indications?
- Are there clinical contraindications?
- Are alternative medications more suitable?
- Have issues of medical coverage been defined?

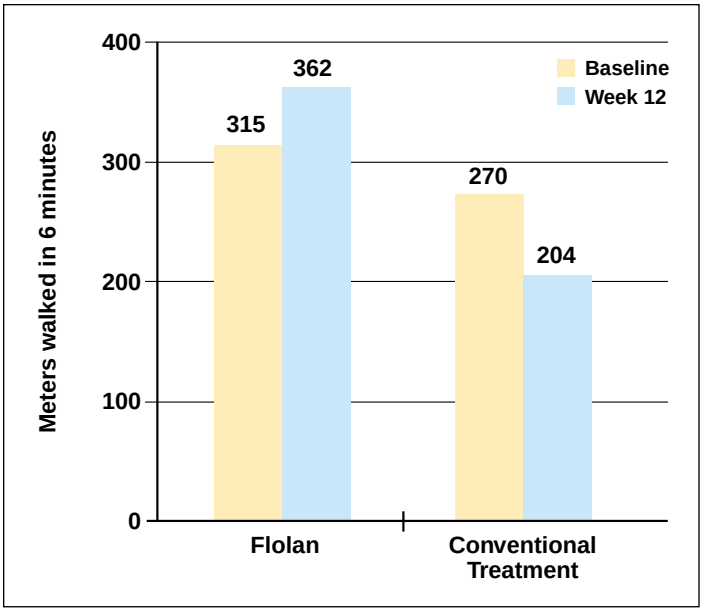

Fig. 2—Comparison between 6-minute walk distances at baseline and 12-week follow-up in patients with PAH treated with epoprostenol vs conventional therapy (*P* < .002).[2]

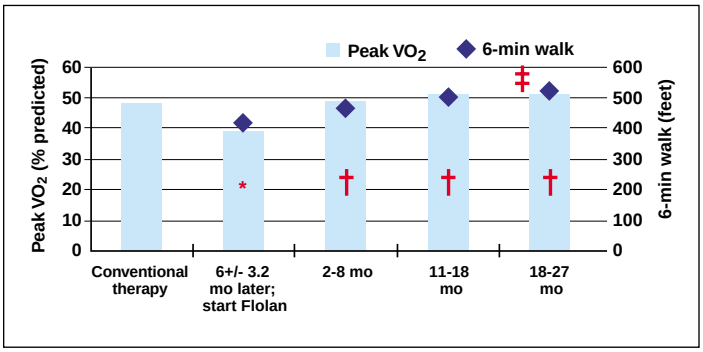

Fig. 3—Effect of epoprostenol on exercise in 16 patients with PPH. At epoprostenol initiation, peak oxygen consumption (VO_2) had declined compared with a previous measurement 6 ± 3.2 months earlier (P* < .05 vs previous measurement). Following initiation of drug, peak VO_2 and 6-minute walk distance both increased (†*P* < .05 and ‡P < .001 vs initiation, respectively).[3]**

- Is the patient able and willing to learn and comply with the regimen?
- Can adequate follow-up be assured?

Clinical indications

Epoprostenol is currently FDA-approved for patients with symptomatic (WHO Class III or IV) primary pulmonary hypertension (PPH) or PAH associated with collagen-vascular disease (the scleroderma-spectrum of diseases). At present, there are no controlled data demonstrating its efficacy in patients with HIV infection, congenital heart disease, or portopulmonary hypertension. Because these indications are similar to those for oral bosentan (Tracleer®) and subcutaneous treprostinil (Remodulin®), additional considerations should be weighed in selecting epoprostenol over these other agents.

Patients with very advanced or rapidly progressive symptoms should be considered for early treatment with epoprostenol since it has proved to be the most effective medical therapy and improved mortality has been demonstrated with its use.[2] Epoprostenol can be added to the medical regimen of patients whose condition has failed to adequately respond or who have not tolerated other medications. This drug should not be used in those with pulmonary venous hypertension as no benefit has been demonstrated and there is potential for worsening.[6,7] Central venous access is essential for placement of a permanent catheter. The presence of superior vena cava or bilateral subclavian vein obstruction (usually in the setting of previous central catheters or pacemaker leads) may be a relative contraindication.

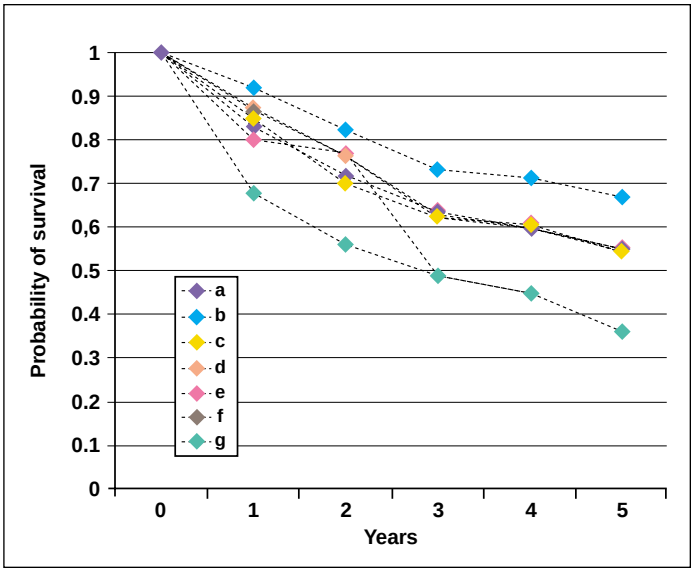

Fig. 4—Probability of survival among PAH patients treated with epoprostenol (a-f) vs untreated patients (g). (a) 195 sequential patients with PAH of various types who started treatment with epoprostenol prior to January 2001 (unpublished data). (b) 97 sequential patients with PPH and full right-heart hemodynamic studies at epoprostenol initiation prior to January 2001 (unpublished data). (c) 178 patients with PPH receiving epoprostenol treatment over period of 8 years.[4] (d) 162 patients with PPH receiving epoprostenol over period of 10 years.[5] (e) 59 patients with PPH treated with epoprostenol.9 (f) 17 patients with PPH treated with epoprostenol.[10] (g) Patients enrolled in the National PPH Registry.[11]

Medical coverage

Epoprostenol is far more expensive than most drugs, its use sometimes exceeding $100,000 per year. If prescribed for appropriate indications (WHO Class III and IV PPH and PAH associated with the scleroderma-spectrum of diseases), medical coverage is usually available. Prior insurance authorization is necessary and can be facilitated by the distributors of the medication. Awareness of reimbursement issues by caregivers is mandatory, and coordination between the patient and the distributor is a vital role of an active pulmonary hypertension clinic.

Patient capability and compliance

Although purely clinical issues regarding treatment selection are pivotal, other factors may take precedence in matching the patient to appropriate epoprostenol treatment. Despite the desire to provide optimal clinically indicated therapy to all patients, not all are safe candidates. In addition, health care

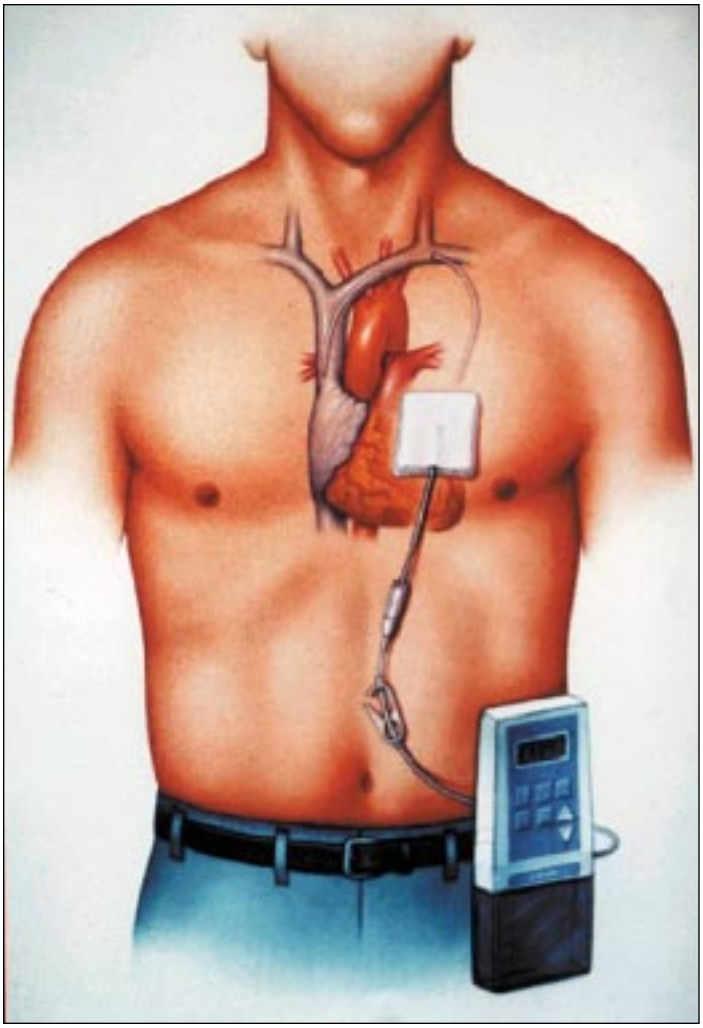

Fig. 5—Infusion apparatus for epoprostenol administration consists of a portable infusion pump and single lumen central venous catheter (generally a Hickman catheter). Note that the catheter exit site is positioned where it is accessible to the patient for self-care.

provider time is a valuable resource; care of one marginally compliant or competent patient may adversely affect the care of others. Thus, careful consideration of factors related to a patient's willingness and ability to undergo therapy as well as the level of family and social support should be addressed before initiation. These factors are best explored by an experienced and sensitive nursing staff with specialization in the management of PAH patients.

Nursing interviews should be conducted with both the patient and a significant other who will assist and support the patient at the outset. A number of issues should be explored with careful questioning. Responses to these questions do not necessarily preclude therapy, but are extremely useful in planning for future patient and staff needs.

Questions to ask after therapy has been explained include:

- Are there physical limitations, such as digital loss because of collagen vascular disease or visual problems or hearing impairment, that may hinder the ability to manipulate syringes, operate the pump, or hear warning alarms?
- Are there problems with the home environment that may preclude safe drug administration and follow-up, such as absence of satisfactory plumbing, poor home sanitation, or lack of access to a telephone?
- Is there a reliable family or social support person to help prepare the medication and manage the infusion pump?
- Are the patient and support persons committed to taking the time each day (approximately 1 to 1.5 hours) to perform necessary procedures?

Questions practitioners should ask themselves about the patient include:

- Is the patient sufficiently at ease to be a receptive learner about a complex treatment strategy, or does stress and agitation warrant deferring?
- Has the patient demonstrated compliance and initiative by keeping scheduled clinic visits and following current treatment recommendations?
- Does the patient actively participate in his or her own care or allow a significant other to manage it?
- Does the patient have a history of substance abuse or mental illness, including depression, that has required medication or hospitalization, which would be risky in the setting of long-term complex intravenous medication infusion?

Patient Education

This process is important and should proceed in an orderly and compulsive fashion. Information for the patient must include the following components:

- Introduction to the concept of long-term drug infusion
- Discussion of realistic expectations
- Education about technical aspects of epoprostenol use
- Potential adverse effects of epoprostenol

Introduction to therapy

Prior to making the decision to proceed with epoprostenol therapy, patients should be shown the actual delivery system, have all procedures demonstrated, and ideally have an opportunity to meet another epoprostenol patient. This may dramatically reduce the anxiety associated with starting long-term intravenous therapy. Patients may be more likely to benefit if they have the opportunity to meet someone of the same sex, disease substrate, and age range. Patients can be given information about the Pulmonary Hypertension Association (PHA), which may assist them in locating another patient in their area.

With the advent of new drug therapy, it is feasible that some patients may ultimately be weaned from epoprostenol, but they should understand that it is very likely going to be part of their daily routine forever, unless they undergo lung or heart-lung transplantation. In our experience, patients must have control over the decision-making process to learn and properly care for the delivery system. To ensure success, written and visual (videotape or compact disc) material to review at home can be offered to supplement face-to-face teaching prior to making a final decision regarding epoprostenol therapy.

Realistic outlook

Patients should have realistic perceptions about the drug. Although epoprostenol has the potential for making a significant difference in quality of life and for improving survival, it has not proved to be a cure for PAH. It is inconvenient, has side effects, and has associated risks. Patients must realize that there may not be immediate improvement in symptoms.

Although the majority of patients improve, it is impossible to predict the magnitude or duration of the therapeutic response. Patients have to understand that initial improvement in symptoms does not guarantee continued improvement or preclude eventual decline. While it is essential to hear this information from the pulmonary hypertension center providers, patients also may benefit from discussion with other patients and caregivers through support groups. They should not, however, base their expectations on results of therapy in other patients.

Technical education

Although the approach to education and drug initiation differs among large centers based on experience and resources, there are some common practices. Patients should be taught by experienced health care providers and ideally by the same people who will be following their care over the long term. At the Mayo Clinic, patients are provided with preprinted step-by-step directions in a manual that covers pump operation, drug reconstitution, and cassette and tubing change. They are encouraged to share a copy of this information with their local physician. Teaching should occur in intensive blocks before and during the actual initiation of the drug. Whether the infusion is initiated on an inpatient or an outpatient basis, it must be done in a monitored setting with immediate access to emergency equipment and care. Long-term epoprostenol infusion should be initiated using CADD I or Legacy pumps.

The process of reconstituting epoprostenol and all facets of pump operation and catheter care must be fully explained and demonstrated. Patients and support persons should be able to demonstrate their proficiency in all phases of epoprostenol administration before they can be considered adequately trained. This ensures that the patient always has a back-up person trained, which reduces patient stress.

Adverse effects

Patients should also be aware of common potential side effects, including jaw pain, headache, hypotension, nausea, diarrhea, and flushing. More long-term side effects may include leg and foot pain, and skin rash. Others, such as high cardiac output failure, anemia, thrombocytopenia, pancytopenia, or weight loss, may be recognized by the clinician with careful follow-up over time. Some of the latter effects may also, however, be due to other underlying disease. Finally, certain adverse effects may be related to the delivery system, including catheter-related infection or sepsis, catheter-related thrombosis, pump failure, and rebound symptoms or death due to sudden discontinuation of epoprostenol.

Drug Initiation

A 6 or 9 French single-lumen tunneled central venous catheter in the subclavian or internal jugular vein is the preferred approach for long-term epoprostenol therapy. The central venous catheter should be tunneled to an exit site that will allow the patient to see the site in order to care for it independently. Sutures should be removed after 4 weeks. Catheters are changed only when they become dysfunctional or infected. Many patients maintain the same catheter for many years. If a tunneled catheter must be removed for a period of time (for example, because of infection) a short-term dedicated catheter, such as a percutaneous intravenous central catheter (PICC) or midline catheter, is appropriate for short-term use. Such catheters have limited stability and are difficult to care for using only one hand.

Epoprostenol infusion through the catheter is typically started in a monitored setting at an infusion rate of 2 to 3 ng/kg/min. Vital signs are obtained before and at least every half hour for at least 2 to 3 hours after drug initiation. Teaching sessions occur on a daily basis until patients and support persons demonstrate proficiency in the techniques of sterile preparation of the medication, operation of the infusion pump, and care of the central venous catheter. At the time of discharge, patients are provided with detailed contact information. Patients are instructed to see their local physicians within the first month of returning home, offering them the opportunity to become familiar with their current status, and to assist with their assessment and monitoring, including anticoagulation.

A proactive approach has been successful with this patient population. Once the patient is fairly comfortable with the procedures and has minimal jaw pain, mild diarrhea, or headache, the epoprostenol dosage is increased by 1 to 2 ng/kg/min. The patient is called or instructed to call within the next week or sooner if dyspnea decreases or the side effects cause discomfort.

Treatment Maintenance and Follow-up

Important issues in long-term management include:

- Communication
- Dose modification
- Interaction with the referring physician
- Follow-up at the clinic
- Emergencies

Communication

While large pulmonary hypertension centers have different communication protocols, virtually all include telephone contact as part of management. At the Mayo Clinic, patients are instructed to call at least every two weeks. The following information is always obtained:

- Verification of current pump rate
- Number and type of vials that are being mixed
- Current weight
- Interim change in symptoms (including functional status) or side effects, and relationship to dose changes
- Verification of prothrombin time monitoring, including recent international normalized ratio (INR)

Dose adjustment

When epoprostenol was FDA-approved, experienced clinicians felt that frequent and consistent dose escalations were advis-

able in order to "stay ahead" of symptoms, rather than to try to catch up once they recurred or worsened. As a consequence of this dosing strategy and because of extended patient survival, substantial numbers of patients began to receive epoprostenol infusion rates of 100 ng/kg/min and higher. Over time, it became apparent that the consequences of high epoprostenol doses in some patients included high output states and fatigue.[5]

Epoprostenol dosing should be individualized to the patient, taking into consideration severity of symptoms, side effects, and underlying disease. Some patients who experience improvement in symptoms during initiation of epoprostenol in the hospital or monitored outpatient setting will report increased symptoms on returning home to a more physically challenging environment. Thus, close regular contact with these patients is imperative.

Role of referring physicians

Local medical providers, including primary care physicians, specialists, and emergency personnel, should be informed about patients' need for epoprostenol and its implications. Patients' current symptoms, medications and doses, the target range for the INR, potential complications, and plan for the future should be provided to primary care and other local practitioners. Local providers should also know how and when to contact the pulmonary hypertension center, particularly for problems that occur after clinic hours. Laminated instruction cards inserted into the pump pack are useful in emergency situations.

Clinic follow-up

Patients are generally seen for follow-up examination in the clinic 1 month after initiation and then every 3 to 6 months, depending on response to treatment. They are called or advised to call every 2 to 4 weeks to report symptoms and side effects, or sooner if problems arise. The frequency of contact depends on the stability of the patient, side effects, and overall comfort level.

During follow-up telephone surveillance, new or worsening symptoms should prompt a visit to the clinic for evaluation. Many centers repeat hemodynamic assessment after 1 year of therapy. Right-heart catheterization is the gold standard for assessment of pulmonary hemodynamics. The expectation at 1 year should be improvement in pulmonary hemodynamics but not normalization of them. Echocardiographic evaluation after approximately 3 to 6 months of treatment can provide useful interim estimation of pulmonary hemodynamics.

Emergencies

All potential emergency situations and proper responses should be discussed and "role-played" with patients during initial teaching. Ideally, local emergency rooms or emergency medical staff should be informed about PAH and its treatment and emergency requirements. Patients sometimes take on this responsibility themselves. If necessary, a letter can be provided to emergency services about the importance of maintaining the infusion at all times and even via a peripheral vein if necessary. Stickers located on the infusion pump show the current dose of epoprostenol as well as warn that the pump cannot be turned off for any reason. Patients are also encouraged to wear a medic alert bracelet or carry a laminated card listing their health problems as well as pump warnings. Urgent situations include central catheters being inadvertently pulled out, a torn or leaking catheter, pump malfunction, and central line infection (particularly tunnel infection or sepsis). Patients need to call 911 or proceed to an emergency room and be certain that the ambulance or emergency personnel are aware that interrupted epoprostenol delivery constitutes an emergency and that intravenous access must be established immediately. The pulmonary hypertension center should be contacted for further instructions if at all possible. A back-up medication cassette and supplies should be brought to the hospital. Infections related to long-term indwelling central lines can be minimized by strict attention to aseptic care.

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