UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Valproic Acid for Delirium

Background:

Delirium is a very common symptom for the palliative care population. Despite preventative measures, it is still common for patients to develop delirium. Pharmacologic management of delirium is a highly debated topic. Mainstay of pharmacologic options include first- and second-generation antipsychotics as well as benzodiazepines despite a lack of evidence to support their efficacy for reducing severity or length of delirium. For patients experiencing non-terminal delirium, there is a need for alternative pharmacologic agents that may improve the agitation with less sedation. Valproic acid (VPA) is an antiepileptic medication that has gained some traction for its use in combating delirium in the ICU setting. Valproic acid is postulated to reverse neuronal processes involved in delirium including a host of neurotransmitters such as dopamine, serotonin, acetylcholine, ɣ-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA). It is generally well-tolerated without many side effects.

Importance:

Delirium is common among palliative care patients and contributes to morbidity and mortality. Palliative care clinicians should be aware of other pharmacologic options to help mitigate delirium. Little (or no) research has been done for valproic acid in the palliative care setting, although we may be able to extrapolate existing literature from other healthcare settings (ie. ICU) to our population.

The Literature:

Am J Hosp Palliat Care. 2022 May;39(5):562-569.

Valproic Acid in the Management of Delirium

Objective: To review the evidence for VPA in the management of delirium

Methods: Systematic review from 1946 to January 12, 2021

- Diagnosis of delirium: CAM ICU in 6 reports, one used DSM-IV-TR criteria, and one used assessment criteria of psychiatry consultation service

Results: n = 10 studies; meta-analysis not possible

- **No RCTs evaluating the effect of VPA in the management of delirium exist**
- **94.8% ICU setting,** mean age 59.7 years (range 27-87 years)
- VPA prescribing practices varied across studies
  - Mean starting dose = 733mg/day, mean dose at follow up (3 to 7 days) = 1061mg/day
  - Loading dose utilized in < 10% of patients, mean loading dose 1765mg
  - Mean duration of therapy was 6.8 days
  - Tapering VPA prior to discontinuation was not common practice
- Prospective open label: N= 13, Disability Rating Score (DRS) decreased in 6/7 patients; 9/13 patients also taking antipsychotics
- Retrospective studies
  - N =254
    - N=40, CAM ICU; delirium resolution was similar between both groups: olanzapine versus VPA
    - N=15, resolution of delirium and improvement in agitation in 100% of cases
    - N=53, CAM ICU; reduction in agitation 51/53 (96%) versus 31/51 (61%), reduction in delirium 36/53 (68%) vs 25/51 (49%)
    - N=46; decreased incidence of delirium 84.8% vs 63.3%, decreased agitation 47.8% vs 16.7%
      - Adjunct therapy: 82.6% antipsychotics, 32.6% benzodiazepines, 39.1% dexmedetomidine
    - N=80; CAM ICU; delirium resolution: 55%, no difference in agitation, 56% of patients received antipsychotics
- Case Series or Reports: N= 10; improvement in agitation in all cases
- Most common side effects: hyperammonemia and thrombocytopenia
- VPA levels: no standardized approach utilized for obtaining VPA levels (trough versus random), and not all articles mentioned VPA levels
- **VPA was most utilized as adjunct to other medications**: antipsychotics, benzodiazepines, dexmedetomidine, ramelteon, gabapentin, mirtazapine, trazodone, sertraline
- Mortality reported in 4 studies with a range of 8-20%, no deaths attributed to VPA. High mortality rate likely related to ICU population

Conclusion: VPA as adjunct or monotherapy for delirium appears relatively safe and an option for treating agitation with hyperactive or mixed delirium based on retrospective studies.

J Pharm Pract. 2022 Sept 26;8971900221128636.

Use of valproic acid for the management of delirium and agitation in the intensive care unit

Methods: Retrospective cohort study of patients who received VPA versus those who did not for treatment for agitation and delirium in the medical and surgical/trauma ICU

- Adult patients (age ≥ 18), admitted to the ICU for ≥ 48 hours included if Richmond Agitation-Sedation Scale (RASS) score ≥ 2, were positive on the CAM-ICU and received ≥ 1 of the following medications during their ICU stay: haloperidol, quetiapine, olanzapine, propranolol, VPA and derivatives, risperidone, dexmedetomidine, or clonidine
- Excluded if prior diagnosis of dementia, concomitantly administered a carbapenem, prescribed VPA for other indications, or prescribed VPA ≤48 hours

Outcomes:

- Primary: delirium and coma free days at 14 days or ICU discharge
- Secondary: agitation and coma free days at 14 days or ICU discharge, ICU length of stay, duration of mechanical ventilation, in hospital mortality, and mortality at 28 days

Results: n = 108 ; average age VPA group 43.7 years and control 45.5 years; 81.5% had new diagnosis of TBI

- Median number of anti-delirium/agitation medications prior to index date:
  - VPA group: 2 (0-3) and control: 1 (0-2)
- **No significant difference between delirium and coma free days in either group**
- **No significant differences between groups for any of the secondary outcomes**
- Safety events in VPA group:
  - 6.1% hepatoxicity, 12.2% thrombocytopenia
- Average dose of VPA was 1643.3mg/day

Conclusion: VPA is associated with similar delirium and agitation-free days compared to other non-VPA anti-delirium and anti-agitation medications, with some adverse effects

Bottom Line:

- It is hard to compare efficacy across studies due to heterogeneity of prescribing practices and outcomes. Available evidence is weak to recommend valproic acid use for delirium. There are no RCTs examining VPA for delirium
- Antipsychotics given most often concurrently with VPA in retrospective studies, so it is difficult to determine causal relationship… or is there a collective effect?
- Although ICU patients are critically ill, this population may not be generalizable to all our patients
- Valproic acid is available in different formulations: intravenous, immediate release capsules, extended release capsules/tablets, oral solution. IV solution is cheapest formulation and may not always be feasible
- Hard to pinpoint causative relationship between ADE, given retrospective nature of studies. Generally, well-tolerated. Of note: valproic acid is teratogenic and contraindicated in pregnancy

CLINICAL PEARL: Evidence is weak to recommend valproic acid use for delirium in the ICU setting