How does this new antibody (LT-a-specific mAb) then improve upon the previous biomolecules developed to block these immune pathways? First, it targets a molecule that is selectively expressed on activated T cells, and hence should selectively kill only the pathogenic T cells. Thus, it is unlikely to cause generalized immunosuppression and is expected to be associated with lower toxicity. Second, it does not interfere with the development of germinal centres; thus, it should preserve the development of affinity maturation and class switching of antibodies in response to infection.

However, we must exercise caution in reading too much into these results. Humans can behave differently from mice and have very different and unexpected results, as occurred with anti-CD28 antibody (TGN1412).[11]

Overall, the new anti-LT-a antibody that inhibits the lymphotoxin pathway appears to be a promising addition to the rapidly growing range of biological compounds that are being developed to control T cell-mediated autoimmune diseases such as insulin-dependent diabetes mellitus, multiple sclerosis and rheumatoid arthritis.

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Acutely ill patients: Rapid sequence intubation with etomidate or ketamine

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SUMMARY

This prospective, randomized, multicentre, controlled, single-blind trial was aimed at comparing early and 28-day morbidity after a single dose of etomidate or ketamine for emergency endotracheal intubation in critically ill adult patients. Over a period of 10 months, 655 patients requiring sedation for emergency tracheal intubation were randomized to receive an intravenous bolus of etomidate (0.3 mg/kg) or ketamine (2 mg/kg). Succinlycholine (1 mg/kg) was administered after the sedative to facilitate tracheal intubation. After confirmation of optimal placement of the endotracheal tube, sedation was provided by midazolam and fentanyl/sufentanil infusions. Those patients who were discharged alive from the intensive care unit (ICU) within 3 days or died before reaching the hospital were excluded from the study so that the outcome of those with the most severe illness was studied. Laboratory variables (haematological and biochemistry), arterial blood gases, results of short adrenocorticotropin hormone test when recommended by the physician, incidence of serious adverse events, intubation difficulty scores and any major interventions done were noted. The primary end-point was the maximum score of the sequential organ failure assessment (SOFA) during the first 3 days of stay in the ICU. The secondary end-points were maximum SOFA score during the stay minus the admission SOFA score, duration of weaning from ventilator, organ support-free days (mechanical ventilation and vasopressors), 28 days all-cause mortality and length of stay in the ICU during the 28-day follow up period.

The results of 469 patients (234 in the etomidate and 235 in the ketamine group) were analysed. Adrenal function was assessed in

232 patients only. The baseline characteristics (demographics, simplified acute physiological score II and SOFA score) did not differ significantly between the 2 groups. The main reasons for intubation in the 2 groups were: coma (69% in both), shock (13% and 26%) and acute respiratory failure (16% and 17%). No statistical difference was noted between the 2 groups regarding the primary end-point (the mean [SD] maximum SOFA score was 10.3 [3.9] for the etomidate *v.* 9.6 [3.9] for the ketamine group). All secondary end-points (mean intubation difficulty score 1 [IQR 0–3] in both the groups), blood pressure and oxygen saturation changes before and after intubation and incidence of cardiac arrest (3% for etomidate *v.* 2% for ketamine) in the 2 groups were similar. However, the percentage of patients with adrenal insufficiency was significantly higher in the etomidate than the ketamine group (OR 6.73.5–12.7). No significant difference in mortality was noted between the 2 groups. Ketamine was found to be a safe and valuable alternative to etomidate for intubation in critically ill patients.

COMMENT

The choice of an ideal induction agent for facilitating intubation in critically ill patients has been an unresolved issue primarily because most such agents (propofol, thiopentone, midazolam and opioids) except ketamine and etomidate lead to hypotension which could be detrimental in critically ill patients. Hypotension during an acute illness, even when transient, increases mortality by 2- to 3-fold.[1–3] The present study concludes that ketamine is a suitable alternative for sedation before intubation in an ICU but does not resolve the controversial issue of an ideal agent for patients with sepsis. Patients with sepsis may be especially prone to post-intubation hypotension, with about 60% requiring vasoactive support afterwards.[3] Etomidate is a hypnotic drug that has a 6-fold better therapeutic index than thiopental or propofol. About 2 decades ago, it was not only the agent of choice for induction of anaesthesia in haemodynamically unstable patients but was popular for sedation in the ICU setting. Etomidate became unpopular due to its association with increased mortality attributed to the profound suppression of adrenal steroidogenesis primarily through its potent inhibition of the enzyme 11b-hydroxylase.[4–6] Adrenal insufficiency is probably associated with increased mortality in critically ill patients especially those with sepsis. In the present study, the final diagnosis of the patients was trauma (104, total in both groups), sepsis (76) and the majority (289) had other diseases. The debate regarding etomidate has revolved around the subgroup of patients with sepsis which in the present study were a very small number. The authors acknowledge that their study is underpowered to infer on the association of etomidate-related mortality in patients with sepsis. The effect of even a single dose of etomidate in patients with sepsis has been at the centre of the controversy.[7–10] Further, etomidate has been found to have inhibitory effects on the bacterial killing capacity of leucocytes which again could affect the outcome in critically ill patients.[11]

Ketamine, as an alternative to etomidate, is an excellent agent with side-effects such as psychodyslepsia, tachycardia and rise in blood pressure, which are of less concern in patients with sepsis requiring intubation. The reason ketamine is not popular is its non-availability in many emergency departments and ICUs, and due to the lack of studies exploring its possible effects in sepsis and on ICU-associated delirium. While future studies might find ketamine to be a reasonable alternative to etomidate for intubation of hypotensive patients with sepsis, currently there is no evidence to support this contention. However, if the clinical option is between ketamine and an agent known to worsen existing hypotension or suppress the adrenal gland, ketamine would be a reasonable choice. A combination of midazolam–fentanyl is useful for sedation before muscle relaxation in such patients. In India, etomidate has been recently marketed for use as an induction agent. Adrenal suppression leading to hypotension due to tuberculosis—occult or otherwise manifesting among patients in the perioperative period or critical care—is not uncommon in India. Therefore, etomidate (single bolus or infusion) in a critical care set up in countries where the incidence of tuberculosis is high should be used with caution and ketamine would be a better option in the ICU setting.

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