ETOMIDATE- A REVIEW OF ROBUST EVIDENCE FOR ITS IN VARIOUS CLINICAL SCENARIOS.

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Etomidate is an imidazole derivative that binds the gamma aminobutyric acid A (GABA A) receptor, resulting in depression of the reticular activating system. It was first introduced into clinical practice in Europe in 1972 and was approved for use in the United States in 1983 and gained increasing popularity due to its good hemodynamic, respiratory and central nervous system stability (1). These qualities have justified its use as an induction agent in anesthesia for haemodynamically unstable patients, especially in the setting of rapid sequence induction (2). Meanwhile it has been proven that etomidate causes reversible and dose dependent adrenocortical suppression by inhibits the 11 β-hydoxylase enzyme that converts 11 β-deoxycortisol into cortisol in the adrenal gland.

In 1983, the letter to the editor from Ledingham and Watt was published in The Lancet describing increased mortality in the setting of continuous sedation for trauma patients after the introduction of etomidate (3). This observations have been a protracted scientific and clinical debate about risk benefit ratios for various indications, administrations and clinical scenarios which still continuous to divide the medical community in pro and con factions.

This article will review the current literature on etomidate and its use in selected clinical stuations.

Etomidate : Structural formula and Clinical effects:

Etomidate is first described in 1965, it was originally developed as an imidazole anti-fungal agent (4). Etomidate is an imidazole derivative that (in particular th more clinically active R^+ isomer) binds the gamma aminobutyric acid A($GABA_A$) receptor, resulting in depression of the reticular activating system. Its rapid onset is secondary to its lipid solubility and is largely nonionized at physiologic pH. Also etomidate exerts sypathomimetic activity on alpha-2B adrenergic receptors held accountable for hemodynamic stability during injection and on transient receptor potential type A(TRPA1) cation channels, which are responsible for nociceptive sensations like occasional venous irritations.

Etomidate leaves myocite contractility and cardiac output largely unchanged, causes only modest decrease in arterial blood pressure (within 10% of baseline).

Ventilation is minimally effected with etomidate (The drug induced decrease in tidal volume is compensated by increase in respiratory rate) and cerebral

metabolic rate, cerebral blood flow, intracranial pressure are decreased (direct cerebral vasoconstrictor). These characteristics of etomidate make it an ideal agent for deep sedation and induction of general anesthesia.
Negative properties of etomidate include lack of analgesic properties, provocation of postoperative nausea; reduce seizure thresholds and extrapyramidal disinhibitory effects, which explain myoclonus. In the case of adrenal supressionthe adrenal glands do not produce enough of the steroid hormones; cortisol. Sequele of adrenal insufficiency include low cortisol levels, hypernatremia, hypoglycemia, hyperkalemia, hypercalcemia, altered mental status, hypotension, and metabolic acidosis.
Common iv induction dose of 0.2-0.3 mg/kg and unconsciousness occurs within the circulation time and also awakening is rapid since it is rapidly metabolized by hydrolysis to a pharmacologically inactive compounds.

Adrenocortical insufficiency and mortality:

Ledingham and Watt were first to report the adrenocortical insufficiency and increased mortality in 1983 (3). Subsequent to this prospective controlled studies at volunteers and healthy surgical patients confirmed the adrenocortical suppression eve after single dose administration of etomidate. It needs lower plasma concentrations to achieve adrenal suppression than hypnosis (10ng/ml to 100ng/ml) and that lasts at least 6 h in healthy patients and > 24 h in those who are critically ill. After these reports the manufacturers changed the drug information leaflet to indicate that etomidate should not be used for long-term sedation or repetitive use.
Systematic review that includes the studies about mortality of etomidate demonstrated obvious limitations: heterogeneity, small sample size or only subgroup analysis, variation of the scores or timing of adrenal insufficiency, limited randomization, blinding, discrepancies in follow-up and 28-day mortality. Only CORTICUS trial in a subgroup analysis demonstrated an association with etomidate and increased mortality in septic shock without an effect of hydrocortisone therapy.

Etomidate use in specific clinical situations:

Rapid Sequence induction (RSI):
The goals of RSI are to facilitate intubation quickly, reduce complications, and improve overall success rate. The anesthetic agent choice for RSI must require both rapid onset of action and hemodynamic stability. Post induction hypotension may lead to mortality or prolonged hospital stay. In a cochrane study that included eight studies in the review and seven in the meta-analysis. Of those seven studies, only two were judged to be at low risk of bias. Overall,

no strong evidence exists that etomidate increases mortality in critically ill patients when compared to other bolus dose induction agents (odds ratio (OR) 1.17; 95% confidence interval (CI) 0.86 to 1.60, 6 studies, 772 participants, moderate quality evidence). In a recent study, Upchurch et al. studied 968 patients, including 526 with etomidate and 442 with ketamine. Hospital mortality was 20.4% among patients induced with ketamine compared with 17.3% among those induced with etomidate (adjusted odds ratio [OR] 1.41; 95% confidence interval [CI] 0.92 to 2.16.
Clinical data attest the to haemodynamic advantages of etomidate at high-risk patients, where as negative effect on major outcomes has not been due to demonstrated by the prospective studies.

In patients with sepsis:
Current evidence suggest that the choice of etomidate as an induction agent in patients with sepsis or septic shock carries the risk of mortality. And increased 28-day mortality rate was noted in patients who received etomidate in Corticosteroid Therapy of Septic Shock (CORTICUS) trial. However Maleraba et al. and Ray et al. did not observe such an increased risk of death following a single dose of etomidate in critically ill patients. Thus the strength of any association between etomidate and adverse outcome can imply, but not prove, causation. Nevertheless following the principle of primum nil nocere we can use alternative induction hypnotics in septic patients.

Anesthesia Induction of patients at cardiovascular risk
Etomidate is often considered as a two-edged sword and its use for induction of anesthesia is controversial. On the one hand etomidate is used for its hemodynamic stability after anesthesia induction and also allows good intubation conditions, especially in more severely ill patients, and on the other it has negative effects on steroid synthesis. Heinrich et al. reported that etomidate has similar outcomes to other drugs in a specific population of 3,054 patients ahead of major cardiac surgery(10). Kaushal et al. reported that Etomidate provides stable hemodynamic parameters and therefore can be use safely for induction in patients with good LV function for CABG/MVR/AVR on CPB without serious cortisol suppression lasting more than 24 hours (11).

Procedural Sedation
Procedural sedation and analgesia (PSA) is defined as the technique of administering sedatives or dissociative agents with or without analgesics to induce an altered state of consciousness that allows the patient to tolarete painful or unpleasant procedures while preserving cardiorespiratory function. American Collage of Emergency Medicine (ACEP) recommends propofol, etomidate, ketofol, ketamine, and alfentanil for PSA of adults. Etomidate is usually combined with fentanyl since it does not have any analgesic effect. In

a recent study by Sanri et al. it is found that etomidate and fentanyl combination had lower respiratory adverse events with better hemodynamic profile (12).

Conclusion:

The etomidate debate is currently in clinical equipoise in which there is genuine uncertainty within the expert medical community. Practitioners should continue to use the induction agents, which they consider is most suitable for the individual patient in the particular circumstances or environments. The story of etomidate is to be continued.

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