Drugs that lower the seizure threshold

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Summary

Drugs with potential to lower the seizure threshold are numerous and diverse. Whether they contribute to clinically overt seizures depends on the dosage in which they are taken, the time-course of their effects, and the susceptibility of the patient. Crucially, however, their contribution to seizure risk is potentially modifiable.

Seizures and the seizure threshold

Terminology

A *seizure* is the clinical manifestation of abnormal, excessive or synchronous neuronal firing in the brain.[1] The clinical features of seizures may include abnormalities of consciousness, movement, sensation, behaviour and autonomic function. *Epilepsy* is the enduring tendency to experience seizures.

The *seizure threshold* describes the minimum intensity of a stimulus required to induce a seizure. It is clinically evident in the context of electroconvulsive therapy, but is otherwise primarily an experimental phenomenon, in which seizures are induced by electrical or chemical stimuli (e.g. with pentylenetetrazole). It is often evaluated during drug development to quantify the extent to which a drug prevents seizures (if this is the intended therapeutic effect) or induces them (as an unwanted effect). As a broader concept, it is useful in clinical practice as a framework to help understand the complex interplay between the patient, their medicines, and their risk of seizures.

Pathophysiology and pharmacology

Seizures occur when there is an excess of excitatory activity relative to inhibitory activity. Glutamate and gamma-aminobutyric acid (GABA) are, respectively, the principle excitatory and inhibitory neurotransmitters in the central nervous system (CNS). Glutamate acts via N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) and kainite receptors to cause an influx of sodium and calcium ions, favouring depolarisation. GABA acts primarily through $GABA_A$ receptors to cause an influx of chloride ions, inducing hyperpolarisation. The mechanisms of action of antiepileptic drugs are not universally understood, but include inference with sodium (e.g. phenytoin, carbamazepine, lamotrigine) and calcium channels (e.g. ethosuxamide); enhancing the effects of GABA

(e.g. benzodiazepines); antagonising glutamate at AMPA receptors (e.g. perampanel); and a combination of these effects (e.g. valproate). Drugs with the opposite effects may induce seizures.

The propensity of a drug to induce seizures depends on its effects on neurotransmission and their time-course (e.g. whether it increases seizure risk during use or on withdrawal), the concentration of drug reaching the brain, and the susceptibility of the individual patient. Susceptibility factors include previous seizures, structural or functional brain abnormalities, and concurrent drug use. In the face of such complexity, it is rare that seizures can be ascribed primarily to the effects of a drug (i.e. 'drug-induced seizures'). Commonly, however, drugs contribute to a shift in excitatory/inhibitory balance which, in that individual at that time, leads to a seizure. In this respect, it is generally more helpful to regard such drugs as having *lowered the seizure threshold*, rather than having incited seizures *per se*.

Many drugs have indirect effects on the seizure threshold, for example by inducing hypoglycaemia, electrolyte disturbances or respiratory depression, or by interacting with antiepileptic therapy. However, this review will concentrate on drugs that lower the seizure threshold via direct effects in the brain.

Specific drugs

Antimicrobials

Beta-lactams

Beta-lactam antibiotics, including penicillins, cephalosporins and carbapenems, interact with the $GABA_A$ receptor to interfere with the inhibitory effects of GABA in a concentration-dependent manner.[2] Correspondingly, they have dose-dependent effects on the seizure threshold.[3,4] However, the CNS penetration of penicillins and cephalosporins is relatively low.[5] As such, most reports of seizures associated with these agents emerge from their use in high doses (often in the treatment of CNS infections) or in renal failure.[6] Carbapenems more readily penetrate the CNS and their use is associated with an increased seizure risk compared with non-carbapenem antibiotics.[7] Among the carbapenems, imipenem is generally thought to have the highest risk. However, this may be because studies conducted on the newer agents (meropenem, ertapenem and doripenem), informed by earlier experience with imipenem, generally excluded patients with a history of seizures. Head-to-head comparisons of imipenem and meropenem do not reveal significant differences in seizure risk.[7]

In addition to their direct effects on the seizure threshold, carbapenems have an interaction with valproate which is sufficiently significant to deserve special mention. It is most readily observed with meropenem, which is associated with a consistent and substantial reduction in serum valproate concentration, in some cases precipitating seizures.[8,9] This interaction occurs whether valproate is administered enterally or intravenously, and its onset and offset are rapid (within days). Its mechanism is uncertain, but its time-course and consistency between routes of administration suggests enhanced elimination or redistribution, possibly into red blood cells, as possible candidates.[9]

Isoniazid

The antituberculous agent isoniazid inhibits pyridoxine phosphokinase, the enzyme which converts pyridoxine to its active form, pyridoxal-5-phosphate. Pyridoxal-5-phosphate is an essential cofactor in the synthesis of GABA from glutamate. The resulting fall in inhibitory activity and rise in excitatory activity leads to a dose-dependent reduction in the seizure threshold. Isoniazid toxicity is characterised by a triad of altered mental status, metabolic acidosis and refractory seizures. Treatment with pyridoxine and a benzodiazepine usually results in prompt seizure termination.

Antimalarials

The antimalarial agents mefloquine and chloroquine can precipitate seizures in people with epilepsy, and have also been associated with seizures in healthy individuals.[10,11] Depending on resistance patterns, doxycycline and atovaquone/proguanil (Malarone®) may be suitable alternatives for malarial prophylaxis in patients at risk of seizures. The half-life of doxycycline is reduced in patients taking carbamazepine or phenytoin; a higher dosage (100 mg twice daily) should therefore be used.[12]

Other antimicrobials

Fluoroquinolones have comparatively high CNS penetration[5] and they may inhibit the $GABA_A$ receptor.[13] Seizures are rare but have been reported, particularly with ciprofloxacin in the context of other susceptibility factors.[6] Macrolides, tetracyclines, aminoglycosides and glycopeptides have not been associated with seizures.[6]

Analgesics

Opioid analgesics

Opioids are associated with diverse effects on the seizure threshold. These vary between drugs, and within drugs according to dosage, experimental model and susceptibility factors. For example, morphine potentiates chemically-induced seizures but protects against electrically-induced seizures[14]; the clinical implications of this are uncertain. Moreover, the relationships between dosage and seizure threshold are complex. Experimentally, morphine has anticonvulsant effects at low doses but is pro-convulsant at high doses, whereas this pattern is reversed for fentanyl and pethidine.[15]

Tramadol is commonly associated with seizures in overdose,[16] and also during therapeutic use. Its supplementary effects in inhibiting noradrenaline and serotonin reuptake, not shared by other opioids, are often cited as an explanation for this. However, in animal models, tramadol, codeine and morphine are similar in their seizure-inducing potential.[17,18] Furthermore, increased extracellular concentrations of serotonin appear protective against seizures,[2] as they may be for antidepressants (see below). These findings suggest that the seizure-inducing effects of tramadol are not mediated through the serotonin pathway. Rather, they, and presumably those of other opioids, may be due to opioid-dependent inhibition of GABAergic pathways[18,19] or histamine H_1-receptor activation.[20]

Non-opioid analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase enzymes, reducing synthesis of prostaglandins from arachidonic acid. The effects of individual prostaglandins vary but, in general, they

increase the seizure threshold, and NSAIDs accordingly have potential to lower the seizure threshold.[21] This effect is seen in various models, in a dose-dependent fashion, for aspirin, diclofenac and indometacin,[21] and there are reports of seizures being caused clinically by these agents during therapeutic use.[22,23] By contrast, ibuprofen and paracetamol have not been shown to lower the seizure threshold and there is some evidence that they may increase it, perhaps because of differential effects on individual prostaglandin synthesis.[24] Mefenamic acid has a non-linear dose–response effect on seizure threshold. In animal models, it suppresses seizures at doses of 20–40 mg/kg,[24,25] whereas at 60 mg/kg[24] — and in toxicity clinically[23] — it can induce seizures.

Methylxantines

The bronchodilator theophylline, and its soluble derivative aminophylline, cause a significant reduction in the seizure threshold in animal models[26] and in electroconvulsive therapy.[27] The mechanism has been ascribed to adenosine A_1-receptor antagonism.[26] This can lead to seizures in patients with and without epilepsy, which can be intractable.[28] This may be because methylxanthines also antagonise the actions of benzodiazepines.[29] Phenytoin is poorly effective and should be avoided. Early use of alternative second-line agents such as phenobarbital, and if necessary induction of general anaesthesia, is advisable.

Antipsychotics

Clozapine has the most marked effects on the seizure threshold, followed by other second-generation antipsychotics.[30,31] First-generation antipsychotics have only a modest effect. Clozapine is associated with concentration-dependent electroencephalographic abnormalities and, in practice, seizures affect 3–6% of clozapine-treated patients.[32,33] Likewise, seizures are commonly noted in studies of spontaneously reported adverse drug reactions,.[34] In patients who experience seizures while taking clozapine, the risks of discontinuing therapy will often be considered greater than the risks of continuing it. In these instances, prophylactic antiepileptic therapy should be offered. Valproate is often a good choice as it is well tolerated and has potentially desirable supplementary effects as a mood stabilizer and antimanic agent.[35]

In contrast to most other antipsychotics, aripiprazole does not lower the seizure threshold during use, and may indeed have anticonvulsant properties.[30,36] However, a rebound pro-convulsant effect may occur on withdrawal.[30]

Antidepressants

The effect of antidepressants on monoaminergic neurotransmission could plausibly modulate the seizure threshold in either direction. Clinical trial data suggest that most commonly used antidepressants are anticonvulsant.[37] Moreover, antidepressant therapy appears to be both safe and beneficial in patients with epilepsy and co-morbid depression.[38] A recent systematic review reaffirmed this, finding no evidence for an increase in seizure frequency in association with the therapeutic use of selective serotonin reuptake inhibitors (e.g. citalopram, fluoxetine, sertraline), selective serotonin–noradrenaline reuptake inhibitors (e.g. venlafaxine, duloxetine), the selective monoamine oxidase A inhibitor moclobemide, or the presynaptic alpha$_2$-adrenoceptor antagonist mirtazapine.[39] Among the tricyclic antidepressants (TCAs), only clomipramine was associated with a reduction in seizure threshold in

therapeutic doses.[39] In contrast to the clinical trial data, observational studies using large population databases have found an increased risk of seizures in association with most antidepressant drugs.[40,41] In a recent study of patients not known to have epilepsy,[40] the risk of seizures was elevated for all antidepressant classes, although low in absolute terms. The conflicting findings from observational and interventional studies have several possible explanations, including differences in population characteristics, duration, and statistical power. It could also be due to residual confounding in the observational studies, arising from the known association between depression and epilepsy.[42] Another consideration is the potential for different effects at therapeutic versus supra-therapeutic concentrations.[39] Seizures are common in cases of antidepressant overdose, particularly with venlafaxine and TCAs.[43] The serotonergic and noradrenergic effects of antidepressants, which predominate at therapeutic doses, probably increase the seizure threshold.[44] In toxicity, other effects such as inhibition of GABAergic and histaminergic transmission may supervene and account for a net reduction in the seizure threshold.[44] It seems plausible that overdose (intentional or unintentional) may be more common in practice than in trials, and captured less completely in observational studies, such that these events could account for the excess of seizures observed.

Bupropion

The atypical antidepressant bupropion, which inhibits reuptake of noradrenaline and dopamine, is now used primarily to aid smoking cessation. It has stimulant effects and a clear dose-dependent relationship with seizure risk. Using a prolonged-release preparation in doses licensed for smoking cessation, overt seizures are uncommon, affecting approximately 0.1% of patients overall.[37] However, the implications of a reduction in seizure threshold may be important for individual patients with other susceptibility factors.

Antiepileptics

The intended therapeutic effect of antiepileptic drugs is to increase the seizure threshold. However, in toxic concentrations, whether through overdose or altered pharmacokinetics, they may paradoxically lower it. Furthermore, some forms of epilepsy can be exacerbated by certain antiepileptic agents. For example, carbamazepine and, to a lesser extent, gabapentin and lamotrigine may exacerbate idiopathic generalised and myoclonic epilepsies.[45] Benzodiazepines and barbiturates, which have important roles in the management of acute seizures, can similarly induce a paradoxical reduction in seizure threshold when taken chronically. Most often, and most predictably, this occurs on withdrawal. Occasionally, however, it can occur during introduction or continuation of therapy.[45]

Anaesthetics

The effects of lidocaine on the seizure threshold vary with concentration in a bimodal fashion. At low concentrations (0.5–5 mg/L), lidocaine suppresses seizure activity, and indeed is moderately effective as a second-line anticonvulsant agent for neonatal seizures.[46] However, at concentrations exceeding 8 mg/L it lowers the seizure threshold and, with escalating concentrations, will ultimately induces seizures in most subjects.[47] Lidocaine-induced seizures are generally brief and self-terminating. Bupivicaine can similarly reduce the seizure threshold in toxicity, although cardiotoxicity is usually the greater concern in these cases.

Volatile general anaesthetic agents such as sevoflurane can induce clinical and electroencephalographic manifestations of seizure activity at low concentrations, but these are promptly suppressed as the concentration increases.[48] A similar but less pronounced effect is evident with intravenous agents such as propofol and thiopentone which, in higher doses, are a mainstay of treatment for status epilepticus. In keeping with this bimodal dose–response pattern, seizures associated with general anaesthesia most often occur during induction or emergence, when the concentration of the anaesthetic agent is low.[49] Pre-treatment with a benzodiazepine has been advocated for patients who may be susceptible to these transient effects.[49]

Conclusion

Many drugs can adversely affect the seizure threshold, although whether this leads to overt seizures depends on the concentration of drug reaching the brain, the susceptibility of the individual to its effects, and how these effects vary over time. In managing patients with epilepsy or other risk factors for seizures, one must be mindful of the potential for medications to lower the seizure threshold, so as not to precipitate avoidable seizures. Likewise, in evaluating patients with seizures, consideration must be given to the seizure-provoking potential of their medications. While their contribution may be small in comparison to other susceptibility factors, the fact that medicines can be stopped or modified according to their risk–benefit balance offers an important route to improving seizure control.

Table 1: Drugs that lower the seizure threshold

Class	Examples	Notes
Antimicrobials		
Beta-lactams	Penicillins, cephalosporins and carbapenems	In the absence of other susceptibility factors, seizures are rare except in high-dose therapy or toxic accumulation.
Antituberculous agents	Isoniazid	Seizures are a manifestation of pyridoxal-5-phosphate deficiency; they respond to pyridoxine and benzodiazepine treatment.
Antimalarials	Mefloquine, chloroquine	Doxycycline and atovaquone/proguanil (Malarone®) are safer options for malaria prophylaxis in people with epilepsy.
Analgesics		
Opioid	Morphine, tramadol, codeine, pethidine, fentanyl	Experimental models show inconsistent effects and non-linear dose–response relationships. However, all opioids appear capable of lowering the seizure threshold under certain conditions.
Non-opioid	Aspirin, diclofenac, indomethacin	Paracetamol and ibuprofen do not appear to lower the seizure threshold. Mefenamic acid has a non-linear dose–response effect on the seizure threshold; it is pro-convulsant in toxicity.
Methylxanthines	Theophylline, aminophylline	Thought to be due adenosine A_1-receptor antagonism. Benzodiazepines may be poorly effective; phenytoin is generally ineffective.
Antipsychotics	Clozapine and, to a lesser extent, other antipsychotics (e.g. risperidone, olanzapine)	Where clozapine is the only effective option, it may be appropriate to continue it together with an antiepileptic agent (e.g. valproate).
Antidepressants	Bupropion Other antidepressants, particularly tricyclics, in overdose	Bupropion (used in smoking cessation) is clearly associated with seizures. Data for other antidepressants at therapeutic dose are conflicting, but seizures are a common feature of toxicity.
Antiepileptics	Carbamazepine Benzodiazepines (e.g. diazepam) on withdrawal of chronic therapy	Most antiepileptics can induce paradoxical seizures in overdose. Also, carbamazepine can exacerbate certain primarily generalised seizure types. Withdrawal from benzodiazepines invariably lowers the seizure threshold.
Anaesthetics	Sevoflurane	Volatile and intravenous anaesthetics invariably suppress seizures at therapeutic doses, but may transiently lower the seizure threshold at sub-therapeutic doses.

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