Acute Drug Administration in Epilepsy: A Review

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Keywords

Epilepsy; Benzodiazepines in epilepsy; Intermittent antiepileptic treatment; Seizure prevention; Cluster prevention; Triggered seizures; Seizure prodromes; Prolonged seizures.

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SUMMARY

Aims: To review acute administration of drugs in epilepsy for indications other than status epilepticus. **Discussion:** This review looks into the application of acute drug administration (ADA) against febrile and prolonged nonfebrile seizures in children, seizure clustering (habitual or at drug withdrawal), catamenial epilepsy, response to seizure “warnings”, and prophylaxis of seizures at perceived increased risk (reflex epilepsies, long-distance travel, lifestyle, and social occasions). The drugs most commonly used for ADA are the benzodiazepines diazepam (oral or rectal), clobazam and buccal or nasal midazolam, and lorazepam. Others include valproic acid, nitrazepam, acetazolamide, chloral hydrate, pyridoxine, and antipyretics. **Conclusions:** The best evidence for the efficacy of ADA exists in febrile and nonfebrile childhood seizures, whereas the evidence in catamenial epilepsy is weak. Prevention of clusters is a well-proven principle but its application has been little studied. Prevention of imminent seizures predicted by well-established triggers, defined risk factors, or premonitory minor seizure activity seems to be at the same time the most intelligent and the least investigated application of ADA and would deserve to be better studied.

Introduction

Rapidly acting drugs with a strong anticonvulsive effect have a well-established role in the treatment of status epilepticus. Benzodiazepines (BZD) are especially used for the initiation of status treatment by the staff of ambulances and emergency rooms. A related use is the diagnostic application of a BZD, often EEG—monitored, when a patient is admitted with suspected nonconvulsive status epilepticus. Injectable BZD like clonazepam (CLZ) are being replaced by others which can be rapidly applied by easier routes: rectal diazepam (DZP), buccal midazolam (MDZ), and nasal lorazepam (LZP).

This article reviews other uses of acute drug administration (ADA) in the treatment of epilepsy which are less well-known and well-established although they may be in more or less common use.

Febrile Convulsions (FC)

The best documented use of ADA is in children with FC. This is a genetically determined condition where a

high rate of recurrence has long been known and given rise to attempts at secondary prevention. Continuous administration of classical antiepileptic drugs (AED) like phenobarbital (PB) or valproic acid (VPA) has been advocated but also strongly been argued against. Not all children relapse after a first FC, so many would be unnecessarily exposed to potentially toxic, sedative and cognitive side effects of these drugs. On the other hand, FC are not always harmless. They may evolve into status epilepticus with a risk of brain damage and, especially when prolonged or accompanied by neurological signs, they may result in chronic epilepsy [1]. The well identified trigger, that is, fever, opens the possibility of preventing seizures without the disadvantages of chronic drug administration. Knudsen and Vestermark [2] in a randomized study of 195 children compared over 1 year the prophylactic effect of continuous PB intake with ADA of oral DZP in the case of fever of 38.5°C or more. Both groups had the same rate of recurrence of FC of the same severity and duration. It was concluded that continuous PB had no advantage over the much better tolerated acute DZP; in addition, 80% of the observed

recurrences with DZP were due to nonadherence to the protocol.

The drawback of this study was the lack of controls without any AED administration. Rosman et al. [3] conducted a placebo-controlled trial of acute oral DZP in 406 children and found a clear prophylactic effect of DZP. However, there were again many instances of FC recurrences due to nonapplication of ADA. Subjects in both groups were withdrawn from the study because of afebrile seizures, side effects of medication, frequent simple FC or recurrent complex FC. Reasons not to apply ADA in children who remained in the study were failure to take the temperature, FCs preceding the rise of temperature, DZP not being at hand, misunderstandings of the instructions, and vomitus. Parents were also sometimes concerned about side effects even if these were only moderate [3] or did not exceed transient sedation [2].

The question remained what effect any coadministered antipyretic medication could have that could contaminate the study of DZP effects. Uhari et al. [4] tried to sort this out in a careful randomized and placebo-controlled investigation of DZP given with and without acetaminophen (paracetamol). The latter had no influence on FC recurrence but unexpectedly the same was true for DZP, possibly because a too low dose had been given.

Another double-blind, randomized study that showed no difference between DZP and placebo in the prevention of recurrence of febrile seizures was published by Autret et al. [5] who believe that the lack of effect was due to parents' nonadherence. DZP had been administered as prescribed in only 1 of 15 patients with recurrences.

Vanasse et al. [6] in an open study demonstrated that Nitrazepam administered to children at risk in the case of fever in comparison with no prevention had similar positive effects as DZP.

Rose et al. [7] prefer Clobazam (CLB) for FC prevention to DZP because of fewer side effects. They established the effect of CLB in a randomized study with placebo control but did not directly compare DZP and CLB.

These investigations looked into the possibility of absolute prevention of further FCs in children where a first FC had revealed the risk, and the results were positive but imperfect. Still some parents were concerned about the side effects of acute BZD administration, and some children would not have had recurrences even without ADA. Another possible and more focused approach is the use of ADA after the onset of a FC with a new febrile illness. The rationale is that simple FCs usually have no sequelae, and what needs to be prevented are complications by prolonged convulsions, and status epilepticus. Oral ADA, however, is too slow-acting for this purpose, and AED injection not applicable at home. This approach,

however, became a serious possibility when rectal DZP became available which is rapidly absorbed and can be kept available in the home of children at risk and administered by the parents [8]. Surprisingly, although the differences in approach were clearly outlined at an early stage [9,10] investigations of rectal DZP [e.g., 11] often did not go for such a rapid termination strategy but just repeated the secondary prevention idea.

Of 38 children with prolonged or repetitive seizures who participated in an open uncontrolled study of home ADA with rectal DZP [12] 14 had complex FC. The authors concluded that this treatment is effective in aborting seizure activity, reduces morbidity and costs associated with hospital visits. Rectal DZP at the time of an actual FC recurrence to prevent prolonged seizures is presently recommended by Camfield et al. [13] as the standard home treatment of febrile seizures "for a well-organized family." Thus, the rapid termination strategy, although less investigated, seems today to prevail over the prevention strategy, apparently due to a combination of proof of principle evidence and the application of common sense.

Other Benzodiazepines than DZP

To administer a drug rectally to a child who is bedridden with fever may not be problematic but more recently there are alternatives for providing rapid BZD action. O'Regan et al. [14] gave nasal MDZ to 19 children with frequent epileptiform EEG discharges and found that these were rapidly interrupted in fifteen cases. On this background, Lahat et al. [15] undertook a thoughtfully designed emergency-room based prospective randomized comparison of nasal MDZ not with rectal but with intravenous DZP in FC. Both drugs were equally efficient in stopping the seizures. Intravenous DZP acted slightly quicker than intranasal MDZ but this was more than made up by the more rapid application of MDZ, so the total time from arrival in hospital to cessation of seizures was shorter with MDZ. The authors make the point that intranasal MDZ would also be applicable at home. McIntyre et al. [16] in a controlled trial compared buccal MDZ to rectal DZP for emergency treatment of seizures in children. Of 219 episodes treated 78 (36%) were febrile episodes. Buccal MDZ was found more efficient but the study was emergency-room based and the best responders to DZP may have been filtered out previously by successful home treatment. However, the efficacy of MDZ was established by this investigation beyond doubt.

Other drugs than BZD

Shimazaki et al. [17] compared rectal chloral hydrate with rectal DZP, both given with fever before a FC, and

found DZP with high significance superior in the prevention of FCs.

Daugbjerg et al. [18] compared the prophylactic effects of rectal DZP with VPA suppositories in a randomized study with inconclusive results which, however, did not indicate that VPA was ineffective.

Pyridoxine deficiency and pyridoxine dependence are well-known causes of seizures in infants, and the finding of abnormal tryptophan loading tests immediately following a febrile seizure seemed to indicate an increased demand for pyridoxine as a possible pathogenic factor in FC of predisposed children. This prompted McKiernan et al. [19] to investigate in a placebo-controlled study the possible protective role of Vitamin B6 supplementation in children with FC. The results, however, were negative even when an abnormal tryptophan load test had been found. Kamiishi et al. [20] gave vitamin B6 in a randomized comparative study acutely to children who in a febrile episode had had a FC. "Some" patients had also received rectal DZP or chloral hydrate, no further details given. Twenty children treated with pyridoxal had no further FC during the episode, whereas 43.2% of 45 untreated controls had recurrent seizures. As it seems, this interesting difference in the action of pyridoxal as ADA and as sustained administration has not been further investigated.

Antipyretics are often coadministered with AEDs with the rationale to reduce temperature and thereby indirectly prevent FCs. The negative finding with acetaminophen of Uhari et al. [4] was mentioned above. Van Stuijvenberg et al. [21] found that the acute administration of ibuprofen also had no prophylactic effect. Strengell et al. [22] in a recent well-controlled study of 231 children who received at first rectal diclofenac or placebo followed by oral acetaminophen, ibuprofen, or placebo without AED confirmed that the effect of these antipyretics did not differ from placebo although the doses applied were higher than in the earlier studies.

Nonfebrile Prolonged Seizures in Children

Prolonged seizures unconnected with febrile illness are much more common in children than in adults, and several of the above-mentioned studies included both febrile and nonfebrile seizures. Other authors looked at nonfebrile prolonged seizures separately, and their results are similar to FC. Jeannet et al. [23] in an open study found nasal (and sublingual) MDZ highly effective in the treatment of acute nonfebrile seizures in children. Scott et al. [24] in a randomized investigation compared rectal DZP

with buccal MDZ. They found that DZP stopped 23 out of 39 events (59%) and MDZ 30 out of 40 (75%), the difference not being statistically significant.

Epilepsies with Clusters of Seizures

The principle, in adults with seizures habitually recurring in series, of preventing these by administration of oral or rectal DZP was proved in two placebo-controlled studies by Milligan et al. [25]. Excellent effect of sublingual LZP in arresting serial seizures in children was found in an open observational study by Yager and Seshia [26]. These authors did not look into the use of this approach as a sustained treatment strategy. Lombroso [27] investigated the effect of treatment at home by oral or rectal DZP (0.2–0.5 mg/kg) of different kinds of status epilepticus, prolonged seizures and clusters of seizures in 76 disposed patients. He compared the time course of 587 events registered in two study years with that of 611 events in the two previous years, in the same patients. Three hundred and sixty seven of these events were clusters of several hours to several days. The treatment was very effective, as seizures continued or relapsed in only 4% of the events (a second dose, however, was given because of relapse in 66 of 517 events). However, the specific figures for clusters are not presented in the article. Dreifuss et al. [28] conducted a randomized placebo-controlled study of rectal DZP for acute treatment of seizure clusters and found it highly effective. Remy [29] recommended to use CLB once or for maximum 2–3 days as add-on therapy for acute treatment of serial seizures, especially when there is a menace of developing status epilepticus. Trimble [30] pointed out that clusters of seizures increase the risk of postictal behavior disturbance and psychosis and recommended a much higher CLB dose, that is, 10 mg in 6 h intervals for 48 h, ending up with 80 mg in 2 days. These authors' dosing advice, however, seems to be based on experience rather than quantitative data. In an observational report Wolf [31] found that a single dose of 10 mg CLB was not always sufficient to break the commencing series and recommended 20 mg; in rare instances the dose needed to be repeated. He recommended a prospective controlled study to further clarify the clinical value of this application of ADA.

Catamenial Epilepsy

A special kind of clustering, that is, seizures in relation to the menstrual cycle, has been described in various types of epilepsy and called "catamenial epilepsy." It is not easy to define and in consequence very variable figures on its frequency have been reported by Foldvary-Schaefer and Falcone [32]. Clustering may occur both

around menstruation and ovulation but exclusively menstruation-bound seizures are very rare [33]. Feely and Gibson were the first to attempt intermittent treatment for this condition. They used CLB and hoped that the intermittent use would prevent tolerance from developing. In a controlled study, they established the superiority to placebo of 20 (–30) mg of CLB given for 10 days “around menstruation” [34], and followed in an open observation 13 women who had responded favorably [35]. It seems that no patient became seizure free, probably because none had exclusively catamenial seizures. Three remained seizure free around menstruation but another three showed increased seizure frequency between the CLB periods. Tolerance did not develop. This application of BZD seems not to have been further investigated [32].

Acetazolamide (AZM) is a rarely used AED with a tradition in the treatment of catamenial epilepsy [32]. Ansell and Clarke [36] anecdotally reported on two women with “marked menstrual aggravation of their seizures” and regular cycles who had “marked benefit” from receiving AZM 5 mg/kg/day on the day before the onset of menstruation and the following day. Lim et al. [37] retrospectively evaluated 20 women with catamenial epilepsy who were treated with AZM. Fifty-five percent received the drug daily and 45%, perimenstrually. None was seizure free but 40% were significantly improved. In this small sample there was no difference in effect between continuous and intermittent treatment. The authors considered a prospective double-blind study but this seems never to have materialized.

To conclude, even as there may be some effect of ADA in catamenial epilepsy [38] the evidence is weak and inconclusive.

Response to “Warnings”

Seizures do not always start abruptly. In focal epilepsies the onset often is with a subjective experience (“aura”) which patients may use for attempts at arresting the seizure, for example, by sensory, cognitive or motor stimuli [39] or by on-demand vagus nerve stimulation [40]. The possibility of intervention is to a large extent dependent on the length of the aura which usually is a rather stable feature in a given patient. Most often auras last only a few seconds or less, but in some patients they last longer, and then ADA is a possible approach. Likewise, generalized tonic-clonic seizures (GTCS) in idiopathic generalized epilepsies may be heralded by a volley of myoclonic seizures or a series of absences which leave the patients or caretakers the possibility of intervention. Another type of seizure “warning” are prodromes

which typically last from 30 min to several hours, allowing for “preventive and therapeutic measures, including drugs, neurostimulation procedures and behavioral intervention ... to interrupt the pre-ictal cascade” [41]. No previous publications regarding this approach were found, but of eight patients with auras and prodromes treated with ADA alone or add-on by Wolf [31] three became seizure free, two were >50% improved, and three remained unchanged.

Epilepsies with Specific Seizure Triggers (Reflex Epilepsies)

Reflex epilepsies are conditions where many or all seizures are triggered by well-defined reproducible sensory or cognitive precipitating mechanisms [42]. This provides a predictability of seizures that can be used for prophylactic ADA, especially when the occasions presenting the provocative stimulus are infrequent. Thus, photosensitive youngsters going to a disco where they are exposed to stroboscopic lights could get prepared taking 10 mg of DZP or CLB to be safe. Photosensitivity being the most frequent type of reflex epilepsy this may often be used but seems never to have been evaluated.

Eating seizures, a less frequent but well-described reflex epileptic entity, seems a less ideal target for ADA since we eat every day. However, Aguglia and Tinuper [43] reported three patients with seizures precipitated by eating whom they treated, in addition to current AEDs with 10 mg CLB taken 1 hour before eating, three times per day in two, and once before lunch in the third. The patients had experienced between one and five eating-provoked seizures per week, and these disappeared. Only in one patient seizures recurred after 2 months. However, due to the long half-lives of CLB and especially its active metabolite Desmethyl-CLB [44] this cannot really be considered an intermittent treatment.

Dhanaraj and Jayavelu [45] used acute CLB administration in hot water epilepsy, in India a rather frequent type of reflex epilepsy where seizures are provoked by bathing when hot water gets poured over the head. They chose patients with exclusively provoked seizures ($n = 10$) and used intermittent CLB as monotherapy. The patients took 10 mg $1\frac{1}{2}$ h before taking a “head bath”. Nine patients became seizure free. One of these had a relapse when he started to take CLB later ($1\frac{1}{2}$ h before the bath) and reached full control again with correct timing. In the remaining patient the therapeutic effect was only partial, consisting in a reduction of seizure severity. The authors conclude that ADA with CLB is the treatment of choice in patients with this syndrome if all seizures are provoked.

Other Prophylactic Acute Administration

According to Levy et al. [46, p. 207] CLB is “ideal for bridging a short period of increased seizure susceptibility (e.g., during examinations, overnight travel, attending a party, switching antiepileptic drugs).”

Prevention of Withdrawal Seizures

Withdrawal seizures are a well-known risk at discontinuation of several classes of substances which somebody has been using for an extended time. Well-known examples are barbiturates and BZD but also alcohol. Typical reasons for AED discontinuation in the treatment of epilepsy are switch to another AED and side effects. Withdrawal seizures can occur even when the discontinued drug had no appreciable therapeutic effect. They can often be avoided by stepwise slow reduction in small decrements. But sometimes, especially with serious toxicity or acute allergic reactions, rapid withdrawal is desired. With some drugs, withdrawal seizures even may occur with very small dose decrements, CLZ being the prototype [47]. Prophylactic ADA, for example, with CLB seems a solution to this problem but has been little investigated.

A special situation is created by AED withdrawal during intensive monitoring with the purpose of provoking seizures for diagnostic reasons or as part of the work-up for possible surgery. The purpose usually is reached with a limited number of seizures which then should be stopped, to prevent status epilepticus. LZP in a concentrated oral solution with “an absorption profile similar IM LZP” has been successfully used with this indication by Schroeder et al [48].

Lifestyle-Provoked Seizures

Disturbances of sleep increase the risk of seizures in many patients, particularly but not exclusively with Juvenile Myoclonic Epilepsy and other idiopathic generalized epilepsies [49], especially when combined with excessive alcohol intake. Some patients with infrequent seizures even have exclusively provoked seizures. Many are perfectly aware of this relation, but that does not necessarily mean that they are willing to abandon party-going which may be a cherished part of their lifestyle. The use of ADA with this indication has not been investigated before but of five own patients with this indication two became seizure free and two had a >50% improvement [31].

Travel

Overnight travel is one of the possible situations resulting in disrupted sleep but no targeted investigations of this risk and its possible prevention by ADA seem to exist.

Air travelling is an important aspect of modern life, both for private and professional reasons, and especially long-distance flights producing jet lags appear to create typical risk situations for seizures. Seizure frequency was increased following flights of 23 volunteer patients over a mean distance of >2400 miles and lasting approximately 6 h in a study of Trevorrow [50]. Prophylactic ADA is not discussed in this study, and its use seems not to have been investigated in any targeted investigation. It is, however, a logical use of ADA, its protective action being established as a principle, and the present author found such recommendations on the internet in numerous patient information sheets, advisers, etc. To consider preflight use of a BZD is one of the counselling topics for people with epilepsy mentioned by Draskowski [51].

Social Indications

Another logical application of ADA is the prevention of seizures in a socially important or potentially stigmatizing situation. Examples which the present author has come across were the participation in church service, theatre, concerts, and sports events but especially occasions where the patient is in focus like when performing at cultural, political or scientific events, at application for a job or presenting a project or result to their superiors, not to forget a patient's own wedding. Many of these are occasions of increased stress which may increase the seizure risk by itself. However, this aspect seems never to have become the subject of a specific investigation.

Potential Problems Associated with ADA

Of the typical side effects of BZD, sedation and drowsiness are mentioned in many of the reports but were in the controlled studies of ADA in FC not different from placebo. Autret et al. [5] who discuss in some detail the problem of insufficient cooperation of parents did not identify side effects as an important reason. Respiratory insufficiency was a concern particularly as rapidly absorbed BZD became available for home use [8–10,16] but according to O'Dell et al, [11], serious respiratory events proved to be extremely rare. Fall in blood pressure or related symptoms like dizziness were reported in isolated cases with rectal DZM [8] and nasal or buccal MDZ [23,24]. Anecdotally, the present reviewer has encountered syncope following ADA with buccal MDZ, when the patient rose from a sitting position after 5 min, and

recommends a longer rest period. No similar reports were found in the literature. Paradoxical agitation in children [5,23] and ataxia [6,7,18] were occasionally seen, and skin irritation around the nostrils with frequent ADA using nasal MDZ was reported in a patient of Jeannet et al. [23]. Considering the indications for which ADA is used, the possible side effects in most cases are a minor concern.

The frequency with which BZD can be applied without developing tolerance has been very little discussed. The highest frequency of successful ADA reported by Wolf [31] was 1–2 per week in three out of 24 patients whereas Dhanaraj and Jayavelu [45] did not comment upon the frequency of head baths successfully protected by ADA which was probably in the same order.

As pointed out by Wolf [31], the use of ADA by patients may involve ambiguous decision-making that requires a learning process before full success can be expected.

Conclusions and ADA in Clinical Practice Today

Febrile and prolonged nonfebrile seizures in children are the indications for ADA which are established with the best investigational evidence. These are also the quantitatively most important indications. Its use in catamenial epilepsy is inconclusive, perhaps due to the rarity of cases with seizures exclusively bound to the menstrual cycle. For the prevention of clusters of seizures there is good proof of principle but a lack of controlled studies to establish the clinical usefulness of ADA.

Prevention of imminent seizures when they can be predicted with some probability by well-established triggers, the presence of defined risk factors or by premonitory minor seizure activity (prodromes, prolonged auras, series of absences, or myoclonic seizures) seems to be at the same time the most intelligent and the least investigated application of ADA. The evidence for this use, add-on or as the only therapy, based on prospective observation [31, 45] is weak but promising and would deserve to become better investigated.

Conflict of Interest

None.

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