“Midazolam resistant” terminal agitation and restlessness

STEP 1 Is this terminal agitation and restlessness?
- Sedating someone who is not in last hours/days may cause iatrogenic delirium
- Is there iatrogenic delirium from other drugs/opioids?
- Is a pre-existing confusion/delirium being exacerbated?
- Is there another correctable cause-physical, emotional, social, spiritual?
- Do I need to add in haloperidol?

STEP 2 Defining midazolam resistance
- “drug of last choice” in 1980’s and 1990’s
- ? “Routine” use in care pathway 2000’s
- No convincing evidence of dose/response curve above 60-100mg/24hours
- Recommended doses Oxford handbook 30-60mg/24h, PCF3 30-60mg/24h
  (reported upper dose range 120mg for hiccup and 240mg for agitation-no supporting data)
- Very high doses will probably only “work” by killing the patient!

STEP 3 Using alternatives:

1. Levomepromazine S/C
   - 25mg stat, 50-100mg/24h (up to 200mg/24h)Oxford Handbook
   - 25mg stat, 50-75mg/24h (up to 300mg/24h) PCF3

   Consider early especially if:
   - concomitant nausea/vomiting (antiemetic)
   - pain (analgesic)
   - delirium (antipsychotic, potent at D2, H1, alpha1 and muscarinic receptors.)

2. Clonazepam S/C
   - 1-4mg/24h (Oxford Handbook)
   - 0.5 mg stat, 2-8mg/24h (PCF3)

   Consider early especially if:
   - Neuropathic pain
   - Can be given as single daily dose (long half life) so where syringe driver contra-indicated

3. Phenobarbitone
   - 100mg stat, 300-600mg/24h (Oxford handbook)
   - 200mg I/M stat 800mg/24h up to 2400mg/24h (PCF3) Page 206
   - Usually third line agent after midazolam/levomepromazine
   - Irritant. Needs a second syringe driver

   Consider early if:
   - Severe and uncontrolled fitting despite benzodiazepines (tolerance to antiepileptic activity of benzodiazepines with continuing use)
4. Hyoscine hydrobromide
   • Not usually indicated
   • Anticholinergic with sedative and retrograde amnesic properties at higher doses
   • 1.2mg/24h (Oxford Handbook)
   • 1.2mg/24h plus 200mcg prn (PCF3)
   • 0.6-2.4mg/24h (British National Formulary)
   • Can cause paradoxical agitation and other anticholinergic side effects

Consider if:
Third or fourth line if coexisting intestinal obstruction and/or severe problems with secretions

5. Propofolol
   • General anaesthetic.
   • Only where all else has failed.
   • Phenobarbitone preferable
   • Needs supervision/anaesthetist advice/expertise

References:
Palliative Care Formulary 3
British National Formulary
There are links to both from
http://www.gp-palliativecare.co.uk/?c=national

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