Critical Review Form
Therapy

Rapid sequence induction in the emergency department: induction drug and outcome of patients admitted to the intensive care unit department: induction drug and outcome of patients admitted to the intensive care unit, *EMJ* 2009;

Objective: **"To assess the possible association between etomidate and adverse outcomes in ED patients undergoing rapid sequence intubation prior to ICU admission". (p. 576)**

Methods: **Investigators conducted a single center retrospective review (with no clear methods – see Gilbert and Worster) of all patients who had RSI in the ED between January 2004 and December 2006 via a prospectively maintained emergency airway registry. Important chart review methods not reported included:**

- **Who maintains and QA's the registry?**
- **What is the purpose of the registry? Are there any confounding influences upon the registry or its keepers (drug company sponsorship)? Has the registry been previously validated for research purposes?**
- **How are chart data abstractors trained and quality assessed?**
- **Are data abstractors blinded to the study hypothesis?**
- **Were standardized data abstraction forms used?**

The following variables were ascertained from the airway registry: patient age and gender presenting diagnosis, APACHE II score and corresponding predicted mortality, induction drug in the ED, post-induction hypotension and hypotension management in these circumstances. The investigators conducted a univariate analysis for each of these variables and then a backward stepwise binary logistic regression analysis to identify independent predictors of hospital mortality.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	No, this was a pre-existing airway registry generated observational cohort.

2.	Was randomization concealed (blinded)?	No, there was no randomization.
3.	Were patients analyzed in the groups to which they were randomized?	Subjects not randomized so no cross-over and all groups were analyzed within their respective treatment arms.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	**No.** Patients who received etomidate (vs. thiopental or propofol, N = 184, 306, 35 respectively) were older (mean age 50 vs. 45 vs. 43, p = 0.008) with higher median APACHE II scores (17 vs. 14 vs. 16, p = 0.002) with higher in-hospital mortality (22% vs. 14% vs. 9%, p = 0.02). Additionally, "etomidate was used more frequently (37%) than thiopental (15%) or propofol (29%) in patients with acute cardiac problems, sepsis, or multiple trauma, and less frequently in patients with seizures or drug overdose (etomidate 28%, thiopental 48%, propofol 54%)". (p. 578) Of rate, the seizure and drug overdose populations had significantly lower mortality rates (3/59 = 51% and 3/152 =20%, respectively). See Table 2 (p. 577)
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes – not randomized or blinded.
2.	Were clinicians aware of group allocation?	Yes – not randomized or blinded.
3.	Were outcome assessors aware of group allocation?	Yes – not randomized or blinded.
4.	Was follow-up complete?	No loss to follow-up reported, but important details of the airway registry and chart review methods are lacking (see above).

II.	What are the results (answer the questions posed below)?	

1.	How large was the treatment effect?	• 575 patients had RSI but only 525 admitted to the ICU.
		• The sampling was male predominant and non-survivors were older with higher APACHE-II scores (Table 1, p. 577).
		• 30% of subjects were drug overdoses, 12% were seizures and 9% had sepsis.
		• The majority of patients had thiopental for RSI induction agent (306 vs. 184 etomidate and 35 propofol).
		• Univariate analysis identified four variables associated with increased mortality: age, APACHE-II score, cerebral hemorrhage and etomidate use (OR 1.89, 95% CI 1.18 - 3.02, p = 0.008).
		• Logistic regression modeling (Table 4, p. 578) did <u>not</u> identify etomidate use as an independent predictor of mortality (OR and p-value not reported), but did identify the following four independent predictors of mortality:
		  ○ Age (OR 1.04, 1.02 – 1.06, p < 0.001)
		  ○ APACHE-II score (OR 1.11, 1.06 – 1.16, p < 0.001)
		  ○ Head trauma (OR 6.54, 1.88 – 22.77, p not reported)
		  ○ Cerebral hemorrhage (OR 12.97, 4.36-38.59, p not reported)
		• Post RSI hypotension was more likely with propofol (OR 2.62, 1.06 – 6.42) then etomidate (0.85, 0.51 – 1.39) or thiopental (0.81, 0.41 - 1.58).

2.	How precise was the estimate of the treatment effect?	Wide CI's for individual variables of logistic regression model reflecting the relatively small sample size for each variable subset.

III.	How can I apply the results to patient care (answer the questions posed below)?	
1.	Were the study patients similar to my patient?	Yes, critically ill adult ED patients at an urban teaching hospital with annual volume of 105,000 and RSI responsibility shared between EM and Anesthesiology physicians. Less clear is the subsequent management of patient's post-intubation (proportion with cerebral hemorrhage who go to surgery, septic patients receiving EGDT, etc.)
2.	Were all clinically important outcomes considered?	Mortality is the most important patient-oriented outcome. The investigators could have reported subset mortality rates for admission diagnosis stratified by induction agent. Furthermore, multiple confounding variables could impact observed mortality. For example, in septic patients the time-to-antibiotics, antimicrobial spectrum appropriateness, and administration of EGDT could all influence mortality and ought to be assessed – particularly in an observational trial subject to many biases that do not plague a well-conducted RCT.
3.	Are the likely treatment benefits worth the potential harm and costs?	"We have found no evidence in this study that etomidate causes worse outcomes than thiopental or propofol" (p. 578). Therefore, "emergency physicians should choose an induction drug based on their own experience of induction drugs and individual patient circumstances, rather than being concerned solely about adrenal suppression". (p. 579)

Limitations

1) **Retrospective review with no stated or referenced methods (Gilbert and Worster) using a non-validated airway register from a single center.**
2) **Dose of induction agent was not recorded.**
3) **Exclusion of emergency surgical patients so these results cannot be extrapolated to them.**

4) **No subset analysis of individual diagnoses, particularly sepsis patients who are supposedly the population most prone to etomidate-related mortality risk.**
5) **No assessment for co-intervention bias (antibiotic timing and choice, EGDT, etc).**
6) **The authors minimize the potential retrospective methodological flaws of their manuscript, while concluding that an RCT "study may be difficult to undertake" without bothering to check for ongoing clinical trials to which they might have referred readers. Such a trial is underway led by the investigators of the PGY-I paper. (Clinical Trials.gov Identifier NCT 00441792).**
7) **No post-hoc assessment of power/sample size or chance of Type II error based upon the available sample size.**
8) **No sensitivity analysis was conducted to assess model stability.**

Bottom Line

Single-center airway registry analysis for 36-months of ED RSI in a critically ill population (median APACHE-II score 18.5 to 20) with a variety of acute disease processes (drug OD, seizure, sepsis, multiple trauma, head trauma, cerebral hemorrhage) that fails to demonstrate etomidate RSI as an independent predictor of mortality. However, a more definitive RCT focused upon septic patients with confounding variable assessment (EGDT, timing of appropriate antibiotics) is needed to definitively answer this question and move beyond the uncertainties of this observational data.