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Review

Drug-induced status epilepticus

Hannah R. Cock

IMBE, St George's University of London, London SW17 0RE, UK
Atkinson Morley Epilepsy Group, St Georges University Hospitals NHS Foundation Trust, London SW17 0QT, UK

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ABSTRACT

Drug-induced status epilepticus (SE) is a relatively uncommon phenomenon, probably accounting for less than 5% of all SE cases, although limitations in case ascertainment and establishing causation substantially weaken epidemiological estimates. Some antiepileptic drugs, particularly those with sodium channel or GABA(γ-aminobutyric acid)-ergic properties, frequently exacerbate seizures and may lead to SE if used inadvertently in generalized epilepsies or less frequently in other epilepsies. Tiagabine seems to have a particular propensity for triggering nonconvulsive SE sometimes in patients with no prior history of seizures. In therapeutic practice, SE is most commonly seen in association with antibiotics (cephalosporins, quinolones, and some others) and immunotherapies/chemotherapies, the latter often in the context of a reversible encephalopathy syndrome. Status epilepticus following accidental or intentional overdoses, particularly of antidepressants or other psychotropic medications, has also featured prominently in the literature: whilst there are sometimes fatal consequences, this is more commonly because of cardiorespiratory or metabolic complications than as a result of seizure activity. A high index of suspicion is required in identifying those at risk and in recognizing potential clues from the presentation, but even with a careful analysis of patient and drug factors, establishing causation can be difficult. In addition to eliminating the potential trigger, management should be as for SE in any other circumstances, with the exception that phenobarbitone is recommended as a second-line treatment for suspected toxicity-related SE where the risk of cardiovascular complications is higher anyways and may be exacerbated by phenytoin. There are also specific recommendations/antidotes in some situations. The outcome of drug-induced status epilepticus is mostly good when promptly identified and treated, though less so in the context of overdoses.

This article is part of a Special Issue entitled "Status Epilepticus".

1. Introduction

That drugs can cause status epilepticus, both convulsive and nonconvulsive, is well recognized and indeed exploited in much of the preclinical work that underpins current understanding about the pathophysiology of epilepsy and drug development. At the simplest level, SE might be an expected risk from drugs which increase central nervous system (CNS) excitation such as glutamate agonists or those which reduce inhibition such as GABA (γ-aminobutyric acid) antagonists, and this is indeed the case in clinical practice. However, there are inevitably many more and sometimes complex mechanisms implicating drugs as a cause of SE, in both therapeutic and overdose situations, but as will be discussed, establishing causation is often difficult with multiple confounders and literature of varied quality. This review will start by discussing these limitations, and, following a brief epidemiological overview, will summarize the literature on drug-induced SE, focusing on those areas where evidence is most compelling and concluding with some general guidance for the practicing clinician.

E-mail address: hannahrc@sgul.ac.uk.

2. Methods and limitations

All articles cited by a previous systematic review on the uncommon causes of SE [1] and additional publications since identified from a search of the published English-language literature on PubMed and Web of Knowledge using the search terms status epilepticus and drug-induced seizure or adverse drug reaction, but excluding preclinical studies (search terms rat and in vivo) other than where directly relevant to drug-induced SE in humans, were personally reviewed. All abstracts and full papers of all potentially relevant publications were reviewed, including a cross-check of cited references. For the purposes of this review, papers relating to nonmedicinal toxins (e.g., botanical and industrial) and radiological contrast media were not included. Studies on SE as a result of withdrawal of medication (antiepileptic or otherwise, including alcohol) and those where the association with SE was considered likely indirect, for example, SE following drug-induced cardiorespiratory suppression leading to hypoxic brain injury or in relation to treatment for neurocysticercosis, were also not included.

During this process, it was quickly apparent that the vast majority of the literature reported isolated cases or small series, and in many

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instances, establishing causality is often challenging. The most commonly used scale for assessing causality in the context of adverse drug reactions (ADRs; Table 1) [2] has a number of limitations in the context of status epilepticus. The majority of cases have alternative nondrug causes such as preexisting epilepsy, other brain diseases, or metabolic derangements; additional drugs are almost always given in an attempt to control seizures, so even if the suspected causative drug is stopped, what leads to cessation of status epilepticus is often unclear, drug levels and dose response are often not ascertained (or ascertainable), and rechallenge is rarely appropriate. Importantly, the Naranjo scale was also never intended to be applied to overdoses though is often misused in this setting in the literature [3]. Only a minority of the reported cases fulfill the criteria for being probably drug-related on this scale. The situation is also not helped by the highly variable quality of individual case reports, including those in highly respected journals. For example, a retrospective review and analysis of 1520 reports of significant ADRs (defined as leading to death, permanent disability, or threat to life) over a 20-year period ending in the mid-1990s [4] found that although over 90% included patient variables such as age, gender, and outcome, less than 25% included other potentially key outcomes such as alcohol status, renal function, recreational drug use, and comorbidities. Similarly, although proposed mechanisms were nearly always discussed, there was insufficient detail on other drug variables such as dose, formulation, and levels. Less than 1% had an "objective" causality assessment.

Given the lack of a validated method and these issues, case selection for this review is necessarily subjective to at least some extent. Reports have been included if judged by the reviewing author as including both 1) objective evidence of SE (requiring EEG for nonconvulsive cases) and 2) likely causality on the basis of a plausible temporal relationship between the drug and onset of SE and known or biologically plausible mechanisms (including, by inference, frequent reports of drug-induced self-limiting seizures). A prior conclusive report of status epilepticus was not considered necessary, and improvement after discontinuing the drug where this was in parallel to initiating antiepileptic treatment was, in itself, considered noncontributory in terms of causation. Where the most recent article on any given agent cites all previous reports, only the latest publication is cited here, though all reports were reviewed to ensure that they met inclusion criteria.

3. Epidemiology

It is perhaps unsurprising, having read the above, that any attempt to ascertain the frequency of drug-induced status epilepticus is fraught with difficulty, further confounded by known challenges in relation to reporting bias; the recognition, diagnosis, and classification of SE; and changes in all over time. However, available data suggest that this is a relatively uncommon phenomenon (Fig. 1A[5]) most often seen in the context of overdoses of psychotropic medications (prescribed and recreational; Fig. 1B [6]) or, as will be later discussed under individual drug classes, accidental toxicity as a result of drug interactions or other comorbidities such as renal impairment in patients with other illnesses. Outcome varies hugely with cause, as is often the case in SE. In the context of overdoses, those presenting as a result of stimulant ingestion; suicide attempts; or with initial hypotension, acidosis, or hyperglycemia, have a worse outcome, likely reflecting a mixture of patient- and drug-related factors [7]. Complications relating to the drug, underlying comorbidities, and consequences of SE all contribute to a case fatality of around 25%, slightly higher than that for alcohol-related SE (20%) in the same series [5].

Table 1
The Naranjo [2] Adverse Drug Reaction Probability Scale.

Question	Yes	No
Any previous conclusive reports on this reaction?	1	0
Did AE appear after the drug was administered?	2	−1
Did AE improve when the drug was stopped or a specific antagonist was given?	1	0
Did AE reappear when the drug was readministered?	2	−1
Are there alternative nondrug causes that could have lead to AE?	−1	2
Did AE reappear with placebo?	−1	1
Were known toxic levels detected?	1	0
Was there a dose response in reaction severity?	1	0
Has the patient had a similar reaction to similar previous drugs?	1	0
Was AE confirmed by any objective evidence?	1	0
Total score		

Any items not known, score 0. Total: 9+ = definite, 5–8 = possible, 1–4 = doubtful, and <1 = doubtful. Of a random stratified sample of 355 published ADR case reports in leading medical journals in 1978, independently scored on this scale, only 30% (range: 20–38% by the reviewer) were considered probable or definite [2].

4. Drugs causing status epilepticus

4.1. Antiepileptic drugs

Many of the published case reports of status epilepticus associated with individual AEDs on closer inspection have substantial confounders such as withdrawal of other AEDs during conversion to monotherapy or as a planned switch or, in the context of progressive or inherently unstable epilepsies, any of which may have at least contributed to the episode. However, there seems little doubt that AEDs can, by themselves, sometimes precipitate SE. This is particularly seen in the context of idiopathic generalized epilepsies inappropriately treated with drugs now well known to exacerbate absence and/or myoclonic seizures (Table 2). That the majority of reports relate to older drugs, and the falling incidence over time hopefully reflect improved awareness of this phenomenon and the increasing emphasis on correct syndromic classification at diagnosis to inform treatment. Importantly, SE, in this context, has a good prognosis. In the two largest reported series based on a retrospective review of video-EEG recordings, the authors identified 12 [8] and 18 [9] cases, respectively, that were all related to carbamazepine with or without other AEDs and that were later mostly seizure-free on the correct medication (typically valproate). Of note, the SE was often atypical and sometimes misdiagnosed initially as dissociative/psychiatric. Most were related to a prior misdiagnosis of localization-related epilepsy based on minor clinical or EEG asymmetry, simple automatisms during absence seizures, or convulsions occurring despite being on valproate. The mechanism, as reviewed by [10], is thought to involve hypersynchronization of neuronal discharges in a thalamocortical loop already predisposed to oscillatory activity as a result of enhanced membrane stabilization (sodium channel blockade) and/or GABA(γ-aminobutyric acid)-ergic effects.

Antiepileptic drug-induced SE occurs not only in patients with localization-related epilepsy (LRE) but also, though less commonly, in individuals with no prior history of seizures (Table 3). Tiagabine features in both contexts most prominently. Although following initial case reports, some disputed that this was anything other than chance, within a few years of licensing [11,12] there were over 30 reported cases of NCSE in LRE. A formal analysis of frequency related to tiagabine exposure (Fig. 2), together with reports of tiagabine precipitating NCSE in patients with non-epileptic attacks [13], in an adolescent following accidental ingestion [14], and in patients where TGB was used as a mood stablizer off label [15,16], leaves the author in no doubt that this is real. There has been some discussion about the distinction between a tiagabine toxic encephalopathy and tiagabine-induced NCSE, in particular because of a gradual on and offset and sometimes poor electroclinical response to benzodiazepines [13]. It is interesting to speculate about whether this reflects tonic inhibition of interneurons switching GABAergic effects from inhibitory to excitatory, but from a practical perspective faced with a clinical picture of new-onset stupor and multifocal myoclonus in association with tiagabine, the distinction is largely academic and management will anyway involve stopping the tiagabine, administering benzodiazepines, and escalation to