Buprenorphine to Reverse Respiratory Depression from Methadone Overdose in Opioid-dependent Patients: A Prospective Randomized Trial

BACKGROUND: Normally, opioid overdoses that lead to respiratory depression are treated with naloxone to reverse the opioid effects. In patients who are opioid-dependent and have used an opioid with a long half-life, naloxone may cause withdrawal symptoms and may require additional doses. Buprenorphine is a longer acting, high potency partial opioid agonist that could potentially be used for opioid overdoses and cause less withdrawal symptoms and persistent effective reversal.

OBJECTIVE: To determine the efficacy and safety of buprenorphine compared to standard naloxone therapy as a respiratory depression reversal agent for methadone overdose in opioid-dependent patients.

METHODS:

- Phase II open-label, parallel arm, controlled clinical trial
- Conducted from November 2015 to December 2018
- Inclusion: opioid-dependent methadone-poisoned patients who developed acute respiratory depression (cyanosis, decreased O2 saturation [less than 90% in the context of acute overdose] and RR < 12 per minute) and needed antidote treatment after presentation to hospital
    - Opioid dependent: chronic use of any opioid drug
- Exclusion: less than 15 years old, those with known co-ingestion of other drugs, those who had aspirated or needed intubation prior to evaluation, and those with known cardiovascular disease
- Not an exclusion: received an initial dose of naloxone before evaluation and subsequently redeveloped respiratory depression a short time later
- 85 patients were randomized into Groups A, B, or C
- **Group A:** IV Naloxone
    - 2mg if RR < 6
    - 0.04 mg if they developed bradypnea (RR of 6 to 12 per minute)
    - Still unresponsive to therapy: 0.4, 2, and finally 10mg doses of naloxone in 2 to 3 min intervals to reverse respiratory depression
    - Continuous infusion starting at a rate of two thirds of the effective bolus dose per hour
    - Tapered (halved roughly every 8h) if the patient was completely symptom-free and venous blood gas analyses (VBGs) were normal
        - More rapid tapering was done if there is evidence of withdrawal.
    - The infusion was ceased when the effective dose was less than 0.25 mg/h.
- **Group B**: IV Buprenorphine
    - 10 µg/kg administered over 6 minutes
- **Group C:** IV Buprenorphine
    - 15 µg/kg administered over 9 minutes
- Primary outcome measure: initial response to the administered antidote.
    - A partial (but adequate) response was indicated by an increase in respiratory rate, with oxygen saturation above 90% but residual sedation
    - A complete response was indicated if there was complete arousal to normal consciousness
- Secondary outcome measure: re-development of respiratory depression/apnea over the admission
    - Persistent respiratory acidosis was defined as a pH of ≤ 7.30 and a pCO2 of ≥ 50 mmHg in spite of ongoing infusion of naloxone or after administration of the buprenorphine doses
- Data analysis:
    - Fisher's exact test to compare proportions
    - Mann-Whitney U test to compare continuous variables
    - Graphical presentation and the log-rank test for time to event analysis (for recurrent respiratory depression)

RESULTS:

- Total number of patients that completed study: 85 (intent to treat) and 81 (per protocol)
    - Group A: 29 (intent to treat) and 27 (per protocol)
    - Group B: 28 (intent to treat) and 27 (per protocol)
    - Group C: 28 (intent to treat) and 27 (per protocol)

- Primary Outcome: complete responses were more common with buprenorphine (93% vs 48%, difference 45%, 95% CI 25 to 67%, P< 0.0001)
- Secondary Outcome: The serial blood gas data supports the consistency of response showing a more consistent PCO2 in the buprenorphine- treated groups

Table 2 Comparison of response to naloxone vs combined buprenorphine groups ($n = 81$)

Outcome	Naloxone ($n = 27$)	Buprenorphine ($n = 54$)	*P* value
Response to bolus antidote doses	Complete 13 (48%) Partial 13 (48%) No response 1(4%)	Complete 50 (93%) Partial 3 (5%) No response 1 (2%)	< 0.0001
Opioid withdrawal	15 (56%)	6 (11%)	< 0.0001
Further apnea	6 (22%)	7 (13%)	0.34
Aspiration	1 (4%)	6 (11%)	0.41
Intubation	8 (30%)	5 (9%)	0.026
Continuing Sedation	9 (33%)	3 (6%)	0.002
ARDS	4 (15%)	0	0.01
Discharged alive with no sequelae (%)	23 (85%)	54 (100%)	0.01

(Taken from source)

- Author's conclusions: Buprenorphine appears to be a useful antidote for methadone-induced respiratory depression. The study also highlights several potential advantages over naloxone. The dosing strategy is much simpler, the response more consistent, severe withdrawal is much less common, and the duration of action is much longer. Outpatient buprenorphine administration to acutely overdosed patients by the patients' family or friends might be a viable alternative to take-home naloxone.

STRENGTHS

- The sample size is typical of phase II studies using continuous outcomes
- Used appropriate statistical analysis for this data

LIMITATIONS

- The method of randomization was sub-optimal and the trial was not blinded
- Higher efficacy and low risk of withdrawal with buprenorphine might be less apparent with other opioids
- Higher or lower or titrated or repeated doses of buprenorphine may be preferred strategies
- They evaluated overdose on only one opioid that is not necessarily the most relevant opioid for overdoses
- Baseline characteristics of the groups showed potentially significant differences

CONCLUSIONS

- Buprenorphine IV infusion vs naloxone IV infusion for secondary use after initial naloxone bolus in patients who are positive to have overdosed on a long-acting opioid such as methadone has shown to be a possible treatment option that could have benefits over traditional naloxone therapy.
- Clinical Practice: Buprenorphine could serve as a viable alternative to naloxone for this patient population, while demonstrating potential beneficial effects concerning less withdrawal and less adverse effects due to the overdose. However, because this study was conducted in one center with a small amount of patients, I would not advise this alternative under normal clinical circumstances until further information is collected.
- The authors state in their conclusion that this is could also be used as an alternative for outpatient use. This is an exaggerated extrapolation, as this study was conducted with weight-based IV infusions in a controlled setting and are not comparable to outpatient versions of these medications or outpatient situations.
- Further studies are required to establish dosing criteria and appropriateness for buprenorphine in this population. A multi-center, double blind, standard controlled with more patients would be ideal to discover more information about this treatment.

Reference:

Zamani N, Buckley N, Hassanian-Moghaddam H. Buprenorphine to Reverse Respiratory Depression from Methadone Overdose in Opioid-dependent Patients: A Prospective Randomized Trial. Critical Care (2020) 24:44.

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