Antiepileptic Drug Management in Hospitalized Epilepsy Patients With Nil Per Os Diets: A Retrospective Review

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Anna M. Bank, MD¹, Jong Woo Lee, MD, PhD²,
Alexa N. Ehler, BS³, and Aaron L. Berkowitz, MD, PhD²

Abstract

Background and Purpose: Antiepileptic drug (AED) management in patients with epilepsy who cannot take their usual oral medications is a common neurologic dilemma in the hospital setting. Strategies to maintain seizure control in patients with nil per os (NPO, nothing by mouth) diet orders include continuation of oral AEDs despite NPO nutrition orders, administration of intravenous AED(s), or temporary administration of benzodiazepines. The frequency with which these strategies are used and their effectiveness in preventing in-hospital seizures is unknown. **Methods:** We conducted a retrospective cohort study to determine AED management strategies and seizure frequency in hospitalized epilepsy patients with NPO diet status admitted to an academic medical center between 2001 and 2016. Clinical documentation was reviewed. Antiepileptic drug selection (medication and route of administration) and presence or absence of seizures were recorded. **Results:** We identified 199 admissions during which epilepsy patients had NPO diet orders. Antiepileptic drug management strategies included continuation of oral medications (50.3% of admissions), intravenous AED monotherapy (22.1%), intravenous AED polytherapy (12.6%), benzodiazepines (1.0%), holding AEDs (4.5%), or a combination (9.5%). Seizures occurred during 14 admissions. Treatment with AED polytherapy prior to admission and changing the patient's AED regimen during admission were associated with increased odds of seizures during admission ($P = .0028$; $P = .0114$). **Conclusions:** These results suggest that patients' home oral AED regimens should be continued when possible in order to minimize the frequency of seizures during hospitalizations.

Keywords

antiepileptic drugs, inpatient, epilepsy

Introduction

Patients with epilepsy have more comorbidities and more frequent hospitalizations than patients without epilepsy.^{1,2} Seizures are common when epilepsy patients are hospitalized, with more than one-third of in-hospital seizures occurring in patients with a known diagnosis of epilepsy.³ In addition to the potential risk to the patient, these seizures can delay necessary treatments for the underlying medical or surgical condition.

When epilepsy patients are hospitalized, they often have altered consciousness, dysphagia, impaired enteral absorption, or perioperative nil per os (NPO, nothing by mouth) status. These conditions can impair their ability to take their usual antiepileptic drugs (AEDs), as the vast majority of AEDs are prescribed in oral formulations.⁴

Thus, AED management in patients with epilepsy who cannot take their usual oral medications is a common neurologic dilemma in the hospital setting. Neurohospitalists, consulting neurologists, and other providers often alter epilepsy

patients' home AED regimens when these patients are admitted with NPO diet status, with the goal of ensuring continued AED therapy and preventing seizures.

Strategies to maintain seizure control in hospitalized patients with NPO orders include continuation of home oral AEDs despite NPO nutrition orders, administration of intravenous formulations of the patient's home AED(s) or alternative intravenous AED(s), or temporary administration of

¹ Department of Neurology, Columbia University Medical Center, New York, NY, USA

² Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

³ Harvard T.H. Chan School of Public Health, Boston, MA, USA

Corresponding Author:

Anna M. Bank, Department of Neurology, Columbia University Medical Center, 710 W. 168th St, Room 741, New York, NY 10032, USA.
Email: amb2304@cumc.columbia.edu

Table 1. Baseline Characteristics of Epilepsy Patients With NPO Orders During Admission.

	Home AED Regimen Continued	Home AED Regimen Not Continued
Admissions	100	99
Sex	78 female (78.0%)	68 female (68.7%)
Age (years) ^a	50.1 ± 16.1 (range: 20-91)	56.6 ± 14.3 (range: 20-87)
Home AEDs (number)	1.46 ± 0.74 (range: 1-4)	1.57 ± 0.74 (range: 1-4)
Admission diagnoses		
Small bowel obstruction	42 (42.0%)	70 (70.7%)
Abdominal surgery	15 (15.0%)	15 (15.2%)
Abdominal pain	14 (14.0%)	3 (3.0%)
Infection	7 (7.0%)	0 (0.0%)
Ileus	6 (6.0%)	4 (4.0%)
Abdominal distension	3 (3.0%)	0 (0.0%)
Perforation	2 (2.0%)	4 (4.0%)
Large bowel obstruction	2 (2.0%)	1 (1.0%)
Gastrointestinal bleed	2 (2.0%)	1 (1.0%)
Other	7 (7.0%)	1 (1.0%)

Abbreviations: AED, antiepileptic drug; NPO, nil per os.

^a*P* < .05.

benzodiazepines.⁵ No data have been published to support the use of one strategy over another, and the frequency with which these strategies are used and their effectiveness in preventing seizures is unknown.

The objective of this study was to determine which inpatient AED management strategy is associated with the lowest odds of seizure during admission. Prior studies have shown that epilepsy patients are more likely to have breakthrough seizures after switching AEDs or after switching to a different formulation of the same AED.^{6,7} Thus, our hypothesis was that continuation of patients' home oral AED regimens would be associated with lower odds of in-hospital seizure than changing to a different AED regimen.

Methods

Patients with epilepsy admitted to an academic medical center between 2001 and 2016 were identified via a clinical data registry using the search criteria "epilepsy and recurrent seizures," "inpatient," and "paralytic ileus and intestinal obstruction without hernia." This search strategy was chosen to obtain a high yield of patients with NPO orders during admission.

Clinical documentation was reviewed in order to confirm that each patient had a diagnosis of epilepsy, was taking oral AEDs prior to admission, and was admitted for an abdominal disorder for which NPO status was documented. If more than one relevant admission was found in a patient's chart, each admission was recorded separately. If a patient had an NPO order more than once during a given admission, AED management during the first NPO period that overlapped with a scheduled AED dose was recorded.

Medication orders were reviewed and AED selection (medication and route of administration) was recorded. Discharge summaries were reviewed and the presence or absence of seizures during each admission was recorded. Seizures after

the NPO order was discontinued were included because these patients had not yet advanced to a full oral diet or were still being treated for intra-abdominal disease, suggesting that enteral absorption may have still been compromised at the time of the seizure.

Because coexisting medical conditions can predispose to breakthrough seizures, the charts of patients who had seizures while admitted were reviewed in order to look for evidence of fevers, infections, severe electrolyte disturbances, or seizure threshold-lowering medications that may have increased the risk of breakthrough seizure.

The study was approved by the institutional review board of Brigham and Women's Hospital. Because of the retrospective nature of the study, informed consent was waived.

Data Analysis

Data were analyzed using IBM SPSS Statistics for Windows Version 22.0 (Armonk, New York) and SAS Version 9.4 (Cary, North Carolina). Chi-square tests were performed for categorical variables and Student *t* tests were performed for continuous variables to determine differences in baseline characteristics between groups. Because some patients had more than one admission over the course of the study period, we used generalized estimating equations (GEEs) with exchangeable correlation structure to assess the association between possible predictors of seizure and seizure during admission.

Three GEE models provided odds ratios and 95% confidence intervals for the association between 2 potential predictors of seizure—preadmission polytherapy AED regimen and changing the patient's home AED regimen during admission—and seizure during admission. Patient identity was used as the clustering variable and admission was used as the unit of analysis. Model 1 was a univariate model with polytherapy as the predictor; model 2 was a univariate model with change

Table 2. AED Management for Patient Admissions During Which a Seizure Occurred.

Pt	Admission	Age	Sex	Reason for Admission	Home AED Regimen	AED Regimen During Admission	Time NPO	Missed Doses	Nasogastric Tube	Diet at Time of Seizure
1	1	55	Male	Small bowel obstruction	Oral carbamazepine 600 mg qAM and 900 mg qPM, oral diazepam 7.5 mg BID and 5 mg at noon	Initially on intravenous levetiracetam 500 mg BID monotherapy, oral carbamazepine 600 mg qAM and 900 mg qPM restarted 1 day later, diazepam initially held due to somnolence but restarted after breakthrough seizure	15 hours, 27 minutes	0	No	Pureed
2	2	68	Female	Small bowel obstruction	Oral levetiracetam, oral oxcarbazepine, oral primidone (home doses unknown)	Initially on intravenous levetiracetam 1500 mg BID, intravenous valproic acid 400 mg BID (without load) started after breakthrough seizure	3 days, 11 hours, 50 minutes	13 doses of oxcarbazepine and primidone	Yes, to suction. No AEDs administered via nasogastric tube.	Regular diet
3	3	54	Male	New diagnosis of abdominal cancer	Oral gabapentin 300 mg TID, oral lacosamide 150 mg BID, oral phenytoin 200 mg qAM and 300 mg qPM, oral topiramate 200 mg BID	Oral gabapentin 300 mg TID, oral lacosamide 150 mg BID, oral phenytoin 200 mg qAM and 300 mg qPM, oral topiramate 200 mg BID	13 hours, 4 minutes	0	No	NPO
4	4	51	Female	Small bowel obstruction	Oral phenobarbital 60 mg BID, oral phenytoin 200 mg BID	Intravenous phenobarbital 60 mg BID, intravenous phenytoin 200 mg BID	3 days, 8 hours, 38 minutes	0	Yes, to suction. No AEDs administered via nasogastric tube.	Regular diet
4	5	58	Female	Small bowel obstruction	Oral phenobarbital 60 mg BID, oral phenytoin 130 mg QHS	Intravenous phenobarbital 45 mg BID, intravenous phenytoin 130 mg QHS	5 days, 16 hours, 33 minutes	1 dose of phenobarbital and phenytoin	No	NPO
4	6	60	Female	Small bowel obstruction	Oral phenobarbital 60 mg BID, oral phenytoin 130 mg QHS	Intravenous phenobarbital 60 mg BID, intravenous phenytoin 250 mg BID	1 day, 11 hours, 41 minutes	0	No	NPO
4	7	61	Female	Small bowel obstruction	Oral phenobarbital 150 mg QHS, oral phenytoin 225 mg QHS	Intravenous phenobarbital 130 mg QHS, intravenous phenytoin 260 mg QHS	1 day, 14 hours, 41 minutes	0	No	Clear sips
4	8	62	Female	Small bowel obstruction	Oral phenobarbital 60 mg BID, oral phenytoin 230 mg QHS	Oral phenobarbital 150 mg QHS, oral phenytoin 260 mg QHS	1 day, 3 hours	0	No	Clear sips
5	9	67	Male	Small bowel obstruction	Oral phenytoin 160 mg daily	Intravenous phenytoin 100 mg q8h	5 days, 5 hours, 34 minutes	0	Yes, to suction. No AEDs administered via nasogastric tube.	NPO

(continued)

Table 2. (continued)

Pt	Admission	Age	Sex	Reason for Admission	Home AED Regimen	AED Regimen During Admission	Time NPO	Missed Doses	Nasogastric Tube	Diet at Time of Seizure
6	10	58	Male	Small bowel obstruction	Oral clobazam 10 mg qAM and 20 mg qPM, oral lacosamide 100 mg BID, oral oxcarbazepine 600 mg BID, oral phenytoin 250 mg QHS (extended-release formulation)	Intravenous lacosamide 100 mg BID, intravenous phenytoin 250 mg daily	8 days, 13 hours, 43 minutes	14 doses of clobazam and oxcarbazepine	Yes, to suction. No AEDs administered via nasogastric tube.	NPO
7	11	55	Male	Abdomino-perineal resection	Oral phenytoin, oral valproic acid (home doses unknown)	Intravenous phenytoin 500 mg QHS, oral valproic acid 100 mg BID	15 hours, 20 minutes	0	Yes, to suction. Valproic acid administered via nasogastric tube.	Clear sips
8	12	62	Female	Small bowel obstruction	Oral phenytoin 100 mg qAM and 300 mg qPM	Intravenous phenytoin 100 mg qAM and 300 mg qPM	7 days, 16 hours, 16 minutes	0	Yes, to suction. No AEDs administered via nasogastric tube.	NPO
9	13	67	Male	Small bowel obstruction	Oral carbamazepine 800 mg daily (extended-release formulation), oral gabapentin 800 mg TID	Initially on intravenous levetiracetam 500 mg BID monotherapy, increased to 1500 mg BID and oral medications restarted after breakthrough seizure	4 days, 23 hours, 42 minutes	4 doses of carbamazepine, 12 doses of gabapentin	Yes, to suction. No AEDs administered via nasogastric tube.	Regular diet
10	14	59	Male	Bowel perforation	Oral lacosamide 200 mg BID, oral levetiracetam 1500 mg BID, oral valproic acid 500 mg daily (extended-release formulation)	Intravenous lacosamide 200 mg BID, intravenous levetiracetam 1500 mg BID, intravenous valproic acid 250 mg BID	5 days, 3 hours, 47 minutes	0	Yes, to suction. No AEDs administered via nasogastric tube.	Unknown

Abbreviations: AED, antiepileptic drug; BID, twice daily; NPO, nil per os; QAM, every morning; QPM, every evening; QHS, every night at bedtime; TID, thrice daily.

in AED regimen as the predictor; and model 3 included both polytherapy and change in AED regimen.

Results

Patients

Baseline characteristics and admission diagnoses are shown in Table 1. Preadmission AEDs in 124 admissions for patients treated with monotherapy prior to admission included levetiracetam (37 admissions, 29.8%), phenytoin (33 admissions, 26.6%), valproic acid (14 admissions, 11.3%), lamotrigine (12 admissions, 9.7%), carbamazepine (11 admissions, 8.9%), gabapentin (8 admissions, 6.5%), phenobarbital (4 admissions, 3.2%), zonisamide (3 admissions, 2.4%), oxcarbazepine (1 admission, 0.8%), and topiramate (1 admission, 0.8%). Among the 75 admissions for patients treated with polytherapy prior to admission, 51 admissions (68.0%) were for patients treated with 2 AEDs, 21 admissions (28.0%) were for patients treated with 3 AEDs, and three admissions (4.0%) were for patients treated with 4 AEDs. No patients were treated with more than 4 AEDs prior to admission.

Antiepileptic Drug Management

In 50.3% of 199 patient admissions, patients had NPO orders for nutrition, but enteral medications were continued, either orally or via nasogastric tube. Nasogastric tubes were placed during 106 admissions (53.3%). Antiepileptic drugs were administered via nasogastric tube during 37 admissions (34.9% of admissions during which nasogastric tubes were used).

Among patients who were treated with AED monotherapy prior to admission, 93.5% were treated with AEDs while admitted. Inpatient AED regimens included continuation of the home oral AED regimen (54.0% of admissions), administration of the home AED in an intravenous formulation (28.2%), administration of a different intravenous AED (4.8%), or a combination (6.5%).

Among patients who were treated with AED polytherapy prior to admission, 98.7% were treated with AEDs while admitted. Inpatient AED regimens included continuation of the home oral AED regimen (44.0% of admissions), intravenous AED polytherapy (33.4%), intravenous AED monotherapy (4.0%), benzodiazepines (2.7%), or a combination (14.7%).

Seizures

Seizures occurred during 14 admissions (7.0%) in 10 patients (11.6%; 1 patient had seizures during 5 different admissions; Table 2). Two seizures occurred during admissions in which the patient's home AED regimen was continued, while 12 seizures occurred during admissions in which the home AED regimen was changed, $\chi^2(1) = 7.792, P = .005$. For the patient who had seizures during 5 different admissions, 1 seizure occurred when the home AED regimen was continued, while 4 seizures occurred when it was changed. Aside from one patient who

Table 3. Predictors of Seizure During Inpatient Admission.

	Seizures, Yes/No	Odds Ratio (95% CI)	P Value
Model 1: Polytherapy	12/63	11.30 (2.52-50.70)	.0015
Model 2: AED regimen changed	12/87	3.95 (1.42-11.02)	.0087
Model 3: Polytherapy AED Regimen Changed		10.68 (2.26-50.38) 3.59 (1.33-9.65)	.0028 .0114

had a magnetic resonance imaging scan suggesting possible posterior reversible encephalopathy syndrome, none of the other patients had documented fevers, infections, electrolyte disturbances, or administered medications that may have increased the likelihood of breakthrough seizures.

A preadmission polytherapy regimen and change in AED regimen were both associated with increased odds of seizure during admission, in both the univariate models and in the combined model (see Table 3, models 1, 2, and 3).

Discussion

Antiepileptic drug management strategies for hospitalized epilepsy patients with NPO orders vary widely even within a single institution, but almost all patients are treated with AEDs. Enteral AEDs are often continued in patients who are unable to tolerate enteral nutrition.

Treatment with AED polytherapy prior to admission and changes in AED regimen during admission were both associated with increased odds of seizure during admission. Patients who are treated with polytherapy likely have seizures that are more difficult to control at baseline, which may help to explain their increased odds of in-hospital seizure.

This study is limited by its retrospective design. Most significantly, because of the limited availability of preadmission clinical documentation, we were unable to determine patients' preadmission seizure frequency and the role that may play in the likelihood of in-hospital seizure.⁸ Additionally, we were not able to control for all possible factors that may affect breakthrough seizure frequency. Patient-related factors, such as low AED levels due to medication noncompliance, and hospitalization-related factors, such as missed doses due to lack of intravenous access, may increase the likelihood of breakthrough seizures.

Our results are consistent with results from prior studies, which have shown an increase in the risk of breakthrough seizures after a change in AED regimen.^{6,7} Taken together, these data suggest that continuation of hospitalized patients' home oral AED regimens—even when they require NPO status—may help to reduce the risk of breakthrough seizures.

Declaration of Conflicting Interests

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