WM CARES
West Midlands Collaborative Actioning Research in End-of-life and Supportive care

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An Exploration into use of continuous subcutaneous Levetiracetam within Palliative Care

Overview

There are many instances within palliative care where seizure management is key to good symptom control and a peaceful death. Acute seizure management is stressful for patients, families and health care professionals alike and the emphasis is on prevention where possible.

Standard practice, when a patient is no longer able to manage oral medication and/or intravenous (IV) access is not considered appropriate, has been to titrate Midazolam via a continuous subcutaneous infusion (CSCI) first line and subsequently to add Phenobarbital second line (1). Although local practice varies, the general consensus seems to be to use 20-30mg Midazolam as a starting dose via a CSCI over 24 hours (1,2) and if seizure activity persists despite further titration to administer 100-200mg intramuscular (IM) Phenobarbital stat followed by 200-600mg via a CSCI over 24 hours.

This practice has anecdotally proved effective in seizure prevention and based on efficacy there is no immediate reason for a change in practice for those patients in the dying phase, however both Midazolam and Phenobarbital can be associated with drowsiness of varying degrees and respiratory depression and although arguably some patients do not experience significant drowsiness from these doses, many would.

Thus in the case of a palliative patient who is not actively dying but has lost a safe swallow and for whom IV access is not desirable (e.g. wishes to go home), for quality of life (QOL) purposes the preference is commonly to remain as alert as possible. Consequently, an efficacious anti-epileptic medication that is not associated with significant drowsiness or other side effects and which can be administered via the subcutaneous (SC) route would be highly advantageous.

Levetiracetam has been used in an attempt to fulfil these requirements.

Diagram 1 Pictogram of phased modality changes as prognosis shortens

Anti-epileptics via oral route	Loss of oral route	Dying phase
Maintains seizures with standard regimens	Maintenance of QOL with targeted SC therapy	Dying phase where SC Midazolam / Phenobarbital more appropriate

Levetiracetam

The anti-epileptic mechanism of action of Levetiracetam is unclear. It binds to the synaptic vesicle protein SV2A which has been linked to epilepsy in animal models (3). It also indirectly modulates GABA (4). It is classified as a broad spectrum anti-seizure medication.

Levetiracetam's remit in seizure management, as per NICE guidance (5), is limited to use as an adjunct for generalised tonic-clonic (GTC) seizures, first line treatment for myoclonic and focal seizures and an adjunct for absence seizures. This guidance is reflected within the British National Formulary (6). At the time of writing, Levetiracetam does not have UK marketing authorisation for use in absence seizures. It has authorisation for monotherapy and adjunctive treatment for focal seizures, with or without secondary generalisation, and adjunctive therapy of myoclonic seizures in patients with Juvenile Myoclonic Epilepsy (JME) and GTC seizures.

Although the licensing is quite specific Levetiracetam has been used extensively off-license for a variety of reasons. For ethical reasons new anti-epileptics can only be tested as adjunctive therapy, however this does not mean they are necessarily unsuitable for monotherapy, just unlicensed for such use. Levetiracetam is currently in this category, however the body of evidence for its use as a single agent for a wide variety of seizure aetiologies is growing.

A literature search using Athens, through health care database search (HDAS), revealed that Levetiracetam has been used as monotherapy in primary generalized epilepsy (7) and partial epilepsy (8), in both paediatrics and care of the elderly (9-10). The body of evidence for its use is growing, with favour swaying towards monotherapy (when comparable efficacy can be achieved) because of fewer risks of adverse events and drug interactions.

The first published case report with suggestion of SC use of Levetiracetam was in 2010 (10), and since then multiple case reports have been described (11-13). Lopez-Saca JM *et al.* (11) speculate that the origin of SC use predates human medicinal use, arising from veterinary medicine (14), when, in order to use SC Levetiracetam, the authors sought exemption under the use of medication in compassionate treatment within European regulations (CE N 726/2004).

Side Effect Profile

The overall efficacy and tolerability of Levetiracetam compares favourably to other anti-epileptics (15).

It has less than 10% protein binding and does not require the CYP450 enzymes for metabolism; a third is metabolised predominantly by non-hepatic hydrolysis and the remainder is excreted by the kidneys unchanged. This is particularly advantageous in polypharmacy situations as Juba KM *et al.* (16) outline in their example of its use in a non-oncological palliative patient, demonstrating the effectiveness of Levetiracetam when other anti-epileptics failed to control seizure activity due to drug interactions through CYP450. Since this superfamily of key proteins and enzymes is integral to many medications used within palliative care, the avoidance of this mechanism of metabolism is advantageous.

The most common undesirable side effects are drowsiness and fatigue (>10%) (17). Anecdotally this drowsiness clinically appears less troublesome than that associated with other anti-epileptics. The most clinically significant side effect is the onset of behavioural disturbances such as aggression, agitation, personality changes or anxiety in 3-4% of patients with epilepsy, which interestingly appears to drop to 0.5% when Levetiracetam is used to treat other seizure causing conditions (18). Contrastingly, Midazolam is estimated to cause paradoxical arousal, agitation and aggression in <10% patients (19-20). This may be an important consideration if deciding to switch a patient to SC Levetiracetam as they approach the dying phase.

Other Modalities

Despite its favourable side effect profile and efficacy, Levetiracetam remains a newer medication which is less established and therefore not the traditional first line treatment (5) for the most common seizure types seen within palliative care (i.e. GTC). This raises the question as to whether other anti-epileptics could/should be used via the SC route in line with existing guidelines. Being able to administer other anti-epileptic via the SC route would expand the possible anti-epileptic armamentarium.

A literature search, performed to explore which other anti-epileptics have been used via the SC route, revealed, unsuprisingly, sparse results, given that this is largely un-licensed practice. There was no level 1, 2 or 3 evidence, rather published research was based on expert opinion and case studies.

Within animal models it appears fairly common practice to use the SC route for Phenytoin (21). Phenytoin is known to be quite irritant and although this is reflected in the literature the reasons are not outlined clearly. The remit for Phenytoin within humans is weighted towards management of GTC seizures, as it is known to worsen other seizure types. Interestingly, there is no clear evidence base to support Phenytoin as more effective at treating GTC seizures than other anti-epileptics. The limited spectrum of action and its potential irritant effects makes this a less favourable choice compared to Levetiracetam.

Sodium Valproate, comparatively, has been used in humans via the SC route, using a 1:1 oral: SC ratio; the IV preparation was used in a case series of six patients (22) with only mild side effects reported. The literature is very limited and there are many more drug interactions associated with Sodium Valproate, again making it less desirable than Levetiracetam.

There are newer anti-epileptic medications, based upon similar chemical structures to Levetiracetam, with reported better side effect profiles (less agitation, aggression and anxiety) appearing on the market. Brivaracetam and Lacosamide are currently being used as adjunct treatment or alternative options if Levetiracetam or other anti-epileptic drugs are not effective. It is unclear at time of writing as to whether these will be able to be administered via the SC route.

How could SC Levetiracetam be used?

Seizure-prone palliative patients can be subdivided into two main groups:

A. Dying patient with long-term seizures, irrespective of cause (e.g. epilepsy, previous cardiovascular accident (CVA) focus etc.)
B. Dying patient with new seizures associated with the dying process (e.g. due to space occupying lesion, new CVA etc.)

The treatment of these differing processes should be appreciated. If the patient is already taking anti-epileptic medication, should there be a conversion regimen from oral/IV anti-epileptic to SC Levetiracetam and when should that occur? There is no evidence or guidelines to facilitate such a structured approach. Indeed the 1:1 ratio of oral to SC Levetiracetam is based on supposition.

In addition, it has been noted that these two groups display slightly differing side effect profiles. As stated earlier, there appears to be an increased risk of adverse behavioural side effects with Levetiracetam in group A. The reason for this is unknown. This difference should be considered on commencement.

On discussion with the lead epilepsy consultant at The Royal Wolverhampton NHS Trust, expert advice would be to titrate Levetiracetam slightly differently depending upon whether the patient was receiving anti-epileptics prior to commencement of SC Levetiracetam.

The dose of Levetiracetam should then be titrated based on seizure control. Our suggestion would be to titrate in 500mg increments every 2-4 days. If seizures are sub-continuous (i.e. almost but not quite continuous) we would recommend a commencement dose of 1000mg. If the scenario is that of infrequent seizure activity we would be more cautious in titrating the dose to minimize side effects. Below is a suggested starting regimen.

Existing Medication Regimen	Starting Dose Levetiracetam CSCI over 24 hours
No anti-epileptics	• Good seizure control - 250mg • Poor seizure control - 500mg • Continuous (status) or sub-continuous – 1000mg
Already on Levetiracetam	Direct conversion 1:1 PO - SC
Single other anti-epileptic	500mg SC Levetiracetam
Multiple anti-epileptics	At least 500mg SC Levetiracetam

Often practically CSCI administration is limited by volume restraints. Keppra® (Levetiracetam) is available in an IV preparation of 100mg/ml in 5ml vials. This renders twice daily SC dosing impractical as common doses of 500mg BD equate to 5ml SC injections. This volume would be against most local hospital guidance, which typically limit SC dosing to 2-3mls due to comfort. For a CSCI, the doses required frequently necessitate administration via two syringe drivers. This may limit patient acceptability and therefore requires careful consideration.

Seizure control in the dying

One interesting, albeit non-evidenced, observation is that the seizure threshold appears to change during the dying phase, with the general consensus that seizure activity becomes less likely when someone is actively dying. The pathophysiology behind this non-tested hypothesis is unknown, but observationally a GTC seizure is a rare event in an actively dying patient.

This potentially raises questions of the role of prophylactic seizure management in the dying phase. Most physicians would be reluctant to not provide some degree of prophylaxis if seizure(s) had previously occurred, however we also typically feel that treatment would be more acceptable if it was not causing any additional drowsiness. Indeed, it is not uncommon to query, in the case of a dying patient who is prescribed prophylactic anti-epileptic medication but has never had a seizure, whether conversion to any regimen in the dying phase is necessary. This scenario should be discussed with patient (if possible) and those close to them and there is ultimately a need, as with all our patients, to weigh up the four principles of medical ethics: beneficence, non-maleficence, respect for autonomy and justice.

Conclusion

Levetiracetam appears effective as a single agent in seizure control. It has a favorable tolerability profile, advantageous route of metabolism and in view of the modalities of administration, a potentially unique remit. This combination makes Levetiracetam particularly suitable for the palliative population and in view of the side effect profile, potentially superior to the more traditional Midazolam / Phenobarbital treatments.

We therefore suggest there is a role for Levetiraectam SC in improving the balance between the four ethical principles in selected patients.

One key practical concern with CSCI Levetiracetam, due to availability of drug concentrations, is that its administration may require multiple syringe drivers, which could potentially alter the balance again.

Furthermore, this ethical balance has to be constantly dynamically assessed as the patient changes. There is currently no guidance, or research, on when a palliative patient should be initiated on Levetiracetam SC in comparison to Midazolam or alternate SC anti-epileptic treatments, whether the two should be used in conjunction, or indeed when there should (or shouldn't) be a decision to return to Midzolam. This is an area of active growing research with the aim to create consistent evidence based guidance.

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