DRUG WITHDRAWAL IN THE EPILEPSY MONITORING UNIT – THE PATSALOS TABLE

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Abstract

Investigation of possible candidates for epilepsy surgery will usually require inpatient EEG to capture seizures and allow full operative planning. Withdrawal of antiepileptic drugs increases the yield of this valuable diagnostic information and the benefits of this should justify any increase in the risk of harm associated with these seizures. We propose an algorithm for enhancing the safety of AED withdrawal in VT admissions while ensuring adequate seizure yields. This algorithm is accompanied by a table which allows utilisation about the knowledge of the clinical and pharmacological properties of each AED to plan dose withdrawal and reduction.

Summary

This document outlines proposed best practice for management of antiepileptic drug (AED) dosing when patients are admitted for monitoring of seizures to an epilepsy monitoring unit (EMU). In the vast majority of cases EMU admissions are safe and, even if seizures occur, will pass off without complication. Previous guidance has concentrated on ensuring practice around technical aspects of EEG monitoring itself and staffing within the unit. In this guidance we aim to outline optimally safe ways of ensuring that EMUs ensure the minimisation of risk to the patients admitted under their care. Risk minimisation requires

i) management of drug reduction,
ii) provision of adequate rescue medication, and
iii) provision of adequate supervision to allow rapid response to generalised seizures.

A table is provided to help plan AED drug withdrawal to ensure that any change in AED effect is timely and safe, taking into account the pharmacological properties of the AEDs in question, and the severity and frequency of the individual's seizures.

Introduction

Admissions to epilepsy monitoring units (EMUs) are a necessary part of the diagnostic and investigative process of most modern epilepsy centres. Video Telemetry (VT) utilises simultaneous video and EEG to capture episodic events for a variety of indications, including the diagnosis of transient episodes of uncertain nature (especially to distinguish epileptic from non-epileptic attack disorder); the classification of epilepsy syndrome; and pre-surgical evaluation in patients with medically refractory epilepsy [1].

This paper discusses the evidence for best practice in managing AED prescribing in patients in patients with epilepsy, where the purpose of admission is recording epileptic seizures in order to localize their onset. The suggestions made are specifically formulated more for patients with epilepsy than Non-Epileptic Attack Disorder, where AEDs will more likely be stopped altogether to confirm a diagnosis of Nonepileptic seizures.

In patients undergoing pre-surgical evaluation to localize the seizure-onset zone, it is helpful to record as many events as possible in the allotted time. The number required depends both on the quality of the video and EEG recording for each episode, and the pre-test probability that the events are unifocal in origin[2].

AED withdrawal increases the probability of recording seizures during a pre-defined duration of admission, so helping to reduce the length of stay[3; 4]. Failure to record adequate seizures has negative consequences for the individual patient; it may prevent a patient from accessing epilepsy surgery, or may precipitate repeated admissions, so prolonging the length of the surgical workup period. Repeated hospital admissions are inconvenient to patients, may result in loss of earnings, be anxiety-provoking, and may require multiple periods of drug withdrawal, thus adding to the burden of disease. What is more, EMU admissions are expensive, requiring multi-day assessments with intensive monitoring, and clinician and physiologist time to interpret prolonged EEG recordings.

Admissions to the EMU carry a small but measurable degree of risk. The MORTEMUS study [5] estimated the incidence of sudden unexpected death in epilepsy (SUDEP) in patients undergoing VT to be 1.2 per 10,000 video telemetry recordings (5.1/1,000 patient years). A recent meta-analysis found around 7% of admissions to the EMU resulted in an adverse event [6], and a UK-based national service evaluation also found that 7% of seizures in the EMU were associated with an adverse event [7]. The most common adverse events reported were status epilepticus (1.5%), postictal psychosis (1.8%), and cardiorespiratory complications (0.04%), falls (1.3%) and seizure related injuries (0.5%) [6]. Such injuries may be severe, such as vertebral compression fractures (11% of patients with a GTCS in one study) [8], or epidural haematoma requiring emergency evacuation, following a seizure-related fall [9].

AED withdrawal in patients undergoing surgical evaluation may not always lend itself to a protocol-driven approach. The number of patient and seizure variables, possible drug combinations, pharmacokinetic factors, and drug interactions that need to be considered in each case complicates the algorithm. A consensus-based recommendation concluded that AED reduction should be individualized to consider both drug- and patient-related factors [10]. AED withdrawal procedures also need to take into account the different admission protocols across EMUs; whether admissions are for planned duration or for a planned number of attacks.

Rate, timing, and supervision of drug withdrawal also vary. Some EMUs have the facility for an inpatient supervised pre-monitoring to withdraw medication. Supervision levels vary between EMUs[11] and those with lower nurse:patient ratios, or without 24-hour observation would need to exercise a higher level of caution in AED withdrawal.

This paper aims to provide practical information to help guide these complex clinical decisions, particularly regarding the pharmacokinetic properties of, and interactions between, AEDs.

We recognise the need to optimise both the safety and the effectiveness of EMU admissions, and would highlight the requirement to understand and take into account the pharmacokinetic properties of each individual's AED regime. We

The effect of AED withdrawal on EMUs

Adverse events vs efficacy

Several studies have reported a medication taper protocol for VT[8; 12; 13; 14], in some cases comparing seizure yield and adverse effects from slower and faster rates of withdrawal[15; 16; 17]. The majority have an observational design, and variation in patient population and drug regimes make it difficult to draw any inferences about the utility and safety of different rates of medication withdrawal from these studies. These studies are underpowered to detect differences in safety measures between different taper protocols, although Guld et al. found that patients who completely withdrew from AEDs had a significantly higher rate of GTCS (52.2% vs 18.2%, p=0.002)[16].

Speed and timing of AED withdrawal

Very rapid drug withdrawal alongside sleep deprivation has been examined. Rizvi et al reported a diagnostic yield of 90.5%, with a low adverse event profile, although lorazepam was required in 60% of patients to abort seizure clusters[18]. Slow AED withdrawal (<30%/ day) in surgical candidates recorded seizures in only 43% of[19] admissions[15]. An EMU in the Netherlands described their experience of withdrawing AEDs at home, up to 4 weeks prior to the admission for VT, depending on the half-life of the AED. During the subsequent 5-day admission, 84% of patients recorded sufficient seizure numbers with only 1.7% of patients having status epilepticus during their hospital admission[20]. In Denmark, an EMU with a non-restrictive setting, in which patients are not confined to bed, recorded no injuries in 976 consecutive patients despite AED withdrawal[21].

A controlled trial of AED withdrawal regimes[22] randomly allocated 140 patients to have AEDs withdrawn sequentially at a rate of 15-30%/ day (slow arm), or >30%/day (rapid arm). Patients in the rapid titration group had a shorter time to first seizure (2.0 +/-1.7 vs 4.6 +/-3.0) and shorter admission (4.7+/-2.6 days vs 6.6+/-3.5 days in the slow arm), but a higher rate of 4-hour seizure clusters. Interestingly, both arms eventually achieved the same mean reduction in medication (68.3% +/- 28% reduction compared to baseline), in order to achieve an adequate recording.

Localisation of the seizure onset and irritative zones

There is substantial evidence that AED withdrawal affects seizure propagation, rather than the seizure onset characteristics, as determined by semiology and EEG. This appears to hold true even when AED withdrawal is associated with increased seizure frequency, secondary generalization and clustering[4; 19; 23; 24; 25]. One study[3] suggested that AED withdrawal, while changing the interictal EEG, continues to localise ictal EEG to the seizure onset zone and lesional zone.

Current practice and guidelines for AED withdrawal

Audits of EMUs in Europe and the USA have shown a wide variation in the way that units deal with AED withdrawal and the provision of rescue medication, with many units lacking standardised precautions (see table 1). Considerable work has gone into outlining best protocols for staffing and nursing cover, seizure detection and on the specific technical requirements for the EEG itself[10; 26; 27], but there has been no specific guidance on AED manipulation, despite the recognised risk of adverse events. A large national cluster-randomized study is currently underway in France, to assess the effect of a standardized protocol versus current practice[28].

Observational studies looking at AED withdrawal regimes face the challenge of describing and analysing highly variable processes. They include patients taking between 1 and 6 AEDs, in up to 59 different combinations[15; 22; 29]. Reductions are often described as a percentage, but it is not always explicit whether each AED should be reduced simultaneously or sequentially. Furthermore, not all AEDs are associated with linear dose/concentration relationships, further complicating the interpretation of drug reductions expressed in percentage terms. In the RCT of rapid vs slow AED withdrawal[22], rapid withdrawal was considered 30-50% daily reduction, while slow taper was considered 15-<30% daily reduction, of sequential AEDs. A consensus-based guideline[10] concluded that 'plans to withdraw AEDs should be individualized to consider patient- and drug-specific factors in relation to need to capture events', and that 'each patient should have an individualized plan for managing acute seizures'. It was indicated that discontinuation of AEDs prior to admission 'should be considered only in exceptional circumstances'. The workshop noted that where drug reduction is needed, the usual practice of most units is to reduce AEDs by 50% on day 1 and 75% on day 2, and to tailor further reduction, stopping one or all AEDs, until the desired number of events are recorded [11].

Recommendations for safe practice

1) Determining whether or not AEDs should be reduced - Assessment of seizures and risk for individual patient

Based on the evidence presented above, and published consensus guidelines, we would propose that clinicians admitting patients to the VTU take into account a range of factors in considering whether AEDs should be withdrawn or reduced. These are summarised in the algorithm in figure 1.

The patient's risk factors for sustaining harm during a seizure should be assessed and considered prior to considering AED withdrawal. Factors shown to be associated with increased risk of adverse events during VT include advanced age, long duration of epilepsy, previous history of psychiatric illness, history of seizure-related injuries or status epilepticus[9], and the presence of osteopaenia[8]. The patient's usual seizure types should be assessed, and clear seizure descriptions recorded prior to admission (particularly with regard to history of GTCS), alongside a record of the patient's recent habitual seizure rate.

There will usually be no need to reduce medications if a patient has frequent seizures (>2/week), depending on the length of the planned admission. If the patient is at high risk, such as a history of SE, consideration should be given to performing monitoring without medication reduction. In such cases the need for implementing a plan for rescue medication is even greater.
At the time of admission, each patient should have rescue medication prescribed, with clear instructions a to when this prescription should take effect (perhaps clarifying number, type, or duration of seizures that would trigger the plan). The rescue medication will vary, but will usually involve some reinstatement of the patient's previous treatment, (e.g. part or full daily dose of baseline medication) with or without additional benzodiazepine.

2) Consent

The risks and benefits of video telemetry with or without AED withdrawal should be discussed with each patient prior to admission, and written informed consent obtained.

3) AED withdrawal regime

Where seizures are relatively infrequent, the risk assessment does not raise significant concerns, and the patient has given consent to medication withdrawal, the physician needs to consider the best strategy for reducing the doses of AEDs. This strategy should take account of a number of factors, particularly drug half-life, duration of pharmacological effect, and tendency to mutual pharmacokinetic interactions. Where available, experience from the patient's previous episodes of VT may also be informative, as may prior knowledge of which AED is most effective in that patient.

We have drawn up the Patsalos Table (table 2), which summarises the pharmacokinetic properties and interactions of AEDs, to inform decisions about medication withdrawal. AEDs have been grouped into 6 categories:

Category 1 are those AEDs where there is concern about an association with withdrawal seizures (benzodiazepines or barbiturates). Reduction of these medications tends to be handled more carefully, despite a lack of direct evidence to confirm this[30] (

Category 2 are those with a very long elimination half-life, which may require effective pre-admission withdrawal to effect changes in admission concentrations (perampanel and zonisamide);
Category 3 have an intermediate half-life, and can usually be stopped abruptly, early in the

admission, in order to achieve an adequate reduction in serum levels within a reasonable time frame;
Category 4 are those with a short half life, in which graded reduction is recommended in order to prevent a precipitous drop in serum levels;
Category 5 are those where the antiseizure effect is unrelated to serum levels (valproate and vigabatrin). The clinical effect of these drugs persists even once the drug has been cleared from the serum (ie their biological half-life is prolonged), and these drugs may need to be withdrawn earlier than their half-life would suggest.

Category 6 are those (phenytoin and stiripentol) which display non-linear (zero-order or saturation) kinetics. As the rate of metabolism is close to the maximum capacity of the enzymes involved in their breakdown, a small adjustment in the dose of the drug may lead to a disproportionately large change in their serum concentration.

Polypharmacy poses more complex problems. Mutual interaction between AEDs will affect the decisions around drug withdrawal. Reduction in enzyme-inducing AEDs (eg carbamazepine, phenytoin) may increase levels of accompanying AEDs, whereas withdrawal of enzyme inhibiting AEDs (eg Valproate) may led to a drop in accompanying AEDs. Such interactions should be anticipated and adjustments made while taking these into account. Particularly where VT admissions last for days, we would see little utility in routinely measuring serum AED levels.

4) Documentation of medication reduction plan and review

The plan for reducing AED dose should be clearly documented prior to admission. Patients should be reviewed by medical staff on a daily basis, and any necessary adjustments made on the basis of seizure frequency. It is important for medical staff to liaise with the neurophysiology department before making decisions about medication changes, to determine whether events have occurred that are unreported by the patient, and to decide whether reported events are the patient's habitual events / events of interest, and whether the EEG recorded is adequate.

5) Prescription of rescue medication

On admission, a prescription should be put in place for rescue medication to be given if seizures worsen. Nursing and medical staff should be aware (or have information easily to hand) of the predefined conditions of administration, the dose, and intended timing of any rescue medication. This prescription may consist of

a) A benzodiazepine (iv lorazepam or buccal midazolam)
b) A full daily dose of some or all of the withdrawn drugs

6) Reintroduction of medications

If AEDs have been withheld for up to 3-4 days, hepatic enzyme activity and serum levels would suggest that it would be safe to reinstate the medication at the full dose[31]. We would suggest a standard period of observation of between 12 and 24 hours after AED therapy has been reinstated while treatment is stabilised, with consideration potentially being given to provision of benzodiazepine rescue medication[11].

7) Audit of practice

Each unit should undertake audits on a regular basis – preferably every 1-2 years to ensure that the rate of provocation of generalised seizures, the staff response times, and the adequacy and accuracy of drug prescriptions are monitored.

Conclusion

AED withdrawal in the EMU increases the probability of seizures occurring, but this cannot be done without also increasing seizure propagation and therefore the risk of generalized and/ or severe or prolonged seizures, and the associated risk of harm. Much work has been done in recent years to address the risk of harm from seizures in the EMU, particularly with respect to nursing care, and levels of supervision, but the nature of generalised tonic clonic seizures is such that this risk will never be eliminated entirely. A conservative approach could be proposed with serial admissions having an increasingly proactive approach to medication reduction. However, such risk avoidance must be balanced against the risk of delaying specific intervention in those who would benefit from it.

Decisions regarding AED withdrawal are a delicate balance of risk vs benefit, and are complicated by the number of patient, seizure, and medication variables that need to be taken into account. A detailed understanding of the pharmacokinetics of antiepileptic medications and their interactions, and an up-to-date knowledge of the evidence base surrounding withdrawal of AEDs will help to facilitate these decisions.

Table 1: Recent audits of practice in the EMU

Study	Bulow	Rubboli	Kouboulashvili	Hamandi
Year	2008	2015	2016	2017
Location	USA	Europe	Europe	UK
Standardized protocol for preadmission screening (seizure frequency/ severity)	Not stated	56%	Not stated	64%
Withdrawal of medication prior to admission	59%	Not stated	52%	Not stated
Protocol for speed of medication withdrawal	20%	Not stated	15%	36%
Signed informed consent for recording	65%	83%	56%	72% (only 48% included AED reduction
Written protocol for treatment of seizure clusters / SE	59%	79%	59%	68%

Table 2

The Patsalos Table

	AED	Approximate half-life (hours)	Half- life with enzyme inducing medication	Effect on metabolism of other AEDs	Withdrawal may INCREASE levels of:	Withdrawal may DECREASE levels of:	Notes
Category 1 **Risk of withdrawal seizures** **High-risk due to possibility that withdrawal seizures may occur. If withdrawal is necessary, reduce doses gradually and with caution**	CLOBAZAM CLB	10-30 (36-46 for N-desmethyl-clobazam pharmacologically active metabolite)	?	None	None	None	
	CLONAZEPAM CLN	17-56	12-46	None	None	None	
	PHENOBARBITAL PHB	70-140	?	Strong inducer	CBZ, CLB, CLN, ESM, FBM, LCM, LTG, LEV, OXC, PHT, RFN, STP, TGB, TPM, VPA and ZNS	None	NB withdrawal of PHB may increase concomitant systemic medications:
Category 2 **Very long half-life** **Long half life will usually prevent adequate withdrawal during a typical duration-limited VTU admission (except in presence of enzyme inducing medication). These drugs may be stopped abruptly with slow reduction in serum level resulting.**	PERAMPANEL PMP	51-129	25	Weak inducer	CBZ, CLB, LTG, VPA	None	
	ZONISAMIDE ZNS	50-70	25-25	?Not in the table	?Not in the table	?Not in the table	

Category 3 **Intermediate half-life** **Can be withdrawn abruptly**	ETHOSUXIMIDE ESM	40-60	20-40	None	None	None	
	ESLICARBAZEPINE ESL	20-24	13-20	Weak inducer Weak inhibitor	LTG, TPM, VPA	PHT	
	LAMOTRIGINE LTG	15-35	8-20 (Increased to 30-90 with VPA)	Minimal	CLN, LEV,VPA	None	
	TOPIRAMATE TPM	20-30	10-15	Strong inhibitor	ESL, ESM, FBM, LTG, PB and RFN		
Category 4 **Short half-life** **Graded withdrawal recommended to avoid rapid drop in serum levels**	ACETAZOLAMIDE	10-15	No effect	None	None	None	
	BRIVATARACETAM	9	?No effect?	None	None	None	
	CARBAMAZEPINE CBZ	8-20 during chronic administration	?	Strong inducer	CLB,, ESL, ESM, FBM, LTG, LEV, OXC, PMP, PHT, PRM, RFN, STP, TGB, TPM, VPA and ZNS	None	Autoinduction of CBZ may lead to faster drop in levels on withdrawal
	FELBAMATE FBM	16-22	10-18	Weak inducer Strong inhibitor	CBZ and VGB	CBZ, CLB, CLN, LTG, PHB, PHT and VPA	
	GABAPENTIN GBP	5-9	No effect	None	None	None	Longer with impaired renal function Half-life is dose dependent due to saturable absorption
	LACOSAMIDE LCM	13	No effect	None	None	None	
	LEVETIRACETAM LEV	6-8	?No effects	None	None	None	Longer with impaired renal function
	OXCARBAZEPINE OXC	8-15	7-12	Weak inducer	CBZ, CLB, LTG, OXC, VPA	None	
	PREGABALIN PGB	5-7	No effect	None	None	None	Longer with impaired renal function – more rapid withdrawal may be justified in such patients
	PRIMIDONE PRM	7-22	3-12	Strong inducer	CBZ, CLB, CZP, ESM, FBM, LCM, LTG, LEV, OXC, PHT, RFN, STP, TGB, TPM, VPA and ZNS	None	PB is a metabolite of PRM and plasma levels are similar. However in presence of EI AEDs PB levels can be 3-5 times higher than PRM
	RUFINAMIDE RFN	6-10	?No effects	Minimal	CBZ, LTG	PHB, PHT	
	TIAGABINE TGB	5–9	2-4	None	None	None	
Category 5 **Atypical pharmacokinetics** **Duration of action and effect of withdrawal is affected by mechanism**	VALPROIC ACID VPA	12-16	5-9	Strong inhibitor	None	ESL, ESM, FBM, LTG, PHB AND RFN	Prolonged action despite short half-life. VPA withdrawal will increase elimination of many concomitant AEDs
	VIGABATRIN VGB	5-8	?	?Not in the table	?Not in the table	?Not in the table	Can be stopped abruptly (prolonged action in chronic dosing as GABA-transaminase levels slowly return to normal

other than the medication half-life (see notes)							
Category 6 Saturation kinetics	PHENYTOIN PHT	30 - 100	?	Strong inducer	CBZ, CLB, CLN, ESL, ESM, FBM, LCM, LTG, LEV, OXC, PGB, PHB, PRM, RFN, STP, TGB, TPM, VPA and ZNS	None	Saturation kinetics may lead to rapid drop in serum levels, therefore graded withdrawal is advised
	STIRIPENTOL STP	4-13	?No effects	Strong inhibitor		CBZ, ESM, PB, PHT, PRM, VPA, CLB	

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Figure 1 – Algorithm for AED Withdrawal in VT Monitoring Unit