Etomidate for Rapid-sequence Intubation in Young Children: Hemodynamic Effects and Adverse Events

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Abstract

Objectives: Physicians commonly use etomidate for adult rapid-sequence intubation (RSI), but the manufacturer does not recommend its use for children under 10 years of age due to a lack of data. The authors present their experience with etomidate for pediatric RSI in order to further develop its risk–benefit profile in this age group. Methods: Trained abstractors reviewed the medical records for all children under 10 years old who received etomidate for RSI between July 1996 and April 2001. Results: 105 children, with an average age of 3 ($\pm$2.9) years, received a median dose of 0.32 ($\pm$0.12) mg/kg of etomidate. The systolic blood pressure increased an average of 4 mm Hg (95% CI = −3.3 to 9.2); the diastolic blood pressure increased 7 mm Hg (95% CI = −3.1 to 11) within 10 minutes of receiving etomidate. The heart rate increased an average of 10 beats/min (95% CI = 4.0 to 17.4). Complications included three patients who vomited within 10 minutes of etomidate administration. There were no cases of documented myoclonus, status epilepticus, or new-onset seizures. Thirty-eight patients received corticosteroids during the hospital course, none for suspected adrenal insufficiency. Three patients died, all from severe brain injury. Conclusions: In children less than 10 years old, etomidate seems to produce minimal hemodynamic changes, and appears to have a low risk of clinically important adrenal insufficiency, myoclonus, and status epilepticus. The association between etomidate and emesis (observed in less than 3% of enrolled patients) remains unclear. For clinical situations in which minimal blood pressure changes during RSI are critical, etomidate appears to have a favorable risk–benefit profile for children under 10 years old. Key words: pediatrics; intubation; etomidate; anesthetic; adverse effects. ACADEMIC EMERGENCY MEDICINE 2003; 10:134–139.

Etomidate was approved for use in the United States in 1983 as an intravenous hypnotic. Several desirable properties make it an attractive agent for rapid-sequence intubation (RSI). Rapid onset,[1] brevity of action,[2] lack of cardiovascular depression,[3] and protection of intracranial pressure[4] all contribute to its growing popularity among emergency physicians.[5] However, researchers have also associated etomidate with an increased likelihood of myoclonus,[6] adrenal suppression,[7,8] emesis,[9] and possibly seizures.[10]

Etomidate for adult RSI has now become both commonplace and accepted by most emergency physicians.[11] However, few researchers have examined etomidate for RSI in pediatric patients, and indeed, the manufacturer does not recommend its use in children under 10 years old due to insufficient data in this age group.[12]

The current study sought to expand the available information on the safety of etomidate for RSI in patients less than 10 years old. The objectives were threefold: first, to evaluate the frequency of immediate adverse events associated with etomidate use for pediatric RSI, including vomiting, seizures, and myoclonus; second, to further document the hemodynamic effects of etomidate on children under 10 years old; and third, to assess for delayed adverse events, including clinically recognized adrenocortical suppression and persistent or recurrent seizures.

METHODS

Study Design. Data were obtained through a standardized retrospective chart review, with extensive efforts made to abide by previously published strategies for improving the quality of chart review research.[13] The institutional review board declared this study exempt from formal review and waived the requirement for informed consent.

Study Setting and Population. All patients less than 10 years old who presented between July 1996 and April 2001 to the emergency department (ED) of a university tertiary care hospital were eligible for study inclusion. The study hospital has an average of 20,000 pediatric ED visits and 300 pediatric trauma activations per year. The American College of Surgeons has designated this hospital as a Level 1

trauma center. Study participants were identified through pharmacy logs and hospital billing records. Patients were included if they were under 10 years of age and had documented administration of etomidate for RSI while in the ED. No patients meeting the inclusion criteria were excluded. The choice of etomidate for RSI was at the discretion of the attending physician, but represents typical practice for our institution.

Study Protocol. Prior to data collection, abstractors underwent training on "practice" medical records using an explicit standardized data collection form. Abstractors trained until the inter-rater reliability for abstracted variables on practice cases exceeded a kappa coefficient of 0.6. All study variables were explicitly defined. All abstractors met periodically to review and discuss any disputes and to ensure uniform handling of data that was missing, ambiguous, or conflicting. Random duplication of abstracting occurred for 15% of the charts to confirm the reliability of data collection. Abstractors considered an immediate or delayed adverse effect to have occurred if there was specific mention of the event in physician, medical student, nursing, or respiratory therapy notes. A standardized list of expressions and synonyms used to define an adverse event was maintained and updated throughout the study.

Measures. Study variables included age, weight, indication for RSI, dose of etomidate, other medications used during the intubation, vital signs immediately prior to intubation, vital signs within 10 minutes of the administration of etomidate (the drug's effective duration),[14] vomiting within 10 minutes of receiving etomidate, number of attempts needed to intubate, failure to intubate, and documentation of seizures, myoclonus, or other unexpected complications during the patient's ED course. Additionally, the nursing and physician notes for the remainder of the hospitalization were reviewed for recurrent or persistent seizures. We defined clinically significant adrenal insufficiency as that causing either death or requiring the administration of corticosteroids for either confirmed or suspected adrenal insufficiency. The medical records were reviewed to locate all patients who died or received corticosteroids during their admission. Patients who received corticosteroids had the physician, nursing, pharmacy, and respiratory therapy progress notes reviewed for documentation of any mention of a clinical suspicion of adrenal insufficiency and for documentation of a specific alternative indication for corticosteroid administration.

Vital signs included the blood pressures and heart rates closest to and prior to the administration of etomidate; and the highest and lowest heart rates and systolic and diastolic blood pressures (SBPs and DBPs) within 10 minutes of etomidate. The mean changes in vital signs and the frequency of outcome variables were calculated along with the 95% confidence intervals (95% CIs). Pearson product–moment correlation was used to search for a relationship between age and change in blood pressure following etomidate administration.

Data Analysis. Microsoft Excel (Redmond, WA) was used for database management. SAS statistical software (SAS Institute, Inc., Cary, NC) was used for Student's t-test, chi-square, and correlation calculations.

RESULTS

From July 1996 to April 2001, 105 children under 10 years old received etomidate for RSI in the ED. Forty-six percent were female, and the mean age ($\pm$SD) was 3 ($\pm$2.9) years (range = 43 days to 10 years). Figure 1 shows the distribution of patient ages. The indications for intubation included trauma (57%), nontraumatic respiratory distress (20%), nontraumatic altered mental status and/or loss of gag reflex (13%), and other miscellaneous presentations (10%). The median dose of etomidate administered was 0.32 ($\pm$0.12) mg/kg (range = 0.04 mg/kg to 1.0 mg/kg). Adjunctive medications included atropine (74%), lidocaine (59%), morphine (3%), and midazolam (7%). Paralytics included succinylcholine (90%), vecuronium (6%), and rocuronium (4%). Forty-eight percent of the patients had documentation of the number of attempts needed to intubate. Of these, 45% were intubated on the first attempt, 34% on the second, 18% on the third, and 2% on the fourth.

Hemodynamic Changes. Fifty-two of the 105 patients had documentation of blood pressure both pre-
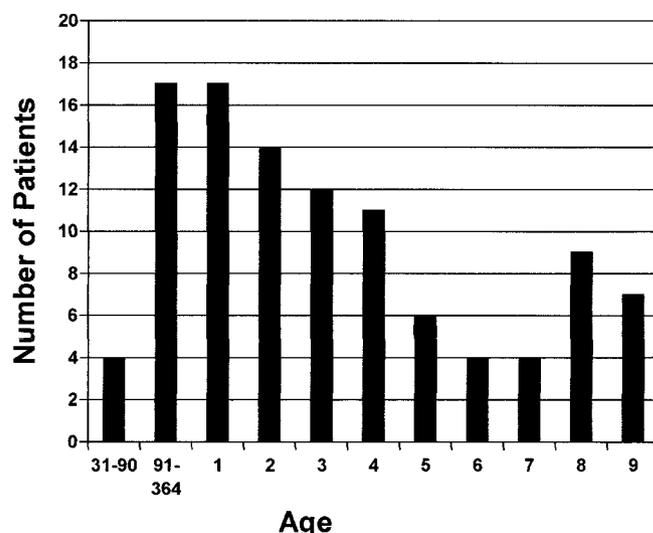

Figure 1. Distribution of patient ages receiving etomidate for rapid-sequence intubation in the emergency department. 31–90 and 91–364 represent days old; all others are in years.

and post-intubation, and within 10 minutes of receiving etomidate. Seventy-five patients had pre- and post-intubation heart rate documented. We compared those children who had complete documentation of vital signs with those who did not, using chi-square and Student's t-test, to determine whether there were systematic differences between these groups. There was no statistical difference (p > 0.05) in age, weight, indication for RSI, dose of etomidate, other medications used during the intubation, vital signs immediately prior to intubation, vomiting within 10 minutes of receiving etomidate, number of attempts needed to intubate, failure to intubate, death, documentation of seizures, myoclonus, or immediate or delayed complications.

Among those patients with complete documentation of vital signs, the mean change in SBP and DBP, when comparing the pre-procedure value with the lowest pressure documented within 10 minutes of etomidate, was an increase of 4 mm Hg (SBP) (95% CI = −3.3 to 9.2 mm Hg) and an increase of 7 mm Hg (DBP) (95% CI = −3.1 to 11 mm Hg). The mean change in heart rate after etomidate administration was an increase of 10 beats/min (95% CI = 4.0 to 17.4 beats/min).

There was no relationship between patient age and the degree of change in SBP (r = 0.22), DBP (r = 0.15), or heart rate (r = 0.09, p > 0.05 for all correlations).

Immediate Adverse Events. Of the 105 intubations, four had immediate adverse events documented (3.8% of the sample, 95% CI = 1.0% to 8.8%), which are described in Table 1. There was no failure to intubate or any documented episode of myoclonus or clinically recognized seizures during the course in the ED.

Delayed Adverse Events. Thirty-eight patients received corticosteroids during their hospital course. Indications for corticosteroids included: wean from a ventilator (reduction of airway swelling) (20), reactive airway disease (8), submandibular swelling due to trauma (1), increased intracranial pressure (4),

upper airway stridor (2), sepsis (1), respiratory syncytial virus (1), and spinal cord injury (1). No patient had documentation of corticosteroid administration or laboratory testing for the clinical suspicion of adrenal insufficiency. Three patients died, all from catastrophic blunt head injury. These patients were believed to have died of their injuries related to the traumatic event, and were not considered to have had complications related to etomidate administration.

Four patients developed seizures after admission, all of whom presented to the ED with seizures and a known seizure disorder. None of these patients developed status epilepticus while in the hospital, and there was no death among these patients.

DISCUSSION

We reviewed 105 cases of etomidate-assisted RSI in children under 10 years of age in an attempt to better define the risks and benefits. We found that, among the 52 patients who had multiple blood pressure measurements within the duration of action of etomidate, there was no significant hemodynamic change. These results parallel those of Sokolove and colleagues, who retrospectively examined 100 patients under the age of 10 and found only a 1-mm Hg drop in blood pressure after etomidate-induced RSI.[15] Researchers have found similar results when they use etomidate for children undergoing general anesthesia for elective procedures,[16,17] and for procedural sedation.[18] Two recent studies reviewed the effects of etomidate for procedural sedation. The first found that one in 38 children needed a fluid bolus for hypotension, although concomitant administration of opiates makes these results difficult to interpret.[19] A second study looked at 51 episodes of procedural sedation in a combination of adults and children and found that the largest drop in blood pressure was in a 6-year-old girl whose SBP dropped from 155 to 107 mm Hg.[20] Thus, the available data suggest that the minimal hemodynamic effects of etomidate, well documented in adults, probably generalize to children under 10 years old.

TABLE 1. Adverse Events Occurring within 10 Minutes of Etomidate Administration

Age	Indication for RSI*	Dose of Etomidate	Concurrent Medications	Adverse Event	Outcome
1 year	Blunt head injury	0.4 mg/kg	Lidocaine, succinylcholine, atropine	Transient desaturation during single successful intubation attempt	Discharged uneventfully
5 years	Blunt head injury	0.24 mg/kg	Lidocaine, succinylcholine, atropine	Vomited after etomidate, prior to intubation	Discharged uneventfully
2 years	Blunt head and chest injury	0.27 mg/kg	Lidocaine, succinylcholine, atropine	Vomited after etomidate, after intubation	Discharged uneventfully
3 years	Blunt head and chest trauma	0.3 mg/kg	Succinylcholine	Vomited after etomidate, after intubation	Discharged with cranial nerve palsy

*RSI = rapid-sequence intubation.

While this suggests that the important advantage of etomidate (the preservation of blood pressure) persists in this age group, the disadvantages are still unclear. The best-documented adverse effect of etomidate involves adrenal suppression,[21–23] which has been shown by laboratory studies to occur following even a single bolus dose (although the clinical implications of this are unclear). Only two studies have examined this issue in young children. Both the current study of 105 children and a similar study of 100 children found no evidence of clinically recognized adrenal suppression in this population.[15] Thus, it appears that the incidence of clinically recognized adrenal suppression in younger children, following a single bolus dose of etomidate for RSI in the ED, is less than 1 in 205 (0.5%, 95% CI = 0% to 1.8%).

Another potential drawback to the use of etomidate involves the potential for immediate complications such as myoclonus, seizures, or emesis. The anesthesia literature contains several reports of myoclonus associated with etomidate.[24–26] Only three reports from the ED setting have examined this issue. The first prospectively studied 48 patients, ten of which were children, who underwent procedural sedation using etomidate. The authors found four cases of myoclonus, one of which they described as "total body stiffness" that lasted about 1 minute.[20] The second study looked at 34 adult patients who received etomidate for RSI, and these authors report one case of myoclonus that did not interfere with intubation.[27] A third review looked at 18 adult ED patients intubated with only etomidate and found a 70% incidence of myoclonus.[28] Our report of 105 pediatric RSIs found no evidence of myoclonus. Concurrent use of rapid-onset paralytics certainly would minimize any myoclonic movements. Practitioners who use paralytics with a slower onset than succinylcholine may encounter myoclonus, but this would likely be clinically insignificant given the pharmacological paralysis of RSI.

While paralytics may counteract the potential difficulties of myoclonus, they may also prevent clinicians from recognizing ongoing seizure activity. Various reports in the anesthesia literature have suggested a potential connection between etomidate and seizures.[29,30] Recently, Laurin et al. compared etomidate with the combination of fentanyl and midazolam for procedural sedation in the ED. They noted that two of the 42 adults who received etomidate had seizures, compared with no patient in the fentanyl/midazolam group.[31] In contrast, an ED study of 51 cases of etomidate-assisted procedural sedation found no seizure (although the one case of "total body stiffness" described above as myoclonus may have actually been a tonic seizure).[20] Dickenson and Singer reviewed the medical records of 38 children who received etomidate in conjunction with

opiates for ED procedural sedation and also found no documentation of seizures.[19] Our study reviewed not only the ED course, but also the remainder of the hospital course, for evidence of status epilepticus or recurrent seizures in children receiving etomidate for RSI. Four children had a recurrent seizure at some point during their hospitalization after receiving etomidate in the ED; all of them presented to the ED with altered mental status secondary to a seizure and a known seizure disorder. No child developed status epilepticus. Although the frequency of documented seizures in this study appears low, the true incidence in patients who are chemically paralyzed could be determined only by concurrent electroencephalography (EEG). However, until further studies determine the degree to which etomidate lowers the seizure threshold (if it does so at all), it would seem prudent to weigh the risks and benefits of etomidate in younger children presenting with a seizure or known seizure disorder. Additionally, in patients intubated with etomidate, physicians should consider intermittently withholding supplemental paralytics, after the initial paralysis of RSI, in order to clinically assess for ongoing seizure activity.

In addition to the reports of myoclonus and seizure activity, researchers have linked etomidate to an increased risk of vomiting.[9,32] One recent double-blind study compared propofol with etomidate for general anesthesia and found that 26.8% of female patients vomited after receiving etomidate, compared with only 10% who received propofol.[33] There have been mixed results among ED studies. For patients undergoing procedural sedation with etomidate, Dickenson and Singer found no vomiting among 38 children,[19] while two other studies report incidences of one in 42[31] and one in 48 sedations.[20] One out-of-hospital study reviewed 44 cases of patients intubated in the field using only etomidate (no paralytics) and found that eight vomited after receiving the medication.[34] Only one small study to date has addressed this issue in patients undergoing RSI in the ED, and the researchers reported no vomiting among 34 intubations.[27] Our investigation found that three of 105 patients vomited within 10 minutes of receiving etomidate, one prior to being intubated. While the concurrent use of paralytics reduces the likelihood of emesis during RSI, paralytics do not completely obviate the issue, particularly in pediatric cases. Any emesis-inducing effect of etomidate that occurs either prior to the onset, or after the effective duration of paralytics, may lead to an increase in clinically significant emesis during intubation. Two common situations may enhance etomidate-induced emesis: preference for slower-onset non-depolarizing paralytics may result in vomiting during the time when etomidate takes effect but paralysis has not yet begun; and multiple intubation attempts (20% of patients in our study) that exceed the duration of paralytic action

result in increased chances of emesis due to oropharyngeal stimulation in a non-paralyzed patient.

LIMITATIONS

Although the study design included significant efforts to comply with published strategies for improving chart review methodology,[13] it suffers from the difficulties inherent in all retrospective studies. Although every effort was made to identify all cases of ED patients receiving etomidate for RSI during our study period, there is the potential for inadvertently omitting cases that were not recorded in the pharmacy logs or billing records. Additionally, the assumption that the lack of any documentation of adverse events equates with the actual absence of these events will always be suspect in retrospective research. Another significant difficulty with observational studies lies in their inability to draw causal relationships. While the appearance of adverse events can provide useful data, their presence does not necessarily imply that etomidate actually caused them. Each of the complications noted in this study may have occurred regardless of the choice of induction agent. Attempts to recognize seizures, without an EEG, in patients who receive paralytics will result in an underestimation of their frequency. Additionally, only 52 of the 105 patients had documentation of both pre- and post-etomidate vital signs. Despite the lack of statistically evident differences between those with complete vital signs and those without, the large number of patients with missing values substantially weakens the conclusions regarding hemodynamic stability. Some patients who did not have vital signs recorded within 10 minutes of etomidate may have had substantial drops in blood pressure that did not result in other complications or death and, therefore, were not detected in our review. Medication effects often vary based on the age of the child, with infants and toddlers reacting differently than older children. While the most frequent age of patients in our study was between 91 days and 2 years, the absolute number of patients in these age ranges is small, making generalization to this population difficult. Finally, the dose of etomidate was not standardized, resulting in a broad range of doses that weakens the strength of our conclusions. Ideally, a prospective randomized blinded study comparing etomidate with other induction agents would solve many of these limitations and yield the most useful information.

CONCLUSIONS

This study describes our ED experience with 105 children under 10 years of age who underwent RSI using etomidate. Etomidate offers a very low risk of clinically recognized adrenal suppression, and a low

risk of seizures. The risk of emesis remains uncertain. For children who had blood pressure documented both before etomidate and within 10 minutes of its administration (52 of 105), there was no significant change noted. Although the manufacturer has not yet recommended etomidate for children in this age range, the available data suggest that for patients who need hemodynamic stability during RSI, etomidate has a favorable risk–benefit profile. For clinical situations that do not require the hemodynamic stability of etomidate, the risk–benefit profile is less clear.

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