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SEX, DRUGS AND R&R (RESUSCITATION & REANIMATION)

The rapidly evolving field of resuscitative endocrinology

What if someday, in the not too distant future, your prehospital care protocols—for cardiac arrest, post-traumatic shock, severe head injury, myocardial infarction, stroke, massive burns and a myriad of other critical illnesses and injuries—all directed you to immediately infuse the patient with an IV dose of the female sex hormone estrogen as routine prophylaxis, and that such doses should be administered as soon as possible after the onset of the critical illness or injury?

That day may not be so far away. During the past decade, a small but rapidly growing cadre of scientists has begun to demonstrate the powerful influences that sex hormones may have in resuscitation medicine. The authors, who have helped pioneer and bring this innovative concept into the clinical arena, have even coined a new term for this evolving field of scientific investigation—"resuscitative endocrinology."

This article will discuss the original hypothesis-generating clinical observations and the basic laboratory evidence supporting the role of sex hormones in resuscitation. In addition, current and upcoming clinical studies will be cited, along with predictions for the use of these promising new therapeutic interventions.

CLINICAL OBSERVATIONS REGARDING SEX-RELATED DIFFERENCES

Sex and cardiac arrest: Nearly 10 years ago, on May 22, 2000, a scientific presentation was delivered at the annual meeting of the Society for Academic Emergency Medicine in San Francisco. The 10-minute oral report was barely noticed by mainstream emergency medicine attendees, but for those at the small breakout session, the results were eye-opening. Contrary to popular wisdom at the time, the study found that *women* had much better outcomes than men in a multi-year, population-based study of out-of-hospital cardiopulmonary arrests involving nearly 5,000 subjects.¹

Although there may have been numerous explanations for these findings, including disparities in chest wall compliance and variations in pharmacobiology, the influence of sex hormones seemed less likely, at least at first, because the average age of the women was about 69 years of age.² However, a continuation of that same study, involving nearly 10,000 subjects, and a corresponding in-hospital study, involving nearly 20,000 in-patients, both demonstrated very striking and distinct survival advantages for the cohort of women of child-bearing age.^{2,3} In fact, in the cases generally reflecting more of a global ischemic insult, such as those presenting with asystole or pulseless electrical activity, essentially all of the survival advantages that women had over men could be attributed to the sub-group of women of child-bearing ages.

Overall, compared with men of a similar age and with older women and men, women of child-bearing age generally have high levels of circulating sex hormones. Although the presumptive role of sex hormones is clearly inferential (hormone levels weren't actually measured), the *profound* differences in both studies have been very compelling.^{2,3} Moreover, as described later in this article, the results have been corroborated by equally compelling laboratory data in which estrogen infused into male animals led to dramatically improved outcomes.⁴⁻¹⁸

Sex and trauma: As in the case of cardiopulmonary arrest, in the realm of trauma, *remarkably high* estradiol (estrogen) levels have now been measured in the cerebrospinal fluid of men who had good outcomes following severe traumatic brain injury (TBI) when compared with normal people and those TBI patients with poor outcomes.¹⁹ How this happens is not understood, but it appears to indicate that the brain seems to know how to protect itself by

secreting or sequestering high levels of estrogen to improve outcomes.

Estrogen appears to have a strong influence in severe physical and physiological insults, and so does progesterone. A clinical trial of progesterone for TBI demonstrated more than a twofold decrease in 30-day mortality, confirming both the safety and efficacy of that sex hormone as well.²⁰

THE SUPPORT OF RESEARCH & EXPERIENCE

A wealth of experimental literature now has demonstrated the effectiveness of therapeutic sex hormone infusions to dramatically improve outcomes in a variety of conditions, ranging from severe TBI, massive hemorrhage, burns and spinal-cord injury to stroke, cardiac ischemia and a host of other critical illnesses and injuries.³⁻¹⁸

The proposed mechanisms of action are numerous, but two key principles should be emphasized: First, the effects of sex hormones are not specific to either cell type or insult. Although perhaps an over-simplification, estrogen, for the most part, works within the mitochondria of every cell in the body, helping to up-regulate (or enhance the action of) cells that might have otherwise become apoptotic (self-destructive) or irreversibly damaged by oxidant-type injury.

Second, given intravenously, the first-pass effect in the liver (believed to be responsible for the pro-thrombotic effects observed with traditional oral administration of estrogen) is bypassed. In essence, a single dose of IV estrogen should not be confused with orally administered hormone replacement therapy (HRT).

As a poignant example of the laboratory studies, in experimental models of severe torso burns, severe and remote inflammatory effects in the brain were noted to be almost entirely blocked by early estrogen administration. Serum levels of the cytokine IL-6 correlate with poor outcomes in burns. But infusions of estrogen inhibit the propagation of this inflammatory marker.²¹

In addition to the experimental literature, estrogen and progesterone have been shown to be relatively safe to use in the general population. Over many decades, in many thousands of patients, IV estrogen has been used extensively without untoward effects in a host of clinical scenarios, including dysfunctional uterine bleeding, uremic hemorrhage, advanced prostate cancer and post-operative bleeding after scoliosis surgery. Further, it's extremely inexpensive, especially when compared with the typical cost of an intensive care unit (ICU) day. Compared with many other pharmacological therapies, estrogen and progesterone are very inexpensive, thus making them exceptional candidates for widespread application (and even liberal routine administration).

THE FUTURE OF SEX HORMONES

During the past year, clinical trials have been implemented in Dallas that are examining the use of IV estrogen (0.5 mg/kg) in people with severe head injury, including those with and without accompanying hemodynamic compromise. Although the results of these ongoing studies are not yet available, the initial experience has, to date, demonstrated safety of the single-dose administration of IV estrogen.

As a result, the National Institutes of Health Resuscitation Outcomes Consortium (ROC) steering committee is now considering the implementation of a multi-center clinical trial of estrogen for both severe head injury and for patients with severe hemodynamic compromise (presumptively, severe hemorrhage). In essence, the concept of resuscitative endocrinology has become mainstream, and the use of estrogen has achieved a certain degree of priority in resuscitation research circles.

Although the current plans for sex-hormone research revolve around trauma scenarios, similar studies will likely be implemented for cardiac arrest, stroke, burns and myocardial infarction. Moreover, the studies, and eventual clinical use, will most likely take place in the prehospital setting, considering that many of the experimental studies have demonstrated that the earlier the intervention is provided, the better the results.

In summary, a growing body of evidence supports the strong influence of sex hormones, particularly estrogen, in cases of resuscitation. Such sex hormones are not only considered to be protective, but also as an active intervention in reanimation and improved outcomes. If the efficacy of sex hormones is definitively proven, they'll likely be used in the prehospital setting and as early as possible after the onset of a critical illness or injury.

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Future studies and clinical use of resuscitative endocrinology will most likely take place in the prehospital setting. The earlier the intervention is provided, the better the results.