Is It Ethical to Administer Vasodilator Drugs to Patients with Primary Pulmonary Hypertension?

Many physicians believe that vasodilator therapy is an accepted approach to the treatment of patients with primary pulmonary hypertension. Despite the lack of evidence that pulmonary vasoconstriction is an important pathogenetic factor in this condition, the use of vasodilator drugs in these patients is rising. Despite reports that vasodilators frequently produce serious adverse hemodynamic and clinical reactions, most (if not all) patients with primary pulmonary hypertension are given at least one trial (and often multiple trials) of vasodilator therapy. Despite the absence of controlled data indicating that long-term treatment with vasodilators produces long-term clinical improvement, patients continue to receive these drugs in the hope that some will benefit. This marked discrepancy between what we know and what we do is easy to understand. In the management of a disease as potentially lethal as primary pulmonary hypertension, it is difficult to stand by and withhold a promising treatment.

But is the use of vasodilator drugs in management of patients with primary pulmonary hypertension so promising? Those who advocate this therapeutic approach point to its apparent successes. In the experience of the Primary Pulmonary Hypertension Registry sponsored by the National Institutes of Health, vasodilators produce a fall in pulmonary artery pressure or in pulmonary vascular resistance in a large number of patients with this disorder. These short-term hemodynamic effects appear to be sustained in the majority of patients who undergo a second right heart catheterization after several weeks or months of therapy. Continued responsiveness to vasodilators has been confirmed in selected individuals for periods up to six years. Furthermore, patients who show the most marked hemodynamic benefits during short-term therapy seem to improve symptomatically during long-term treatment. Some investigators have even suggested that prolonged therapy may favorably alter the natural history of the disease; the survival of patients with primary pulmonary hypertension in the 1980s appears to be longer than those whose diagnosis was made in the 1960s and 1970s. These encouraging observations have raised sincere hopes that treatment with vasodilator drugs can produce clinically meaningful benefits in some of these severely ill patients. Unfortunately, all previous studies that have used vasodilator drugs in the treatment of primary pulmonary hypertension have been uncontrolled, and thus, it remains uncertain that the benefits that have been reported were related to therapy or the process by which therapy was administered. For example, although impressive circulatory effects have been observed following vasodilator therapy in many patients, similar hemodynamic changes may also occur spontaneously in the absence of vasodilator drugs. Further, although some patients seem to improve symptomatically after treatment with vasodilators, similar clinical benefits may be seen during ineffective therapy.

Finally, although patients who respond to vasodilators have a longer survival than patients who fail to show hemodynamic benefits, this favorable prognosis seems to be related to intrinsic characteristics of the pulmonary vasculature rather than to continued treatment with vasodilator drugs. All of these observations have raised doubts (in the absence of controlled studies) about the utility of vasodilator therapy. The only convincing evidence to date that vasodilators may be beneficial in patients with pulmonary hypertension has been the demonstration of hemodynamic improvement during long-term treatment with these drugs. Most physicians would not expect such sustained benefits to be seen in the absence of effective treatment.

Such expectations, however, need to be reevaluated in light of the interesting paper by Danktzer and colleagues in this issue of Chest (p 1185). These investigators carried out serial right heart catheterizations in six patients with primary pulmonary hypertension whose long-term treatment was interrupted to determine if the hemodynamic effects that were observed could be directly related to the administration of vasodilator drugs. No patient in this study, however, showed a rise in pulmonary artery pressure or pulmonary vascular resistance when vasodilator therapy was withdrawn or showed a decline in these variables when treatment was reinstituted. How can these observations be explained? The authors offer two possibilities: either the hemodynamic changes observed during long-term treatment were spontaneous or the drug therapy induced a prolonged remission of the disease. The authors were skeptical about the
first possibility, since the magnitude of the changes they observed after two to four months exceeded the spontaneous variability they previously observed during 48 h of observation. However, the spontaneous variability of most cardiovascular end points increases dramatically as a function of time; after several months, extreme changes are needed to ensure that any observed effect can reasonably be attributed to treatment. How, then, can the authors be certain that the hemodynamic changes that they observed during long-term vasodilator therapy were related to treatment? The only solution, as the authors suggest, is to perform a placebo-controlled trial.

It is noteworthy that all of the patients evaluated by Danktzer and coworkers felt they were better while taking their medication, whether or not they improved hemodynamically. How can this be explained? Danktzer et al performed measurements only at rest, and it is possible that the clinical benefits that they observed were related to an improvement in exercise hemodynamics that they did not evaluate in their study. On the other hand, it is equally possible that the symptomatic benefits they noted were related to a placebo effect. Many patients receiving a new drug improve (in part) because they have entered a new therapeutic environment, which (by increasing the expectation of benefit) reduces anxiety concerning symptoms. The creation of such a therapeutic environment occurs commonly in clinical practice but is greatly exaggerated in the setting of a formal research trial, in which the personal attention provided to the patient reaches very high levels. Evidence of such a placebo effect may be apparent even when objective measures of exercise tolerance are used. How, then, can we be certain that the symptomatic benefits reported by the authors were related to the use of vasodilator drugs? The only solution is to perform a placebo-controlled trial.

Is it likely that such a placebo-controlled trial might produce results that would differ so markedly from the uncontrolled clinical impressions that have been reported in the literature? The situation faced by physicians when contemplating the use of vasodilators in primary pulmonary hypertension is reminiscent of that faced by practitioners a decade ago when vasodilators such as prazosin were introduced in the treatment of left ventricular failure. Uncontrolled studies of prazosin reported marked hemodynamic and clinical benefits, which seemed to be sustained during long-term therapy and were paralleled by a substantial increase in exercise tolerance. Some investigators thought that the value of prazosin was so clearly demonstrable that placebo-controlled trials were unnecessary. Ten years later, we now know that most patients with chronic heart failure do not improve during long-term prazosin therapy. The hemodynamic benefits that were reported a decade ago were probably related to spontaneous changes that are now known to occur in patients with heart failure who undergo right heart catheterization. The improvement in exercise tolerance that was observed in the early reports is now known to occur predictably in patients with heart failure who enter clinical studies even if they receive no effective treatment. Placebo-controlled trials were needed to show that prazosin neither improved the clinical status nor altered the long-term outcome of patients. Fortunately, prazosin was well tolerated by most patients with heart failure. In contrast, many patients with pulmonary hypertension do not tolerate treatment with vasodilator drugs.

Are placebo-controlled trials of vasodilator therapy in patients with primary pulmonary hypertension ethical? Is it reasonable to enroll patients who respond hemodynamically to treatment into a study in which half will receive long-term treatment with placebo? A placebo-controlled study can be considered unethical only if the relation of benefit to risk is established. It would be unethical to withhold treatment with drugs that we know are effective, especially if we know that they are reasonably safe. None of these concerns, however, is applicable to the use of vasodilators in patients with primary pulmonary hypertension, in whom the benefits of treatment are uncertain but the risks are well known. On the other hand, is it not unethical to use a potentially dangerous drug in a seriously ill patient unless the benefits of treatment have been proved? Physicians must struggle with this dilemma every time they choose to use a vasodilator drug to manage primary pulmonary hypertension.

Milton Packer, M.D.
New York

Division of Cardiology, Department of Medicine, Mt Sinai School of Medicine.
Reprint requests: Dr. Packer, Division of Cardiology, Mt Sinai Medical Center, One Gustave L. Levy Place, New York City 10029

REFERENCES

1 Packer M. Does pulmonary vasoconstriction play an important role in patients with primary pulmonary hypertension? A skeptic's view of vasodilator therapy. Chest 1985; 88:655S-68S
6 Chan NS, Mc Lay J, Kenmure AC. Reversibility of primary
pulmonary hypertension during six years of treatment with oral diazoxide. Br Heart J 1987; 57:207-09

New Modes of Mechanical Ventilation for ARDS
How Should They Be Evaluated?

Over the past ten years, there has been a recurring interest in new methods of mechanical ventilation for patients with severe respiratory failure from the adult respiratory distress syndrome (ARDS). The search for new approaches to ventilatory support for ARDS patients has evolved, in part, from a general frustration with our inability to reduce the mortality from this syndrome. However, the well-intentioned efforts to find better means for providing mechanical ventilation for patients with ARDS seem somewhat misguided, since many studies have shown that mortality in most ARDS patients can be attributed to uncontrolled infection and multiorgan failure, not primarily to respiratory failure. Nevertheless, the effort to find more effective methods of ventilatory support for ARDS patients has an interesting history that is worth reviewing briefly.

In the extracorporeal membrane oxygenation (ECMO) study that was carried out in the 1970s, the control group was treated with conventional mechanical ventilation, while the ECMO-treated patients received lower tidal volumes with a lower mean airway pressure. Interestingly, the incidence of barotrauma and mortality was the same in the two groups. Subsequently, some investigators advocated high levels of positive end-expiratory pressure (PEEP) (as high as 40 to 45 cm H₂O) with the goal of reducing the intrapulmonary shunt fraction to less than 15 percent. Although there was initial enthusiasm that the high levels of PEEP improved survival in ARDS, the studies were uncontrolled. Subsequently, Nelson and co-workers did a randomized study of high vs moderate levels of PEEP and found no effect on duration of mechanical ventilation or on overall mortality. Furthermore, a prospective trial of the prophylactic value of 8 cm H₂O PEEP in patients at high risk for developing ARDS showed no benefit of PEEP in preventing ARDS.

In the early 1980s, there was considerable interest in high-frequency ventilation as an alternative to conventional ventilation, partly because patients could be treated at lower peak airway pressures, which some investigators thought might result in less barotrauma and perhaps less ventilation-induced lung injury. However, subsequent work demonstrated that oxygenation with high-frequency ventilation is strongly influenced by the mean airway pressure that is applied, especially in patients with ARDS. Significant improvement in oxygenation could be achieved with high-frequency jet ventilation, but primarily if this was associated with an increase in the mean airway pressure, which in turn often had a deleterious effect on venous return and cardiac output. Furthermore, a well-designed prospective, randomized study of 309 patients showed that there was no significant difference in the total duration of intensive care or survival in patients treated with high-frequency jet ventilation compared with conventional volume ventilation. Also, a recently published prospective NIH-sponsored study showed no benefit of high-frequency ventilation compared with conventional ventilation in neonates with hyaline membrane disease. Moreover, MacIntyre and associates recently concluded that jet ventilation does not offer important clinical benefits over conventional volume ventilation in adult patients with respiratory failure, with the possible exception of those patients with a large bronchopleural fistula.

And now, most recently, there has been a growing interest in the use of pressure-controlled, inverse ratio ventilation as another alternative for providing mechanical ventilation in patients with severe respiratory failure and ARDS. In a recent issue of Chest, Tharratt and co-workers published a retrospective study of