Acute Administration of Benzodiazepines as Part of Treatment Strategies for Epilepsy

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Alternative epilepsy therapies; Benzodiazepines in epilepsy; Cluster prevention; Intermittent antiepileptic treatment; Seizure prevention; Seizure prodromes; Triggered seizures.

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This work is dedicated to Prof. Dr. Dieter Janz, Berlin, on the occasion of his 90th birthday on April 20, 2010.

Ad-hoc administration of benzodiazepines (BZD) is well established in status epilepticus, but intermittent BZD use in the treatment of chronic epilepsy is little known beyond catamenial epilepsy. We aim to assess the use of acute drug administration (ADA) in the treatment of 24 patients with epilepsy (9 idiopathic generalized, 14 focal symptomatic/cryptogenic, 1 migraine-epilepsy) receiving ADA for (1) prevention of generalized tonic-clonic seizures (GTCS) after minor seizures, (2) prevention of seizures at perceived risk, (3) prevention of seizure clusters. Standard ADA was 10 mg oral clobazam (CLB); one patient received 10 mg rectal diazepam. Concomitant antiepileptic drugs (AED) remained unchanged whenever possible. Ten patients used ADA always correctly, 7 mostly, 7 sporadically or not. Outcome considering seizure control was positive in 44% of all patients (59% of those who actually used ADA): 5 patients seizure free, 1 free of disabling seizures, 4 with >50% reduction in seizure frequency. Eleven had minor or no improvement, 3 patients could not be rated. Thirteen (of 19 possible) patients attempted prevention of seizures or clusters, 10 with full or >50% success (52.6 resp. 76.9%). Prevention of clusters sometimes required higher or repetitive CLB dosing. Self rating of patients who did use ADA was positive or very positive in 88.2%. Retention rate was 66.7% of all patients, and 88.2% of those using ADA. The best results were obtained in idiopathic generalized epilepsy (IGE) patients with seizures habitually triggered by typical factors (sleep deprivation, alcohol) but also some others were successful. The only adverse effect was gait ataxia in a multiple-handicapped patient. ADA is an elegant and often successful but underused treatment option for selected patient groups where it can make the difference between becoming seizure free or not. Depending on the individual case it can be applied as monotherapy or in combination with a basis AED. A controlled investigation should follow.

Introduction

The *ad hoc* administration of a rapidly acting antiepileptic agent is an established part of the treatment of status epilepticus and comparable acute seizure events [1]. Typically, benzodiazepines (BZD) such as diazepam (DZP) and clonazepam (CZP), more recently lorazepam and midazolam are used that can be administered intravenously or by alternative (rectal, buccal, or nasal) rapid pathways. BZD are drugs of choice for this purpose because they are effective antiepileptic agents and the tolerance to them which typically develops with extended administration is no issue in an acute situation.

The intermittent use of BZD in the treatment of epilepsy is less well-known [2]. Clobazam (CLB) that can only be given orally and therefore, is unsuitable for status epilepticus has been tried for periodic administration in catamenial epilepsy [3–6], but with unconvincing results. Patients with well-defined mechanisms of seizure facilitation who are opposed to regular drug intake may profit from preventive intermittent BZD [7].

Little has been published about the acute use of such drugs as part of a comprehensive treatment strategy along with continuous antiepileptic drug (AED) administration.

This article reports on the author's own results with the use of intermittent BZD in the treatment of epilepsy.

Materials and Methods

In a prospective observational study, the present author has since January 1, 2004 registered and followed all outpatients personally treated in the epilepsy clinics of Copenhagen University Hospital Rigshospitalet and the Danish Epilepsy Centre, Dianalund with a regimen of, or including acute drug administration (ADA). ADA was prescribed to patients who still had seizures and were not surgical candidates in one of the following preconditions: patient opposed to drug treatment and wanting to avoid it, get out of it, or at least avoid dose increase; patient aware of triggering factors of seizures but unable to control them; patient with seizure recurrence in clusters. Included in this study are all patients who were registered up to December 31, 2008, in order to ensure a minimal observation period of 12 months. The first patient was enrolled on March 17, 2004 and the last on November 20, 2008.

Patients received a precise epilepsy syndrome diagnosis based on the seizure history, including seizure descriptions by witnesses when obtainable, and a standard electroencephalogram (EEG) protocol that includes 5 min hyperventilation and intermittent light stimulation and, in case of inconclusive findings, repetition after sleep deprivation to obtain a sleep recording. In all patients with a clinical diagnosis other than idiopathic generalized epilepsy (IGE), an MRI with a special epilepsy protocol is part of the diagnostic workup. Patients are seen at intervals of up to 1 year, typically 6 months, depending on the clinical indication. The regular means of seizure count and compliance control of both clinics include a standard seizure calendar to be presented at every visit, use of a drug dispenser, and routine morning trough-level determinations.

There were three indications for ADA, that is

1. Prevention of generalized tonic-clonic seizures (GTCS) after minor seizures (absence, myoclonic, simple focal, or aura)
2. Prevention of seizures in patients with perceived risk of seizures or triggering factors.
3. Prevention of clusters of seizures

The mode of application of BZD depended on the individual situation. Standard was a single oral dose of 10 mg CLB. If rapid action was required for GTSC prevention (indication 1), 10 mg DZP were applied rectally. If 10 mg of CLB proved ineffective, the dose was increased to 20 mg or changed to 2 mg CZP. In the case of seizure clusters habitually lasting for more than 1 day, repetitive CLB doses were prescribed.

To obtain the patients' consent and full cooperation, the rationale, procedures and possible risks of ADA were

explained to them in detail. They were instructed to use ADA with caution to avoid the development of tolerance by too frequent exposition.

To be included in this analysis, a patient needed to have a minimum of two seizures in the 12 months preceding ADA, and outcomes were rated for the last 12 months preceding the evaluation date. For all patients, it was noted if they had used ADA as prescribed (always, partly, or never), and if they had used it beyond the prescription. The patients gave a self-rating of ADA (very satisfactory, satisfactory, indifferent, and unsatisfactory) and reported if they felt they had been successful with seizure or cluster prevention. They were asked if they wanted to continue with ADA. A narrative of their experiences with ADA was recorded.

As a strategy, concomitant AEDs remained unchanged, but for clinical reasons this was not always possible. Changes that occurred and their possible influence on the outcome are reported in results.

Outcome was evaluated according to intention to treat, that is, patients who for some reason did not follow the prescription or dropped out before 12 months observation were not eliminated but are included in the analysis.

The outcomes were rated according to indication:

1. Prevention of GTCS after minor seizures: a modified Engel scale was used of Ia no seizures, Ib no disabling seizures, II >50% seizure reduction, III no improvement, IV deterioration.
2. Prevention of seizures at perceived risk: the same scale was used plus a rating of prevention: ++ always successful, + successful in >50% of instances, – unsuccessful.
3. Prevention of clusters: for seizure outcome, the same scale was used as with 1, for prevention the same as with 2, only referring not to seizures but clusters.

Results

Twenty-four patients were included, and 21 were followed from 12 to 66 months (mean: 29.6 months). Three patients dropped out before 12 months but are included in the evaluation. The clinical and demographic data are presented in Table 1. There were 10 males and 14 females. Seventy-five percent of the patients were older than 30 (mean 43.3, range 18–83 years), and two-thirds had epilepsy for more than 10 years (mean 18.9, range 3–44 years). Nine patients had idiopathic generalized epilepsy, and 14 symptomatic or cryptogenic focal epilepsy. One had GTCS habitually evolving out of migraine (migraine-epilepsy, [8]). Seventy-five percent had more than one seizure type. Seizures were infrequent

Table 1 Patient overview

	Group1 (8)	Group2 (8)	Group3 (8)	All (24)
Sex (m:f)	2:6	4:4	4:4	10:14
Age at entry				
Mean (range)	39.3 (18–68)	35 (26–66)	48.4 (32–83)	43.3 (18–83)
≤30	3	3	-	6
31–50	3	2	6	11
>50	2	3	2	7
Duration in years				
Mean (range)	17.3 (2–41)	12.3 (4–25)	26.6 (5–44)	18.9 (2–44)
≤10	3	4	1	8
11–20	2	2	2	6
21–30	1	2	-	3
>30	2	-	5	7
Syndromes				
Idiopathic generalized (9)				
JAE	2	-	-	2
JME	1	2	-	3
EGTCSA	-	2	-	2
Unspecified	2	-	-	2
Focal (14)				
Temporal	2	2	4	8
Frontal	-	1	1	2
Occipital	-	1	-	1
Multilobar	-	-	2	2
Multifocal	-	-	1	1
Migraine-epilepsy (1)	1	-	-	1
Baseline sz frequency (12 months)				
2–10	7	5	-	12
11–50	1	3	6	10
>50	-	-	2	2
Number of sz types				
1	1	3	2	6
2	4	3	3	10
>2	3	2	3	8

Group 1: Intervention at seizure prodrome/aura.

Group 2: Prevention of seizures at perceived risk.

Group 3: Prevention of clusters.

JAE: Juvenile Absence Epilepsy.

JME: Juvenile Myoclonic Epilepsy.

EGTCSA: Epilepsy with generalized tonic-clonic seizures on awakening.

The longer duration of epilepsy in group 3 is significant compared with group 2 (ANOVA, $P = 0.03$).

(2–10 per year) in half of the cases. The patients happen to be equally distributed over the three indication classes. Ten patients (42%) used ADA always as prescribed, seven (29%) did partly but not always use it correctly, and seven (29%) used it only sporadically or not at all. Three patients in group 1 (Prevention of GTCS after minor seizures) sometimes also used ADA for prevention of seizures at perceived risk.

Three patients used ADA frequently, that is, 1–2 × per week, six applied it with moderate frequency (1–3 × per month), and eight occasionally (1–11 × per year).

The drug used for ADA was CLB in 21 cases, rectal DZP in one, and in two both rectal DZP, oral CLB, and oral CZP were tried.

Overall Ratings

Seizure Control

Five patients became totally seizure free (Ia) and one, free of disabling seizures (Ib). Four had a >50% reduction in seizure frequency (II), and in 11 the seizure

frequency was unimproved (III). In three, the seizure frequency could not be determined. Thus, improvement of seizure frequency (outcome classes I and II) was achieved in 44% of all enrolled patients, and in 59% of those who actually applied ADA. Development of tolerance was not observed with the restricted exposition to BZD applied.

Prevention

Prevention of seizures or clusters was applicable in 19 patients of whom, however, six had not attempted it. Of the remaining 13 patients, four had always, and six in >50% success with prevention, two failed, and one could not be rated. The 10 successes represent 52.6% of all applicable and 76.9% of all who tried.

Self-Rating

Of the 17 patients who actually applied ADA, seven found it very satisfactory, eight satisfactory, one was indifferent, and one gave a negative rating. The positive ratings represent 62.5% of all patients and 88.2% of those who applied ADA.

Retention

Fifteen patients decided to continue with ADA and two did not. Of the seven who did not apply ADA, six continue to do so, and one decided at follow-up to start with ADA. The retention rate, thus, is 66.7% of all patients and 88.2% of the ones who used ADA.

Unconfirmed Potential Factors of Outcome

The number of different seizure types and the baseline seizure frequency (Table 1) did not influence the outcome. Successfully treated patients were not different in duration of epilepsy (mean 19.0 years, range 3–39 vs. 18.9 years, range 2–49).

ADA and Epilepsy Type

In the nine patients with IGE, ADA was used either as prevention of GTCS after minor seizures or as seizure prevention at perceived risk. Seven adhered to the prescription fully or partly and were successful with seizure prevention (three seizure free, one free from disabling seizures, two with >50% seizure reduction, and one with no improvement of seizure frequency but successful seizure prevention, for example, with intercontinental travels).

In the group of focal epilepsies ($n = 14$) all three indications for ADA exist. Nine patients adhered to prescription, of which one had outcome class Ib and another, class II. One patient became seizure free without ADA by avoidance of trigger situations. All others were unimproved. However, success with prevention of seizures or clusters was reported by six and failure only by two, one could not be rated.

The patient with migraine-epilepsy became seizure free (Ia) with ADA at onset of migraine aura.

Prevention of GTCS after Minor Seizures

There are eight patients in this group. Five had idiopathic generalized epilepsy with GTCS that were preceded by series of either absences or myoclonic seizures; in all five, the rare GTCS were triggered by lack of sleep, in three together with social drinking, in two also following intercontinental flights. Two had temporal lobe epilepsy (TLE) with GTCS preceded by auras of sufficient duration to allow for ADA intervention, and one had migraine-epilepsy. Seven used 10 mg oral CLB and one, 10 mg rectal DZP. Two IGE patients and the patient with migraine-epilepsy are totally seizure free, two IGE patients had a >50% seizure reduction, and in one the seizure frequency was unimproved. This patient, however, had used CLB in situations of perceived risk, for example, intercontinental flights or occasions of reduced sleep, had in these cases not had a seizure and rated ADA as positive. Of the two TLE patients, one with seizures of much variable frequency never used CLB. The other reported positive experiences with the prevention of GTC, but in <50% of instances. He is rated as unimproved but gives a positive self-rating and continues with ADA.

Concomitant AEDs

One patient received ADA as monotherapy, and one discontinued other treatment due to the success of ADA. Drugs remained unchanged in three (two with excellent outcome), and in another three were adjusted to reach better effect, which, however, was only obtained in one (Table 2).

In summary, the treatment in five of these eight patients was successful, but in one the improvement could not be ascribed to ADA. Two were unimproved, both with irregular use of ADA, and one who never took the BZD could not be rated. All three patients who used ADA exactly as prescribed became seizure free. Most of the successful patients had IGE.

Table 2 Concomitant AEDs and outcome ratings

AED	Group 1	Group 2	Group 3
None	1: II	1: III	0
Unchanged	3: Ia,Ia,III	5: Ia,II,II,II,III	5: Ib,III,III,III,III
Discontinued	1: Ia	0	1: III
Adjusted for better effect	3: II,III,III	1: Ia	2: II,III
Reduced for side effects	0	1: III	0

Rating scale (modified Engel scale):

Ia: seizure free.

Ib: free from disabling seizures.

II: >50% reduction of seizure frequency.

III: smaller or no reduction of seizure frequency.

The improvements in all but three cases cannot be due to changes in the comedication.

Prevention of Seizures at Perceived Risk

Of the eight patients, four had IGE, two TLE, and one each occipital lobe epilepsy (OLE) due to arteriovenous angioma (operated) and posttraumatic frontal lobe epilepsy (FLE). The prescribed ADA was 10 mg CLB in all instances. The reported triggering factors were lack of sleep/social drinking in five, extraordinary psychophysical stress in two, and exposure to complex linguistic input at social occasions in one patient with left TLE. Five of these patients reported that they only had provoked seizures but in two of them this perception was not quite convincing. These two and a patient with Juvenile Myoclonic Epilepsy (JME) with classical seizure provocation never used the prescribed ADA but one of them (with TLE) had instead successfully avoided the triggering factors and was seizure free at follow-up. Of three patients who applied CLB correctly two with IGE became seizure free, and one with TLE had a 65% seizure reduction. The patient with FLE who has been followed for 60 months, experienced successful intervention in a first period, then stopped using ADA in a period of very low seizure frequency, and is now successfully using it again. Her seizure outcome is rated unimproved but her self-rating is clearly positive and she continues with ADA.

Of the three patients who convincingly reported only provoked seizures, two used ADA as prescribed and are seizure free, the third hesitated and did not yet use it.

Concomitant AEDs

One patient takes no drugs, and in six the initial AED dose remained unchanged. The remaining patient obtained reliable prevention by ADA after a dose increase of concomitant lamotrigine, indicating full seizure control as a combined effect of continuous AED treatment and ADA.

In summary, the best results (class Ia) were again obtained by patients with IGE, but also one TLE patient with a well-defined trigger was markedly improved. No patient failed who used ADA correctly. Six of eight patients continue with ADA. In one patient, reduction of seizure propensity by a baseline AED was a prerequisite for successful seizure prevention by ADA.

Prevention of Clusters of Seizures

The eight patients in this group are the oldest, have epilepsy longer than the others, and have a higher seizure frequency. All had focal epilepsies (four TLE, one FLE, three multilobar or multifocal) with seizures occurring in clusters at intervals, in three cases as the only pattern and in five with interspersed isolated seizures. The ADA in all cases was CLB 10 mg after the first or second seizure, depending on the individual pattern of clustering. In cases of clusters spreading over >1 day the dose was repeated following an individualized schedule. In three cases, the 10 mg dose proved not sufficiently effective and was increased to 20 mg. Three patients never used ADA, four used it always as prescribed and one, mostly. Two were fully successful with cluster prevention, which in one resulted in a class Ib rating (free of GTCS). In this patient whose clusters habitually lasted from 1 to 4 days, a first dose of 10 mg CLB will prevent further seizures but is repeated at bedtime. Sometimes a third dose is taken on day 3 if there is another simple focal seizure. The clusters in two patients were not prevented by ADA, and in one of them, a multihandicapped patient, CLB resulted in increased ataxia. These patients stopped the use of ADA after 4 and 7 months, respectively.

Concomitant Medication

See Table 2. In one patient, termination of a current treatment with 20 mg CLB daily proved a precondition of successful cluster prevention, which occurred after a washout period of 4 months.

In summary, in this group ADA is used as a palliative approach and the outcome is rated by cluster prevention rather than general seizure reduction. The goal was reached in three of the five patients who actually used ADA, and in one this meant that he became free of disabling seizures (outcome class Ib). In the two others ADA failed in spite of correct application, and in one of them the only serious side effect of ADA in this cohort (ataxia) was registered. For three patients, 10 mg CLB that usually was a sufficient dose in the two other groups turned out to be too low. A patient with clusters outlasting 1 day repeats the dose once or twice.

Problems with ADA

Like all nonsurgical therapies the success of ADA depends to a large extent on the patients' adherence to the prescription. Seven of our patients (29%) never applied ADA. The reasons were either that during the observation period the situation for its application did not occur or so rarely that the patient had forgotten the prescription, or that the patient for some reason was not willing to apply it, or developed an own strategy of avoiding trigger situations (two cases). Another seven patients did not always correctly use ADA, mostly because they had difficulties in deciding if the situation was such as it should be applied or not. This can be an objective difficulty since the situation to which they have to respond may not be a "yes/no" but, rather, a "more/less" situation, for example of the intensity of an aura sensation or the frequency of habitual absences. Only three of these patients obtained an overall improvement although they all reported positive experiences with ADA. This situation may still improve due to further discussion with the patients.

In some cases, the incipient seizure activity to which the patients are supposed to react impairs their cognition and their ability to adequately respond. In these cases the assistance of a family member or other caretaker may be required.

Discussion

The patients' advanced age and the long duration of their epilepsies at start of ADA show that this therapy approach is little known and little used. In contrast, this observational study indicates that ADA is a particularly well-focused, often successful treatment option for selected patient groups, that is, (1) Patients with GTCS preceded by minor seizures (absence, myoclonic, simple focal, or prolonged auras); (2) patients whose seizures habitually are conditioned by well-defined trigger mechanisms (perceived risk); and (3) patients with seizures occurring in clusters.

The best candidates appear to be patients with one of the juvenile and adult syndromes of IGE, especially if most or all seizures are triggered by the conditions, which are typical for these syndromes, that is, sleep deprivation with or without alcohol or increased psychophysical stress. For these patients, ADA can make the difference between being seizure free or not. Not all of them but some can even stop continuous AED intake and remain seizure free. These patients are represented in both groups 1 and 2, the difference between the groups being mainly if ADA is applied prophylactic in situations of perceived risk, or in response to incipient seizure activ-

ity. Some patients will prefer the first option, others the second, some use it at both occasions.

The most important point seems to be that the indication for ADA is well-defined, that the well-motivated and well-instructed patient is able to recognize it, and applies ADA consistently.

Another potential use of prophylactic ADA, independent of perceived increased seizure risk, is seizure prevention preparing for a social situation or performance (concert, church service, public appearance, sports) where having a seizure would be a major inconvenience or carry an increased risk of trauma. However, no such patient is included in this cohort.

The third group is quite different. Here the primary purpose of ADA is not curative, but palliative. If the majority of a patient's seizures are part of a cluster it makes an important difference if ADA after a first seizure reduces clusters to single seizures. The small group reported included both a well-functioning patient whose clusters of simple focal seizures habitually terminated with a GTCS and who is now free of these, and a moderately handicapped patient whose mobility outside the house is greatly improved since she can be confident not to get another seizure that day, having used ADA.

However, compared with the partially overlapping groups 1 and 2, and considering that only five patients actually used ADA, the group of cluster prevention is very small and a larger prospective study is a desiderate although an older proof-of-principle study exists [9].

The standard ADA used in this cohort was oral CLB in a dose of 10 mg. For prevention of clusters, a higher dose of 20 mg was sometimes needed, and in patients with clusters extending over more than 1 day, repetitive administration can be required. Parenteral ADA is indicated when immediate action is required. This was applied to one patient in this cohort who received DZP 10 mg rectal. For convenience, buccal midazolam would now mostly be preferred.

ADA must not be seen as an alternative to regular AED treatment. In many patients, especially those who not only have seizures conditioned by triggers, a baseline reduction of seizure propensity by some ongoing AED is necessary, and full seizure control is achieved by ADA which takes care of exceptional occasions when the basis medication does not suffice. It seems, however, that some patients can even use this elegant method as monotherapy.

The author is fully aware of the limitations of the observational approach taken here where in particular placebo effects could be at play. The scope of this study is therefore mostly explorative of an area that appears under investigated and not easily lends itself to a controlled approach. Of the three indications discussed here,

cluster prevention seems to be the one where a randomized comparative study seems best feasible and is planned to be undertaken.

Conflict of Interest

The author has no conflicts of interest to declare.

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