Investigation of the pharmacokinetics and pharmacodynamics of epidural methadone in healthy volunteers

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Introduction and Hypotheses:

Neuraxial hydrophilic opioids (e.g. morphine) typically have long durations of action and spread within the neuraxis, providing widespread analgesia over many dermatomes and also supraspinal adverse effects.

Neuraxial hydrophobic opioids (e.g. fentanyl) provide more segmental analgesia with fewer side effects, but they typically have shorter durations.

Methadone is a long-acting, hydrophilic, and polar opioid. It may provide the best of both worlds – prolonged, segmental analgesia with fewer adverse effects. Studies in rats suggest this is the case, but human studies are lacking.

Hypothesis: Epidural methadone will elicit a more segmental analgesic effect than morphine (though with similar duration), operationalized as a greater change in heat pain tolerance (ΔHPT) at the dermatome of injection (L3)as compared to the change at a distant dermatome (V2).

Primary Outcome:

ΔAUC_{HPT} - the difference between the AUC of the curve for time vs change in HPT at L3 versus V2 dermatomes for methadone vs morphine for the first 12 hours after administration.

Secondary Outcomes:

ΔAUC_{PPT} - as above, but for pressure pain threshold (PPT).
Markers of supraspinal/systemic effects – pupil diameter, respiratory rate, $ETCO_2$, and central adverse effects.
Correlation between clinical effect and plasma drug concentration (pending).

Inclusion/Exclusion Criteria:

Inclusion: 1) Age ≥ 18 years; 2) BMI 18.5-30.0.

Exclusion: 1) Known cardiac/hepatic/renal disease; 2) diabetes mellitus; 3) chronic pain; 4) contraindications to epidural, local anesthetic, or opioids; 5) pregnant or lactation; 6) history of substance use disorder or positive screen using 4-question Simple Screening Instrument for Substance Abuse (SSI-SA); 7) inability to provide reliable HPT at each tested dermatome at screening or prior to beginning each testing visit.

Study Design:

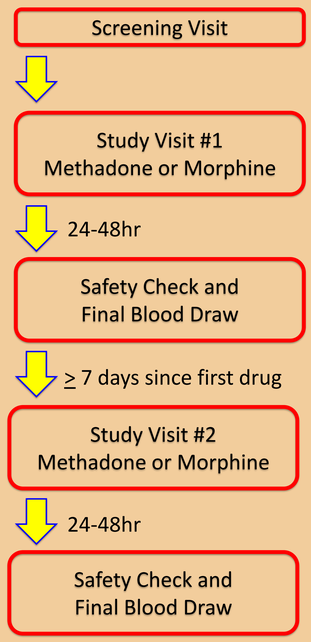
Prospective, double-blind, randomized, crossover study of 13 healthy volunteers completing both study arms. Study was performed at Washington University in Saint Louis and was approved by the WUSM IRB (#201802099).

Study drug administered as bolus via epidural catheter at L3-L4 interspace – either 4mg methadone or 4mg morphine (study days > 1 week apart).

Assessments made pre-drug administration (x 2) and 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours after drug administration.

Assessments included: respiratory rate and end-expired CO_2 (nasal cannula with capnography), pupil diameter (pupilometer), HPT at L3 and V2 dermatomes (TSA-II), PPT at L3 and V2 dermatomes (pressure algometer), drug concentration (venous blood sample, also drawn at 18hr and once between 42-72hr).

Patients reported AEs at any time.



Results:

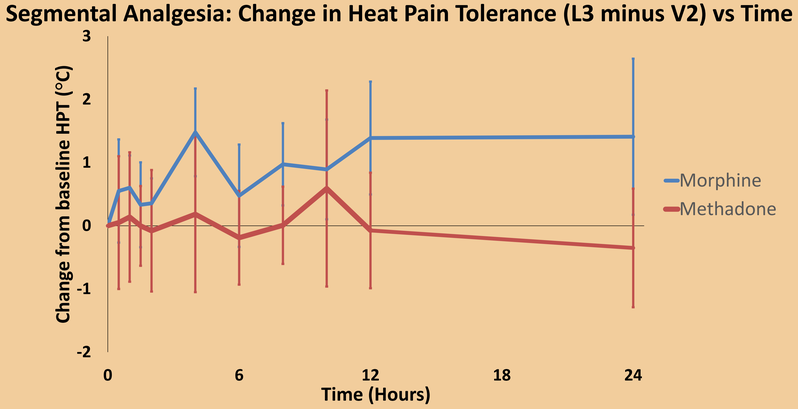


Figure 1 – Difference in change from baseline HPT at L3 vs V2 for 24 hours after administration of epidural morphine (blue) and epidural methadone (red). Positive numbers indicate greater relative analgesia at L3; negative numbers indicate greater relative analgesia at V2. Error bars – $CI_{95\%}$.

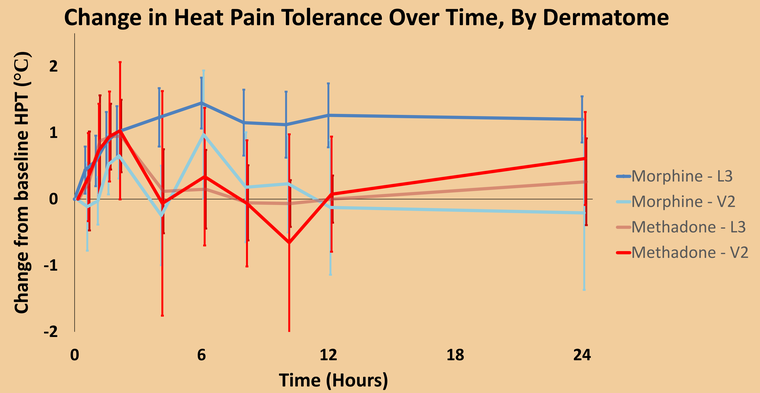


Figure 2 – Change from baseline HPT at L3 (dark shades) and V2 (light shades) for 24 hours after administration of epidural morphine (blue) and epidural methadone (red). Positive numbers indicate greater relative analgesia at L3; negative numbers indicate greater relative analgesia at V2. Error bars – $CI_{95\%}$.

Adverse Effect	Morphine	Methadone	p-value
Nausea	6 (46%)	0 (0%)	0.01
Pruritus	4 (31%)	0 (0%)	0.10
Urinary Retention	3 (23%)	0 (0%)	0.22
Subjective Sedation	0 (0%)	0 (0%)	1.0
Any Opioid Effect	8 (62%)	0 (0%)	0.002

Table 1 – Number (proportion) of participants experiencing AEs from epidural morphine (blue) vs epidural methadone (red). "Any opioid effect" includes any of the other listed effects. All p values are for Fisher exact test.

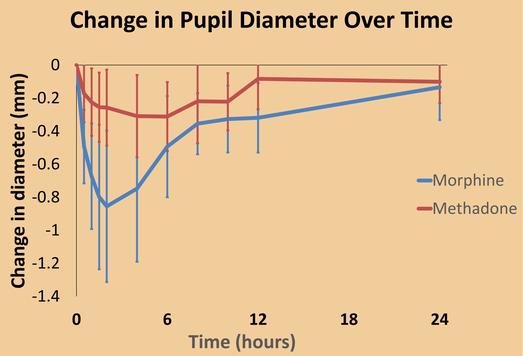


Figure 3 – Mean change in pupil diameter over time after morphine (blue) and methadone (red). Error bars – $CI_{95\%}$.

Results:

ΔAUC_{HPT} for hours 0-12 for morphine and methadone were not significantly different (morphine: 10.2 deg-hr, CI_{95} +5.6 to +14.8 deg-hr versus methadone: 1.4 deg-hr, CI_{95} -7.3 to +9.4 deg-hr; p = 0.09). Morphine provided significantly more analgesia at the L3 dermatome (13.4 deg-hr, CI_{95} +9.2 to +17.5) than did methadone (2.5 deg-hr, CI_{95} -3.1 to +8.1; p = 0.03), while the two provided comparable analgesia at the face (morphine: 3.2 deg-hr, CI_{95} -2.4 to 8.7 deg-hr; methadone: 1.5 deg-hr, CI_{95} -10.0 to 13.0; p = 0.35).

Morphine caused greater miosis over the first 12 hours than did methadone - AUC of change in pupil diameter vs time curve was -6.2mm-hr (CI_{95} -9.2 to -3.2mm-hr) for morphine vs -2.9mm-hr (CI_{95} -4.8 to -0.9 mm-hr; p = 0.009) for methadone.

Neither methadone nor morphine induced clinically significant respiratory depression over the first 12 hours as measured by respiratory rate (morphine: +7.6 bpm-hr, CI_{95} -7.2 to + 22.3 bpm-hr; methadone: +1.6 bpm-hr, CI_{95} -23.5 to +26.7 bpm-hr; p = 0.5) or $EtCO_2$ (morphine: +15.5 mmHg-hr, CI_{95} -2.8 to +33.8 mmHg-hr; methadone: +11.2 mmHg-hr, CI_{95} -1.3 to +23.6 mmHg-hr; p = 0.7).

More participants had opioid-related AEs (nausea, pruritus, urinary retention) with morphine (46%, CI_{95} 19-73%) than with methadone (0%). The most common AE with morphine was nausea (46%). No participants reported subjective sedation.

Discussion and Conclusions:

Bolus epidural methadone did not demonstrate greater relative segmental analgesia to heat pain than did bolus epidural morphine. There was a trend toward greater segmental analgesia for morphine driven by greater analgesia at the dermatome of injection and comparable analgesia at distant dermatomes, but due to high inter-participant variability this was not statistically significant.

Non-analgesic markers of supraspinal opioid spread (pupillometry, AEs) suggest greater neuraxial spread of morphine than of methadone.

While significantly more patients experienced nausea/vomiting, pruritus, and urinary retention with morphine, this must be interpreted with caution because these may not have been equianalgesic doses.

Acknowledgements:

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