

Commentary: Nesiritide and Lessons Unlearned

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Abstract: Drawing from nesiritide and other recent case studies, the author describes problems associated with prematurely adopting drugs, the seductive nature of the intermediate endpoint, and the influence of pharmaceutical industry marketing on clinical practice.

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Introduction

Pop. That's the sound of another therapeutic balloon bursting. This time it's nesiritide (Natrecor®), human B-type natriuretic peptide, for decompensated congestive heart failure. A meta-analysis published in the April 20, 2005 issue of JAMA concluded that compared with nonionotrope-based therapy, nesiritide appeared to be associated with an increased risk of death (1).

Unfortunately, nesiritide shows that we as doctors have not learned the lessons of the past. Now history, in the form of another treatment failure, has repeated itself. What are those

lessons? Beware the lure of the intermediate endpoint; selective reading is bad for doctors and their patients; and finally, the Golden Rule – she who has the gold makes the rules – still applies.

The Lure of the Intermediate Endpoint

Nesiritide was approved in the United States by the Food and Drug Administration (FDA) in 2001 on the basis of data showing that compared to intravenous nitroglycerin or placebo, that there was a statistically significant improvement in both capillary wedge pressure and self-reported dyspnoea (2). However, nesiritide had not been

demonstrated to have any hard clinical benefits over nitroglycerin in terms of mortality or fewer repeat hospitalizations (3). In short, nesiritide was approved on the basis of intermediate, or surrogate, endpoints. Intermediate endpoints are

acceptable when they have been conclusively linked to clinical outcomes. So, for instance, lowering blood pressure by whatever mechanism leads to improvements in morbidity and mortality; decreasing viral loads has been shown to reduce mortality in patients with HIV/AIDS.

But there are also many instances where surrogate endpoints have proven deceptive. Perhaps the best known recent example is the use of hormone replacement therapy for postmenopausal women in the hope of preventing cardiovascular disease. At one time, this approach seems reasonable based on the positive results that estrogen demonstrated on cholesterol levels. But the publication of the Women's Health Initiative trial showed that line of reasoning to be fallacious; women receiving estrogen and progestin had an excess of cardiovascular disease compared to those on placebo (4). In the mid 1980s doctors were routinely prescribing flecainide and encainide based on data that showed a high efficacy in suppressing a variety of arrhythmias. Once again, clinical outcomes were not assessed until the Cardiac Arrhythmia Suppression Trial found that mortality was higher on these agents than on placebo (5). Closer to home, emergency physicians often insert pulmonary artery catheters (PAC) to measure a variety of physiologic variables in the hopes of improving outcomes. While PACs do not jeopardize survival neither do they appear to provide any benefit when used in patients with shock or the acute respiratory distress syndrome (6).

Selective reading is bad for doctors and their patients

One of the reasons for the enthusiasm for nesiritide appears to have been doctors' perception that it improved or preserved renal function and reduced the need for diuretics. But the labeling approved by the FDA noted that "Natreacor 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 Natreacor may

be associated with azotemia" and that there was no difference in net diuresis between nitroglycerin and nesiritide. But the FDA did not require the company to highlight these concerns possibly assuming that doctors would thoroughly read the product information and use that

information in clinical practice (7). Sales of U.S. \$400 million for nesiritide in 2004 seem to suggest that the FDA's hopes were misplaced (8). Indeed, when concerns were raised about nesiritide at the 2004 American Heart Association Scientific Session they were met with a "vehement negative response" (7). One 2005 review article opined that nesiritide "improves renal hemodynamics and tubular function. As a result, nesiritide quickly reduces clinical symptoms and improves mortality in patients with acute CHF" (9).

Selective hearing on the part of doctors is nothing new. After flecainide and encainide were shown to increase mortality 80% of surveyed doctors in the North American Society of Pacing and Electrophysiology were continuing to use these drugs in patients already taking them, 90% still initiated therapy with these drugs and a substantial percentage continued to use them for unapproved uses (10). Despite an extensive informational campaign carried out by the FDA warning of the risks of using the analgesic dextropropoxyphene there was no change in prescribing rates, the no-refill recommendation had no impact on refill rates and the risk of overdose death remained constant (11).

One of the sources that doctors do seem to pay attention to is journal ads. Despite protestations from doctors that they are not influenced by this source of information companies were willing to spend just under \$450 million on journal ads in the United States in 2003 (12) because they know that for each additional dollar that they put into this form of promotion they can generate up to \$12 in return (13). Four page ads for nesiritide trumpeted its alleged benefits with headlines such as "Natreacor delivered rapid hemodynamic improvement: reduction in filling pressures (PCWP) within 15 minutes" and "Natreacor delivered greater improvement in dyspnea." (Advertisement in *Circulation* December 4, 2001).

Experts reviewed 102 journal ads in 10 leading medical journals and concluded that in 44% of

cases it was felt that the ad would lead to improper prescribing if a physician had no other information about the drug other than that contained in the advertisement. Overall, reviewers would not have recommended publication of 28% of the advertisements and would have required major revisions in 34%

before publication (14). The majority of original research cited to substantiate claims in pharmaceutical ads is funded by or has authors affiliated with the product's manufacturer (15).

The Golden Rule – she who has the gold makes the rules

The meta-analysis done by Sackner-Bernstein and colleagues and published in JAMA was not the only such review of nesiritide. Scios, the company marketing the product, also did its own meta-analysis. While the one done independently showed a 1.81 (95% CI 1.02 to 3.27, $p = 0.04$) relative risk for death as compared to placebo the company sponsored one had a relative risk of 1.26 (95% CI 0.80 to 2.00) and a nonsignificant p value of 0.33. The difference resulted from the fact that the Scios analysis included open-label trials and ones involving out-patient use (3).

The fact that company funded research produces results favourable to the sponsor should not come as any surprise. In a meta-analysis published in the BMJ in 2003, Lexchin and colleagues showed that the summary odds ratio for favourable outcomes for research with industry sponsorship was 4.05 (95% CI, 2.98 to 5.51). Their results applied across a wide range of disease states, drugs and drug classes, over a period spanning at least two decades and regardless of the type of research being assessed—pharmacoeconomic studies, clinical trials or meta-analyses of clinical trials (16).

Subsequent to their study, at least four other similar articles have appeared. Als-Nielsen et al analyzed 370 randomized controlled trials (RCTs) in 25 meta-analyses in the Cochrane Library (17). The experimental drug was recommended as treatment of choice in 16% of trials funded by nonprofit organizations and in 51% with for-profit sponsorship. Trials funded by the later type of organization had a 5.3 greater chance (95% CI, 2.0 to 14.4) of recommending the product being tested as the treatment of choice compared to trials with nonprofit

sponsorship. A second study looked at sponsorship and quantitative outcomes in pharmacoeconomic studies of SSRIs. The conclusion was that over the range of questions that were posed – SSRIs versus tricyclics, new versus old antidepressants and the outcome of modeling studies—the answer was the same; industry sponsored studies were more likely to

report favourable results that were non-industry sponsored studies (18). Bhandari et al analyzed 158 randomized controlled trials in five major medical journals that were published between January 1999 to June 2001 and after adjusting for study quality and sample size, reported that the odds ratio in favour of industry funded trials reporting a positive outcome was 1.6 (95% CI, 1.1 to 2.8) (19). Most recently, a group of Canadian researchers examined 372 clinical trials involving atypical antipsychotics of which one-third were sponsored by industry. The reported outcomes of the sponsored trials highly favoured the manufacturer's product (20).

Conclusion

Emergency doctors, by the nature of our work are frequently faced with critically ill patients. The therapies that we have on hand are often to inadequate to deal with the extreme nature of their problems. Thus, when something new and apparently better comes along we are eager - sometimes overly eager- to embrace the new. That may well be for the better; think of thrombolytics for acute myocardial infarction or rapid sequence intubation for patients with compromised airways. But nesiritide shows that newer is not always better. We should know this from previous experience, but sometimes, to our patients' detriment, we forget it. George Santayana, the 19th century American philosopher, said "those who cannot remember the past are condemned to repeat it." When it comes to new drug therapy doctors must sometimes plead guilty to forgetting the past.

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