ADJUNCTIVE VALPROATE FOR THE TREATMENT OF AGITATED OR HYPERACTIVE DELIRIUM

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The problem...
63 y/o female, ICU 3 weeks

Septic shock secondary to wound infection - collapsed
- Hypoxic Brain Injury
- Fell from bed in ICU sustained fractured ankle – surgery: external fixation
- Acute Renal Failure

Sustained agitation and delirium in ICU
- Confused, climbing bedrails, punching at staff, kicking, pulling lines and EF, vocalising
- Required physical restraints
- Initiated antipsychotic for agitation (haloperidol, largactil, olanzapine and quetiapine all given at various times over admission – charted regular quetiapine)
AGITATED OR HYPERACTIVE DELIRIUM: CASE 1

- Developed Neuroleptic Malignant Syndrome (NMS) 48hrs post-Quetiapine
- Prolonged QTc
- Antipsychotics contra-indicated
- On continued attempts to awaken - no improvement in agitation
  - clonidine
  - dexmedetomidine
  - benzodiazepines
  - propofol
  - analgesia (opiates)
- Unable to find any new underlying, untreated or ongoing cause of prolonged delirium
  - Referral to C/L – any other pharmacological option?
Previous experience with Valproate for various forms of behavioural disturbance, agitation & aggression

- Brain Injury Rehab Units
- Patients with Dementia
- Bipolar Affective Disorder
- Adjunct to management of Delirium Tremens as adjunct to benzodiazepines

Use in multifactorial hyperactive delirium?
SO WHAT IS VALPROATE?

- Sodium salt of Valproic Acid
- Derived from Valeriana officinalis
- Anticonvulsant since 1962
- FDA approval 1978
- Australia registered for epilepsy and mania
- USA also approved prevention migraines
Available multiple formulations: tablet, liquid, IV injectable
Bioavailability between preparations almost same – doses equipotent
Highly protein bound (>90%)
Small volume distribution
Enters CNS via passive diffusion and active anion exchange in brain capillary endothelium
Half life 9-16 hours
Extensive hepatic metabolism (<5% via kidneys)
- Glucuronidation
- Mitochondrial beta-oxidation pathways
PROPOSED DELIRIOLYTIC ACTION

- Blockade voltage-gated Na Channels
- Blockade (T-type) calcium channels
- Increased GABA synthesis
- Blocks GABA degradation
- GABA modulator
  - Induces presynaptic release
  - Does not affect GABA receptor per se (like benzodiazepines do via allosteric modulation of the receptor – which can explain the deliriogetic effect of benzos)
- Modulates serotonergic and dopaminergic transmission
- Attenuates effect of glutamate on NMDA receptors
ACUTE SIDE EFFECTS VALPROATE

- Nausea/vomiting
- Sedation
- Thrombocytopenia
- Hyperammonaemia
- Elevated LFTs
- Pancreatitis
- Drug reactions – note carbapenems
- Contraindicated in pregnancy
Initiated valproate 200mg BD
Up-titration to 500mg BD after 3 days
Monitored FBC, LFTs, ammonia – no issues
At higher dose started to get some reduction in agitated behaviour and able to be transferred from ICU to medical ward
No further improvement over next 3 weeks – never oriented
Cardiac arrest in hospital - deceased
<table>
<thead>
<tr>
<th>Paper</th>
<th>Year</th>
<th>Type</th>
<th>N</th>
<th>Resolved</th>
<th>Avg. time resolution</th>
<th>Dose</th>
<th>Side effects</th>
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</thead>
<tbody>
<tr>
<td>Sher et al.</td>
<td>2015</td>
<td>Case Series: Retrospective Case</td>
<td>16</td>
<td>13 (81%)</td>
<td>6.2 days</td>
<td>1133 – 1258 mg/day</td>
<td>Nil reported</td>
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<tr>
<td></td>
<td></td>
<td>Review</td>
<td></td>
<td></td>
<td>(4.2 d excl. outlier)</td>
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<tr>
<td>Bourgeois et al.</td>
<td>2005</td>
<td>Case Series</td>
<td>6</td>
<td>5 (83%)</td>
<td>3-5 days</td>
<td>500 – 2000 mg/day</td>
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</tbody>
</table>
| Gagnon et al.         | 2017  | Retrospective Cohort Study         | 53  | Did not assess | Significant improvement by day 3 | Loading 1800 mg or 28mg/kg. Maintenance dose 1500 mg/day | 2 (5%) elevated transaminases  
7 (13%) thrombocytopenia  
6 (12%) hyperammonaemia |
| Crowley et al.        | 2017  | Retrospective Observational Analysis | 17  | 50%      | “Observed downtrend in prevalence of delirium” | 5.8 – 17.4 mg/kg/day  |                                                   |
| Alam A, Puri NV.      | 2014  | Case series – Bickerstaff Brainstem encephalitis | 2   |          |                      | 500mg bid iv         |                                                   |
| Fitz et al. (Abstract only) | 2011 | Retrospective Review – Valproate vs Olanzapine time to resolution | 18 V 22 O | 72% | Resolved by day 7 | Not reported in abstract |                                                   |
**LITERATURE REVIEW SUMMARY**

- All retrospective &/or case series – no prospective or randomised trials
- Multifactorial delirium across different settings: ICU vs medical wards
- Low numbers (N=53 largest study; total cases N=134)
- Low power
- Publication bias likely
- Methodological differences – especially objective delirium measures
- Natural course of delirium (self-resolving)
- Minimal information regarding time to resolution or outcomes (most studies recorded subjective improvement within 48 – 72 hours)
- Variation in doses of Valproate used
- Heterogeneity cases, protocols, medications, outcome measures
Case series (C/L service)
Hyperactive delirium cases where usual pharmacological management was ineffective or contraindicated
N=6
5 (83%) resolved
Avg. 3-5 days
Dose 500mg – 2000mg/day
No reported side effects

BOURGEOIS ET AL (2005)
Retrospective Review
Valproate vs Olanzapine time to resolution
72% resolution by day 7 – similar both groups
Abstract only in conference paper – dose of valproate or side effects not reported

Safety and efficacy of valproic acid for treatment of delirium in critically ill patients

Fitz, K.
Harding, A.
2011
Journal Critical Care Medicine
Retrospective Case Review

Treatment refractory hyperactive delirium – valproate added to treatment

N=16

81% resolved

All cases showed improvement in agitation

Avg time to resolution 6.2 days (4.2d excluding one outlier)

Dose avg. 1200mg/day

Nil side effects reported

SHER ET AL (2015)

Adjunctive Valproic Acid in Management-Refractory Hyperactive Delirium: A Case Series and Rationale

Yelizaveta Sher, M.D., Anne Catherine Miller, M.D., Sermsak Lolak, M.D., Andrea Ament, M.D., José R. Maldonado, M.D.
Retrospective Observational Analysis

N=17

Day of valproate initiation – 76.5% met criteria for agitation, 52.9% screened positive for delirium

By Day 7 reduced to 70% and 20% respectively

‘Observed downtrend in prevalence of hyperactive delirium’

Dose 5.8 – 17.4 mg/kg/day (70kg person = 400–1200mg/day)

No side effects reported

Concurrent reduction in opiates, sedatives and antipsychotics
GAGNON ET AL (2017)

- Retrospective Cohort
- N=53
- Case selection: agitated/hyperactive delirium where delirium was worsening despite prior pharmacological management
- Valproate given in addition
- Did not assess resolution
- Significant improvement by Day 3
- Loading dose 1800mg – followed by maintenance of 1500mg/day
  - 2(5%) elevated transaminases
  - 7(13%) thrombocytopenia
  - 6(12%) hyperammonaemia
  - None had any adverse outcome from these effects
CASE 2

Hope for a better outcome
AGITATED OR HYPERACTIVE DELIRIUM: CASE 2

- 73 yo male, prostatectomy (adenocarcinoma)
- Previous history prolonged post-surgical delirium 1 year prior
- Day 3 post-op developed severe agitated/hyperactive delirium
- Organic screens/investigations normal
- Standard delirium management (non-pharmacological)
- Worsening over next 48 hours
  - Approx 1-2 hrs sleep per day
  - Climbing bedrails
  - Aggressive, hitting staff
  - Manic like features – rapid speech, loud, disinhibition
  - Destroying equipment and mattress
- No response to high doses sedation – lorazepam, diazepam (AWS), olanzapine, quetiapine, haloperidol, clonidine, melatonin – C/L referral
AGITATED OR HYPERACTIVE DELIRIUM: CASE 2

- Valproate 1000mg BD
- Dramatic reduction in agitated behaviour within 24 hours
- Sleep improved
- By 48 hours required reduction in all other antipsychotics and benzos
- At 72 hours was oriented T/P/P but still quite drowsy
- Rapid down titration of valproate – 500mg BD, 200mg BD, 200mg nocte
- Ceased olanzapine and benzos
- Discharged on no medication by day 7 full recovery
- No side effects noted from addition of valproate
PEARLS...

- Treatment refractory severe agitation/hyperactive delirium
- High dose initially (500mg – 1g) BD in addition
- IV, PO, via NG tube (liquid)
- Wean down rapidly when response evident (aim to cease in hospital)
- Monitor?
  - Ammonia levels
  - Abdominal pain
  - Thrombocytopenia (FBC)
  - LFT’s
  - Valproate blood level? – not useful unless prolonged treatment required > 7 days
  - Excessive drowsiness – wean all sedatives
THE CONCLUSION...
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REFERENCES

There's someone for everyone, and the person for you is a psychiatrist.