Stress Free: To Be or Not to Be?

This issue of the journal includes two reports that document that etomidate attenuates the usual adrenocortical stress response to surgery. Wagner and White report that etomidate, but not thiopental, completely prevents the adrenocortical response to ACTH stimulation one hour after even a single injection of etomidate for anesthetic induction.1 Fragen and co-workers report that anesthetic induction with etomidate, as compared with thiopental, prevents the increases in cortisol and aldosterone that occur postoperatively.2 One must understand the background and history of etomidate in order to appreciate the significance of these results.

Etomidate, a nonbarbiturate imidazole compound, was introduced into European clinical practice in 1972. Careful studies in a small number of patients confirmed the clinical impression that this drug was associated with remarkable cardiovascular stability.3 The intravenous infusion of etomidate produced only a 9% increase in heart rate, a 14% increase in cardiac index, and a 12% decrease in systemic vascular resistance. LVEDP, dp/dtmax and mean arterial pressure were unchanged from the awake state. The absence of deleterious circulatory effects was even more apparent in the coronary circulation. Etomidate increased coronary blood flow by 19% because of an equivalent decrease in coronary vascular resistance, while myocardial oxygen consumption was unchanged from the awake state. The result was a decrease in oxygen extraction (−11%) by the heart and an increase (+21%) in oxygen saturation in the coronary vein. The combination of minimal systemic hemodynamic effects plus apparent salutary effects on coronary hemodynamics contributed to the popularity of etomidate as an induction agent for extremely ill patients and for those with ischemic heart disease. There were disadvantages of the drug also, but these appeared to be acceptable when compared with its virtues. Pain at the intravenous injection site, hiccupping, cough, tremor, increased muscle tone, and rather marked involuntary muscle movements were inconveniences, but the overall advantages appeared to outweigh the disadvantages at least for some patients. However, a more serious concern about the safety of etomidate was voiced in 1985.

Ledingham and Watt, in a letter to Lancet, reported that the mortality of multiple trauma patients requiring mechanical ventilation was increased when etomidate was used for prolonged sedation.4 In a subsequent letter, Ledingham and colleagues reported their suspicion that etomidate was associated with depressed adrenocortical function.5 Their hypothesis was based on the observation that serum cortisol was decreased in critically ill patients who received etomidate as compared with others who were sedated with narcotics and/or benzodiazepines. However, all of these results were clouded by the heterogeneity of the patient populations, the use of historic controls, the absence of randomization of drug treatments ( Were the more critically ill patients sedated with etomidate precisely because of its cardiovascular stability?) and by the open (nonblinded) nature of these observations. The presentation of these results in letters, rather than in rigorously peer reviewed publications, emphasized the preliminary nature of the observation.

The investigations reported here were randomized prospective trials of etomidate versus thiopental for induction and/or supplementation of anesthesia during short operations in healthy women. The results indicate that etomidate produced a generalized depression of adrenocortical function as evidenced by decreased plasma concentration of cortisol and aldosterone in the early postoperative period9 and by the failure of ACTH to increase the concentrations of either cortisol or aldosterone1 after even a single induction dose of etomidate.

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We are left with a dilemma. Should we champion etomidate as a valuable drug to produce "stress-free anesthesia" (a popular term in current anesthetic parlance), or should we abandon its use because it depresses adrenocortical function? As is often the case, an absolute answer rarely is provided by single investigations. More commonly, the answer becomes evident as the amount of scientific evidence increases. The results reported here should be confirmed (or verified) by other human or animal studies in order to verify their validity. Other questions should be answered as well. Do these changes occur in men as well as women? Is there evidence of electrolyte abnormalities (hyponatremia, hypochloremia, and hyperkalemia), decreased renal function, or altered intermediary metabolism to substantiate the presence of functional adrenocortical insufficiency, as opposed to simple changes in the plasma values of circulating hormones? Are there further data to suggest a causal relationship between prolonged etomidate sedation and increased mortality in the previously described critically ill patients? All of these questions require answers before we can arrive at an answer that will be acceptable to an unbiased and rigorously skeptical scientist. However, the existing evidence is strong enough to influence my practice pattern and my approach to anesthetic induction.

It is well established that adrenalectomy or adrenal insufficiency results in decreased tolerance to environmental stresses such as cold, heat, infection, trauma, or exercise. As Hans Selye described so elegantly,6 stress is associated with increases in ACTH, corticotropin-releasing factor, and cortisol, and, by some still poorly understood mechanism, these are protective responses that are essential to life. That the perioperative period is a time of considerable emotional stress and increased adrenocortical activity is well established.7 Indeed, in my own laboratory I have observed that adrenalectomized rats were unable to tolerate even a simple barbiturate anesthetic in the absence of operation when their brethren with intact adrenal glands tolerated rather extensive anesthesia and operation without difficulty.

Operations and injuries are not "stress free"; some of our drugs may suppress the response to stress, but they do not eliminate the stress itself. While some have touted the virtues of anesthetics that blunt the stress response, it is difficult for this observer to accept the concept that the absence of an adrenocortical response to ACTH stimulation could be considered an advantage for any patient who might undergo operation, no matter how minor the procedure might be. What we as anesthesiologists might view as a minor operation can result in a significant emotional, if not physiologic, stress for the patient. The problems of intraoperative and/or postoperative adrenocortical suppression could be even greater in patients undergoing more extensive operative procedures or those with underlying cardiovascular instability (exactly the situations for which etomidate appeared to be of special value). I shall not use etomidate in my practice until there are convincing data that refute the current concerns about its influences on the adrenal cortex and their possible implications for postoperative morbidity and/or mortality or the mortality associated with prolonged sedation produced by this drug. Simply put, there are too many other ways to induce anesthesia or provide prolonged sedation, even in seriously ill patients or in those with coronary artery disease, to justify the use of this drug in my practice.

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References

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Are Volatile Anesthetics Really Calcium Entry Blockers?

Volatile anesthetics can increase the incidence of ventricular ectopic beats (dysrhythmogenic effect), but they paradoxically can decrease the occurrence of ectopy (antidysrhythmic effect) under certain settings also. Such seemingly contradictory behavior can present a practical problem to anesthesiologists confronted with patients with coronary artery disease. When will administration of these drugs be of potential harm or benefit to patients in regard to myocardial performance? The article of

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