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Sequential intrarectal diazepam and intravenous levetiracetam in treating acute repetitive and prolonged seizures

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Summary

In this retrospective study of institutionalized patients with mental retardation, we present the efficacy and safety of sequential treatment with intrarectal diazepam (IRD) gel (Diastat) and intravenous levetiracetam (IVL) in comparison with either treatment alone for acute repetitive or prolonged seizures (ARPS). We defined ARPS as ≥ 3 seizures of any type within 1 h or a single seizure of any type lasting ≥ 3 min. Eighty-eight ARPS episodes were treated in 25 patients (14 female, age 21–72 years), with mainly symptomatic generalized epilepsy. There were no adverse events directly attributable to the administration of IRD or IVL. Seizure recurrence within 4 h of treatment, the primary outcome measure, was significantly lower after combined sequential IRD + IVL treatment (3 of 36) compared to IRD alone (6 of 24, $p = 0.048$) or IVL alone (10 of 28, $p = 0.039$). There was no statistically significant difference between the individual IRD and IVL treatments ($p = 0.604$). The estimated odds ratio (OR) indicated that the risk of seizure recurrence was higher after IRD or IVL monotherapy compared to combined IRD + IVL treatment. Subsequent emergency room (ER) transfers following seizure recurrence were least likely after IVL treatment (10%) compared to combined IRD + IVL (67%) or IRD (83%) treatment. These findings suggest that although IRD or IVL monotherapy is efficacious, the combination is superior in controlling ARPS in this special group of institutionalized patients. In addition, we speculate that a more reliable onset of action after IVL treatment results in rapid seizure control and fewer ER transfers, despite seizure recurrence.

Keywords

Acute repetitive seizures; Seizure clusters; Prolonged seizures; Intrarectal diazepam; Intravenous levetiracetam; Refractory epilepsy; Mental retardation; Intellectual disability

The goal of treating acute repetitive or prolonged seizures (ARPS) is to prevent evolution into status epilepticus. Evidence suggests that a prolonged seizure responds less favorably to first-line therapy and that stopping the seizure prior to arrival at the hospital results in a

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favorable outcome (Lowenstein & Alldredge, 1993; Alldredge et al., 2001). Acute repetitive seizures, often called seizure clusters, may present as multiple seizures in a short time, frequent minor seizures or minor seizures with a distinct pattern recognized as heralding major seizures (Cereghino et al., 1998; Dreifuss et al., 1998). The definition of prolonged seizures is more elusive, although the data from children suggest that a seizure lasting 5–10 min should be considered prolonged (Shinnar, 2007). However, based on the proposed 5-min seizure duration as the operational definition of status epilepticus (Lowenstein et al., 1999), one can argue that a prolonged seizure should have a duration of <5 min. Although intravenous (IV) administration is preferable in preventing impending status epilepticus, alternative routes of delivery (e.g., intrarectal, intranasal, and buccal) need to be considered, particularly for home-based therapy. Currently, rectal diazepam gel (Diastat) is the only approved medication in the United States for the out-of-hospital treatment of acute repetitive seizures. Among the IV formulations, levetiracetam (LEV) has been the most recent addition, although it is not approved for treating status epilepticus.

In this retrospective study, we investigated the efficacy and safety of sequential treatment with intrarectal diazepam (IRD) gel (Diastat) and intravenous levetiracetam (IVL) for ARPS in institutionalized patients. Prompted by the relatively low success with IRD monotherapy, and the concerns about using IV formulations due to potential adverse effects (e.g., respiratory depression with lorazepam, cardiac conduction abnormalities with phenytoin), we amended the ARPS treatment protocol in our center to include sequential administration of IRD followed by IVL. Although the rationale for this approach existed in the animal model (Mazarati et al., 2004), the clinical application of this became more practical with the availability of IV LEV.

Methods

Setting and ARPS protocol

This study was conducted at the Hazelwood Center (Louisville, KY, U.S.A.), a state-run residential treatment facility. Institutional review board approval was obtained. At our center, ARPS is defined as ≥ 3 seizures of any type within 1 h, or a single seizure of any type lasting ≥ 3 min, and the recommended intervention consists of administration of IRD, transfer to a 24-h nursing unit within the facility, establishment of immediate IV access, infusion of IVL over 15 min, and transfer to the nearest emergency room (ER) if the seizures remain uncontrolled at the end of the IVL infusion. Two exceptions to this protocol are recognized based on the physician's assessment: (1) direct transfer to the ER when IV access is not feasible and seizures persist for ≥ 10 min after IRD; (2) direct administration of IVL (without prior IRD) for patients with established IV access who are already under continuous supervision for other reasons. Therefore, the treatments for ARPS could fall into one of the three study arms: IRD + IVL; IRD only; IVL only. The dose of IRD was based on the manufacturer's recommendations, rounded to either 5 or 10 mg. The dose of IVL was one-half the total daily concomitant oral dose, rounded to 500, 1,000, or 1,500 mg; for patients not on concomitant oral LEV, a dose of 500 mg was used.

Patient population

The study population consisted of patients with severe mental retardation and refractory epilepsy, personally followed by the authors. From the database, we identified the consecutive episodes of ARPS that occurred over an 18-month period (April 2007–September 2008). The outcome after each ARPS episode was noted from the chart entries. When ER transfers occurred, the reason for the transfer was ascertained from the chart, but the subsequent outcome in the ER was not tracked.

Inclusion/exclusion criteria

All ARPS episodes that were treated by either IRD or IVL, or both, were eligible for inclusion. We excluded those episodes for which the treatment was initiated after a delay of >10 min from the time of recognition of ARPS.

Outcome measure

After intrarectal administration of diazepam gel, the peak plasma concentration occurs in 45–70 min and falls to a steady-state level by 4 h (Cloyd et al., 1998). After IV administration of 2,000–3,000 mg of LEV over 15 min, the peak plasma concentration occurs in 15 min, falls to a steady state level by 1 h, with a terminal half-life of 8 h (Ramael et al., 2006). Based on this, we chose our primary outcome measure as seizure recurrence during the 4-h observation period after the initiation of treatment. As an extended measure of efficacy, we also evaluated the ER transfers that resulted from uncontrolled seizures within the treatment window (see preceding protocol) or recurrent seizures occurring after the end of treatment.

Statistical analysis

The data were analyzed by using SAS 9.2 (SAS Institute, Cary, NC, U.S.A.), based on a logistic regression mixed model, which included a patient random effect to account for the correlation among multiple observations from the same patient. The model parameters were estimated using the generalized estimation equation (GEE) method, which is robust against misspecification of the correlation structure. A p-value <0.05 was considered statistically significant.

Results

Among the 89 ARPS treatments, one was excluded because the treatment was not initiated promptly after the recognition of ARPS. Therefore, 88 ARPS treatments in 25 patients (14 female, 11 male), aged 21–72 years (mean 44 years), were available for analysis (Table 1). The treated ARPS episodes consisted of generalized tonic–clonic, atonic, tonic, absence, and complex partial seizures. The concomitant AEDs ranged from two to five. Seven patients had vagus nerve stimulator implants. The range of ARPS treatments per patient was 1–10 (median 3).

Of the 88 ARPS treatments (Table 2), 36 were in the IRD + IVL arm (19 patients), 24 in the IRD arm (14 patients), and 28 in the IVL arm (11 patients). The three arms were similar with respect to patient age, gender, and number or type of concomitant AEDs. Twenty-four and 79 ARPS treatments were administered to patients already on concomitant oral benzodiazepine (diazepam or clonazepam) and oral LEV, respectively. The mean dose of IRD (0.17–0.18 mg/kg) was similar between the IRD + IVL and IRD arms. The mean dose of IVL (19.7 mg/kg) was the same between the IRD + IVL and IVL arms. For the logistic regression mixed model, we performed a selection of variables consisting of age, gender, seizure types, epilepsy diagnosis, and treatment effects, and found only the treatment effects to be statistically significant. Based on this, seizure recurrence within 4 h of treatment was found to be significantly lower in the IRD + IVL arm (3 of 36) than the IRD arm (6 of 24, $p = 0.048$), the IVL arm (10 of 28, $p = 0.039$), or the combination of the individual IRD and IVL arms (16 of 52, $p = 0.032$). However, the difference in seizure recurrence was not statistically significant between the individual IRD and IVL arms (6 of 24 vs. 10 of 28, $p = 0.604$). The estimated odds ratio (OR) showed that the risk of seizure recurrence was higher in both the IRD [5.72, 95% confidence interval (CI) 1.01–32.39] and the IVL arms (8.90, 95% CI 1.12–70.98) compared to the combined IRD + IVL arm. Concomitant treatment with oral LEV or benzodiazepines in the IVL arm, or concomitant treatment with oral

benzodiazepines in the IRD arm did not affect the outcome ($p = \text{NS}$, Fisher's exact test); however, only one ARPS episode was treated in the IRD arm without concomitant oral LEV, precluding meaningful statistical analysis.

There were eight ER transfers in the three arms. All of these ER transfers were confined to those ARPS episodes that resulted in seizure recurrence; in other words, none of the ARPS episodes that were successfully treated initially required subsequent ER transfers. Of these seizure recurrences, 2 of 3 (67%) in the IRD + IVL arm, 5 of 6 (83%) in the IRD arm, and 1 of 10 (10%) in the IVL arm required ER transfers. There were no adverse events directly attributable to the administration of either IRD or IVL such as respiratory depression, allergic reaction, or injection-site reaction.

Discussion

Our study suggests that sequential treatment with IRD and IVL is feasible and well tolerated for treating APRS in institutionalized patients. The mean dose of IRD (0.17–0.18 mg/kg) in the IRD + IVL and IRD arms was similar, although slightly lower than the recommended dose (Diastat package insert). We believe that this was due to the lower comfort level of the physicians in prescribing the recommended dose (0.2 mg/kg) of IRD based on the risk of potential respiratory depression in this population of institutionalized patients. The mean dose of IVL (19.7 mg/kg) in the IRD + IVL and IVL arms was the same, but this could not be compared to a recommended standard as there is no weight-based dosing guideline for IVL in adults (Keppra package insert). Overall, sequential treatment with IRD + IVL was more efficacious than treatment with either IRD or IVL alone in preventing seizure recurrence within 4 h of treatment. There was no statistically significant difference in seizure recurrence between the individual IRD and IVL monotherapy arms. The risk of seizure recurrence was higher after IRD or IVL monotherapy in comparison to sequential treatment with IRD + IVL. Taken together, these findings suggest that although IRD or IVL monotherapy is efficacious, the combination is superior in controlling ARPS in this group of institutionalized patients with mainly symptomatic generalized epilepsy. This is supported by an experimental study that showed potentiation of anticonvulsant effects of diazepam by LEV when both the medications were administered in subtherapeutic levels to rats in a self-sustaining status epilepticus model (Mazarati et al., 2004). Synergism between the benzodiazepines [with γ -aminobutyric acid (GABA)ergic mechanism of action] and LEV can also be inferred based on another study in mice, which suggested a weak modulation of GABA responses by LEV (Rigo et al., 2002). Further evidence supporting this potentiation has also been reported in humans in a retrospective study of 18 episodes of status epilepticus in 16 patients where IV LEV successfully controlled the seizures that failed to respond initially to benzodiazepines (Knake et al., 2008).

In the context of the preceding discussion, one would expect that concomitant treatment with oral benzodiazepines in the IVL arm or concomitant treatment with oral LEV in the IRD arm would have led to synergism, and, therefore, favorable outcomes; however, this was not the case in the former scenario, whereas the latter could not be evaluated statistically. Similarly, concomitant treatment with oral LEV in the IVL arm, or concomitant treatment with oral benzodiazepines in the IRD arm did not affect the outcome, implying that additional doses of the same medication may still be beneficial in treating acute episodes. Overall, these findings suggest that pharmacokinetic factors (e.g., timing of administration of concomitant medication with respect to the acute treatment) may play a role in addition to the potentiation outlined earlier.

With respect to the ER transfers, we were unable to ascertain from the records whether the ER transfers occurred because of persistent seizures at the end of the treatment or because of

seizure recurrence after achieving initial seizure control. However, the results showed that there were far fewer ER transfers in the IVL monotherapy arm (10%) compared to the combined IRD + IVL or the IRD monotherapy arms (67–83%). It is worth noting that IVL was infused readily in the IVL group, since the patients already had IV access (see protocol above), resulting in reliable and rapid delivery of the drug. In contrast, in the combined IRD + IVL and the IRD monotherapy arms, although IRD was administered initially, IVL was either administered after a time delay (since a new IV line had to be placed) or not administered at all (due to difficulty in obtaining IV access). We speculate that the initial administration of IVL (with a more reliable onset of action after direct IV infusion) may be superior to the initial administration of IRD (which requires intrarectal absorption) in achieving rapid seizure control, and therefore, preventing ER transfers. However, the small number of ER transfers in this study precludes definitive conclusions.

The results of our study are applicable only to mentally retarded patients with epilepsy who tend to have certain types of seizures (e.g., tonic, atonic, and atypical absence) not typically encountered in the general population. Because of the retrospective nature of our study, we cannot make definitive conclusions regarding whether the seizure type, the number of concomitant medications, or the timing of the treatment in relation to the administration of the concomitant medications affect outcome. Prospective studies in a larger population of patients would be needed to confirm our findings; such studies can address these issues as well as differentiate the efficacy of treatment on repetitive versus prolonged seizures. Nevertheless, in the context of limited therapeutic options available in the residential facilities, our findings suggest a beneficial role for the sequential administration of IRD and IVL in treating acute repetitive and prolonged seizures.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this article is consistent with those guidelines.

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Table 1

Patient characteristics

Pt #	Age	Gender	Seizure types	Epilepsy diagnosis	Concomitant AEDs	No. of treatments
1	45	M	GTC, atonic	SGE	CBZ, LTG, LEV	3
2	22	M	GTC, tonic	SGE	DZP, LTG, LEV	8
3	43	M	Tonic	SGE (LGS)	LTG, LEV, TPM	3
4	49	M	Absence	SGE	LTG, LEV, PB, PHT, TPM	4
5	25	M	GTC, tonic	SGE (LGS)	CZP*, LTG, LEV, TPM, VPA*, ZNS*	4
6	35	F	GTC	SGE	LTG, LEV, TPM	4
7	49	M	GTC, tonic	SGE (LGS)	LTG, LEV, PGB	4
8	21	F	Tonic	SGE	DZP, LEV, VPA	4
9	46	F	CPS	SPE	CBZ, LTG, LEV	4
10	57	F	GTC	SGE	GBP, LEV, OXC	2
11	55	F	GTC	SGE	CBZ, LTG*, LEV, PB*, PHT*, ZNS	5
12	21	M	CPS	Unknown	LTG, LEV*, PB, VPA	10
13	63	M	GTC, tonic	SGE	LEV, PHT, VPA	3
14	45	F	GTC, tonic	SGE (LGS)	CZP, LTG, LEV, VPA*	8
15	36	F	Tonic	SGE	LTG, LEV	2
16	44	F	GTC	SGE	GBP, LTG, LEV	2
17	27	F	CPS	Unknown	CBZ, LEV	2
18	38	M	GTC	SGE (LGS)	LTG, LEV, PB, VPA	1
19	46	F	CPS	Unknown	LEV, VPA	3
20	61	F	Tonic	SGE	LTG, LEV, PHT, PGB, TPM	2
21	43	F	GTC	SGE (LGS)	DZP*, LEV, PHT, PGB, TPM	4
22	72	F	GTC, CPS	Unknown	CBZ, GBP, TPM	3
23	45	M	Tonic	SGE (LGS)	LEV, PB, VPA	1
24	47	F	GTC	SGE (LGS)	LTG, PGB, VPA	1
25	58	M	Tonic	SGE	LTG, LEV, TPM	1

GTC, generalized tonic-clonic; CPS, complex partial seizure; SGE, symptomatic generalized epilepsy; SPE, symptomatic partial epilepsy; LGS, Lennox-Gastaut syndrome; CBZ, carbamazepine; CZP, clonazepam; DZP, diazepam; GBP, gabapentin; LTG, lamotrigine; LEV, levetiracetam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PGB, pregabalin; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

* Concomitant only during some treatments.

Table 2
Results of treatment in 88 ARPS episodes

	IRD + IVL	IRD	IVL
Number of treatments	36	24	28
Number of patients treated	19	14	11
Gender	F = 10, M = 9	F = 9, M = 5	F = 6, M = 5
Age, years (mean age)	21–72 (42)	21–61 (40)	21–72 (39)
Seizure types treated	GTC, tonic, atonic, absence, CPS	GTC, tonic, CPS	GTC, tonic, CPS
Number of concomitant AEDs	2–5	2–5	2–4
Concomitant AEDs	CBZ, CZP, DZP, GBP, LTG, LEV, PB, PHT, PGB, TPM, VPA, ZNS	CBZ, CZP, DZP, GBP, LTG, LEV, OXC, PB, PHT, PGB, TPM, VPA, ZNS	CBZ, DZP, GBP, LTG, LEV, OXC, PB, PHT, PGB, TPM, VPA
Number of treatments on concomitant oral BDZ (DZP or CZP) (%)	6 (17)	15 (63)	3 (11)
Number of treatments on concomitant oral LEV (%)	32 (89)	23 (96)	24 (86)
Dose of IRD administered, mg (mean)	5–10 (8)	5–10 (9)	None
Dose of IRD administered, mg/kg (mean)	0.08–0.27 (0.17)	0.10–0.27 (0.18)	None
Dose of IVL administered, mg (mean)	500–1500 (1014)	None	500–1500 (982)
Dose of IVL administered, mg/kg (mean)	8.5–34.7 (19.7)	None	8.1–33.6 (19.7)
Seizure recurrence within 4 h, n*	3	6	10
Emergency room (ER) transfers, n (% of seizure recurrences)	2 (67)	5 (83)	1 (10)

ARPS, acute repetitive or prolonged seizures; IRD, intrarectal diazepam; IVL, intravenous levetiracetam; GTC, generalized tonic-clonic; CPS, complex partial seizure; BDZ, benzodiazepine; CBZ, carbamazepine; CZP, clonazepam; DZP, diazepam; GBP, gabapentin; LTG, lamotrigine; LEV, levetiracetam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PGB, pregabalin; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

* p = 0.048 for IRD + IVL versus IRD; p = 0.039 for IRD + IVL versus IVL; p = 0.604 for IRD versus IVL.