HIGHLIGHTS

Hemodynamic and Analgesic Actions of Epidurally Administered Clonidine

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EISENACH *et al.* (page 277) have undertaken an important study to define the clinical pharmacology of epidurally administered clonidine in humans. The goal of the study was to define the pharmacokinetics and pharmacodynamics of epidurally administered clonidine on experimental pain, sympathetic reflexes, respiration, and cardiovascular control in nine healthy volunteers. Clonidine, 750 μg, was administered epidurally with arterial plasma and cerebrospinal fluid sampling for drug concentrations and pharmacokinetic analysis. Pharmacodynamic measurements included blood pressure, heart rate, relative finger and toe blood flow, and response to cold temperature pain testing. For comparison, 10 different volunteers also were studied with an intravenous infusion of alfentanil with measurement of venous plasma concentration and similar pharmacodynamics.

The authors found that clonidine decreased the reported pain in the lower extremity but not in the upper extremity, suggesting a spinal site of action for the drug. Using an effect compartment model, cerebrospinal fluid concentrations were related to the degree of analgesia, the predicted minimally effective clonidine effect site concentrations for analgesia was approximately 76 ng/ml. Clonidine increased the relative finger and toe blood flow, decreased blood pressure and heart rate, produced sedation, and mildly increased arterial P_{CO_2}. In the volunteers receiving alfentanil, pharmacodynamic effects were similar, except that more profound respiratory depression was seen. This study demonstrates the relevance and importance of high-resolution, sophisticated, and invasive studies in human volunteers. The quantity or quality of information obtained in this study most likely could not have been obtained in a similar number of patients. This study clearly demonstrated that clonidine produces regional analgesia by a local, spinal action and a generalized inhibition of sympathetic nervous system activity and reflexes.

Focal Cerebral Ischemia in Rats: Effect of Hypervolemic Hemodilution with Diaspirin Cross-linked Hemoglobin *Versus* Albumin on Brain Injury and Edema

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WHILE there are numerous medically sound reasons for reducing patient exposure to homologous blood, including immune suppression, transfusion reactions, and hepatitis transmission, fear of transmission of the human immunodeficiency virus has prompted the greatest changes in transfusion practices and the greatest investment in the development of substitutes for blood. Acellular hemoglobin solutions have been under investigation for nearly 100 yr, with a few promising but limited clinical studies. In 1991, in response to the burgeoning research (stimulated in part by the acquired immunodeficiency syndrome epidemic), the Food and Drug Administration's Center for Biologics Evaluation and Research published "Points to Consider in the Safety Evaluation of Hemoglobin-based Oxygen Carriers"[1] to help guide the development of these new biologics. Today, three such products are in clinical trials and others soon will be.

Early clinical trials included reports of toxicity, especially renal toxicity, which is now thought to have been caused by dissociated hemoglobin dimers and contaminants. Most of the current generation of candidate hemoglobin derivatives are cross-linked or polymerized to limit renal excretion, and far more sophisticated purification procedures are in place to prevent or remove contaminants. Cross-linking the dimers together not only prevents their dissociation but can mimic the erythrocyte's 2,3-DPG, right-shifting the ox-

ygen dissociation curve of hemoglobin to enhance oxygen delivery. In addition to natural human hemoglobin, transgenic human hemoglobin (from pigs), mutant human hemoglobin (from *Escherichia coli*), and bovine hemoglobin are among the source materials under investigation.

It is likely that these hemoglobin solutions will not be limited to the usual blood transfusion indications, and the term "blood substitute" may prove to be something of a misnomer. Because the cellular blood type antigens are removed, the hemoglobin solutions may be delivered in emergencies, without the delay for typing and cross-matching inherent to blood transfusion. Thus, potentially, the blood substitutes could be given in the pre-hospital setting, substituting instead for saline, and restoring blood pressure while reducing the fluid overload. Such efficacy has been shown in animal studies[2] using diaspirin cross-linked hemoglobin (DCLHb),[3] the hemoglobin solution used in the focal cerebral ischemia study by Cole *et al.* (page 335). DCLHb is currently in clinical trials for use in trauma resuscitation.

In the Cole *et al.* study, DCLHb decreased focal cerebral ischemic injury and edema in a carefully controlled rat model of intraoperative stroke. Previously, Cole has shown that DCLHb increases cerebral blood flow in this same model.[4] Improved perfusion of other tissues has been observed in different animal models as well,[5] and may be at least partially the result of decreased viscosity and partially due to the binding of nitric oxide by hemoglobin. In addition, because of the relative sizes of hemoglobin and erythrocytes, with some 260 million hemoglobin molecules per erythrocyte, the acellular hemoglobin solution may be able to bypass blockages that prevent erythrocytes passage. Thus, such nonindications for blood transfusions as the treatment of stroke, myocardial infarction, and sickle cell crisis are under investigation as potential applications for these revolutionary new fluids. Another indication may be coronary balloon angioplasty, in which the hemoglobin solution, because of its small size and low viscosity, can be pumped through the narrow lumen of the angioplasty catheter to oxygenate the tissues at risk downstream of the inflated balloon. A potential role in the treatment of septic shock also has been hypothesized.

In summary, the hemoglobin-based oxygen carriers may present opportunities for new therapeutic approaches to a number of difficult-to-treat disease conditions, in addition to reducing patient exposure to homologous blood. With several candidate solutions already progressing through clinical trials, the prediction of availability by 1996 is not unreasonable.

References

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