Starting Buprenorphine Immediately after Reversal of Opioid Overdose with Naloxone


Heroin or Fentanyl* overdose reversed with naloxone
*or other short-acting opioid

Are any patient exclusion criteria present?
- Benzodiazepine, other sedative or intoxicant suspected
- Altered mental status, depressed level of consciousness, or delirium
- Unable to comprehend potential risks and benefits for any reason
- Severe medical illness such as sepsis, respiratory distress, organ failure present or suspected
- Report of methadone use
- Not a candidate for buprenorphine maintenance treatment for any reason

NO TO ALL

Is the patient awake with signs of opioid withdrawal? (i.e. COWS >4)

NO

YES

Is the patient agreeable to treatment with buprenorphine?

NO

YES

16mg SL Buprenorphine
Administered as a single dose or in divided doses over 1-2 hours. (Start with 0.3mg IV if unable to tolerate SL.)

Observe in ED until patient shows no clinical signs of excessive sedation or withdrawal (typically 2 hours).
OK to administer additional doses of Bup up to 32mg.
Engage, use motivational interviewing, and link to ongoing care.

Provide supportive care, observe and reevaluate

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The minimum inclusion criteria for ODNaloxoneBup is an otherwise healthy patient with no suspected co-ingestions and no recent methadone use with a normal level of consciousness, normal mental status, and the ability to provide informed consent.

Administration of buprenorphine (Bup) to patients intoxicated with alcohol, benzodiazepines or other sedative can result in potentially dangerous respiratory depression. Patients with acute illness or severe chronic illness such as infection, heart failure, liver failure, respiratory failure or acute renal failure can experience unpredictable sedation and respiratory depression.

Patients with altered mental status are not able to provide a reliable history or adequately consider the risks and benefits to provide informed consent. Patients taking methadone should be supported to continue methadone treatment; overdose is not an indication to switch to buprenorphine and may disrupt care.

Additionally, the interaction with buprenorphine and methadone is not well understood and potentially adverse antagonistic (withdrawal) interactions can occur.

Be prepared

There are two “worst case scenario” adverse events possible with ODNaloxoneBup:

1. Additive sedation with respiratory depression, and

2. Precipitated withdrawal. While neither of these has been reported at this time, any ED should be prepared and willing to adequately manage these potential complications. Reversal of buprenorphine is accomplished with high-dose naloxone (2-3mg IV push followed by 4mg/hr infusion) (9,10). Precipitated withdrawal is treated with empirically titrated with a multimodal approach that may include: benzodiazepines, alpha-2 agonists (clonidine, dexmedetomidine, lofexidine), high affinity full agonist opioids (hydromorphone), ketamine, and dopamine antagonists (e.g. metoclopramide or haloperidol).
Why this works

Once naloxone has reversed opioid overdose (regardless of whether withdrawal signs/symptoms have been precipitated), initiation of buprenorphine should yield a relative increase in mu-opioid receptor (MOR) agonism and be experienced as stabilization or withdrawal relief. *In vitro* (+NaCl), naloxone exhibits 5-fold higher MOR affinity than morphine and comparable MOR affinity as sufentanil and, under these same physiological conditions, buprenorphine exhibits 6-fold higher MOR affinity than naloxone.

Following naloxone displacement and reversal of opioid overdose, buprenorphine is therefore expected to displace naloxone from available MORs (and residual naloxone effect should wash out rapidly due to its pharmacokinetics; see figure above). Once bound to MORs, buprenorphine’s high-affinity, longer-acting MOR occupancy should effectively prevent return of full agonist toxicity (provide opioid blockade) even if relatively high concentrations of full agonist remain in the circulation.

The positive treatment responses we have observed suggest the possibility that as naloxone is metabolized and/or displaced from MORs a mixed state of buprenorphine partial agonism and full opioid agonism (from the residual opioid that caused the overdose) occur, thereby avoiding an abrupt transition from full to partial agonism that would have been experienced as precipitated withdrawal.

REFERENCES


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