Nesiritide and Worsening of Renal Function
The Emperor’s New Clothes?

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When we walk the streets at night in safety, it does not strike us that this might be otherwise. This habit of feeling safe has become second nature, and we do not reflect on just how this is due solely to the working of special institutions.

—Georg W.F. Hegel (1770–1831),
The Philosophy of Right (1821, trans. 1942)

Concern about the safety of commonly used and heavily promoted medications has grown in recent years, culminating with the recent events surrounding the cyclooxygenase-2 (COX-2) inhibitors. Patients, physicians, politicians, and government bodies are asking how newly approved medicines can be belatedly found unsafe and at the same time be prescribed widely on the basis of what is perceived as misinformation about their efficacy relative to older agents with which there is far greater experience. Is the approval process flawed, are medical practitioners so uninterested or unconcerned, or is essential information systematically withheld or misrepresented?

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The article by Sackner-Bernstein and colleagues1 in this issue of Circulation provides useful insight into the processes of drug approval, marketing, and physicians’ acceptance of new therapies. These authors used data from clinical trials of nesiritide (human B-type natriuretic peptide; BNP) to examine the effect of this agent on renal function. The unique feature of their analysis is that it is based neither on a direct review of the study data nor on data from peer-reviewed publications but rather primarily on data contained in US Food and Drug Administration (FDA) reviews and the sponsor’s briefing document, both of which are accessible to the public on the FDA Web site (specific links are provided in their article). Their analyses found consistent and statistically significantly increased risks of worsening renal function with nesiritide as compared with the control groups in these trials, as defined by an increase in serum creatinine (SCr) of >0.5 mg/dL. Increases in relative risk of ~40% to 50% were observed in relationship to controls treated with both positive inotropic agents and noninotropic drugs, including nitroglycerin, and at both the approved doses of nesiritide and all doses studied. Overall, SCr increases >0.5 mg/dL were noted in 169 (21%) of 797 patients treated with nesiritide and 69 (15%) of the 472 control patients.

Unfortunately, there are important limitations to these analyses because of the nonavailability of the primary data, which the authors acknowledge. These limitations include the use of a single arbitrary definition of worsening renal function (one chosen by the FDA medical reviewers), inability to identify and adjust for baseline differences in the treatment groups, and limited information on events or interventions that occurred after the treatment periods. The last point is particularly relevant because many patients who exhibited this magnitude of increase in SCr did so only several days or longer after the end of the study infusions. Furthermore, only limited information about the clinical or renal outcomes of the patients experiencing worsening renal function is available. As determined by the investigators, substantially more nesiritide-treated patients (32 of 288, 11.1%) required a “medical intervention” for the worsening of renal failure as compared with the control group (6 of 144, 4.2%). There was no difference in the need for dialysis, however, which was instituted in 14 of 561 nesiritide patients (2.5%) and 8 of 360 control patients (2.2%), although the small numbers of these events makes it impossible to exclude clinically important differences in the need for dialysis.

Despite, or in part because of, the unorthodox methods used, we believe the Sackner-Bernstein study warrants attention. Renal function deteriorates frequently during the treatment of patients hospitalized for heart failure. Increases of ≥0.1 mg/dL occur in ~70% of patients admitted for heart failure.2 Nearly 40% experience increases ≥0.3 mg/dL, a change that is associated with increased length of stay and both higher in-hospital and postdischarge mortality rates.3–4 The development of worsening renal function during treatment occurs not only in patients with severe systolic dysfunction with presumed low cardiac output and renal perfusion but also at similar rates and with similar prognostic significance in patients with preserved ejection fraction.5–6 The most powerful predictor of this phenomenon, commonly called “the cardiorenal syndrome,” is preexisting chronic kidney disease, which is often related to hypertension and diabetes. Worsening renal function also has become a major barrier to the use of treatments known to prolong survival, including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers, and aldosterone blockers. These agents not only improve survival but also can be renal protective with long-term use. Therefore, withdrawal of these therapies is associated with a poor prognosis.7
The finding of more frequent worsening of renal function cannot be taken lightly. Increases in creatinine do not necessarily portend a poor outcome, as the trials with angiotensin-converting enzyme inhibitors have taught. Furthermore, multiple confounders, such as hypotension and overdiuresis, may be responsible for the increased creatinine. BNP exerts multiple potentially beneficial actions on the kidney, including inhibition of renin synthesis, vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole of the glomerulus, and decreased sodium reabsorption at the proximal tubule and collecting duct. However, the evidence that BNP improves renal function or facilitates natriuresis in the setting of decompensated heart failure is limited at best. Ultimately, transient increases in creatinine may have no clinical significance, unless they serve as a harbinger of worse clinical outcomes.

Indeed, the potential clinical importance of the renal function changes was identified as a point of discussion at the 2001 FDA Cardiovascular and Renal Drugs Advisory Committee meeting, at which nesiritide was approved. It was noted that in the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial, there were trends toward a longer length of stay after infusion in patients treated with nesiritide as compared with nitroglycerin (10.0 ± 8.4 versus 8.1 ± 7.0 days, P = 0.0008) and in 30-day mortality (22 of 273 [8.1%] in the nesiritide group versus 11 of 216 [5.1%] in the nitroglycerin group, P = 0.2), although the relationship of these findings to the changes in renal function was not analyzed. Several advisory committee members expressed concern about these findings, including one who stated, “... if we decided at the end of the day to suggest to the FDA that this drug is approvable at this time, then I would want to mandate obtaining more data about this particular issue.” In response to this and comments by other committee members, Dr Lipicky, who was then director of the Cardiorenal Division of the FDA Center for Drug Evaluation and Research, replied, “We hear your concern, and I think that’s noted.”

Nesiritide was approved by the FDA in 2001 for the “intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.” The FDA-approved labeling states that in these patients, nesiritide “reduced pulmonary capillary wedge pressure and improved dyspnea.” Since its approval, many physicians have enthusiastically adopted the use of nesiritide in their clinical practice, in some cases as a routine therapy for patients admitted for decompensated heart failure. For many physicians, a primary reason for using this agent has been its perceived ability to improve or preserve renal function and reduce requirements for diuretics; however, there are few data to support these perceptions. Indeed, the package insert states in the precautions section that:

Nesiritide may affect renal function in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with Natrecor may be associated with azotemia. When Natrecor was initiated at doses higher than 0.01 µg/kg/min (0.015 and 0.03 µg/kg/min), there was an increased rate of elevated serum creatinine over baseline compared with standard therapies, although the rate of acute renal failure and need for dialysis was not increased.

The clinical laboratory section of the package insert states:

In the PRECEDEnt trial, the incidence of elevations in serum creatinine to >0.5 mg/dL above baseline through day 14 was higher in the Natrecor 0.015-µg/kg/min group (17%) and the Natrecor 0.03-µg/kg/min group (19%) than with standard therapy (11%). In the VMAC trial, through day 30, the incidence of elevations in creatinine to >0.5 mg/dL above baseline was 28% and 21% in the Natrecor (2 µg/kg bolus followed by 0.01 µg/kg/min) and nitroglycerin groups, respectively.

Furthermore, the FDA labeling explicitly states that there was no difference in net diuresis between nesiritide and nitroglycerin during the first 24 hours of the VMAC trial. In addition, the 6-month mortality rates for the VMAC trial are also reported in the package insert (nesiritide 25.1% [95% CI 20.0% to 30.5%]; nitroglycerin 20.8% [95% CI 15.5% to 26.5%]). Thus, the FDA included some of the data that raised the advisory committee members’ concerns, but it neither determined that these findings warranted including a warning in the labeling nor followed the suggestion that further studies be mandated. In sum, the FDA acted as if practicing physicians would carefully read the precautions in the package insert and that this information would influence clinical practice.

The article by Sackner-Bernstein and colleagues essentially uses the data reviewed by the FDA and expands on the information in the package insert to raise the issue of the safety of nesiritide in a different public forum—the peer-reviewed medical literature. When the same information was presented at the 2004 American Heart Association Scientific Sessions, it was met with a vehement negative response, indicating that many physicians do not accept these findings and believe that nesiritide is not only safe but also beneficial in protecting or even improving renal function. Indeed, these convictions are supported by review articles, continuing medical education materials, and expert opinion pieces, such as a recent article from a peer-reviewed journal that states that nesiritide “improves renal hemodynamics and tubular function. As a result, nesiritide quickly reduces clinical symptoms and improves mortality in patients with acute CHF.” No reference is made to the FDA-approved package insert, which states the contrary, or to the first specifically designed controlled study to assess the effect of nesiritide on renal function. That study found no difference in urine output, renal plasma flow, or glomerular filtration rate in a double-blind, randomized, crossover study of nesiritide compared with placebo.

What can be done to correct this disconnect between the clinical trial data and the safety concerns noted by the FDA and the actual practices of physicians? Many are calling for the FDA to establish higher standards for the demonstration of safety for new therapies, particularly if the therapies demonstrate improvement only in symptoms rather than in clinical outcomes. Indeed, the European Medicines Agency, the European equivalent of the FDA, has specifically required that data on worsening renal function (development of renal insufficiency and need for dialysis) and mortality data be obtained at 30 days and 6 months in new drug applications for acute cardiac failure. The European Medicines Agency is awaiting the results of a 2-trial program, the European Trial of Nesiritide in Acute Decompensated Heart Failure, that will enroll 1900 patients with acute decompensated heart failure to nesiritide or placebo before...
considering it for approval for the European market. This would avoid much of the recent controversy about drug safety and clarify whether adverse laboratory findings such as the worsening of renal function are in fact a signal for adverse clinical outcomes. Such a requirement would necessitate much larger and more expensive trials, no doubt delaying or even preventing the development of worthwhile new therapeutic agents.

Another possibility is more aggressive labeling by the FDA in package inserts; perhaps what is not known about the safety of new agents should be more emphatically highlighted. A warning statement that the effects of the medication on survival and other clinical outcomes are not known could be included, accompanied by any data of concern, even if the findings do not reach statistical significance. Although such a change is clearly within the purview of the FDA, history suggests that it may not have much impact. Another approach could be to place greater restrictions on marketing or better enforce existing regulations. These restrictions could apply to company-sponsored symposia and lectures, informational materials, and especially direct-to-consumer advertising. These restrictions are limited by First Amendment free-speech issues and the vast resources that would be required to implement the restrictions. Although none of these approaches is ideal, a combination needs to be implemented to improve the future health of the public.

The article by Sackner-Bernstein and colleagues points to another possible approach. The authors systematically examined data that have long been accessible. Their bringing this information into the scientific literature makes it likely that the presentation of these data will receive more publicity and reach many more practitioners than the actual FDA-approved labeling. It is also likely that this article will encourage other investigators to analyze FDA data that have not been adequately reported or that may take on new significance in light of subsequent trials and clinical experience. Ideally, these analyses could be conducted in collaboration with FDA experts, although the current bureaucratic environment may make this impractical. If, as is being discussed, a vigorous drug safety office is established, then it may benefit greatly from collaboration with knowledgeable investigators. There is also significant potential for misuse and abuse by investigators and competitors as well as others with inadequate expertise to interpret such results. Sackner-Bernstein and colleagues and the editors of Circulation deserve credit for submitting these results to appropriate peer review and publishing this provocative analysis, which informs the debate about the drug-approval process and the role of our special institutions to protect the public safety with respect to prescription medications.

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References


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