Nicardipine (Cardene) for Hypertension in Critically Ill Patients

Mark A. Malesker, PharmD, Professor of Pharmacy and Medicine, Creighton University Medical Center, Omaha, Neb.

Parenteral nicardipine (Cardene Premixed Injection, EKR Therapeutics) has demonstrated both efficacy and safety for quickly reducing blood pressure among critically ill patients with acute hypertension. To test whether outcomes with nicardipine justified its higher acquisition costs, Dr. Malesker identified 159 consecutive patients receiving nicardipine in the intensive-care unit (ICU) at two Omaha hospitals along with an equal number of consecutive patients receiving other parenteral antihypertensive agents. These medications included enalaprilat (Vasotec), esmolol (Brevibloc), fenoldopam (Corlopan), labetalol (Trandate), nitroglycerin (Nitro-Bid), and nitroprusside (Nitropress). Outcome measures included time to initial oral antihypertensive therapy, length of hospital stay (LOS), need for a second or a substituted agent, major complication rates, and total in-patient hospital costs.

Nicardipine showed significant benefit for time to oral antihypertensive therapy, time spent in the medicine ward and total LOS (Table 1). In addition, a larger number of patients in the non-nicardipine group (59%) required a second or a substituted antihypertensive agent compared with the nicardipine patients (34%) (P = 0.001). Major complications were more common in the non-nicardipine group (18% vs. 8%; P = 0.018), and in-hospital costs were 17% lower with nicardipine (P < 0.001).

As with earlier research in adolescents and adults, a study of add-on omalizumab (Xolair, Novartis) in children from six to 12 years of age with inadequately controlled moderate-to-severe, allergic asthma showed reductions in the rate of clinically significant exacerbations.

Omalizumab, a recombinant humanized monoclonal IgE antibody, is approved in the U.S. as an add-on therapy for patients with moderate-to-severe, IgE-persistent allergic asthma with a positive skin-prick test or in vitro reactivity to a perennial aeroallergen with symptoms inadequately controlled with inhaled corticosteroids (ICS).

The trial, which compared the long-term (52-week) efficacy and safety with placebo in children six to 12 years of age, included a 24-week fixed steroid phase and a 28-week adjustable-steroid phase. During the latter period, the ICS dose was adjusted according to National Heart, Lung, and Blood Institute (NHLBI) guidelines for steroid reduction. All of the children had moderate-to-severe, allergic asthma of at least a year’s duration that had been inadequately controlled even though they had received at least a medium-dose ICS, fluticasone (e.g., Advair, GlaxoSmithKline) of 200 mcg/day or more, or equivalent, with or without other controller medications. Omalizumab at a dose of 75 to 375 mg (n = 384) or placebo (n = 192) was given subcutaneously once every two or four weeks for 52 weeks, according to the patient’s body weight and total serum IgE level at the first visit.

The primary efficacy outcome was the exacerbation rate during the fixed-steroid phase. During this 24-week phase, omalizumab patients experienced a 31% decrease in the rate of clinically significant asthma exacerbations compared with those receiving placebo (0.45 vs. 0.64, rate ratio [RR]; P = 0.007). The advantage persisted over 52 weeks as well (0.78 vs. 1.36 for a 43% reduction; P < 0.001). In an interview, Dr. Malesker noted variable responses with enalaprilat, a risk of extravasation with esmolol, hypotension with labetalol, rapidly developing resistance to nitroglycerin, and toxicity in patients with impaired hepatic or renal function with nitroprusside.

He concluded, “In addition to the lower overall treatment cost, the higher acquisition cost of nicardipine is offset by a greater monotherapy success rate and a lower rate of complications.”

Add-on Omalizumab (Xolair) for Moderate-to-Severe, Allergic Asthma in Children

H. Milgrom, MD, National Jewish Medical and Research Center, Denver, Colo.

Andrea Anderson, PharmD, Senior Medical Liaison, Genentech, Sterling, Mass.

As with earlier research in adolescents and adults, a study of add-on omalizumab (Xolair, Novartis) in children from six to 12 years of age with inadequately controlled moderate-to-severe, allergic asthma prolonged the time to first exacerbation compared with placebo (193 days vs. 178 days).

Table 1 Nicardipine and Non-Nicardipine Therapy and Hospital Times

<table>
<thead>
<tr>
<th>Non-Nicardipine Group (N = 159)</th>
<th>Nicardipine Group (N = 159)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours to start of antihypertensive therapy</td>
<td>22.2 ± 6.5</td>
<td>19.7 ± 6.5</td>
</tr>
<tr>
<td>Hours in intensive-care unit</td>
<td>31.8 ± 14.4</td>
<td>37.9 ± 22.8</td>
</tr>
<tr>
<td>Hours in medicine ward</td>
<td>166.6 ± 41.9</td>
<td>136.7 ± 47.4</td>
</tr>
<tr>
<td>Total hospital hours</td>
<td>198.5 ± 49.5</td>
<td>174.6 ± 61.3</td>
</tr>
</tbody>
</table>

Mr. Alexander is a freelance medical writer living in New York City.
Acquired Postsurgical Coagulopathy

A series of presentations on acquired coagulopathy in postsurgical patients suggests a long-lasting risk following the use of topical hemostat bovine (cattle-derived) thrombin, with a potential for significant clinical and economic consequences. Bovine thrombin–associated immune-mediated coagulopathy (IMC) is thought to be related to the formation of antibodies to bovine thrombin that cross-react with native human coagulation factors, potentially leading to severe bleeding. The FDA’s boxed labeling for topical bovine products includes precautions against re-exposure among patients with pre-existing antibodies.

Persistence of Antibodies to Topical Hemostat Bovine Thrombin

- C. Duane Randleman, MD, Cardio-Thoracic Surgeons PC, Birmingham, Ala.

Dr. Randleman’s analysis of prior clinical trials evaluated data from 205 patients with definite or highly likely surgical exposure to a bovine thrombin product in the previous three years. His study noted that 15.6% of patients retained anti–bovine thrombin product antibodies with more than a 100-fold range in antibody titer. Antibodies to bovine thrombin were found in 21% of patients who had undergone surgery in the previous year and in 6% of patients who had undergone a surgical procedure three or more years earlier.

Dr. Randleman concluded, “Clinicians should be aware that antibodies to bovine thrombin products may persist for years following exposure.”

Coagulopathy after Surgery: Clinical and Economic Outcomes

- Emily Beth Devine, PharmD, MBA, PhD, University of Washington, Seattle, Wash.

The absolute risk of IMC among patients with acquired coagulopathy, as well as its incidence and economic impact, remains unknown. Dr. Devine’s pilot study was designed to characterize the clinical impact of acquired coagulopathy in hospitalized surgical patients and to compare the use of resources among patients who experienced coagulopathy after surgery with patients who did not.

Dr. Devine reviewed the medical records of 5,367 patients who had undergone surgery (neurological, spinal, cardiovascular, abdominal/gastrointestinal, musculoskeletal, or orthopedic) and who were admitted to Harborview Medical Center in the first six months of 2008. Twenty-six patients with postsurgical elevations of prothrombin time (PT) and activated partial thromboplastin time (aPTT) were identified and compared with 26 matched controls. The mean time to coagulopathy after surgery was 7.1 days, with 96.2% of patients requiring admission to the ICU postoperatively (mean, 11 days). The median duration of coagulopathy was four days, (range, 1–42 days).

Compared with controls, patients with coagulopathy had a significantly longer overall LOS, postoperative LOS, a higher number of total days spent in the ICU, and reduced survival rates in the hospital (Table 2). Complications were also much more common in these patients: pulmonary problems developed in 50% of the coagulopathy group and in 8% in controls, and acute renal failure occurred in 26% of the coagulopathy patients but in none of the controls.

Coagulopathy patients used more resources than controls ($112,280 vs. $38,357; P < 0.001). Most of the difference was accounted for by ICU and ward charges. Furthermore, more than two-thirds of the expenses were incurred from time of the coagulopathy to discharge from the hospital.

Dr. Devine concluded that acquired coagulopathy was associated with significant increases in LOS in the ICU and the hospital in greater utilization of resources.

Bovine Thrombin–Associated Coagulopathy After Surgery

- M. Scot Maxon, PharmD, Associate Director of Medical Affairs, ZymoGenetics, Inc., Seattle, Wash.

The findings of Dr. Devine were consistent with those in Dr. Maxon’s economic impact study of data derived from the literature describing 48 cases of bovine thrombin–associated IMC. In an interview, Dr. Maxon pointed out that because the incidence of IMC is unknown, conventional Markov cost-effectiveness modeling of IMC treatment is not possible. Formulary committees, however, must still decide whether to add topical hemostatic agents.

“What we could do was a cost avoidance model based on incremental cost,” Dr. Maxon said.

He suggested that P&T committee members could base their decisions on these study results or they could put their own specific cost numbers into the model. In this analysis, patients with IMC were classified as those with bleeding (n = 21) and those without bleeding (n = 28). For patients with bleeding, median costs were $92,333 (range, $41,592–163,072); for nonbleeding patients, median costs were $56,668 (range $16,584–129,828).

Dr. Maxon emphasized that even those patients who merely have abnormal laboratory values consume more resources. He commented:

<table>
<thead>
<tr>
<th>Table 2 Comparison of Mean Hospital Length of Stay</th>
<th>Coagulopathy Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall length of stay</td>
<td>34.8 ± 22.6 days</td>
<td>11.8 ± 8.5 days</td>
</tr>
<tr>
<td>Postoperative length of stay</td>
<td>31.5 ± 15.8 days</td>
<td>9.8 ± 7.1 days</td>
</tr>
<tr>
<td>Total stay in intensive-care unit</td>
<td>15.3 ± 8.5 days</td>
<td>4.2 ± 4.3 days</td>
</tr>
<tr>
<td>Hospital survival rate</td>
<td>80.8%</td>
<td>100%</td>
</tr>
<tr>
<td>P value versus controls</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Physicians become concerned and want to find out the cause of the prolonged clotting times. They may try to immunomodulate by giving intravenous immune globulin, or they may even give blood products, such as platelets, which will supply factor V. Whichever, you end up with prolonged length of stay, the primary cost in both groups.

Dr. Maxon noted that cost totals were conservative, because the economic model included only quantifiable resources with referenceable costs per unit. He explained that another problematic aspect of IMC was the delay in the progress of immune reactions during which some patients who develop antibodies to bovine thrombin go on to form cross-reacting antibodies to native human thrombin. Research suggests that the earliest occurrence is about five days after exposure. Patients may return with consequences as divergent as epistaxis or retroperitoneal hematoma.

Dr. Maxon concluded:

This economic model suggests that even a single nonbleeding case of bovine thrombin IMC may increase resource utilization costs. You don’t know for sure who’s had prior exposure to bovine thrombin, but some evidence suggests that as many as one in six surgical patients has developed antibodies to it.

There is no commercially available test for determining the presence of bovine thrombin antibodies. ZymoGenetics, which produces a recombinant topical thrombin, supported this research.