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INTRODUCTION

Benzodiazepines, including diazepam (DZP), lorazepam (LZP), and midazolam (MDZ), are considered the initial drugs of choice for status epilepticus (SE) treatment. A number of trials have demonstrated their safety and efficacy; however, the failure rate ranges from 10-55%.[1,2] This may be attributable, in part, to sub-optimal benzodiazepine dosing and timing of administration.

The Neurocritical Care Society (NCS) and American Epilepsy Society (AES) have published evidence-based guidelines for benzodiazepine use in SE that specify drugs, doses, and routes of administration.[1,2] Initial benzodiazepine treatment should consist of either a 10 mg dose of intramuscular (IM) MDZ for patients weighing > 40 kg or 5 mg for those 13-40 kg; or intravenous (IV) LZP 0.1 mg/kg/dose (maximum 4 mg/dose) or IV DZP 0.15-0.2 mg/kg/dose (maximum 10 mg/dose).[1,2] The LZP and DZP doses can be repeated if the initial dose fails to stop the seizure. Although not included in the guidelines, based on pharmacokinetics, 10 mg IV MDZ dose can be considered adequate therapy.[3]

Reports have documented underdosing of benzodiazepines used in SE; however, comprehensive information, regarding patient age, setting, drugs, doses, timing of doses, and routes is limited.[4,5] This report describes patterns of benzodiazepine use in SE in a geographically diverse population.

METHODS

The Established Status Epilepticus Treatment Trial (ESETT) provided an opportunity to systematically observe benzodiazepine administration in patients subsequently determined to have SE unresponsive to benzodiazepines.[6] Using pre-enrollment data from ESETT subjects, we describe benzodiazepine treatment with respect to: 1) drug choice, dose, and route of administration, 2) timing and setting in which the drugs were administered, and 3) patient weight (< or ≥ 40 kg for LZP, ≤ or > 40 kg for MDZ, and < or ≥ 66.7 kg for DZP). NCS and AES guidelines were used to define underdosing for our analyses. These weight-based cutoffs were per published guidelines.[1,2]

Because patients could receive more than one benzodiazepine, the cumulative dose was determined using LZP equivalents to account for differences in drug potencies. Transmucosal benzodiazepines, e.g. DZP or intranasal/buccal MDZ, given prior to emergency medical services (EMS) arrival are included in the calculation of cumulative benzodiazepine dose. For patients weighing ≥ 32 kg, 10 mg MDZ or DZP were considered equal to 4 mg LZP.[1,2] For patients weighing < 32 kg, 0.3 mg/kg of DZP IV or 0.2 mg/kg of MDZ IV or 0.3 mg/kg of MDZ IM were considered equal to 0.1 mg/kg LZP IV.[1,2] There was no upper limit for the benzodiazepine dose required to qualify for ESETT enrollment. While the ESETT protocol stipulated a minimum cumulative adequate dose for enrollment (Data supplement S1), instructions on the rate and frequency of dosing were not provided. ESETT sites were expected to dose benzodiazepines as

per their local standards of care. The settings in which benzodiazepines were administered were categorized as: 1) Prior to EMS, 2) EMS, and 3) Emergency Department (ED).

Data were collected from subjects enrolled at 41 US academic and community hospitals. For this analysis, the ESETT database was frozen on December 12, 2016. Data were analyzed using SAS version 9.4 to compute descriptive statistics.

RESULTS:

This analysis included 207 ESETT subjects: 88 children, 95 adults aged 18-65, and 24 older adults aged ≥ 66 (Data supplement S1). There were 511 administrations with an average (mean ± standard deviation) of 2.47 ± 1.04 doses per subject. LZP comprised of 61% of doses, followed by MDZ (31%), and DZP (8%). Most DZP doses (65%) were given prior to EMS arrival, whereas 68% of MDZ doses were given by EMS personnel, and 94% of LZP doses were administered in the ED. A comparison of routes of administration reveals that 95% of LZP doses were administered IV, while 5% (N=17) were by IM, IN, or buccal routes. With regards to MDZ, 41% of doses were given IM, 45% were by the IV route and the remaining 14% by IN or buccal routes. The rectal route was used for 69% of DZP administrations. Of these, 78% and 96% were in patients younger than 12 and 18 years, respectively.

First Dose of First Benzodiazepine: Among all subjects, 102 received their first dose of any benzodiazepine in the ED. Overall, 29.8% of first doses met minimum recommendations per guidelines. Of these, 86.7% of DZP, 14.5% of MDZ and 23.2% of LZP administrations met the minimum dose recommendations. Figure 1 shows that for subjects < 40 kg the guideline recommended LZP (≥ 0.1 mg/kg) or MDZ (≥ 5 mg) dose was administered as a first dose in 41.9% and 12.5% of the cases, respectively. In contrast, for those weighing ≥ 40 kg the recommended LZP (≥ 4 mg) or MDZ recommended (≥ 10 mg) dose was administered in 14.7% and 15.4% of the subjects, respectively. A DZP dose ≥ 10 mg was administered in 60% of the subjects ≥ 66.7 kg, while 96% of DZP administrations were ≥ 0.15 mg/kg in those < 66.7 kg.

Dose per Administration: Seventy-seven percent of DZP, 10.7% of MDZ and 21.8% of LZP doses administered were at or above the recommendations (Data supplement S1). Prior to EMS, most administrations were DZP (25/37) given at or above the minimum recommended doses, whereas in both the EMS and ED settings, most of the administered benzodiazepine doses were below recommendations.

Cumulative Benzodiazepine Doses: Cumulative dosing patterns were examined using LZP equivalents (Data supplement S1). Among 138 adults and older children weighing ≥ 32 kg, the cumulative dose in LZP equivalents was < 4 mg in 9%, 4 mg in 42%, 5-6 mg in 25% and > 7 mg in 24%. In 68 children weighing < 32 kg, the cumulative dose was < 0.1 mg/kg in 18%, 0.1 to < 0.2 mg/kg in 44%, 0.2 to < 0.3 mg/kg in 28% and > 0.3 mg/kg in 10% of subjects.

DISCUSSION

The results of this study suggest that many patients with SE who fail benzodiazepine treatment are not receiving recommended initial doses of benzodiazepines. The observed practice was not consistent with published evidence-based guidelines which stipulate that the initial treatment of SE begin with a benzodiazepine administered as early as possible, as a single full dose, and by an appropriate route.[1,2] In contrast, we found a pattern of administering multiple, small doses with approximately 70% of patients receiving a lower than guideline recommended first dose of the first drug. If, however, rectal DZP is excluded, the first doses of MDZ and LZP, mostly administered by EMS and/or ED personnel, were below guideline recommendations 80% of the time. Administration of subsequent doses continued the pattern of underdosing. Regardless of the number of administrations, approximately 12% of patients never received the required cumulative dose needed to meet ESETT eligibility criteria. This potentially reduced response to benzodiazepines as delay in administering appropriate therapy is thought to place patients at risk for longer seizures and poor outcomes.[7]

Our results extend the findings from earlier reports on initial management of SE.[4,5] In a multicenter study of adults, the investigators found that > 80% of patients with SE received a lower than recommended LZP dose.[4] Langer and Fountain, in a retrospective study of generalized convulsive SE in 170 children and adults found that only 11% of the patients, all children, received an adequate initial benzodiazepine dose.[5] The problem of benzodiazepine underdosing in SE may be attributable to the perceived risk of cardio-respiratory compromise associated with benzodiazepines.[8] However, Alldredge *et. al* showed that the rate of respiratory or circulatory complications was nearly doubled (p=0.08) in untreated SE patients versus those treated with benzodiazepines.[8] We also noted that on 17 occasions LZP was administered by IM, IN, or buccal routes. These routes do not support rapid LZP absorption and are inappropriate for SE therapy.[9]

LIMITATIONS

Our analysis is limited to SE patients who continued to have seizures despite benzodiazepine treatment. Since initial benzodiazepine underdosing is likely associated with treatment failure, our population may overestimate the rate of underdosing among patients treated for SE. While this limits the generalizability of our findings, benzodiazepine underdosing is particularly important in this subpopulation in whom seizures continue and may progress to refractory SE with attendant high rates of morbidity and mortality. Conversely, this analysis may underestimate the rate of underdosing because only those given an adequate cumulative benzodiazepine dose were eligible for ESETT enrollment. It is possible that eagerness to enroll subjects could bias toward lower cumulative benzodiazepine doses. However, in this scenario, EDs would be more likely to administer larger individual doses in order to meet the minimum adequate dose sooner and should not affect EMS practice. Lastly our sample size precluded the analysis of specific factors such as regional effects on dosing patterns.

CONCLUSIONS

Benzodiazepine underdosing for the treatment of SE was common in this geographically diverse set of EDs. This phenomenon may contribute to decreased efficacy. Further, the low doses used per administration in both ED and EMS settings suggests this represents practice culture rather than an artifact in practice driven by study enrollment. Hence, greater educational efforts and overcoming systematic and structural barriers are needed to change clinical practice.

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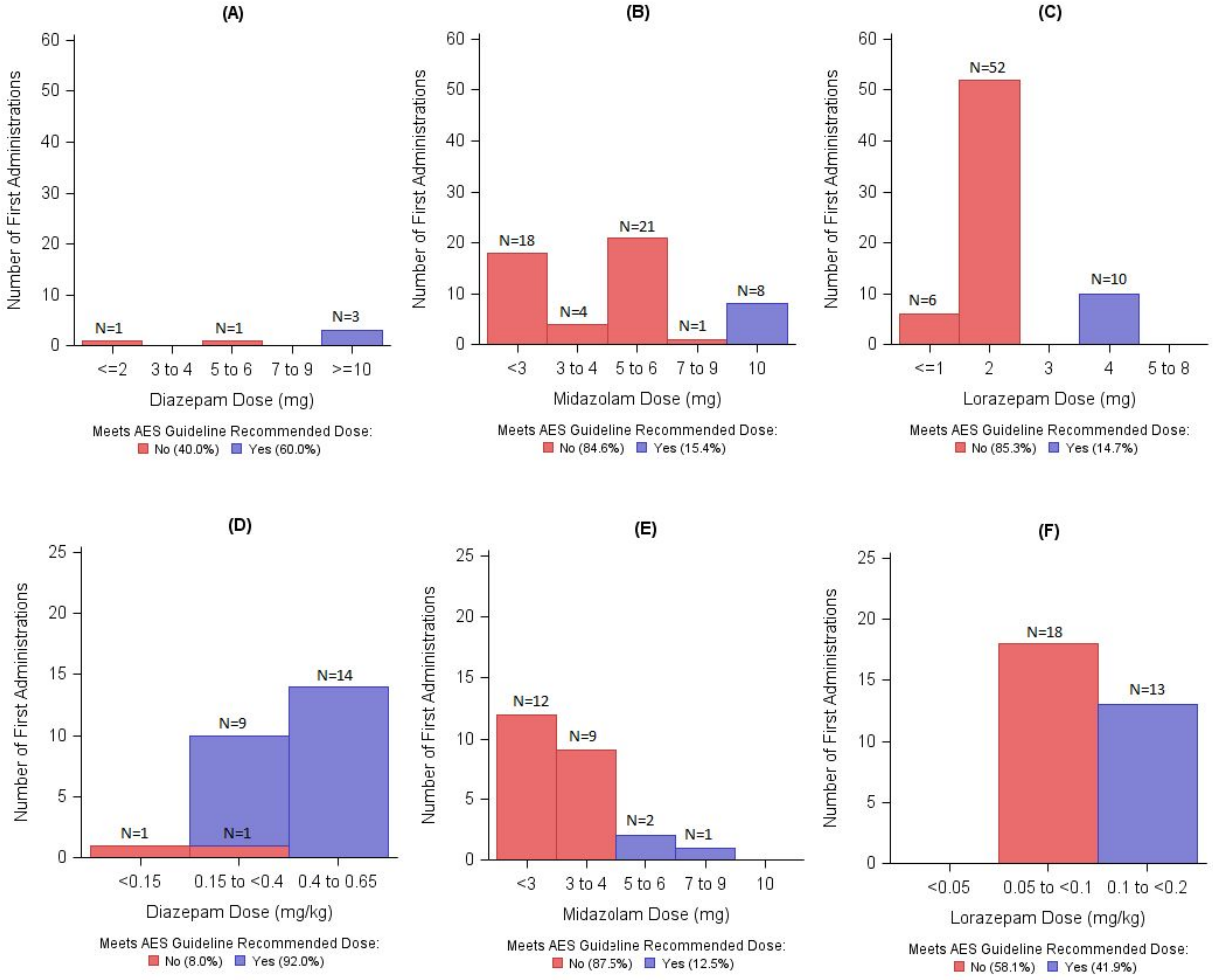
FIGURES

Figure 1: Distribution of first dose of the first administered benzodiazepine (DZP, MDZ or LZP) as actual doses. Top panel: fixed dosing, bottom panel: weight-based dosing. A:DZP doses for those ≥ 66.7kg (IV) or ≥ 50 kg (rectal); B: MDZ doses for those > 40 kg; C: LZP doses for those ≥ 40 kg; D: DZP doses for those < 66.7 kg (IV) or < 50 kg (rectal); E: MDZ doses for those ≤ 40 kg; F: LZP doses for those < 40 kg . Categorized as met (blue) or did not meet (red) guidelines.



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Abstract

Objective

Early termination of status epilepticus requires administration of an adequate benzodiazepine dose by an appropriate route. Prior reports suggest that benzodiazepine dosing in status epilepticus often differs from published guidelines. We describe patterns of diazepam (DZP), lorazepam (LZP), and midazolam (MDZ) use in prehospital and emergency department (ED) settings based on clinical care that occurred prior to enrollment in a trial of patients with benzodiazepine-refractory status epilepticus.

Methods

Benzodiazepine dosing information was collected from adults and children prior to enrollment in the Established Status Epilepticus Treatment Trial (ESETT), a multicenter study of 2nd-line drug therapy in established status epilepticus. Data on individual and cumulative benzodiazepine doses, number of doses, timing, setting, and routes of administration were analyzed. Settings included prior to ambulance arrival, emergency medical service (EMS), and ED. Published guidelines served as the basis for defining recommended doses.

Results

There were 511 benzodiazepine administrations (312 LZP, 159 MDZ, 40 DZP) given to 207 patients. Benzodiazepine use varied by setting: 67% of DZP doses were given prior to EMS arrival, 82% of MDZ doses were administered by EMS personnel, while 86% of LZP doses were administered in the ED. For the first administered dose of the first benzodiazepine, 86.7 % of DZP, 15.4 % of MDZ and 23.2 % of LZP met the minimum dose recommended by published guidelines. Underdosing also occurred with subsequent benzodiazepine administrations.

Conclusions

Benzodiazepine underdosing, particularly as an initial dose, was common in this geographically diverse set of patients who failed benzodiazepine treatment and were subsequently enrolled in ESETT. This phenomenon may contribute to reduced efficacy, potentially resulting in prolongation of status epilepticus.

Key words: Status Epilepticus, Benzodiazepines, Dose, Emergency Medicine

INTRODUCTION

Benzodiazepines including diazepam (DZP), lorazepam (LZP), and midazolam (MDZ) are considered the initial drugs of choice for ~~initial~~ status epilepticus (SE) treatment.[1,2] A number of trials have demonstrated their safety and efficacy ~~as initial therapy as compared to placebo or other anti-seizure drugs~~; however, the failure rate ranges from 10-55%.[3–9] This may be attributable, in part, to sub-optimal dosing and timing of benzodiazepine administration.[10–13]

~~Failure to quickly abort status epilepticus results in increased morbidity and mortality.[14] Hence, it is critical to administer an adequate benzodiazepine dose by an appropriate route in a timely manner.~~ The Neurocritical Care Society (NCS) and American Epilepsy Society (AES) have published evidence-based guidelines for benzodiazepine use in ~~status epilepticus~~SE that specify ~~recommended~~ drugs, doses, and routes of administration ~~(Table 1)~~.[1,2,14] Initial benzodiazepine treatment should consist of either a ~~single~~ 10 mg dose of intramuscular (IM) MDZ for patients weighing > 40 kg or 5 mg for those ~~weighing~~ 13-40 kg; or intravenous (IV) LZP 0.1 mg/kg/dose (maximum ~~dose of~~ 4 mg/dose) or IV DZP 0.15-0.2 mg/kg/dose (maximum ~~dose of~~ 10 mg/dose).[1,2] The~~se~~ LZP and DZP doses can be repeated if the initial dose fails to stop the seizure. Although not included in the guidelines, based on pharmacokinetics, 10 mg IV MDZ dose can be ~~is also~~ considered ~~an~~ adequate therapy.[15,16] ~~If these 3 options are unavailable, the guidelines recommend giving a single 15 mg/kg dose of IV phenobarbital or a single dose of rectal diazepam 0.2-0.5 mg/kg (max 20 mg/dose) or intranasal (IN)/ buccal MDZ~~.[1,2]

~~Previous~~ R~~r~~eports have documented underdosing of ~~that~~ benzodiazepines used in ~~status epilepticus~~SE ~~are often underdosed as compared to recommendations,~~ .[10,17–20] h~~H~~owever~~,~~ comprehensive information~~, including comparisons of children and adults,~~ regarding patient age, ~~the~~ setting, drugs, doses, timing of doses, and routes is limited.[10,17–20] ~~The aim of t~~This report describes ~~was to better understand the~~ patterns of benzodiazepine use in ~~status epilepticus~~SE in a geographically diverse group of patients.

METHODS

The Established ~~Status Epilepticus~~Status Epilepticus Treatment Trial (ESETT) ~~was a comparative effectiveness study of fosphenytoin, levetiracetam, and valproic acid in adults and children aged 2 years and older with benzodiazepine-refractory status epilepticus. The trial protocol did not prescribe or define how patients are to be treated with benzodiazepines but required an adequate cumulative dose of benzodiazepines prior to enrollment. The trial therefore~~ provided an opportunity to systematically observe benzodiazepine administration in ~~clinical practice among~~ patients subsequently determined to have ~~status epilepticus~~SE unresponsive to benzodiazepines.[21] Using pre-enrollment data from ESETT subjects ~~enrolled in ESETT~~, we describe benzodiazepine treatment with respect to 1) drug choice ~~of drug~~, dose, and route of administration, 2) ~~the~~ timing and setting in which the drugs were administered, and 3) patient weight (< or ≥ 40 kg for LZP, ≤ or > 40 kg for MDZ, and < or ≥ 66.7 kg for DZP). NCS and AES guidelines were

used to define underdosing for our analyses. These weight-based cut offs were ~~determined by the maximum recommended dose for each benzodiazepine~~ per published guidelines.

~~Pre-enrollment data from ESETT subjects were used as the basis for our analyses. The ESETT primary inclusion criterion was patients with persistent or recurrent seizures in the emergency department at least 5 minutes, and no later than 30 minutes, after a cumulatively adequate benzodiazepine dose that could consist of 2 or more individual doses.[22] There was no upper limit for the benzodiazepine dose required to qualify for ESETT enrollment. While the ESETT protocol stipulates a minimum cumulative adequate dose for enrollment (Table 1), it did not provide instructions on benzodiazepine dosing. ESETT sites were expected to dose benzodiazepines as per their local standard of care and per clinical guidelines. NCS and AES guidelines served as the criteria we used to define underdosing for our analyses. Transmucosally administered benzodiazepines such as rectal DZP or intranasal/buccal MDZ given at home or elsewhere prior to emergency medical services (EMS) arrival are included in the calculation of cumulative adequate benzodiazepine dose, but at least one dose must have also been given by EMS personnel or in the emergency department (ED) between 5 and 30 minutes prior to ESETT enrollment.~~

~~Given that~~ Because patients could receive more than one benzodiazepine, the cumulative dose was determined using LZP equivalents to account for differences in drug potencies. Transmucosal benzodiazepines, e.g. rectal DZP or intranasal/buccal MDZ given prior to emergency medical services (EMS) arrival are included in the calculation of cumulative benzodiazepine dose. For patients ~~adults and older children (~~weighing ≥ 32 kg~~)~~, 10 mg MDZ or DZP were considered equal to 4 mg LZP.[1,2] For patients ~~younger children (~~weighing < 32 kg~~,)~~ 0.3 mg/kg of DZP IV or 0.2 mg/kg of MDZ IV or 0.3 mg/kg of MDZ IM were considered equal to 0.1 mg/kg LZP IV.[1,2] There was no upper limit for the benzodiazepine dose required to qualify for ESETT enrollment. While the ESETT protocol stipulateds a minimum cumulative adequate dose for enrollment (Data supplement S1) ~~(Table 1), it did not provide~~ instructions on the rate and frequency of ~~benzodiazepine~~ dosing were not provided. ESETT sites were expected to dose benzodiazepines as per their local standard of care. ~~and per clinical guidelines.~~ The settings in which ~~the~~ benzodiazepines were administered were categorized as: 1) Prior to EMS, 2) EMS, and 3) Emergency Department (ED). ~~The prior to EMS category includes settings (e.g. home, school, work) in which a benzodiazepine was administered by nonmedical caregivers.~~

Data ~~for this analysis~~ were ~~as~~ collected from patients enrolled at 41 US academic and community hospitals participating in ESETT~~,, including many children's hospitals located throughout the United States.~~ For this analysis, the ESETT ~~study~~ database was frozen on December 12, 2016. ~~Pre-enrollment patient characteristics were analyzed.~~ Data were analyzed using SAS version 9.4 to compute descriptive statistics. ~~A Chi-squared test was used to compare the proportion of patients given the recommended first dose of the first administered benzodiazepine between weight-based versus fixed dosing groups.~~

RESULTS:

~~At the time of~~ T~~t~~his analysis included~~,~~ 207 ESETT subjects ~~had been enrolled in ESETT~~: 88 ~~(43%) were~~ children, 95 ~~(46%) were~~ adults aged 18-65, and 24 ~~(12%) were~~ older adults aged ≥ 66 (Data supplement S1) ~~and above~~. ~~Within this group, at least one dose of each drug was given as follows: LZP to 172 (83%) subjects, MDZ to100 (48%) subjects; and DZP to 34 (16%) subjects.~~ There were ~~a total of~~ 511 administrations with an average (mean ± standard deviation~~SD~~) of 2.47 ± 1.04 doses per subject. LZP comprised of 61% ~~of the total number~~ of doses, followed by MDZ (31%), and DZP (8%). ~~Table 2 shows the distribution of administrations based on setting, route of administration, and age. Additional details are provided in *supplementary Table 1*.~~ Most DZP doses (65%) were given prior to EMS arrival, whereas 68% of MDZ doses were given by EMS personnel, and 94% of LZP doses were administered in the ED. A comparison of routes of administration reveals that 95% of LZP doses were administered IV~~intravenously across all age groups in all settings~~, while 5% (N=17) of LZP administrations were by IM, IN, or buccal routes. With regards to MDZ, 41% of doses were given IM ~~(primarily by EMS personnel)~~, 45% were by the IV route and the remaining 14% by IN or buccal routes. ~~For all IM MDZ doses in all settings (N=65), 71% were given to patients aged 18 years or older. In contrast, IN or buccal MDZ administration was more common in children (20 administrations) than in adults (2 administrations).~~ The rectal DZP route was used for 69% of ~~DZP~~ administrations. Of these, 78% and 96% were in patients younger than 12 and 18 years respectively. ~~and 96% were in those younger than 18 years of age.~~

First Dose of First Benzodiazepine: Among all ~~the 207~~ subjects, 102 received their first dose of any benzodiazepine in the ED. Overall, 29.8% of first doses met minimum recommendations per guidelines. Of these, 86.7% of DZP, 14.5% of MDZ and 23.2% of LZP administrations met the minimum guideline dose recommendations. ~~As shown in~~ Figure 1 shows~~,~~ that for subjects < 40 kg the guideline recommended LZP (≥ 0.1 mg/kg) or MDZ (≥ 5 mg) dose was administered as a first dose in 41.9% and 12.5% of the cases, respectively. In contrast, for those weighing ≥ 40 kg the recommended LZP (≥ 4 mg) or MDZ recommended (≥ 10 mg) dose was administered in 14.7% and 15.4% of the subjects, respectively. A DZP dose ≥ 10 mg was administered in 60% of the subjects ≥ 66.7 kg, while 96% of DZP administrations were ≥ 0.15 mg/kg in those < 66.7 kg. ~~Among subjects who were administered weight-based doses (n=80), 50.0% received the recommended first dose; whereas only 16.8% of those given a fixed dose (n=125) received a recommended first dose, largely due to LZP and DZP dosing. The odds for an adequate dose for those in the weight-based dose group are 4.95 (95% C.I.= 2.61, 9.41) times as those in the fixed-dose group. Weight information was missing for 1 subject and dose and route information were missing for another subject.~~

Dose per Administration: ~~Figure 2 shows the number of administrations for each drug that met the guideline recommendations. Of the 510 administrations with known dosages, 76.9%~~ Seventy seven percent of DZP, 10.7% of MDZ and 21.8% of LZP doses administered were at or above the recommendations (Data supplement S1). Prior to EMS, ~~–~~most administrations were ~~patients~~

~~primarily received~~ DZP (25/37) given at or above the minimum recommended dose~~s in most cases~~, whereas in both the EMS and ED settings, most of the administered benzodiazepine doses were below ~~the~~ recommendations.

Cumulative Benzodiazepine Doses ~~Used in ESETT~~: ~~For the purposes of comparing all 3 benzodiazepines, we examined~~ Cumulative dosing patterns were examined using LZP equivalents (Data supplement S1). ~~The distribution of cumulative administered benzodiazepine doses is shown in Figure 3~~. Among 138 adults and older children weighing ≥ 32 kg, the cumulative dose in LZP equivalents was < 4 mg in 9%, 4 mg in 42%, 5-6 mg in 25% and > 7 mg in 24%. ~~Similarly, i~~In 68 children weighing < 32 kg, the cumulative dose was < 0.1 mg/kg in 18%, 0.1 to < 0.2 mg/kg in 44%, 0.2 to < 0.3 mg/kg in 28% and > 0.3 mg/kg in 10% of subjects. ~~Twelve younger children and 12 adults, 24 patients total (11.7%) did not receive a cumulative adequate benzodiazepine dose and will be protocol deviations in the analysis of primary outcome for ESETT.~~

~~*Time to Cumulative Adequate Dose after the First Dose:* The median elapsed time from the first dose to the dose that achieved the adequate cumulative benzodiazepine dose (≥ 4 mg or ≥ 0.1 mg/kg LZP equivalents) was 6 minutes, the interquartile range (IQR) was 0-8 minutes, and the overall range was 0 to 112 minutes. When analyzed by weight group, the median elapsed time in those weighing ≥ 32 kg was 8 minutes (IQR: 2-21, overall range: 0-112), which was higher and more variable than the median time of 0 minutes (IQR: 0-13.5, overall range: 0-65) for subjects weighing < 32 kg.~~

DISCUSSION

The results of this study suggest that many patients with ~~status epilepticus~~SE who fail benzodiazepine treatment are not receiving recommended~~,~~ initial doses of benzodiazepines. ~~Sites were instructed to give benzodiazepines consistent with guidelines and their usual practice.~~ The observed practice~~, however,~~ was not consistent with published evidence-based guidelines which stipulate that the initial treatment of ~~status epilepticus~~SE begin with a benzodiazepine administered as early as possible, as a single full dose, and by an appropriate route for the benzodiazepine being used.[1,2] ~~Further emphasizing the importance of adequate dosing, the guidelines stipulate that if the first dose fails to stop seizures within 5 minutes, a second full dose of IV LZP or DZP should be administered.[1,2]~~

~~In contrast, in this multi-center study of adults and children with convulsive benzodiazepine-refractory status epilepticus, w~~In contrast, we found a pattern of administering multiple, small~~ler than recommended benzodiazepine~~ doses~~. The pattern begins~~ with approximately 70% of patients receiving a lower than guideline recommended first dose of the first drug. If h~~H~~owever, rectal DZP is excluded, ~~this percentage is inflated because all the patients (N=25) getting rectal diazepam prior to EMS arrival received the recommended dose. In contrast, t~~the first doses of MDZ and

LZP, mostly administered by EMS and/or ED personnel, were below guideline recommendations 80.~~1~~% of the time. Administration of subsequent doses continued the pattern of underdosing. Regardless of the number of administrations, approximately 12% of patients never received the required cumulative dose needed to meet ESETT eligibility criteria~~. Moreover, attainment of cumulative dose required for enrollment in the trial took 18 minutes or longer after the first dose in approximately 25% of adults and children, which~~ This potentially reduced response to benzodiazepines as delay in administering appropriate therapy is thought to place patients at risk for longer seizures and poor outcomes. ~~Although underdosing was pervasive, a larger proportion of children received recommended doses as compared to adults.~~

Commented [ES1]: Again findings should be presented in the results section not the discussion.

~~Delay in administering appropriate therapy is thought to place patients at risk for longer seizures and poor outcomes.[12,13,23–30] If an initial benzodiazepine dose does not terminate a prolonged seizure; higher subsequent doses may be required. This could be due to changes in benzodiazepine pharmacodynamics.Although underdosing was pervasive, a larger proportion of children received recommended doses as compared to adults. Benzodiazepines exert their anticonvulsant effect by allosterically increasing the affinity of gamma-amino-butyric acid (GABA) to the GABA type A ($GABA_A$) receptor leading to an increased ion channel opening frequency.[31] The resulting influx of chloride ions causes inhibition of action potentials.[32] However, prolonged seizures result in enhanced endocytosis of synaptic $GABA_A$ receptors, thus reducing benzodiazepine potency.[33–36] This internalization is associated with decreased effectiveness of DZP and, presumably, other benzodiazepines.[37,38] For example, in a rat model the DZP ED_{50} for terminating seizures was 10-fold higher, 40 mg/kg vs. 4.2 mg/kg, when administered after 45 minutes of continuous seizures as compared to 10 minutes.[37] Furthermore, rapid receptor plasticity has been attributed to activation of some secondary messengers during prolonged seizures.[39] As status epilepticus continues, the activity and number of N-methyl-D-aspartate (NMDA) receptors and excitatory amino-acid synaptic concentrations likely increase making early termination the goal so as to avoid established status epilepticus.[31,32]~~

Our results ~~, involving 41 EDs across the United States, confirm and~~ extend the findings from earlier reports on initial management of ~~status epilepticus~~SE.[10,17–20] In a multicenter study of adults, ~~Alvarez *et. al*~~the investigators found that > 80% of patients with SE received a lower than recommended LZP dose ~~was frequently underdosed in the management of status epilepticus with similar rates of underdosing across the 3 centers involved (> 80%).[10] In a retrospective analysis of 100 adults treated for status epilepticus at a single center, Rao and colleagues found that 7% did not receive a benzodiazepine as initial therapy and only 31% received an adequate initial dose of benzodiazepine.[17] Braun et al reported consistent underdosing of benzodiazepines in 44 adults with convulsive status epilepticus treated by EMS or in the ED of an inner city hospital.[18] Similarly, studies in children have also found that benzodiazepine dosing practices deviate from guidelines.[26,33]~~ Langer and Fountain, in a retrospective~~, observational~~ study of generalized convulsive ~~status epilepticus~~SE in 170 children and adults ~~treated at a single center,~~ found that

~~50% of the patients received multiple, small doses of benzodiazepines.[19]~~ ~~O~~only 11% of the patients, all children, received an adequate initial benzodiazepine dose.[19]

The problem of benzodiazepine underdosing in ~~status epilepticus~~SE may be attributable to ~~to one or more causes. One factor is~~ the perceived risk of cardio-respiratory compromise associated with benzodiazepines.[30,34,35] However, Alldredge *et al* showed that the rate of respiratory or circulatory complications was nearly doubled (p=0.08) in untreated ~~status epilepticus~~SE patients ~~left untreated~~ versus those treated with benzodiazepines.[3] We also noted that on 17 occasions LZP was administered by IM, IN, or buccal routes. These routes do not support rapid LZP absorption and are inappropriate for SE therapy ~~Another factor may be the lack of familiarity with what constitutes equipotent dosing of MDZ. In our study we found many occurrences of 2 or 4 mg MDZ doses given to the same patient suggesting a perception that MDZ and LZP doses are interchangeable. These and related status epilepticus management issues can be addressed through staff training/empowerment and making it part of standard EMS practice.~~

~~We also noted that on 17 occasions LZP was administered by IM, IN, or buccal routes. These routes do not support rapid LZP absorption and are not appropriate for status epilepticus therapy~~.[36–39] ~~Newer benzodiazepine formulations in development specifically designed for treatment of seizure emergencies such as IN DZP, IN MDZ and an IM auto-injector MDZ, may facilitate early administration of recommended doses.[40]~~

LIMITATIONS

~~This study has several limitations. First, the~~ Our analysis is limited to SE patients ~~with status epilepticus~~ who continued to have seizures despite benzodiazepine treatment ~~with benzodiazepines~~. Since initial benzodiazepine underdosing is likely ~~to be~~ associated with treatment failure, ~~the study~~ our population may overestimate the ~~overall~~ rate of underdosing among ~~all~~ patients treated for SE ~~status epilepticus in emergency settings~~. While this limits generalizability of our findings, ~~However, the danger of underdosing of~~ benzodiazepine underdosings is ~~of~~ particular importantee in thise subpopulation ~~studied here,~~ in whom seizures continue and may progress to ~~established and~~ refractory ~~status epilepticus~~SE with attendant high rates of morbidity and mortality. Conversely, t~~T~~his analysis may ~~, on the other hand,~~ underestimate the rate of underdosing because only those patients ~~ultimately~~ given an adequate cumulative benzodiazepine dose ~~of benzodiazepines~~ were eligible for ~~enrollment in~~ ESETT enrollment~~. It is remarkable that 11.7% were inappropriately enrolled without meeting the adequate benzodiazepine dose eligibility criterion, which likely reflects the penetration of underdosing in the underlying practice culture~~. ~~Also, I~~it is possible that eagerness to enroll subjects ~~in the trial~~ could bias toward lower cumulative benzodiazepine doses ~~of benzodiazepines. This effect cannot be excluded but~~ However, in this scenario EDs would be more likely to administer ~~is unlikely as such a bias in culture would seemingly lead to~~ larger individual doses in order to meet the minimum adequate dose sooner ~~,~~

~~rather than smaller incremental benzodiazepine administrations, shorter intervals between administrations than what was observed~~, and ~~w~~should not ~~have been expected to~~ affect EMS practice~~. The observed low doses per administration in both ED and EMS settings, suggests practice culture rather than an artifact in practice driven by enrollment in ESETT. Another limitation is that the~~ Lastly our sample size precluded the analysis of ~~as to whether~~ specific factors such as regional effects on ~~influence~~ benzodiazepine dosing patterns. ~~The lack of a comparator group precludes extrapolation to a larger population of individuals getting initial treatment of status epilepticus. Time from seizure to adequate dose may be an important factor but that information was not available.~~

CONCLUSIONS

~~In summary, b~~Benzodiazepine underdosing for the treatment of ~~status epilepticus~~SE was common in this geographically diverse set of EDs. This phenomenon may contribute to decreased efficacy. Further, the low doses used per administration in both ED and EMS settings suggests this represents practice culture rather than an artifact in practice driven by study enrollment~~ in the study~~. Hence, greater educational efforts ~~-~~and overcoming systematic and structural barriers are needed to change clinical practice. ~~Better treatment options and understanding of optimal status epilepticus treatment may decrease instances of underdosing and improve clinical outcomes.~~

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TABLES

Table 1. Guideline Recommended Doses and ESETT Protocol Eligibility Criteria

		Guideline Recommended Doses per Administration*	ESETT Eligibility Criteria for Minimally Adequate Cumulative Dose **	
Drug	**Route**		**Dose for ≥ 32 kg Patients (mg)**	**Dose for < 32 kg Patients (mg/kg)**
Diazepam	IV Rectal	0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once If IV route not available, then 0.2-0.5 mg/kg/dose, max: 20 mg/dose	10	0.3
Lorazepam	IV	0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once	4	0.1
Midazolam	IV IM IN/Buccal	IM Dosing: 10 mg for > 40 kg, 5 mg for 13-40 kg Dosing not specified	10 10	0.2 0.3

* Brophy GM et al. ,Neurocrit Care 2012;17(1):3–23 and Glauser T et al., Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

**Cut-off criteria for the transmucosal routes were the same as those for the intravenous route

Table 2: Distribution of Total Number of Benzodiazepine Doses by Route of Administration, Setting and Age Group (N=511 administrations in 207 patients)

	Lorazepam		Midazolam		Diazepam		Total	
	N= 312		N= 159		N= 40		N=511	
	n	%	n	%	n	%	n	%
Route of administration								
Intravenous	295	95%	72	45%	12	31%	379	74%
Intramuscular	15	5%	65	41%	0	0%	80	16%
Transmucosal*	2	1%	22	14%	27	69%	51	10%
Setting								
Prior to EMS	4	1%	9	6%	26	65%	39	8%
EMS	14	5%	108	68%	9	23%	131	26%
ED	294	94%	42	26%	5	13%	341	67%
Age group								
Pediatric**	97	31%	66	42%	27	68%	190	37%
Adult	215	69%	93	58%	12	30%	320	63%

EMS- Emergency Medical Services; ED- Emergency Department
*Transmucosal administration for diazepam was per rectum, while intranasal or buccal routes were used for lorazepam and midazolam.
**The pediatric group includes ages less than or equal to 17, the adult group includes those greater than 17.
Administration information for one case was missing due to unknown dose and route.

FIGURES
(PLEASE SEE ATTACHMENTS FOR FIGURES)

Figure 1: Distribution of first dose of the first administered benzodiazepine (DZP, MDZ or LZP) as actual doses. Top panel: fixed dosing, bottom panel: weight-based dosing. A:DZP doses for those ≥ 66.7kg (IV) or ≥ 50 kg (rectal); B: MDZ doses for those > 40 kg; C: LZP doses for those ≥ 40 kg; D: DZP doses for those < 66.7 kg (IV) or < 50 kg (rectal); E: MDZ doses for those ≤ 40 kg; F: LZP doses for those < 40 kg . Categorized as met (blue) or did not meet (red) guidelines.

Figure 2: Total number of administrations that met (blue) and did not meet (red) guideline recommendations for DZP, MDZ and LZP (N=511) *(Numbers on top of the bars represent % administrations for each drug)*

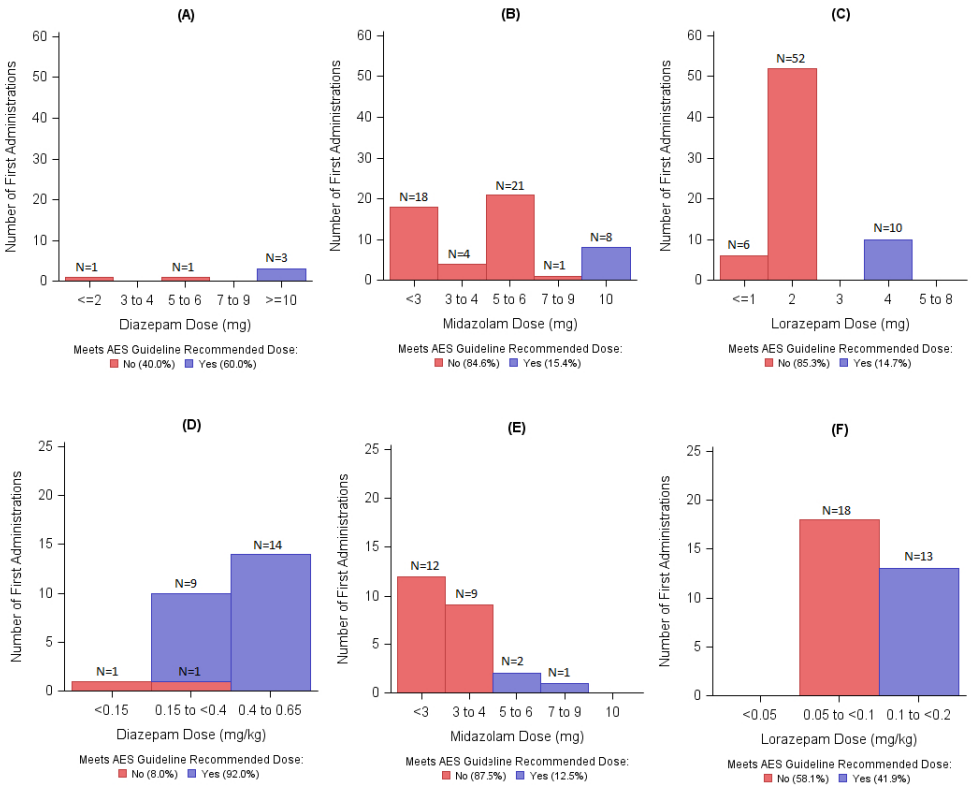
Figure 3: Distribution of the cumulative benzodiazepine dose in lorazepam equivalents for subjects weighing ≥ 32 kg (top panel) and < 32 kg (bottom panel)

Supplementary table

Supplementary Table 1: Distribution of total number of benzodiazepine doses by route of administration, setting and age group

			Age Group (years)		Total
			<=17*	>=18	
Total Administrations			N=190	N=320	N=510*
Drug	Route	Setting			
Diazepam	IV	EMS	1	6	7
		ED	0	5	5
	PR	Prior to EMS	24	1	25
		EMS	2	0	2
Midazolam	IV	Prior to EMS	0	7	7
		EMS	19	21	40
		ED	8	17	25
	IM	EMS	15	37	52
		ED	4	9	13
	IN/Buccal	Prior to EMS	2	0	2
		EMS	14	2	16
		ED	4	0	4
Lorazepam	IV	EMS	2	10	12
		ED	93	190	283
	IM	Prior to EMS	0	3	3
		EMS	1	0	1
		ED	0	11	11
	IN/Buccal	Prior to EMS	1	0	1
		EMS	0	1	1

***One administration missing due to unknown dose and route.**



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SUPPLEMENTARY MATERIAL

Figures

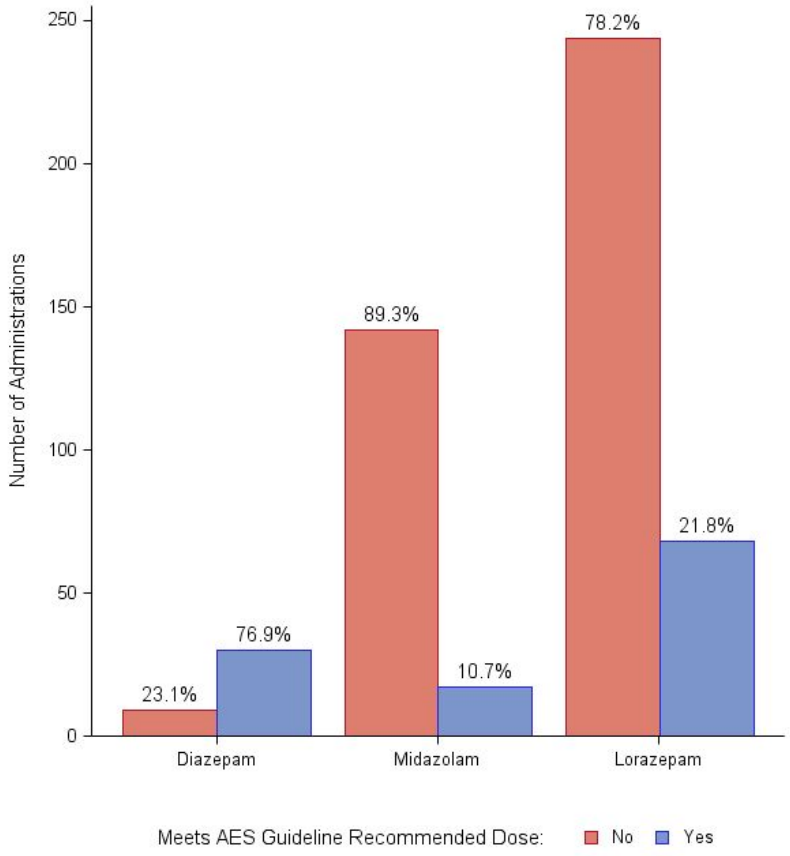

Figure S1: Total number of administrations that met (blue) and did not meet (red) guideline recommendations for DZP, MDZ and LZP (N=511) *(Numbers on top of the bars represent % administrations for each drug)*

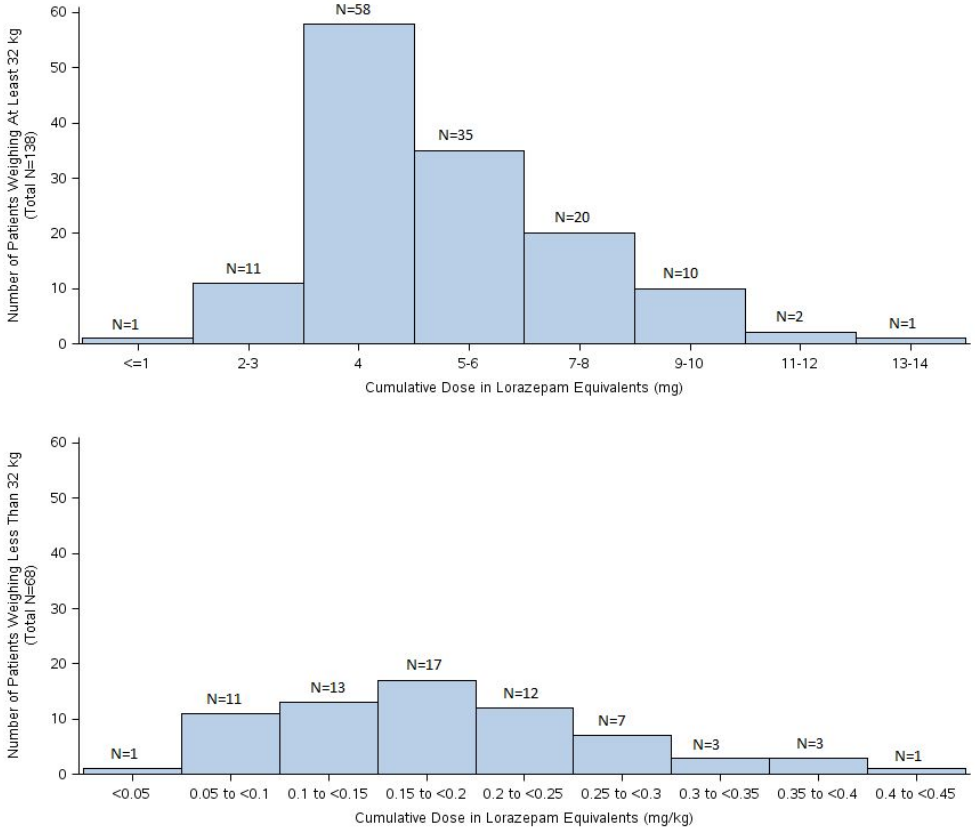

Figure S2: Distribution of the cumulative benzodiazepine dose in lorazepam equivalents for subjects weighing ≥ 32 kg (top panel) and < 32 kg (bottom panel)

Tables

Table S1. Guideline Recommended Doses and ESETT Protocol Eligibility Criteria

		Guideline Recommended Doses per Administration*	ESETT Eligibility Criteria for Minimally Adequate Cumulative Dose **	
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Lorazepam	IV	0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once	4	0.1
Midazolam	IV IM IN/Buccal	IM Dosing: 10 mg for > 40 kg, 5 mg for 13-40 kg Dosing not specified	10 10	0.2 0.3

* Brophy GM et al. ,Neurocrit Care 2012;17(1):3–23 and Glauser T et al., Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 48–61

**Cut-off criteria for the transmucosal routes were the same as those for the intravenous route

Table S2: Distribution of Total Number of Benzodiazepine Doses by Route of Administration, Setting and Age Group (N=511 administrations in 207 patients)

	Lorazepam		Midazolam		Diazepam		Total	
	N= 312		N= 159		N= 40		N=511	
	n	%	n	%	n	%	n	%
Route of administration								
Intravenous	295	95%	72	45%	12	31%	379	74%
Intramuscular	15	5%	65	41%	0	0%	80	16%
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Setting								
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Age group								
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EMS- Emergency Medical Services; ED- Emergency Department
*Transmucosal administration for diazepam was per rectum, while intranasal or buccal routes were used for lorazepam and midazolam.
**The pediatric group includes ages less than or equal to 17, the adult group includes those greater than 17.
Administration information for one case was missing due to unknown dose and route.