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A Century of Arginine Vasopressin Research Leading to New Therapeutic Strategies

DRS. Oliver and Schäfer[1] reported more than 100 yr ago that extracts of the pituitary gland had potent vasopressor effects, and this action was restricted to extracts from the posterior pituitary lobe.[2] Having been known only as *vasopressin* for the first 20 yr after its detection, its strong antidiuretic effects and beneficial actions in diabetes insipidus resulted in the renaming of vasopressin as *antidiuretic hormone*.[3] In 1951, the specific peptide fraction of posterior pituitary preparations attributed to the antidiuretic action was isolated.[4] The first complete synthetic preparation of the hormone by Vincent du Vigneaud *et al.*[5] was accomplished in 1954. These researchers received the Nobel Prize for their work 1 yr later. Until approximately 15 yr ago, vasopressin was used to treat polyuria in patients with diabetes insipidus[6] and to reduce blood loss in patients with gastrointestinal bleeding.[7] There was interest in vasopressin as a pro-peristaltic drug during the 1970s and 1980s,[8] but this soon diminished because of the drug's unpredictable effects.[9] The beneficial effects of vasopressin in shock patients was originally described in 1957 as a brief report,[10] but it was only in the 1990s that vasopressin was used clinically for the potent vasopressor effects it was originally described for almost 100 yr ago.

Stimulated by reports in patients with cardiac arrest[11] and vasodilatory septic shock,[12] the clinical use of arginine vasopressin (AVP) and its analogs as vasopressor drugs has increased substantially during the past 15 yr. In this issue of ANESTHESIOLOGY, Drs. Treschan and Peters give a comprehensive overview of clinical strategies for which AVP has already been successfully applied.[13] AVP has also been used as a supplementary vasopressor in patients with cardiogenic shock,[14] cardiocirculatory failure after successful cardiopulmonary resuscitation (Viktoria Mayr, M.D., Resident, Department of Anesthesiology and Critical Care Medicine, Innsbruck Medical University, Innsbruck, Austria, verbal personal communication, May 26, 2006), drug intoxication,[15,16] and during surgery of carcinoid tumors.[17] Because an anesthesiologist may face any of these pathophysiologic states, it is of paramount importance to be familiar with the physiologic and pharmacologic characteristics of AVP and its analogs.

Despite numerous reports and small studies describing the successful and potentially lifesaving effects of AVP in cardiovascular shock states seemingly incompatible with survival, the concept of AVP as a "magic bullet" must be avoided, and AVP should be used only at recommended dosages for indications that have been defined through clinical investigations. Before introducing AVP into standard treatment protocols, the results of major clinical outcome studies must be awaited. However, the difficulties of proving significant survival benefits of a rescue therapy in multicenter trials is readily apparent. Furthermore, for some indications, *e.g.*, anaphylactic shock or drug intoxications, it is unlikely that large clinical studies can ever be performed. It should also be remembered that it is unlikely that a drug used in diseases where the disturbance of homeostasis is as complex as in cardiac arrest, severe shock states, or multiple organ dysfunction syndrome will be free of side effects. The first overview of significant side effects of a supplementary AVP infu-

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sion in patients with advanced vasodilatory shock has recently been presented,[18] but results of major studies are needed to assess the risk-to-benefit ratio of AVP in critically ill patients.

Currently, three multicenter trials evaluating the effects of AVP in cardiac arrest, septic shock, and uncontrolled hemorrhagic shock are being performed. The Vasopressin and Septic Shock Trial, a multicenter, triple-blind, randomized controlled study in intensive care units across Canada and Australia, examines the effectiveness of AVP (0.03 U/min) as a supplementary vasopressor on 28-day and 90-day survival in patients with septic shock. Finalization of patient randomization is expected soon, but initial promising results of the interim analysis have been reported. The hypothesis being tested is that compared with norepinephrine treatment alone, supplementary infusion of low-dose AVP (0.03 U/min) would increase 28-day survival from 40% to 50%. In France, an investigation studying the combination of AVP and epinephrine *versus* epinephrine alone during prehospital cardiopulmonary resuscitation is under way; 2000 patients have already been enrolled, and first results are expected in late 2006. In summer 2006, our study group will initiate a multicenter trial in Europe to analyze the effects of AVP in prehospital trauma patients with uncontrolled hemorrhagic shock who do not respond to standard treatment.[19]

Since its discovery more than 100 yr ago, AVP is increasingly acknowledged as a valuable adjunct vasopressor in catecholamine-resistant shock states. AVP is an excellent example of how an orphan drug can be developed to improve the treatment of our patients.

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