Bench to Bedside: Principles and Practice of Epoprostenol Therapy, from Maximizing Benefit to Minimizing Side Effects


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Ivan Robbins, MD, Director, Pulmonary Hypertension Center, Vanderbilt University, Nashville, Tennessee, conducted this discussion. The panel included David Langleben, MD, Director, Center for Pulmonary Vascular Disease, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; Michael McGoon, MD, Consultant in Cardiology, Mayo Clinic, Rochester, Minnesota; and Abby Krichman, RRT, Pulmonary Hypertension Coordinator, Duke University Medical Center, Durham, North Carolina.

Dr Robbins: I have always been interested in why investigators decided to try intravenous prostacyclin, or epoprostenol (Flolan), as long-term treatment.

Dr McGoon: It was recognized as a very potent vasodilator, with the additional theoretical benefits of being one of the most potent endogenous platelet inhibitors. So it made some sense to use it in a disease in which vasoconstriction was felt to be a predominant causal mechanism.

Dr Langleben: It was a serendipitous concurrence of a novel molecule and a pharmaceutical company that held very basic research in high regard. Prostacyclin, as an endogenous vasodilator was initially described in 1976. The major clinical phase in pulmonary hypertension began later in that decade, extending to the mid-80s. So it took a while to work its way down to clinical use. I think it was its potent vasodilator effect with a probable short duration of action that made it very attractive as an acute vasodilator for testing.

Dr McGoon: The other serendipitous aspect of this drug is that it came when we were getting disillusioned with other vasodilators, most specifically hydralazine. So the concept of a short-acting pulmonary vasodilating agent, which was actually replacing deficient endogenous production of prostacyclin, made a lot of sense.

Dr Robbins: How did you come up with the dosing scheme?

Dr McGoon: Initially it had been identified during the acute-stage dose-ranging studies that preceded our involvement. It became clear very soon when using epoprostenol that if you gave too big a dose you were going to get a lot of side effects and you had to creep up on the dose if you were gong to get benefit over the long haul. About 2 to 3 ng/kg/min was the initial starting dosage in the early studies and is clearly the way to go. Typically, most patients, by the time they were dismissed from our initial care, were receiving around 6 ng/kg/min when they went home, and after that point we incremented gradually by 1 or 2 ng/kg/min every week or so, particularly if a patient was still symptomatic, which was frequently the case. Later, based on conversations with other clinicians nationwide, we evolved into more or less routinely increasing the dosage regardless of symptoms. The idea was that we wanted to stay ahead of symptoms preventively and continue to have a vasodilator effect that would hopefully impart some vascular remodeling and permanency to the decreased resistance. Eventually it was recognized that there was a state in which symptoms of high cardiac output could overtake the benefits of decreased resistance. It has always been observed that the predominant effect of administering epoprostenol was to increase cardiac output with modest decreases in pulmonary pressure at best, resulting in a decrease in calculated pulmonary resistance.

Dr Robbins: Abby, what has the experience been at Duke?

Ms Krichman: Initially, in the early days of epoprostenol dosing, the prevailing practice was to continue increasing dosages on a regular basis and just tolerate the adverse side effects. We certainly have come full circle. Now we try to maintain the lowest dose (of epoprostenol) possible to ameliorate symptoms but also to minimize the side effects.

Dr Langleben: Our practice was exactly as Mike described initially.

Dr Robbins: We were just looking at our 5-year experience, and our average dose is probably somewhere around 25 ng/kg/min. We have very few people receiving more than 50 ng/kg/min.

Dr Langleben: Our early patients, the ones who have had 10 or 11 years of treatment, have reached higher dosages. Most of the recent patients are not at that dose level, though. Our average is probably 45 to 60 ng/kg/min after many years. After a year of therapy most people are receiving about 20 ng/kg/min.

Dr McGoon: We are all over the board, to be perfect-

ly honest. It is such a moving target at this time, when we have the option of combining or transitioning to other medications. We can talk about averages, but at least in our case, the standard deviation of doses at any given time is extremely broad.

Dr Robbins: Should we talk a bit about combined therapy?

Dr McGoon: It is at an early stage. We are still learning about it. One pattern we have seen is that when we add another agent to epoprostenol, even one that is not a prostenoid, like bosentan, for example, there can be an exacerbation of what we would normally call epoprostenol side effects, such as flushing, headache, and gastrointestinal disquietude.

Dr Langleben: The concept of attacking an illness through a variety of mediators and mechanisms is standard for other types of illnesses. Perhaps, because of the relative rarity of pulmonary hypertension or the lack of availability of easy therapy, we have not been able to consider combined therapy until now.

Ms Krichman: There are a lot of physicians out there who think they can just give patients bosentan and completely wean them from epoprostenol. We may be able to accomplish that in some patients, but with very careful monitoring.

Dr Robbins: You are absolutely right.

Ms Krichman: We ought to make it clear that we are using combination therapy to hopefully improve outcomes, not solely to wean epoprostenol.

Dr Langleben: Would everyone agree that epoprostenol remains our gold standard for the medical treatment of advanced functional class III and IV patients?

Dr Robbins: Yes.

Dr Langleben: So, has everyone around the table seen failures of other therapies already and resorted to epoprostenol?

All: Yes.

Dr McGoon: Our prediction was, and I think it is coming true, that the oral therapy, bosentan, would be used widely, but that not all hopeful expectations would be met. There has been more recently the feeling that "Well, we haven't seen all the benefit we want, so maybe we should think about adding or transitioning to epoprostenol."

Ms Krichman: At our center, and probably for most of you as well, when somebody's more of an early Class III patient, our preference is always oral therapy first, but for those with later Class III symptoms, we are initiating epoprostenol in most cases.

Now we try to maintain the lowest dose (of epoprostenol) possible to ameliorate symptoms but also to minimize the side effects.

Dr McGoon: That would be my preference, and that is what I express to most patients.

Ms Krichman: There are always patients who refuse epoprostenol and want to try oral therapy first. In most cases we're amenable to a short trial of oral therapy with careful follow-up and monitoring.

Dr McGoon: The key, particularly if you are going to start with conservative therapy, is the follow-up. The whole process of the pulmonary hypertension specialty clinic has to be geared to establishing communication with the patient about the treatment options, the pros and cons, and then to very intensive follow-up and reevaluation.

Dr Langleben: What are your standards for follow–up?

Dr McGoon: Of course, it varies from patient to patient. We follow patients in terms of clinical symptoms with 6-minute walk testing at intervals of 3 to 6 months and with echocardiography, usually at 6 months. If there is disparity among clinical impression, examination, and echocardiographic data, we will do right-heart catheterization.

Dr Langleben: We prospectively follow patients with echocardiography at least every 6 months. Our population numbers aren't huge, but we can tell who is doing well on the basis of the Doppler echocardiography-derived index of myocardial performance (the TEI index)) and how their ventricles are coping.

Dr McGoon: At some centers, some clinicians clearly feel that regular, periodic right-heart catheterization for hemodynamically precise characterization provides additional information about cardiac output.

Ms Krichman: I think a lot of centers do that.

Dr McGoon: We don't do it on everybody because the specific number doesn't really help me too much, compared with the global assessment of a patient's status, which includes many factors. I think all of us employ multiple criteria in deciding how patients are doing and what changes, if any, in therapy should be attempted.

Dr Langleben: The other thing we pay particular attention to on our echocardiograms is an estimate of cardiac output.

Ms Krichman: What is the prevailing thought about patients who continue to have severely enlarged right ventricles, but who symptomatically are doing okay?

Dr Langleben: With those patients, we follow the TEI index. In many of these patients the index is greatly and abnormally elevated. If the index is slightly improved, despite the fact that they have right ventricular dilatation, we gently increase the dosage. If the index hasn't really improved with epoprostenol, we give them a couple of months, then that is an indicator to list them for early transplantation, regardless of

their symptoms. Then we more aggressively increase the epoprostenol dosage to try to buy them time to get their transplant.

Dr Robbins: David, I am just not impressed with aggressive dosing. And by going up on the dose aggressively, we find you get a lot more side effects.

Dr Langleben: We do increase the dose more rapidly than we would in more stable patients. We don't get a lot of epoprostenol side effects beyond jaw pain and a little bit of diarrhea.

Ms Krichman: We see a lot of musculoskeletal pain.

Dr McGoon: The problem is knowing in the individual patient whether you have reached the optimal dosage. I agree with David that if a patient is not doing well, then you don't know that a higher dose won't work until you have tried. So it does stimulate a strategy of going up on the dosage. If you find the side effects overwhelm the benefits, or if you really don't get any additional benefits from the inconvenience or expense of a higher dosage, then it may make sense to try tapering off again.

Ms Krichman: I think we should talk about general dosing strategies for patients who have just started receiving epoprostenol. We usually have a 3- to 4-day hospitalization with a goal of sending patients home taking 4 to 6 ng/kg/min of drug, somewhere in that range. For sicker patients we'll be more aggressive, titrating up during the initiation period. Once they are home, we call patients weekly for at least a month following initiation of therapy and go up 1 or 2 ng/ kg/min a week. Dosing is very individualized, depending on symptoms and side effects. Once symptoms are somewhat under control, we back off on dose titration, typically to every 2 weeks and then every month. When we reach a dosage where there is a balance of symptomatic improvement and minimal side effects, we stop going up.

Dr Robbins: That is pretty close to what we do, and what is probably done in a lot of centers.

Ms Krichman: Except for the very sickest patients, there is no need to rapidly titrate epoprostenol

Dr McGoon: Oh, I agree.

Dr Robbins: You raised a very good point, Abby, the fact that these patients need very close follow-up. You can't just send patients home taking 3 or 4 ng/kg/min and then say, "Okay, we'll see you back in a month or so."

Ms Krichman: It doesn't work well for physicians taking care of epoprostenol patients without some kind of physician extender. There is clearly a role for health care professionals who work very closely with physicians and who talk with patients on a regular basis and see them in clinic periodically. This is not an easy disease to manage.

Dr McGoon: I have no hesitation whatsoever in saying that our pulmonary hypertension clinic was established primarily to have nurses in a setting with focused interest.

Ms Krichman: Yes. And that has to be the message to community physicians or physicians who aren't at tertiary care centers.

Dr Robbins: What about infection from the long-term indwelling catheters? How do you manage that at your centers?

Dr McGoon: The first step is obviously prevention, and that comes with education of the patient about strict aseptic control. But even under the best conditions, the catheter can get infected. Our response depends on the circumstances. If it is a localized exit-site infection, we will make substantial efforts to preserve the catheter and treat with antibiotics to prevent it from getting worse. Certainly if there is any evidence of systemic infection, the catheter is out and intravenous antibiotics are given.

Dr Robbins: Education is key. The only time we have had problems is with patients who didn't understand or ignored the signs of the problem and then came in and were quite ill.

Ms Krichman: Overall, how many catheters have you had to pull because of systemic infection?

Dr McGoon: If I had to guess the percentage of patients who have had that, it would be 3% or 4 % maybe. I have some patients who have been receiving the drug for more than 10 years who have never had a change in catheter. But thenthere are others who have had two or three infections in one year.

Dr Robbins: Have the indications for use of prostacyclin changed over the years for you?

Dr McGoon: Yes, it has evolved to broader indications. As published experience increased with secondary pulmonary hypertension and randomized studies increased with collagen vascular disease, the labeling expanded our options and we were able to use the drug more broadly. Now we consider its use in nonsurgical thromboembolic disease or interstitial pulmonary fibrosis and so on, in which pulmonary hypertension may be a big component. The more other things you have wrong, the less the beneficial effect.

Dr Langleben: I am not sure their longevity will be the same as that of primary pulmonary hypertension patients in the sense that the other medical issues related to their principal illness will likely affect survival.

Dr Robbins: Any other issues that anyone feels are important to bring up?

Dr McGoon: One source of problems for us has been when patients unexpectedly see other physicians who don't know what to do in an urgent situation. You just have to listen to

patients when dealing with epoprostenol. They actually know what they are doing.

Ms Krichman: That is an important part of the education of patients and caregivers that sometimes does not happen, really taking the time to explain what a peripheral IV is, when you need to get it put in, and that sort of thing.

Dr Langleben: We give patients a preprinted card that they carry with their pumps. It states in big bold letters, "DO THIS NOW." Patients are instructed to go to their nearest hospital emergency room if they have a problem with the infusion lines or catheter, and to show the card immediately on arrival. The system works.

Ms Krichman: Another topic we might touch on is the side effects of prostacyclin and how we are treating them. The initial approach is to lower the dose of epoprostenol if tolerated. Musculoskeletal pain is a big issue. Mostly we are using gabapentin (Neurontin).

Dr Robbins: We have used COX-2 inhibitors. They help some people, and then we move on to amitriptyline with an occasional patient, and then to gabapentin.

Ms Krichman: Is anybody using tramadol (Ultram) or opioids?

Dr McGoon: Not in any routine way. We have a low threshold for using gabapentin.

Dr Langleben: What about for diarrhea?

All: Loperamide (Imodium).

Dr McGoon: We sometimes use jaw pain as an index of whether patients are getting enough. If they are not having jaw pain, we have serious concerns whether enough is being used.

Ms Krichman: We used to do that, and then there were those patients who did not have jaw pain but were doing great.

One thing I know we have all seen as a side effect is ascites. The important issue is determining whether ascites is from worsening heart failure or from epoprostenol. Those seem to be the most difficult to sort out.

Dr McGoon: If someone is not doing well, we wonder (a) is the patient getting it and (b) if they are, whether it may be at too low a dose.

Dr Robbins: Any other big side effects?

Ms Krichman: One thing I know we have all seen as a side effect is ascites. The important issue is determining whether ascites is from worsening heart failure or from epoprostenol. Those seem to be the most difficult to sort out.

Dr Robbins: We have seen it somewhat, but more often we have seen it in the face of severe right heart failure.

Ms Krichman: We certainly have seen such patients, but now we are seeing patients who are not in right heart failure and have significant ascites.

Dr McGoon: Yes, I agree, Abby. And patients require frequent paracentesis.

Dr McGoon: You know, I think it is a testimonial. To be frank, epoprostenol has never been exposed to what we would consider a scientifically rigorous clinical study. There was no placebo, there was no blinding involved and so on, and yet I think most of us are convinced, based on our experience, that it works. Part of the reason we are convinced is that in spite of what seem to be fairly horrendous side effects, patients still feel they are benefiting from the medication. The other reason I think it is physiologically beneficial is our experience when some patients' infusions have been surreptitiously interrupted. For example, we've had a couple of instances when the line was inadvertently pulled out from the vein but remained subcutaneous, so the patient was unknowingly no longer getting an infusion. The patients felt worse, as though their symptoms had returned until the infusion was resumed. That was my "controlled" study.