Antinociception *versus* neurocognitive effect of biased mu-opioid receptor oliceridine *versus* morphine – Utility Function Analyses

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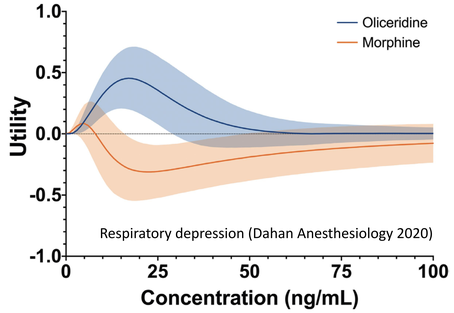
1

Morphine and oliceridine have different molecular effects despite both acting at the mu-opioid receptor:

1. Morphine activates **TOLL-like receptor 4** on microglia cells , causing a proinflammatory response, possibly causing neurocognitive effects. **Oliceridine has a lesser effect at these receptors.**
2. Oliceridine, but not morphine, is biased towards the G-protein intracellular pathway, causing less respiratory depression (See diagram 2)

2



Respiratory depression (Dahan Anesthesiology 2020)

3

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THE UTILITY FUNCTION OF ANTIHYPERTENSIVE THERAPY *

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U = Gains - Losses

U = Benefit - Risk

Risk = harm of untoward event x probability of event

Risk = expected medical harm

Utility = Benefit - Harm

Utility = P(B) – P(H)

FIGURE 1. The general definition of utility (U).

4

Opioid-induced neurocognitive dysfunction is an important opioid adverse effect

- motor instability (inability to mobilize or a high likelihood of falling)
- dizziness/lightheadedness

- memory loss and confusion
- delirium
- progression of already existing cognitive impairment

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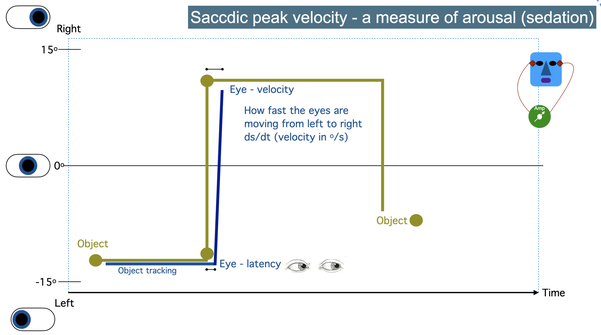
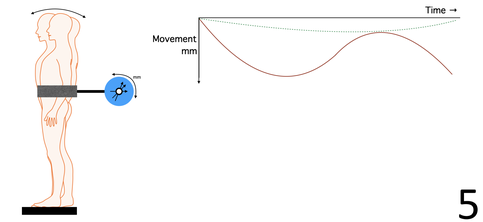
Saccdic peak velocity - a measure of arousal (sedation)



Body sway - measure of stability



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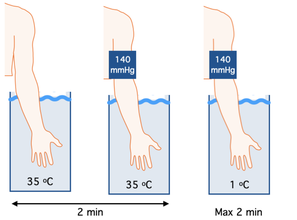
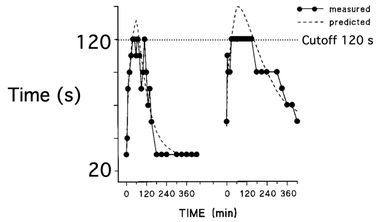
Cold pressor test - anti-nociception





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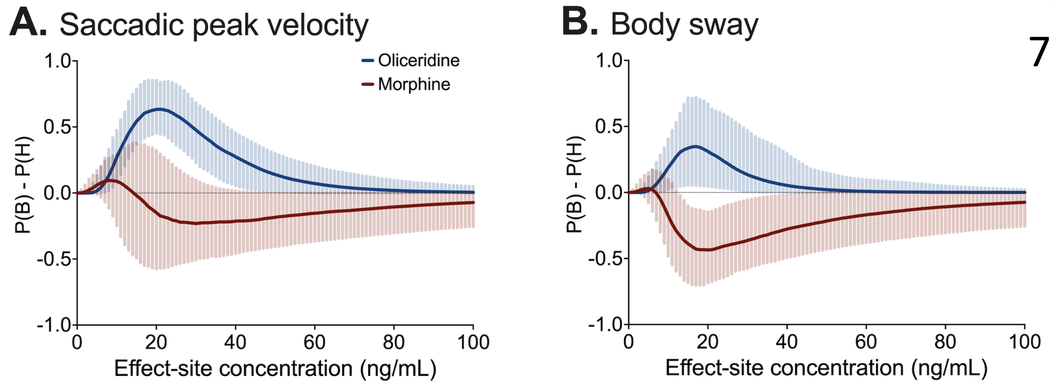

Conclusions: **These utilty data indicate that over the clinical concentration range, oliceridine is an analgesic with a favorable safety profile over morphine when considering analgesia and neurocognitive function.**

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