

TOLERABILITY OF RAPID ZONISAMIDE (ZNS) TITRATION IN HOSPITAL SETTING

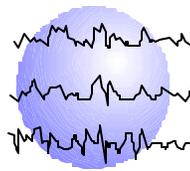
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ABSTRACT

RATIONALE

It is sometimes better to introduce new antiepileptic drugs (AEDs) in a limited timeframe utilizing rapid titration while patients are hospitalized, thereby obtaining better seizure control and limiting adverse events (AEs). Zonisamide (ZNS), a new AED, is used in this study. The objective is to better understand the rapid titration within a hospital setting for patients treated with ZNS.

METHODS

Fifty-five adult patients with medically intractable partial epilepsy, aged 20 to 91 years (average age 43.5) (24 male, 31 female patients), were admitted to the hospital for the addition of ZNS to obtain better seizure control. The titration schedule was individualized for each patient based on his/her tolerability for the drug, AEs, and seizure control. ZNS was started at 100 mg/day on day 1 of the titration. Days to complete titration ranged from 1 to 9 days, with the average being 5.8 days. Maximum ZNS dosages ranged from 100 to 700 mg/day, with the average being 350 mg/day. Patients were on from 1 to 4 other AEDs. Six patients were on 1 AED (11%), 27 on 2 AEDs (49%), 16 on 3 AEDs (29%), and 6 were on 4 AEDs (11%). Inpatient ZNS blood levels were available for 28 patients, with the average level being 11.7 mcg/mL.

RESULTS

Of the 55 patients started on ZNS while in the hospital, only 3 (5%) were discontinued prior to discharge: 1 for a noticeable increase in seizure activity, 1 for confusion, and 1 for decreased spontaneity and sleepiness. Nine patients (16%) discontinued ZNS prior to or at the first clinic visit. Normal timeframe for first clinic visit after hospitalization was 6 to 8 weeks. Reasons for discontinuation were: 2 patients with noticeable increase in seizure activity, 2 with tinnitus, 2 with no noticeable improvement in seizures, 1 with active EEG and incontinence, and 1 with incontinence, vomiting, mood swings, and appetite fluctuations. The last patient switched back to her previous AEDs 1 week after hospital discharge. Twenty-one of the 55 patients (38%) had a greater than or equal to 50% reduction in seizures, including 6 patients who were seizure free. Nine patients (16%) had improved seizure control and 6 (11%) had no change. Seven (13%) had a decrease in seizure control, including 2 patients who were noncompliant with their medications and 1 who needed a replacement of the vagus nerve stimulator. Thirty-six patients had blood levels drawn by their first clinic visit. The average level was 21.9 mcg/mL, which reflects the average dose of 386 mg of ZNS.

CONCLUSIONS

A rapid titration of ZNS in the hospital environment can be achieved safely with minimal adverse effects along with the expectation of significantly improved seizure control.

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INTRODUCTION

People with epilepsy often make the transition to new medication on an outpatient basis. This transition may take days or even weeks to accomplish. New antiepileptic drugs (AEDs) sometimes yield better seizure control and fewer adverse events (AEs) when introduced quickly, using rapid titration while patients are hospitalized. Zonisamide (Zonegran[®], ZNS) is a novel AED with multiple mechanisms of action and a broad spectrum of activity against many seizure types. The drug has been available in Japan since 1989 and is approved in the United States for the adjunctive treatment of partial seizures in adults with epilepsy. In the hospital setting we implemented a rapid titration of ZNS. This report summarizes those results.

METHODS

This study included 55 adult patients (24 males and 31 females) with medically intractable partial epilepsy, aged 20 to 91 years (mean=43.5 years), who were admitted to the hospital for the addition of ZNS to obtain better seizure control. ZNS was added to the patients' current AED regimen at a starting dosage of 100 mg/day. The ZNS titration schedule was individualized for each patient based on his or her tolerability of the drug, AEs, and seizure control. ZNS titration was completed in the hospital for all patients, and duration of titration ranged from 1 to 9 days (mean=5.8 days). Table 1 provides a summary of patients' AED regimens.

All patients were discharged after being seizure free for at least 24 hours on the new AED regimen. Patients completed follow-up clinic visits beginning 6 to 8 weeks after hospital discharge to assess efficacy of treatment. Efficacy of ZNS was assessed via reduction in patients' seizure frequency from baseline, using patient seizure diaries. Baseline seizure frequency was based on phone contacts or caretaker seizure diaries for the 3 months prior to hospital admission. Safety of ZNS was assessed via reports of AEs.

RESULTS

Mean duration of hospitalization, including titration days, was 13.8 days (range= 6 - 33 days). Of the 55 patients started on ZNS while in the hospital, only 3 (5%) (Figure 1) were discontinued prior to discharge (Table 2). Nine additional patients (16%) discontinued ZNS prior to or at the first clinic visit (Figure 1). Reasons for discontinuation in these patients are shown in Table 3. One patient, who experienced incontinence, vomiting, mood swings, and appetite fluctuations, switched back to her previous AEDs 1 week after hospital discharge. Seven patients experienced other AEs while hospitalized but did not discontinue ZNS. These AEs included feeling "spacey" in 1 patient (2%), nausea in 3 patients (5%), vomiting in 1 patient (2%), and difficulty sleeping in 2 patients (4%).

Thirty-six patients had ZNS blood levels measured by their first clinic visit; mean level was 21.9 mcg/mL, which reflects these patients' average ZNS dosage of 386 mg/day.

CONCLUSIONS

The results of this study indicate that rapid titration of ZNS in the hospital environment can be achieved safely. The AEs reported in this study were similar to those seen in previous studies employing lower ZNS dosages and/or slower titration schedules.^{1,2} AEs were minimal for the majority of patients in the present study, and ZNS resulted in improved seizure control. Further study of rapid ZNS titration is warranted.

REFERENCES

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Table 1. Patient AED Regimens

Mean (range) maximum ZNS dosage (mg/day)	350 (100-700)
Mean (range) inpatient serum ZNS concentration (mcg/mL)*	11.7 (5.0-38.2)
Mean serum ZNS concentration measured by first clinic visit** (mcg/mL)	21.9 (Range unavailable)
Patients on AEDs in addition to ZNS*** [n (%)]	
1 AED	6 (11)
2 AEDs	27 (49)
3 AEDs	16 (29)
4 AEDs	6 (11)
* Available for 28 patients	
** Available for 36 patients	
*** Does not include vagus nerve stimulators used by 7 patients	

Table 2. Reasons for Termination of ZNS During Hospitalization

Reason	Patients n (%)
Noticeable increases in seizure activity	1 (2)
Confusion	1 (2)
Sleepiness and decreased spontaneity	1 (2)

Table 3. Reasons for Termination of ZNS Prior to or at First Clinic Visit (Outside the Hospital)

Reason	Patients n (%)
Noticeable increases in seizure activity	2 (4)
Tinnitus	2 (4)
No noticeable seizure improvement	2 (4)
Active EEG* and incontinence	1 (2)
Incontinence, vomiting, mood swings, and appetite fluctuations	1 (2)
*Revealed subclinical status epilepticus	

Figure 1. Continuation and Termination of ZNS (N=55)

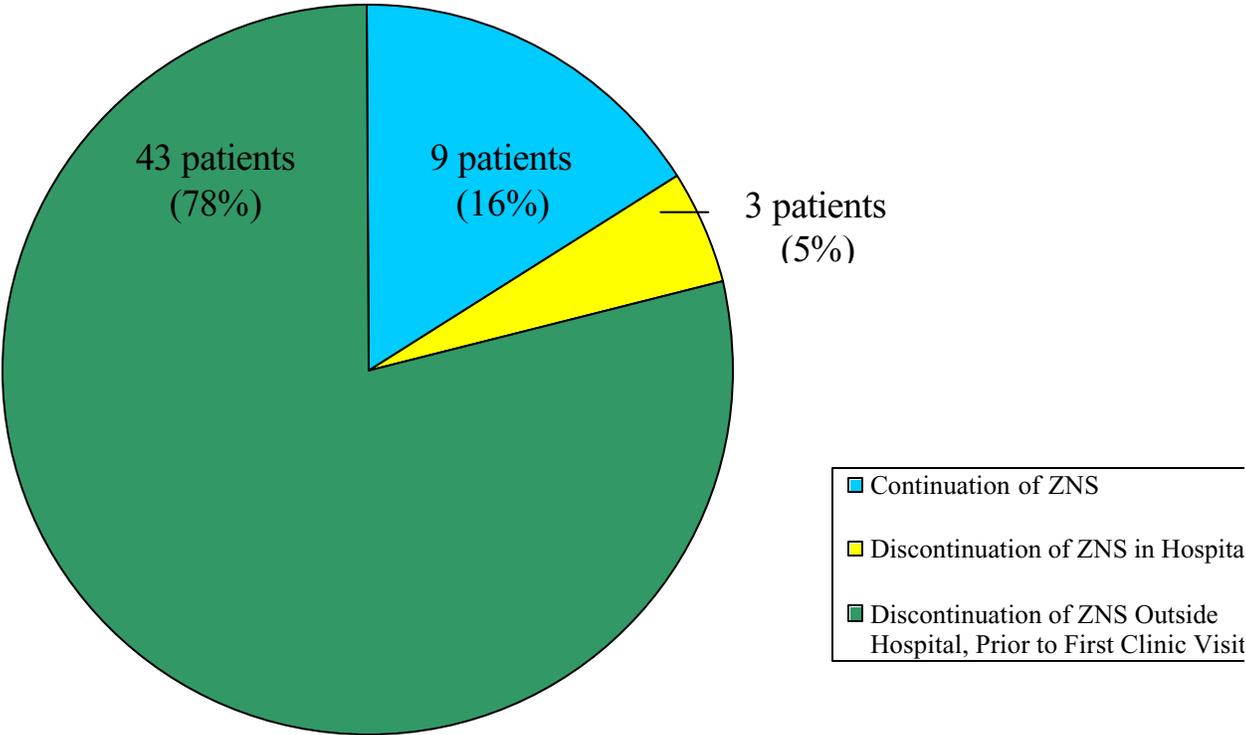
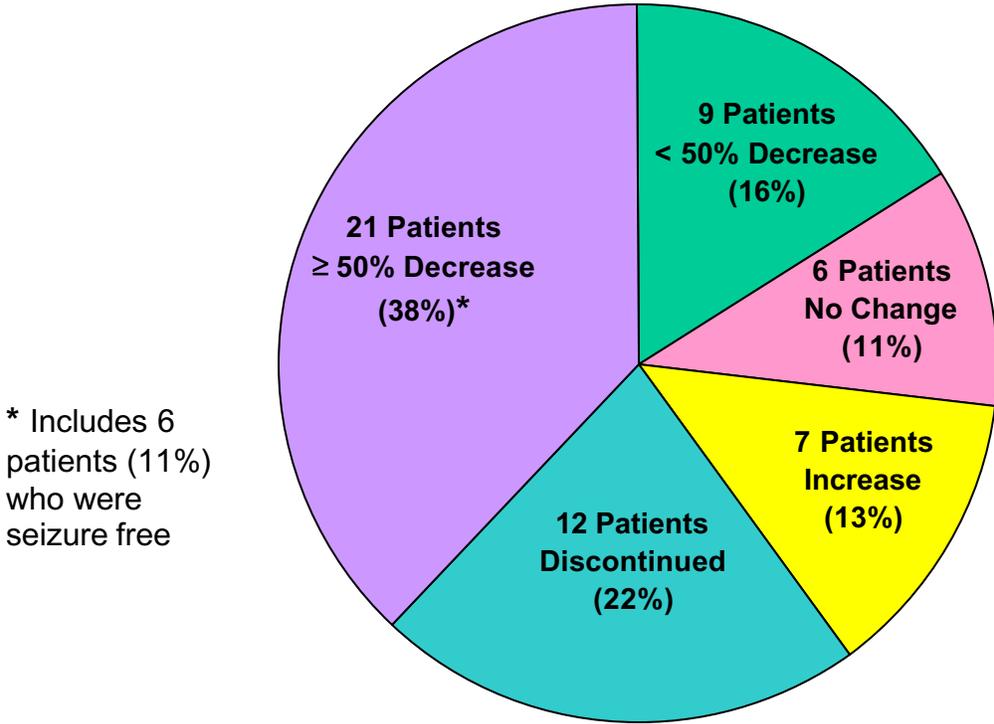


Figure 2 Changes in Seizure Frequency (n = 55)



* Includes 6 patients (11%) who were seizure free