Abstract

Objectives: To determine whether midazolam, when used as an induction agent for emergency department (ED) rapid-sequence intubation (RSI), is used in adequate and recommended induction doses (0.1 to 0.3 mg/kg), and to compare the accuracy of the dosing of midazolam for ED RSI with the accuracy of dosing of other agents. Methods: The authors conducted a systematic query of a prospectively collected database of ED intubations using the National Emergency Airway Registry data, gathered in 11 participating EDs over a 16-month period. A data form completed at the time of emergency department intubation (EDI) enabled analysis of patients’ ages, weights, and indications for EDI, as well as the techniques and drugs used to facilitate EDI. Data were analyzed to determine whether midazolam is used in recommended doses during RSI. Patients intubated with midazolam alone were compared with patients who received other induction agents for RSI. Results: Of 1,288 patients entered in the study, 1,023 (79%) underwent RSI. Of the 888 RSI patients with an age recorded, midazolam was used as the sole induction agent in 140 (16%). The mean (±SD) dosages of midazolam used in RSI were 2.6 (±1.7) mg in children (age ≤ 18) and 3.7 (±2.5) mg in adults (age ≥19); the mean (±SD) dosages by weight were 0.08 (±0.04) mg/kg in children and 0.05 (±0.03) mg/kg in adults. More than half (56%) of the children, and nearly all (92%) of the adults, received dosages lower than the minimum recommended dosage (0.1 mg/kg). Of patients who received barbiturates, only 21% of children and 21% of adults received a dose lower than the minimum recommended. When combined with another induction agent, midazolam was dosed similarly to when it was used alone: mean adult doses were 3.1 (±1.2) mg and 0.04 (±0.02) mg/kg. Conclusions: Underdosing of midazolam during ED RSI is frequent, and appears to be related to incorrect dosage selection, rather than to a deliberate intention to reduce the dose used. Key words: RSI; rapid-sequence induction; ED; emergency department; midazolam; dose. ACADEMIC EMERGENCY MEDICINE 2003; 10:329–338.

Midazolam is commonly used as an induction agent for emergency department intubation (EDI). The section on induction dosing in the midazolam drug monograph states:

In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3 to 0.35 mg/kg for induction, administered over 20 to 30 seconds and allowing 2 minutes for effect. In resistant cases, up to 0.6 mg/kg total dose may be used for induction, but such larger doses may prolong recovery. Unpremedicated patients over the age of 55 years usually require less midazolam HCl for induction. An initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less midazolam HCl for induction. An initial dose of 0.2 to 0.25 mg/kg will usually suffice. In some cases, as little as 0.15 mg/kg may suffice.1

The recommended dose of midazolam for induction in major textbooks is 0.1 to 0.3 mg/kg, encompassing the manufacturer’s recommendations, and allowing substantial (threefold) dose variation for various clinical circumstances.2-5 In stable ED patients undergoing rapid-sequence intubation (RSI), the upper ranges of this dosing recommendation are indicated, consistent with the use of full induction doses of other agents used for ED RSI (e.g., etomidate 0.3 mg/kg, sodium thiopental 3–5 mg/kg).

Most potent sedative agents used for EDI are not commonly used in the ED for purposes other than sedation. Although there have been a few reports of the use of propofol or ultrashort-acting barbiturates for ED procedural sedation, only midazolam is widely used for this alternate purpose.6–8 Ketamine is frequently

From the Brigham and Women’s Hospital (RMW), Boston, MA; Harvard Affiliated Emergency Medicine Residency Program (MJS, RMW), Boston, MA; the Mount Auburn Hospital (MJS), Cambridge, MA; University of Utah (EDB), Salt Lake City, UT; University of Arizona (JCS), Tucson, AZ; University of North Carolina (RJV), Chapel Hill, NC; and Children’s Hospital (VC), Boston, MA. Received February 7, 2002; revision received September 20, 2002; accepted October 20, 2002. Presented at the SAEM New England regional conference, New Haven, CT, April 1998; and the SAEM annual meeting, Chicago, IL, May 1998.

Address for correspondence: Mark J. Sagarin, MD, Department of Emergency Medicine, Mount Auburn Hospital, 330 Mount Auburn Street, Cambridge, MA 02138. Fax: 413-473-9369; e-mail: mark_sagarin@hms.harvard.edu.

Address for reprints: Ron M. Walls, MD, Department of Emergency Medicine, Brigham & Women’s Hospital, 75 Francis Street, Boston, MA 02115. Fax: 617-278-6911; e-mail: rwalls@partners.org.
used for pediatric sedation, but is rarely used in sedation of adults because of undesirable side effects.9–11

Over more than ten years of teaching courses on airway management, one of us (RMW) has observed that physicians usually correctly identify the recommended doses of induction agents for use in ED RSI, and report using these doses. However, when midazolam is discussed as an induction agent, the doses identified by clinicians are generally much less than the recommended induction dose (0.2–0.3 mg/kg), and almost always less than the minimum induction dose (0.1 mg/kg). Physicians almost uniformly report using these markedly reduced doses of midazolam, despite their use of the recommended doses of other induction agents.

Adequate dosing of the induction agent is important for several reasons:

1. The patient becomes unaware of the resuscitative events, including neuromuscular blockade and intubation.12 Patients paralyzed and intubated while awake or inadequately sedated, in contrast, may experience emotional and psychiatric disturbances.13–15

2. Adverse hemodynamic responses to intubation, especially catecholamine release with resultant hypertension and tachycardia, are significantly attenuated by adequate doses of induction agents.16–20

3. Laryngoscopy and intubation during RSI are attempted at the earliest possible time after the neuromuscular blocking agent is administered. In these circumstances, the effects of the induction agent are additive to those of the neuromuscular blocking agent. Thus, appropriate doses of effective induction agents improve laryngoscopic grade at intubation.21–26

Accordingly, we undertook a study using data acquired during the National Emergency Airway Registry (NEAR I) project pilot phase (NEAR I) to determine the pattern of use of midazolam among emergency physicians at our participating centers. Our purpose was to determine the patterns of use of midazolam in EDI and to assess compliance of emergency physicians with recommended dosages for midazolam when it is used as the induction agent for ED RSI. A secondary purpose was to determine whether any observed underdosing is a result of reduction of the midazolam dose when midazolam is being used in combination with other induction agents. Finally, we wanted to compare the use of midazolam with that of other induction agents, to determine whether there is consistency in terms of use of recommended induction doses of all agents. Where underdosing was identified, we attempted to determine whether underdosing was predicted by specific patient characteristics, such as hypotension or mental states.

METHODS

Study Design. The first phase of the National Emergency Airway Registry (NEAR I) was initiated in June 1996 as a consortium of 11 academic EDs in the United States. All departments are staffed by full-time emergency medicine (EM) attending physicians and are affiliated with fully accredited EM residency training programs. Non-EM resident physicians also rotate through the majority of these departments and participate in EDIs. Participating institutions are certified as Level I (n = 7), Level II (n = 3), or Level III (n = 1) trauma centers and have an aggregate ED census of 610,000 patient visits per year (range 25,000 to 120,000). Pediatric patients are treated in nine of the EDs, which include one designated children’s hospital. Each hospital maintains individual protocols regarding the policy and procedures for ED airway management. EDIs are performed by resident physicians at the discretion of, and supervised by, attending physicians.

For the purposes of data collection, standard definitions were agreed upon and a data form was developed using an iterative process participated in by most of the centers. Intubations done using any sedative agent, but without neuromuscular blocking agents, were defined as “sedative only” intubations (SED). Intubations without any pharmacologic aid were classified according to whether they were nasal (NTI) or oral, and if oral were identified as “oral–no medication” (NOM). The data form required physicians to identify when a rapid-sequence technique (RSI) was used, and data entry personnel verified that neuromuscular blockade was used to ensure that the designation “RSI” was appropriate.

This study was approved by the institutional review board (IRB) of each participating institution.

Study Setting and Population. The patients analyzed in this study were derived from the set of patients in the NEAR I registry who were intubated orally using a rapid-sequence technique, defined as intubation facilitated by the use of neuromuscular blockade, and indicated as RSI by the intubating physician. Only patients whose age was recorded were included, to allow the study patients to be analyzed as pediatric (age ≤ 18) and adult (age ≥ 19) subgroups.

The “RSI: midazolam only” group was the central group evaluated in this study. It was defined as all patients enrolled in the registry who were intubated orally after receiving neuromuscular blockade plus midazolam, with no other induction agents. These patients could receive additional noninduction agents, such as atropine or lidocaine, in addition to neuromuscular blockade and midazolam.

A second group, called the “RSI: midazolam & other” group, was defined as all patients enrolled in
the registry who were intubated orally after receiving neuromuscular blockade plus midazolam and another agent capable of being an induction agent. These patients could receive other noninduction agents, such as atropine or lidocaine in addition to neuromuscular blockade, midazolam, and the other induction agent(s).

In order to compare the dosing of midazolam with that of other induction agents known to cause hypotension, a third subset of patients, called the “RSI: other benzodiazepine or barbiturate” group, was defined as those patients who were intubated orally after receiving neuromuscular blockade plus diazepam, methohexital, or thiopental as the only induction agent. The recommended induction dosages for diazepam, methohexital, and thiopental are 0.2–0.5, 1.0–3.0, and 3.0–5.0, respectively.1–4,27 The lower end of each range was defined as the cutoff for adequate dosing. Patients could receive other noninduction agents, such as atropine or lidocaine, in addition to neuromuscular blockade and the induction agent.

A fourth group, called the “RSI: no midazolam” group, was defined as all patients who did not receive midazolam in RSI. Note that the “RSI: other benzodiazepine or barbiturate” group is a subset of this fourth group, which also includes patients induced with ketamine, fentanyl, or etomidate.

Study Protocol. During the pilot phase of NEAR, data were gathered prospectively over a 16-month period (June 1996–September 1997) on patients requiring EDI who presented to the 11 participating institutions. After each EDI, the physician who intubated the patient completed a data form that included the patient’s age, gender, weight, indication for intubation, technique of airway management, number of attempts, complications, and names and dosages of all medications used to facilitate intubation.

Weights were determined from discussion with the patient’s family or friends present at the time of the intubation, or by the physician’s best estimate. These estimates are the weights physicians used to calculate drug dosing for induction agents, and therefore are the best for assessing the patterns of physicians’ dosing. No attempts to verify estimated weights were made through further chart review: few critically ill patients are weighed at the time of intubation, and many are never weighed in the intensive care unit (ICU).

Data Analysis. Demographic data for the four groups such as mean age, gender, and mean weights were compared. Within each group, the primary indication for intubation was analyzed in two ways: 1) trauma vs. nontrauma indications, and 2) neurologic versus nonneurologic disease. For the latter analysis, all patients were divided into two groups: a) the “potentially neurologically altered” or “PNA” group (patients with head injury, drug/toxin, stroke, status epilepticus, or coma) and b) the “not neurologically altered” or “NNA” group (all other indications for intubation). This was designed to permit analysis of midazolam dosing with respect to mental status (i.e., to allow for deliberate reduction of the dose because of obtundation existing before initiation of RSI). In these analyses of demographic data, we excluded any patients for whom the necessary data were not available.

Student’s t-test and chi-square analysis were used for all statistical comparisons. The p-value for statistical significance was set at 0.05. Ninety-five percent confidence intervals (95% CIs) for means and for proportions were calculated using standard published formulae.28

RESULTS

A total of 1,288 EDIs from 11 participating centers were prospectively entered into the database. Of 1,288 patients overall, 1,023 (79%) were intubated orally using RSI. Of these 1,023 patients, 888 (87%) had the age properly documented. These 888 patients constituted the overall study group: it included 124 children and 764 adults. Of these 888 patients, 140 (16%) were intubated orally with midazolam as the sole induction agent (“RSI: midazolam only” group). This included 18 children and 122 adults. One patient was excluded because dosage was not recorded. For analyses of dosage by weight, 13 patients were excluded because the estimated weight was not recorded.

When midazolam was the sole induction agent for RSI (“RSI: midazolam only” group), the mean dosage of midazolam used was 2.6 (±1.7) mg (95% CI = 1.8 to 3.4 mg) in children and 3.7 (±2.5) mg (95% CI = 3.2 to 4.2 mg) in adults (Figure 1). Seventy-seven percent of patients (95% CI = 69% to 84%) received exactly 2 mg, 4 mg, or 5 mg of midazolam. The mean dosages by weight were 0.08 (±0.04) mg/kg for children (95% CI = 0.06 to 0.10 mg/kg) and 0.05 (±0.03) mg/kg for adults (CI = 0.05 to 0.06 mg/kg). Midazolam dosages lower than the minimum recommended (<0.10 mg/kg) were administered to 56% of children (95% CI = 30% to 80%) and 92% of adults (95% CI = 85% to 96%) (Figure 2). The mean age of children who were underdosed was 13.6 (±5.5) years, whereas the mean age of children who were adequately dosed was 2.9 (±2.1) years (t-test p < 0.0005), suggesting that an absolute dosage was being selected, rather than a weight-based dosage.

Table 1 compares demographics of the groups of adults intubated via RSI for whom age was recorded: a) with midazolam as the only induction agent (“RSI: midazolam only”); b) with midazolam in combination with another potential sedative/induction agent (“RSI: midazolam & other”); c) with a benzodiazepine or barbiturate other than midazolam as the only
induction agent ("RSI: other benzodiazepine or barbiturate"); and d) all those who did not receive midazolam as part of RSI ("RSI: no midazolam"). Note that group c is a subset of group d. Patients intubated with midazolam alone were older and less likely to be trauma victims compared with patients intubated with other agents. Patients intubated with midazolam only were also less likely to have neurological disorders than patients intubated with other benzodiazepines and barbiturates. There was no significant difference in estimated weight or gender between groups.

Table 2 compares the same groups in children intubated via RSI. There is no "RSI: midazolam & other" group; this group was excluded because the number was inadequate for analysis (2 patients). Like adults, children intubated with midazolam alone were less likely to be trauma victims compared with patients intubated with other agents. There was no significant difference in age, weight, gender, or the proportion of patients who were potentially neurologically altered (PNA) between groups.

Of the 888 patients in the study group, all of whom received neuromuscular blockade, 47 (5%) were intubated orally with midazolam in combination with another sedative/induction agent ("RSI: midazolam & other" group). Because only two of these 47 were pediatric patients, meaningful analysis of the pediatric group was impossible, so only adult patients were analyzed. There were 44 adult patients with dosages recorded, including 35 adult patients with both dosage and weight recorded. The agents that were combined with midazolam were fentanyl (33), etomidate (7), and ketamine (4). Mean (±SD) dosages of these drugs used in combination with midazolam were as follows: fentanyl, 123 (±49) μg; etomidate 22 (±8) mg; and ketamine 115 (±44) mg. Mean (±SD) dosages by estimated weight of these drugs used in combination with midazolam were fentanyl, 1.8 (±0.8) μg/kg; etomidate 0.3 (±0.2) mg/kg; and
ketamine 1.4 (±0.7) mg/kg. The mean dosage of fentanyl is well below the induction dose of 15–30 μg/kg, demonstrating that the fentanyl was used in low doses when it was combined with midazolam. The etomidate and ketamine dosages are full induction range dosages. Overall, mean (±SD) midazolam dosage in these patients was 3.1 (±1.2) mg (95% CI = 2.7 to 3.5 mg); mean dosage by weight was 0.04 (±0.02) mg/kg (95% CI = 0.04 to 0.05 mg). The mean dosage of midazolam used in combination with fentanyl was 3.3 (±1.4) mg, in combination with etomidate was 2.6 mg (±1.1) mg, and in combination with ketamine was 2.5 (±1.0) mg.

Among patients intubated with RSI, there were 27 children who received thiopental as the sole induction agent; there were 17, 39, and 37 adults who received diazepam, methohexital, and thiopental, respectively. These patients formed the “RSI: other benzodiazepine or barbiturate” group. No patients received one of these drugs in combination with another sedative or barbiturate. Many studies have reported the hemodynamic effects of midazolam at dosages of 0.15–0.30 mg/kg. In relatively healthy, normovolemic patients, midazolam at these dosages causes either no change or only modest decreases in mean arterial pressure (MAP) (≤10 mm Hg). In studies of patients with limited cardiac reserve, induction with 0.2 to 0.3 mg/kg of midazolam causes mean decreases in MAP ranging from about 10 mm Hg to about 20 mm Hg. These modest hemodynamic effects were seen using dosages of midazolam that were two to three times the dose (0.1 mg/kg) we used in the adult patients. One additional study of patients with severe mitral stenosis showed a decrease in MAP of only 6 mm Hg after induction with 0.07 mg/kg of morphine plus 0.1 mg/kg of midazolam; MAP rapidly returned to baseline after intubation.

If underdosing of midazolam were caused by a concern about hypotension, one would expect

<table>
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<th>TABLE 1. Demographic Data: Adults</th>
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| n  | Age (Mean, yr) | Gender (% Female) | Weight (Mean, kg) | Trauma (%) | PNA* (%)
|----|----------------|------------------|-----------------|-----------|--------|
| RSI: midazolam only | 122 | 60.4 | 42 | 73.4 | 13 | 31
| RSI: midazolam & other | 47 | 53.5† | 34 | 73.1 | 20 | 23
| RSI: other benzodiazepine or barbiturate | 93 | 50.1‡ | 34 | 73.2 | 40‡ | 55‡
| RSI: no midazolam | 595 | 49.4‡ | 35 | 73.1 | 35‡ | 42

*PNA, potentially neurologically altered, includes head injury, drug/toxin, stroke, status epilepticus, and coma.
†p < 0.05, compared with the RSI: midazolam only group. RSI = rapid-sequence intubation.
‡p < 0.0005, compared with the RSI: midazolam only group.

**DISCUSSION**

We found a high incidence of midazolam underdosing when this drug was used for RSI. A potential explanation is that physicians are concerned about the potential for causing hypotension with the use of midazolam, and therefore deliberately reduce the dose. While some hypotension accompanies benzodiazepine induction, it is generally not a serious problem. Many studies have reported the hemodynamic effects of midazolam at dosages of 0.15–0.30 mg/kg. In relatively healthy, normovolemic patients, midazolam at these dosages causes either no change or only modest decreases in mean arterial pressure (MAP) (≤10 mm Hg). In studies of patients with limited cardiac reserve, induction with 0.2 to 0.3 mg/kg of midazolam causes mean decreases in MAP ranging from about 10 mm Hg to about 20 mm Hg. These modest hemodynamic effects were seen using dosages of midazolam that were two to three times the dose (0.1 mg/kg) we used as our cutoff for underdosing, and four to six times the mean dose we observed emergency physicians using in adult patients. One additional study of patients with severe mitral stenosis showed a decrease in MAP of only 6 mm Hg after induction with 0.07 mg/kg of morphine plus 0.1 mg/kg of midazolam; MAP rapidly returned to baseline after intubation.

If underdosing of midazolam were caused by a concern about hypotension, one would expect

<table>
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<th>TABLE 2. Demographic Data: Children</th>
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| n  | Age (Mean, yr) | Gender (% Female) | Weight (Mean, kg) | Trauma (%) | PNA* (%)
|----|----------------|------------------|-----------------|-----------|--------|
| RSI: midazolam only | 18 | 9.2 | 44 | 44.6 | 31 | 50
| RSI: other benzodiazepine or barbiturate | 27 | 8.1 | 19 | 33.4 | 56 | 74
| RSI: no midazolam | 104 | 10.3 | 23 | 40.4 | 70‡ | 53

*PNA, potentially neurologically altered, includes head injury, drug/toxin, stroke, status epilepticus, and coma.
†p < 0.005, compared with the RSI: midazolam only group. RSI = rapid-sequence intubation.
similar underdosing of barbiturates, which are well known for causing hypotension. In head-to-head comparisons versus midazolam, thiopental causes either similar or greater degrees of hypotension.\textsuperscript{29–31,33,38,41} Yet among both children and adults in our study, the incidence of underdosing of barbiturates (methohexital and thiopental) was significantly less than the incidence of underdosing of benzodiazepines (diazepam and midazolam). Emergency physicians in this study use a markedly reduced dose of barbiturates only a small fraction as often as they do with benzodiazepines. We therefore suspect that it is unlikely that emergency physicians reduce their induction dosages of midazolam solely out of a concern about the potential to cause hypotension.

Another possible explanation for midazolam underdosing is that the patients who receive midazolam as the sole induction agent are a select group who are perceived to require less sedation than others, in that they are already obtunded before intubation is initiated. If so, one would expect a disproportionate share of these patients to have neurologic injury, alteration, or disease. In fact, we found that a comparable percentage of patients in the “RSI: midazolam only” study group were “potentially neurologically altered” when compared with other study groups, even using our generously inclusive definition. Thus, there is no evidence that the patients receiving midazolam had greater obtundation of mental status before intubation than did patients in other groups.

The demographic data in Table 1 suggest those patients receiving midazolam are, on average, approximately ten years older than those receiving other agents. Some of these patients, especially those with underlying cardiac dysfunction, may require lower dosages of the induction agent in order to maintain an adequate blood pressure. However, the lowest adequate induction dose that is recommended even in this group is 0.1 mg/kg, and we set our “adequate” dose at this level. Most patients in this study received less than this minimally acceptable dose.

Thus, we suspect that the underdosing of midazolam observed in this study is related to physician factors rather than patient factors. This is a surprising finding, given that the doses of other induction agents used are within recommended ranges. Unlike most other ED induction agents, benzodiazepines are frequently used for other medical purposes, and emergency physicians may tend to use the familiar dosages commonly used for procedural sedation when planning induction of anesthesia. This explanation is supported by the following three findings:

1. That similar dosages of midazolam were used whether or not it was combined with another sedative/induction agent. When a full dose of another induction agent is used, the midazolam is presumably administered as a complementary sedative or pre-induction agent.
2. That diazepam, which is also used for purposes other than induction, is also regularly under-
dosed, whereas barbiturates, which are rarely used for other purposes, are much less commonly underdosed. Furthermore, in the less common situation in which barbiturates are used for procedural sedation, the dosing is close to the low end of the induction dosing (unlike the benzodiazepines, in which sedation dosing is substantially lower than induction dosing).

3. That the dosages used seem to reflect an absolute milligram amount, rather than a calculated mg/kg amount. This third point is emphasized by the pediatric data, in which fairly constant doses were administered across all pediatric age groups, reaching adequate mg/kg doses only in young (lightweight) patients.

Midazolam and diazepam are used for sedation of agitated patients, sedation for procedures, and seizure control. For obvious reasons, the dosages recommended for these purposes are lower than the dosages recommended for typical induction. Forty-two percent of adults in our study received 2 mg or less of midazolam when it was the sole anesthetic induction agent, regardless of their mental status before intubation. It is feasible that emergency physicians extrapolate the commonly used sedation dosages of midazolam to induction, because they are comfortable or familiar with these doses, but if so, they do not consider that the patient will likely be aware when he or she is intubated.

In RSI, the induction agent should render the patient unconscious, preferably within 1 minute. This optimizes intubating conditions, minimizes adverse responses to intubation, and creates comfort without recall for the patient. When midazolam is used for induction in RSI, the dosage necessary to achieve unconsciousness is at least 0.1 mg/kg, and double or triple this dose is recommended in generally healthy, hemodynamically stable patients.1

Taken together, these findings suggest that when physicians use an agent for two related (sedation) purposes, dosing recommendations may become obscured. When a benzodiazepine is used for procedural sedation, the express purpose is to achieve an endpoint of blunted responses and recall, but preservation of protective airway reflexes. When used for induction, the endpoint is to achieve general anesthesia, in which the patient is unresponsive to noxious stimuli and without protective airway reflexes. Choice and dose of induction agent have been unequivocally shown to influence intubating conditions, even in the context of neuromuscular blockade, so the selection of an inadequate dose of induction agent may make intubation unnecessarily difficult. In addition, patient perception and recall may not be fully blunted, and undesirable hemodynamic responses to intubation may ensue. It is noteworthy that when other agents are used, such as thiopental or etomidate, the full-recommended induction dose is generally given. Dosing may be clearer in these circumstances because these agents are generally used in the ED only for induction for intubation.

Another possible confounder with respect to physician selection of the appropriate induction dose of midazolam may be the product packaging. The administration of midazolam in dosages of 2, 4, or 5 mg in 77% of patients further supports this notion of blurring of sedative and induction doses but also suggests that the amount dispensed in a vial (most commonly 2 or 5 mg) may affect the dosage chosen. In the setting where a minimum 14-mg dose of midazolam is indicated for induction of a relatively healthy 70-kg patient, it is possible that emergency physicians and nurses are uncomfortable administering seven vials of this drug at one time, particularly when sedative applications require only one or two vials. Drugs used only in the ED for induction, such as etomidate and thiopental, are provided in "induction" dose-sized vials (20 mg for etomidate, 250 mg for thiopental) and were much more appropriately dosed.

Because the patients appear unresponsive as a result of their complete neuromuscular blockade, many physicians do not appreciate that the patient may actually remain awake. At the dosages used by emergency physicians in these 11 centers (mean of 0.05 mg/kg), most adult patients receiving midazolam are probably not asleep when they are intubated. Patients undergoing RSI generally receive the induction agent and neuromuscular blockade almost simultaneously approximately 1 minute before intubation. Gamble et al.42 assessed 20 patients' degrees of sedation up to 5 minutes after they received various dosages of midazolam. One minute after these patients received 0.15 mg/kg (three times the mean used in this study, albeit in healthy patients), none were asleep and only 10% were very drowsy. After 5 minutes, 20% were asleep and 50% were very drowsy. Other studies of induction with 0.15 mg/kg of midazolam have had similar findings.35,43 In one study of children, 83% receiving 0.15 mg/kg and 33% receiving doses three to four times greater than this (i.e., 0.45 to 0.60 mg/kg) did not fall asleep at 3 minutes.44 Taken together, these observations suggest that very few patients in our study received enough midazolam to actually be asleep at the time of intubation, with the caveat that our patients were generally sicker than the patients in these controlled studies and thus would tend to be more sensitive to induction agents.5 Fortunately, midazolam is a fairly potent amnestic agent, and perhaps physicians are overly optimistic in counting on the amnestic properties of midazolam to ensure that patients do not recall the unpleasant experiences of neuromuscular paralysis and oral intubation.

Some have argued that it is inconsequential whether the patient is asleep as long as the airway
is controlled safely. There are several potential problems with this approach. First, RSI requires early laryngoscopy, and the induction agent facilitates intubation. Several recent studies clearly demonstrate the effect of induction agent in facilitating laryngoscopic view, even in the presence of neuromuscular blockade.\textsuperscript{21–26} Adequate dosing of the induction agent, in this case midazolam, improves laryngoscopic view and the likelihood of successful early intubation. Second, the stress of paralysis and laryngoscopy without sedation results in catecholamine release, hypertension, tachycardia, and possibly elevated intracranial pressure in the acute phase. This is by no account desirable, and is largely preventable with proper use of induction agents.\textsuperscript{16–20} Finally, awareness during neuromuscular blockade is a very frightening experience that can lead to serious emotional and psychiatric sequelae.\textsuperscript{12–15}

**LIMITATIONS**

There are several limitations to our study. Although we believe that we obtained prospective data on consecutive intubations performed in each ED, we did not conduct an audit to determine the proportion of EDIs entered into the study. It is possible that there is a reporting bias in that those EDIs that were entered were not typical of all EDIs at these centers. If a reporting bias existed, however, one might expect even greater degrees of midazolam underdosing as physicians using dosages below those recommended might avoid reporting.

Weights were estimated by the physician performing the intubation. Although there is no way to validate these weights, and they may be inaccurate, they are nevertheless the weights the clinicians would have used in calculating drug dosages, and thus tend to validate, rather than invalidate our observation. For the reasons mentioned previously (death in the hours to days after intubation, changes in mass in the ICU, that some patients are never weighed), there was no way to obtain more accurate weight measurements.

Missing data points on our data forms may have affected our results. Many patients whose ages, weights, genders, indications for intubation, and drug dosages were not recorded were eliminated from analysis of these variables. Although the vital signs before intubation were requested on the NEAR data form, they were variably completed. We therefore were unable to directly assess whether midazolam was chosen as the induction agent in patients with lower blood pressures, and whether this was the rationale for underdosing.

We also requested Glasgow Coma Scale scores as a marker of neurologic compromise, but these values also were unreliably recorded. We therefore used the indication for intubation as a surrogate marker of altered mental status. Certainly, there are many patients with nonneurologic complaints who develop stupor because of their medical illness, such as hypoxia or shock; these patients were not captured in the “potentially neurologically altered” category. We were unable to directly capture the mental status of each patient enrolled in the study. Furthermore, although we ruled out the possibility that there was a disproportionate share of potentially neurologically altered patients in the “RSI: midazolam only” group, it is feasible that there was some quality or character not detected by our data form in many of these patients’ presentations that resulted in a high incidence of deliberate dose reduction. However, this would not explain dose reduction to levels below the minimum recommended on such a large scale.

It might have been feasible to obtain some of the additional information on vital signs and pre-intubation mental status though retrospective chart reviews, but due to the multicenter nature of the study and privacy concerns, this was technically impossible as it would have required multiple repeated petitions to IRBs, contact with and consent from hundreds of patients, and a nationwide network of research assistants.

This study was conducted at university-affiliated EDs, many with faculty members interested in airway management. These findings may not be representative of EDs in the community, or even all university-affiliated EDs. One would expect that the NEAR pilot centers would pay close attention to appropriate airway management, and it is therefore probable that rates of midazolam underdosing are even higher in the larger community. It is possible, in contrast, that less experienced resident physicians at the NEAR pilot centers are those choosing the relatively low doses of midazolam for induction. If this were the case, however, one would expect that their supervising attending physicians would be present and correct this error.

The comparison between the “RSI: midazolam only” and “RSI: midazolam & other” dosing may be underpowered to detect a difference in dosing of midazolam between these two groups; that is, there exists a possibility of type II error. The midazolam dosing between these groups was so similar that even if a statistical difference were to exist in larger sample sizes, it would be unlikely to be clinically relevant. This comparison is also limited by the fact that the majority of “RSI: midazolam & other” patients received fentanyl in the low dosages (mean of 1.8 μg/kg) that are used for pretreatment and are well below what is necessary to achieve unconsciousness. Furthermore, the “RSI: midazolam only” patients were significantly older than the “RSI: midazolam & other” patients. It is possible that, were these patients younger, they would have received larger midazolam dosages, and a difference would have emerged between these groups.
The analysis of the “RSI: other benzodiazepine or barbiturate” group also has limited power given the small sample sizes, but the large difference in frequency of underdosing between benzodiazepines and barbiturates (Figure 3) resulted in significant differences despite broad confidence intervals. In addition, the “RSI: midazolam only” patients were significantly older than this group. It is possible that, were these patients younger, there would have been a smaller difference between these groups. It seems unlikely that age entirely explains this substantial difference observed. The “RSI: midazolam only” patients were also significantly less likely to be trauma victims than the patients in this group. It is possible therefore, that part of the greater underdosing of midazolam can be attributed to more cardiovascular medical illness in the “RSI: midazolam only” group. Also, etomidate is commonly used in trauma indications, which tend to occur in groups of younger patients, thus leaving the older nontrauma patients to receive midazolam.

The power of many of the comparisons of pediatric patients is limited due to small sample sizes.

CONCLUSIONS

More than half of children, and nearly all adults, intubated using rapid-sequence technique with midazolam as the sole induction agent received dosages lower than the minimum recommended for intubation of severely compromised patients. This appears due to physician factors, in that the dose selected is simply too low, without apparent clinical indication for the dosage reduction. This systematic underdosing is not observed with agents such as sodium thiopental that are used only for anesthetic induction, and packaged for this purpose, raising the likelihood that the use of midazolam for procedural sedation and the mode of packaging of midazolam combine to result in dosing selection that is inadequate for rapid-sequence intubation. Emergency physicians would be well advised to review the dosing recommendations for midazolam and to undertake education of ED staff with respect to the correct dosing of midazolam for emergency RSI.

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