"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

Watson M, Lucas C, Hoy A, Back I (2005) *Oxford Handbook of Palliative Care* Oxford University Press Oxford

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