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Subcutaneous sodium valproate in palliative care: A systematic review

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Abstract

Background: Seizures are an important palliative symptom, the management of which can be complicated by patients' capacity to swallow oral medications. In this setting, and the wish to avoid intravenous access, subcutaneous infusions may be employed. Options for antiseizure medications that can be provided subcutaneously may be limited. Subcutaneous sodium valproate may be an additional management strategy.

Aim: To evaluate the published experience of subcutaneous valproate use in palliative care, namely with respect to effectiveness and tolerability.

Design: A systematic review was registered (PROSPERO CRD42023453427), conducted and reported according to PRISMA reporting guidelines.

Data sources: The databases PubMed, EMBASE and Scopus were searched for publications until August 11, 2023.

Results: The searches returned 429 results, of which six fulfilled inclusion criteria. Case series were the most common study design, and most studies included <10 individuals who received subcutaneous sodium valproate. There were three studies that presented results on the utility of subcutaneous sodium valproate for seizure control, which described it to be an effective strategy. One study also described it as an effective treatment for neuropathic pain. The doses were often based on presumed 1:1 oral to subcutaneous conversion ratios. Only one study described a local site adverse reaction, which resolved with a change of administration site.

Conclusions: There are limited data on the use of subcutaneous sodium valproate in palliative care. However, palliative symptoms for which subcutaneous sodium valproate have been used successfully are seizures and neuropathic pain. The available data have described few adverse effects, supporting its use with an appropriate degree of caution.

Keywords

Valproic acid, seizures, pain, palliative care

What is already known about the topic?

- In palliative care patients for whom there is a need for non-oral antiseizure medications, and a preference to avoid intravenous access, options are primarily limited to benzodiazepines.
- In circumstances where the sedative effects of benzodiazepines are to be avoided, the use of subcutaneous levetiracetam have been reported.
- There are limited guidelines available regarding the possible use of subcutaneous sodium valproate.

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What this paper adds?

- Several studies have described successful use of subcutaneous sodium valproate in palliative care to manage seizures.
- While limited, the available data described few adverse effects, aside from an isolated local reaction that is resolved with a change of site.
- Current routine medication resources may not reflect this potential use of sodium valproate, and palliative care has unique medication considerations that may not apply to medication administration in other settings.

Implication for practice, theory or policy

- Although data are limited, existing studies present enough evidence to argue for the inclusion of subcutaneous valproate in the palliative care armamentarium for selected circumstances.

Introduction

Achieving adequate seizure control during palliative care is of vital importance.[1] Particularly in the setting of neurological disorders, patients may have a variable ability, or lack of ability, to swallow oral medications. In palliative care patients for whom there is a need for non-oral antiseizure medications, and a preference to avoid intravenous access, options may be limited outside of benzodiazepines. Given the sedative effects of benzodiazepines, the use of less sedating options like subcutaneous levetiracetam have been reported.[2] Similarly, subcutaneous sodium valproate may be another proposed option in circumstances where intravenous access and sedative effects are to be preferentially avoided.

Sodium valproate is a widely used antiseizure medication, often recommended as first-line therapy for generalised epilepsy.[3] Sodium valproate may also be used in some instances of severe neuropathic pain,[4] although evidence to support its use as a first-line agent is lacking.[5] It is commonly administered orally,[6] however, intravenous administration may also be used, such as during status epilepticus.[7] Other reported administration routes include rectal and subcutaneous.[8,9] There are limited guidelines available regarding the possible use of subcutaneous sodium valproate.

This systematic review aimed to evaluate and summarise the available published experience regarding the use of subcutaneous valproate in a palliative care setting, namely with respect to effectiveness and tolerability.

Materials and methods

Study design, search strategy and selection criteria

Prior to being conducted, this systematic review was prospectively registered with the PROSPERO (CRD 42023453427). This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplemental Information 1 for PRISMA checklist).[10] The databases PubMed, EMBASE and Scopus were searched from inception to 11.08.2023. The search employed was based upon the following terms: *(valpro* OR epilim OR dyzantil OR epival) AND (subcut* OR hypoderm*) AND (palliat* OR end-of-life OR hospice OR comfort OR terminal OR symptomatic OR supportive).* Please see Supplemental Information 2 for additional details regarding inclusion criteria and data extraction.

Results

Search results and study characteristics

There were 429 articles identified. Subsequently, there were eight studies that underwent full-text review. There were six studies that were considered to fulfil inclusion criteria (see Supplemental Information 3). These studies included four case series and one cross-sectional study (see Table 1). One of the studies that fulfilled inclusion criteria, O'Connor et al.,[11] presented a subset of the patients reported in another study, O'Connor et al.,[12] and therefore will not be discussed separately. Risk of bias analysis of the included studies showed that they were often of at least moderate risk of bias (see Supplemental Information 4). However, this potential for bias must acknowledge the limitations of the publication types in which the cases were described, which was often a poster or abstract format. Study reporting was most often limited by lack of detail, particularly with respect to methodology description and the presentation of baseline patient characteristics.

Effectiveness

There were three studies that described the use of subcutaneous sodium valproate for seizure control. Kondasinghe et al.[9] describe the use of continuous subcutaneous infusions of sodium valproate in six patients (range 500 mg–2500 mg/24 h, median 1100 mg/24 h; see Table 2), in whom 5/6 (83%) had their seizures controlled. O'Connor et al. describe seven patients in whom sodium valproate was used by continuous subcutaneous infusion as doses varying from 600 mg/24 h to 1200 mg/24 h. In this study 7/7 (100%) of patients achieved seizure control following initial dose adjustments.[12] One study described the use of

Table 1. Study characteristics.

Journal Study information	Patient factors		Subcutaneous valproate administration		
	No. of patients and age	(a) Seizures (b) Causes of seizures (c) Comorbidities	Daily dose and preparation of valproate	Dosing regimen	Duration of treatment
Cran et al. 2018 United Kingdom; Retrospective Cohort Study	Total of 26 adults -14 levetiracetam -7 midazolam -2 sodium valproate -2 combination levetiracetam and midazolam -1 no anticonvulsants	(a) Yes (b–c) Not specified	600 mg/day	Continuous subcutaneous infusion	Not specified
O'Connor et al. 2017 Uncertain; Prospective Case Study	Patients (ages 57.7 ± 14.1)	(a) Yes (b) Primary or metastatic brain tumours -6 glioblastoma multiforme -1 non-small cell lung cancer (c) Not specified	600–1200 mg/day with median 600 mg/day. -2 patients had increased dosages during treatment period to control seizures	Continuous subcutaneous infusion	3–17 days
Davis and et al. 2018 United Kingdom; Prospective Case Study	6 adults	(a) No (b) Variable -4 metastatic cancer -1 cervical myelopathy -1 osteoradionecrosis of base of skull (c) Not specified	Commenced at a dose of 200–600 mg/24 h -Doses were up-titrated individually between 400–1500 mg/day (maximal increments of 300 mg/day) -Starting dose of 400 mg/day found to offer clinically relevant improvement in pain control	Continuous subcutaneous infusion	Not specified
Kondasinghe et al. 2022 Australia; Retrospective Case Study	Total of 12 adults -8 levetiracetam -6 sodium valproate -2 combination of both	(a) Yes (b) Most commonly due to primary brain tumours (c) Variable -5 glioblastoma multiforme -2 non-small cell lung carcinomas -1 anaplastic astrocytoma -1 metastatic melanoma, -1 squamous cell carcinoma -1 dementia with underlying epilepsy -1 subdural hematoma	500–2500 mg/day with median of 1100 mg/day -20–50 mg/mL concentration	Continuous subcutaneous infusion	2–4 days with median of 3.5 days
Pouchoulin et al. 2014 France; Cross-sectional Study	Total of 324 adults -64 subcutaneous infusions	(a–c) Not specified	Not specified	4 discontinuous administration and 7 continuous infusion	Not specified

Table 2. Subcutaneous sodium valproate efficacy and tolerability.

Study	Efficacy of subcutaneous valproate (a) Indication (b) Quantitative/Qualitative Results	Tolerability of subcutaneous valproate (a) Nature of adverse events / side effects (b) Frequency of events
Cran et al. 2018	(a) Seizure control (b) Results are not specifically presented for valproate subset. - Seizures were controlled in 69% of patients with initial doses prescribed. - 46% died within a week of parenteral anticonvulsant prescription. - 92% died but did not state how long after treatment	(a–b) N/A
O'Connor et al. 2017	(a) Seizure control (b) Overall, 100% of patients had resolution of seizures eventually. - 5 out of 7 (71.4%) patients were seizure free initially. - In the remaining 2 patients, seizure activity resolved with an increased dosage	(a) No adverse events or local reaction in all 7 patients (b) N/A
Davis et al. 2018	(a) Neuropathic pain management (b) 5/6 (83.3%) patients experienced clinically significant improved pain control within 48 h. - 2/2 (100%) patients' allodynia resolved (1 of whom had severe residual nociceptive pain due to rapidly progressive disease). - 2/6 (33.3%) patients required an increase in opioid dose	(a) No complications attributable to this treatment (b) N/A
Kondasinghe et al. 2022	(a) Seizure control (83%) and pain management (17%) (b) Effectively controlled seizures in 83% of patients.	(a) Variable - Skin erythema at infusion site (b) 1/6 patient
Pouchoulin et al. 2014	(a-b) Not specified	(a) Reported adverse reactions included pain and induration. Abscesses and necrosis only with discontinuous administration[a] (b) More local adverse effects with discontinuous administration (65 instances) as opposed to continuous administration (16 instances), no instances of abscess or necrosis with continuous infusions.[a]

[a]Note that the tolerability is not specifically reported for subcutaneous valproate in this study.

continuous subcutaneous infusions including sodium valproate (600 mg/24 h), but did not present results specifically with this medication.[13] However, in their group of 25 patients that received medications including sodium valproate, levetiracetam and midazolam, seizures were described to be controlled in 69% of cases following initial doses. In one study of patients with neuropathic pain, continuous subcutaneous infusion of sodium valproate (dose range from 400 mg/24 h to 1500 mg/24 h), 5/6 (83.3%) of patients had a clinically significant improvement in pain within 48 h.[14]

Tolerability

Four studies reported on the tolerability or adverse effects associated with subcutaneous sodium valproate.[9,12,14,15] The three of these studies that presented results on valproate in isolation, comprising a total of 19 patients receiving subcutaneous sodium valproate, reported one adverse effect. Kondasinghe et al.[9] described one patient who experienced erythema at the subcutaneous line insertion site, which then resolved when a new subcutaneous access was obtained and the same concentration of sodium valproate provided subcutaneously at the second site. One study reported on adverse effects in a cohort of patients receiving a diverse range of subcutaneous medications, which included a subset who were receiving subcutaneous valproate. This group of patients had a number of local site reactions described; however, it was not possible to determine which reactions were associated with sodium valproate. In this study, it was described that local site reactions were less frequent with continuous infusions as opposed to discontinuous administration.[15]

Discussion

Summary of main findings

The results of this review have demonstrated that there is relatively little evidence regarding the use subcutaneous sodium valproate; however, the evidence that is available suggests that subcutaneous sodium valproate may be a reasonable consideration for selected patients. Current routine medication resources may not reflect this potential use of sodium valproate.[16] In particular, palliative care has unique medication considerations that may not apply to medication administration in other settings. The majority of studies used subcutaneous sodium valproate for seizures in patients with difficulty tolerating oral medications. There were also reports of benefit derived for neuropathic pain with subcutaneous sodium valproate use. Studies that specifically reported on the tolerability of a subcutaneous sodium valproate group described very few adverse effects, aside from an isolated local reaction. One study described its dilutant, using 0.9% saline or water for injections.[12] Practical considerations regarding subcutaneous valproate administration are discussed further in Supplemental Information 5.

Strengths and limitations

All primary peer-reviewed articles with palliative care patients treated with subcutaneous valproate were included irrespective of language. The main limitation of the review is in the low level of evidence of the studies that were available for inclusion. The review process itself is limited by the potential for publication bias influencing the results of the review.

Implications for future research

In the first instance, further descriptive data would add value to the current literature regarding the use of subcutaneous sodium valproate. Future observational studies may provide useful information through the specific description of patient cohort characteristics, dose conversions, concentration and dilutants. Real-world data regarding its use would aid in estimating the frequency of adverse effects, such as local site reactions. If a situation arose in which a patient was receiving subcutaneous valproate and required a blood test for another indication, measure a sodium valproate level may also provide additional information.

Conclusion

There are several studies that have described the successful use of subcutaneous infusions of sodium valproate in the palliative care setting. Palliative symptoms for which the use of sodium valproate via this route have been described include the management of seizures and neuropathic pain. Ultimately, in view of the limited data at this stage, this route of administration of sodium valproate would at best be an adjunct to other strategies being used to manage palliative symptoms. However, should the situation arise in which it is necessary, there are limited data to support its use with an appropriate degree of caution. The existing studies present enough evidence to argue for the inclusion of subcutaneous valproate in the palliative care armamentarium for selected circumstances. Future research in this area would be aided in the first instance through the presentation of additional descriptive data.

Author contributions

S.T., J.N., C.T., B.S., J.K., A.G., T.D., T.Z., R.G., S.E., M.K., I.M., A.H., S.S. G.C. and S.B. made substantial contributions to the conception and design of the work, acquisition of data, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content, gave final approval for the version to be published and agreed to be accountable for all aspects of the work.

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