C8 Pain – KETAMINE DOSING STRATEGIES

(T.R.O. for Marshfield Clinic Palliative Medicine Fellowship)

For patient selection, use your own judgment. Minimal data exists as of 2014 to guide selection.

The most likely groups to benefit include:

1. Patients with clear evidence of opioid hyperalgesia and central sensitization
2. Patients with persistent severe (>7/10) malignant pain despite:
    a. large doses of opioids (>1000mg MDEs)
    b. and DESPITE opioid rotation (including methadone trial whenever feasible) and
    c. at least two primary adjuvant analgesic being used (gabapentin/ pregabelin AND venlafaxine/duloxetine, +/- oral anticonvulsant)

Parenteral Dosing

- **Marshfield Clinic dosing**
    - Discuss side effects very thoroughly with the patient prior to orders to prepare (but not to needlessly alarm) patient and family for the likely psychotomimetic effects. Reassure frequently if needed during the infusion.
    - Start at **0.5 mg/kg intravenous or SQ over 6** hours (i.e. 2mg/kg/day equivalent BUT for 6 hours ONLY).
        - Note: this is the most effective dose from Mercadante's study extended over a safer infusion time (6 hours vs 30 minutes), yet shortened from the Australian protocol (below) calling for a 24 hour trial (of a fixed, but similar dose).
    - Order 1 mg of lorazepam at the beginning of infusion and every 3 hours x 2 subsequent doses prn psychotomimetic side effects. Alternatively, may give 2 mg of Haloperidol. Order glycopyrrolate 0.2-0.3 mg subcutaneous every 6 hours prn excessive salivation or lacrimation.
    - Check psychotomimetic side effects and vitals every 1 hour x 3, pain intensity every 2-3 hours.
        - **Stop infusion if** P>110, systolic blood pressure increased by more than 25% of baseline, sustained RR <7, agitation or severe, intolerable psychotomimetic side effects.
    - AFTER the initial 6 hours, **if sustained (at least 12 hours) pain improvement** by 50% or more during the initial infusion is achieved, continue with intravenous (or SQ) infusion at the initial dose of **2 mg/kg/ day for 48 (72)** hours, then convert 1:1 subcutaneous to oral tid.
        - Note that this dose for an average weight person yields a rate close to the Australian protocols (± 100 mg/day). Oral conversion is a matter of dispute. We tend not to decrease the dose at the point of parenteral to enteral conversion.
    - AFTER the initial 6 hours, **if pain not improved** and no severe side effects, **start 4 mg/kg/day infusion** over the next 18 hours (effectively doubling the initial dose).
    - After the initial 24 hours, **if pain not improved** and no severe side effects, start 6 mg/kg/day infusion over the next 24 hours

        - After the initial 48 hours, **if pain still not improved** and no severe side effects, start 9 mg/kg/day infusion over the next 24 hours – IF the patient re-consents to this high dose

        - If pain recurs, titrate upwards by 50%-100% every 24 hours, up to 500m/day and up to 5 days of treatment of the maximum (500) dose. If not effective, STOP.

        - **If sustained pain improvement** by 50% or more for at least 24 hours of the intravenous (or SQ) infusion at 4mg/kg/day or higher, stop the infusion for 4-6 hours to confirm that pain control persists and if so, convert 1:1 to oral tid.

    - Intermittent dosing: 0.25-0.50(0.60) mg/kg IV Q6hrs, (very rare at MCPMF)

ORAL (outpatient) Dosing

- Oral dose, may start at 10-20 mg PO TID or 0.5mg/kg TID-QID (little evidence for a specific dose exists)
- Titrate by 50% every 48 hours until side effects or up to 500mg/day, whichever comes first
    - liver disease: dose reductions with hepatic impairment due to prolonged duration of action

- The (negative) **RCT** C8 Pain Ketamine NOT Effective JCO12.pdf used the following **protocol**:
    - Start at 100 mg/24 hours SQ infusion for 24 hours
    - IF pain intensity NOT improved but at least 2/10 points, increase to 300mg/24hrs at 24 hours
    - IF pain intensity NOT improved by at least 2/10 points, increase to 500mg/24hrs after the initial 48 hours elapsed
    - Continue at the dose at which pain improved (by at least 2/10)
    - Discontinue after 24 hrs of 500mg/24 or total on-ketamine interval of 5 days, IF no improvement
        - MCPMF addendum: Transition to oral dose at 5th day with 1-to-1 conversion of the effective parenteral dose