The Best of Times, the Worst of Times: the Wealth and Poverty of Heart Failure Pharmacotherapies

Is there a Role for Vesnarinone?

To paraphrase Charles Dickens in his classic, A Tale of Two Cities, "It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness. . ." 1775 was not an auspicious year for European royalty. However, progress, as is inevitable, ruled the day and the evolution of governing concepts created dramatic new governing paradigms. The same can be said for current heart failure therapeutic treatments. We have made dramatic progress since the 'dark ages' of the 1950s, when rudimentary diuretics and noxious inotropic agents proved the mainstay for dropsical patients with congestive heart failure. In some senses, we have now painted ourselves into a dark corner by demonstrating the add-on accrual benefit of multiple pharmacotherapeutic agents in heart failure patients. It is now 'standard of care' to have a patient on, at the least, an angiotensin-converting enzyme (ACE) inhibitor, a β adrenergic blocker, and should congestion be present, a diuretic (with its requisite mineral supplements), digoxin, aldosterone antagonist, and perhaps even an angiotensin-receptor blocking agent. This ignores agents required for co-morbidities and ancillary difficulties such as diabetes mellitus and chronic obstructive pulmonary disease. It is not unusual to see a clinician prescribe a dozen different medications for patients with significantly symptomatic congestive heart failure. How has this come to be? Simply put, we have been continually excited but then disappointed with therapies that have emerged. Repeatedly, we have demonstrated the incompleteness of therapeutic impact. For example, if we look at one-year mortality in the Studies of Left Ventricular Dysfunction Treatment Trial, which was completed in 1991, the mortality rate for the diuretic and digoxin group was just over 15%, and was reduced by 21% to approximately 13% when an ACE inhibitor was added to the protocol. In the Cardiac Insufficiency Bisoprolol Clinical Trial, completed in 1999, the one-year mortality rate was reduced from this 13% point by 33% to approximately 8% simply by the addition of a β blocker to an ACE inhibitor, digoxin, and diuretic protocol. Results have further improved with the addition of an angiotensin-receptor blocker to the base protocol, as studied in the CHARM trial in 2003. However, one-year mortality for heart failure patients overall remains in the 5–7% range despite aggressive therapies and multiple medications. Furthermore, in the population more generally, in which outcomes are usually worse than those noted in clinical trials, databases (such as Framingham) have suggested a reduction in 5-year heart failure mortality in

symptomatic men from approximately 70% in the 1960s to a little under 60% in the 1990s. These statistics remind one of the dismal outcomes that patients with heart failure, particularly symptomatic congestive heart failure, suffer and emphasize the importance of a continued search for new therapeutic approaches.

Obviously, not all patients given individual drugs or their combinations respond. We do not understand the heterogeneity of heart failure patients that explains variable outcomes. The need to re-explore responses to drugs studied in the past, and develop new therapeutic strategies, is extraordinarily important in view of the remaining high morbidity risk. It is in that context that an overview of vesnarinone should be undertaken. Indeed, we are re-exploring the uses of drugs discarded in the past because of concerns regarding safety and efficacy, with at least three agents undergoing new scrutiny: vesnarinone, enoximone, and levosimendan. All three drugs had been abandoned at one time because of conflicting clinical trial observations and, in particular, the suggestion of adverse outcomes in some studies. Did we try the wrong doses in our clinical trials? Did we select the wrong patients? Were underlying therapeutic agents confounding? In the end, is there any hope for these agents?

Vesnarinone is a fascinating quinolinone derivative with many distinct myocardial actions. As more specifically detailed in this monograph, phosphodiasterase type 3 inhibition (which is weak) leads to increased vesnarinone-induced myocardial contractility, and accompanying that is a prolongation of the action potential, with minimal negative chronotropic and vasodilatory activity. Interestingly enough, cytokine production seems to be attenuated with vesnarinone. As is now well known and is overviewed in this compendium, two large-scale randomized clinical trials came to two diverse conclusions regarding the utility of vesnarinone in congestive heart failure patients. The Vesnarinone Study Group Trial suggested a dose-dependent benefit, whereas the Vesnarinone Trial suggested increased mortality in a stepwise fashion as the dosage escalated. However, those of us participating in these clinical trials could not help but observe the number of patients claiming a substantial improvement in the symptomatology of devastating congestive heart failure. Interestingly, many patients at the conclusion of the Vesnarinone Trial who were known to be taking vesnarinone went to great lengths to obtain the drug in a compassionate use format. Perhaps that is indicative of a response, although, obviously, one can make no definitive conclusion from isolated anecdotes.

Therefore, in the setting of advanced heart failure, when patients are particularly symptomatic and all other tactics and hope has been exhausted, what do we do?! In that setting it is perhaps justifiable to try agents that have, at the very least, some suggestion of clinical benefit, and vesnarinone surely might be one of those drugs. Further study can hopefully clarify which patient is specifically at risk of arrhythmic events that might predispose to greater adverse events when treated with vesnarinone. It is not unreasonable to speculate that the combination of vesnarinone and a β blocker would actually prove highly efficacious and beneficial! Likewise, in the current heart failure arena, in which

the utilization of implantable cardioverter defibrillating devices, with or without biventricular pacing to resynchronize the heart electrically, might provide a safety margin, which coupled with a drug like vesnarinone would improve patients' symptoms and well being while protecting them from arrhythmic death.

Arguably, it is time to reconsider agents that have been discarded. Perhaps we have thrown the baby out with the bathwater, so to speak, and what was necessary was a better study of safer ways to administer the drug, be that with different dosing protocols, in more highly select patient populations, or in conjunction with strategies designed to attenuate arrhythmias and other aspects of detrimental heart failure pathophysiology. This supplement plumbs the nuances of this concept. Perhaps vesnarinone is a beneficial drug that was abandoned prematurely. Hopefully, more detailed clinical studies will subsequently re-emerge, and we can reassess the potential of an agent that so many patients anecdotally thought was stupendous.

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