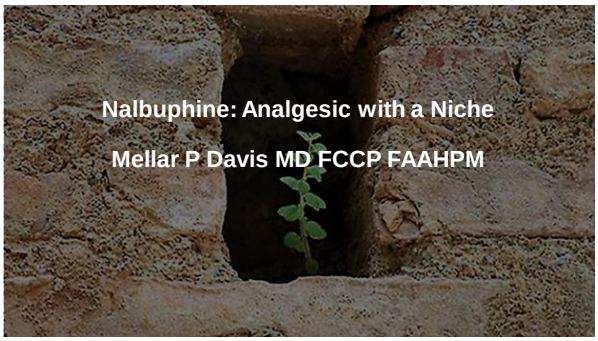


Summary of Advantages

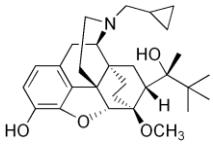
- Safe in renal failure- fecal excretion
- Analgesia equal to morphine with fewer side effects
- Reduced constipation
- Reduced but not absent addiction risk
- Reduced psychotomimetic side effects relative to morphine
- Can be taken orally (though not licensed)
- Ceiling on respiratory depression
- Conjugated to inactive metabolites- may be relatively safe in hepatic failure

Summary of Advantages

- Safe in cardiovascular disease-no hypotension, reduced cardiac output
- Reduces neuropathic pain
- Reduced risk of opioid related urinary retention
- Reduces pruritus in renal failure and with opioids
- Reverses respiratory depression of oxycodone, morphine, fentanyl and hydromorphone
- Poor street value-mu receptor antagonist
- Reduced withdrawal risk and physical dependence

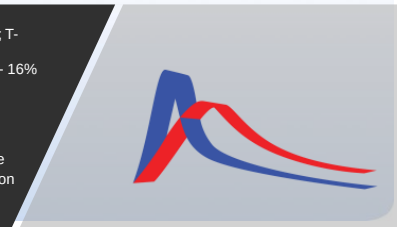
Nalbuphine

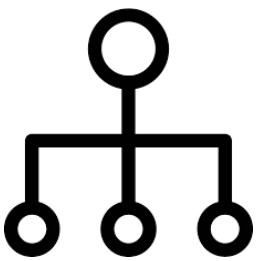
- Classified as a mu receptor antagonist/ kappa receptor agonist
- Related to nalorphine, butorphanol and buprenorphine
- 6-transmembrane mu receptor ligand
- Cyclobutylmethyl substitution on nitrogen ring
- 6-alpha hydroxyl group on 'C' ring
- Naloxone structure



Pharmacokinetics

- Parenteral nalbuphine; T-max 30- 46 minutes
- Oral bioavailability- 12- 16% in young, 46% elderly, oral/IV 5:1 or 6:1
- T1/2 2-4 hours
- 50% protein bound
- T ½ increases with age
- Clearance dependent on hepatic perfusion
- Renal clearance 4-7%





Pharmacokinetics

- Inhibition of UGT 2B7 increases nalbuphine 4-5 fold
- Enterohepatic recirculation with T1/2 longer with oral than parenteral
- Major metabolites are conjugated and inactive
- Largely undergoes fecal elimination

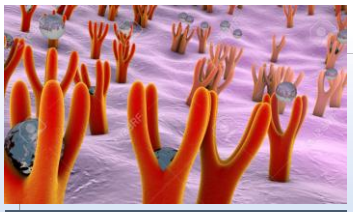
Pharmacokinetics in Renal Failure

- Oral SR tablets 30mg up to 240mg/day
- 15 hemodialysis patients,9 healthy controls
- Slow rise in plasma levels 4-9 hours
- Double-peak consistent with enterohepatic recirculation
- Steady state 2-3 days
- Renal failure increased exposure by 65% (C-max) and 83% (AUC), T1/2 1.6 fold greater
- Dialysis clearance- 1%
- No drug accumulation
- Dose dependent improved uremic pruritus, no respiratory depression

Nalbuphine: Oral and Parenteral Pharmacokinetics

Parenteral (10mg)
T ½ 2-3 hours
Bioavailable- 70-100%

Oral (45mg)
T ½-7.7-6.9 hours
Bioavailable-16.4-15.5%



Pharmacodynamics

- Opioid receptor affinity: mu Ki 6.3 nM, kappa Ki 61 nM and delta 163 nM
- Devoid of sigma 1 receptor binding
- 6-transmembrane mu receptor agonist (similar to butorphanol and buprenorphine)
- Selective mu receptor blockade does not influence analgesia
- Higher doses of naloxone are needed to reverse analgesia relative to morphine

Pharmacodynamics

- Nalbuphine and 6-beta naltrexol are neutral mu receptor antagonists and naloxone and naltrexone are inverse agonists in the opioid tolerant
- Opioid tolerant individuals have constitutionally active mu receptors which are blocked by inverse agonists (naloxone) but not neutral antagonists
- Nalbuphine can reverse potent opioid respiratory depression at low doses (0.1mg/kg) without inducing withdrawal
- Antagonist activity is 0.03 times that of naloxone in animals

Nalbuphine Antianalgesia

- Specific to males
- Pain 1 hour to 90 minutes after injection which is transient
- Optimal dose is lower in women (10mg) than men (20mg) ? related
- Antianalgesia is blocked by low dose naloxone (ratio 12.5 to 1), chlorpromazine (10mg), haloperidol (1mg), nociceptin receptor blockers and low dose morphine (2mg)

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Nalbuphine Analgesia Compared with Morphine

Systematic Review, Meta-Analysis and Bayesian analysis for credible limits

- 15 RCT, 820 patients,
- 10 trials for pain efficacy,
- 6 for pruritus,
- 12 for nausea,
- 10 for vomiting,
- 3 for respiratory depression

Nalbuphine Analgesia Compared with Morphine

Pain

- 10 RCTs, 618 patients, 299 received nalbuphine
- Pain relief RR 1.01 (95% CI 0.91-1.11), heterogeneity 40%, p=0.09
- Credible interval RR 1.102 (95% 0.6697-1.627) based on 1000 simulations
- No publication bias

Nalbuphine Analgesia Compared with Morphine

Nausea

RR (nalbuphine to morphine) 0.75 (95% CI 0.6-0.997) p=0.048

Vomiting

RR 0.65 (95% CI 0.5-0.85) p=0.001

Pruritus

RR 0.17 (95% CI 0.09-0.34) p=0.000

Respiratory depression

RR 0.27 (95% CI 0.27-0.57) p=0.003

Analgesia in Cancer Pain and Orthopedic Pain

- 6 studies, 186 patients
- Patients remained on nalbuphine up to 6 months
- Oral doses were 15-60mg q4h and up to 90mg as a single dose
- 4/186 developed analgesic tolerance
- 4/186 who stopped nalbuphine developed withdrawal symptoms

Schmidt W 1985

Analgesic in Cancer

- Twenty patients treated parenterally 16-188 days
- Doses ranged from 5-45mg
- Average daily dose 66mg / day
- Maximum dose 320mg/day

Stambaigh J 1982

Adverse Effects

- Respiratory depression is similar with 10mg of nalbuphine and 10mg morphine but there is a ceiling with nalbuphine at 30mg, not with morphine
- Very little respiratory depression at 1.24mg / kg and higher
- Less nausea and vomiting
- Less adverse effect on GI motility than morphine, codeine , buprenorphine and butorphanol
- No urinary retention

Schmidt W 1985
Beaver W 1978

Adverse Effects

- Few psychotomimetic effects (1% or less)
- Does not produce hypotension, reduce stroke volume, right heart pressures, bradycardia, tachycardia or EKG changes
- Less euphoria , little physical dependence and withdrawal

Schmidt W 1985
Errick J 1983
Fahmy N 1980

Adverse Effects

- Sedation (36%), nausea, vomiting
- Precipitate opioid withdrawal in morphine tolerant individuals if rotating at equianalgesic doses (1 to 1)
- Will not treat an ongoing abstinence syndrome unlike buprenorphine
- Dysphoria in addicts

Cowan A 1976
Villarreal J 1968
Jasinski D 1972, 1979

Abuse

- Reported in South Asia due to poor regulation of licit opioids through India. Other opioids are codeine, buprenorphine and dextropropoxyphene
- Isolated in Derry, Ireland
- In weightlifters and bodybuilders who use nalbuphine to reduce anabolic side effects
- Health care workers with easy access

Larance B 2011
McElrath K 2006
Wines J 1999

Equianalgesic

- Morphine to nalbuphine- 0.8 to 1- 1 to 1
- Nalbuphine 15mg po is equal to 60-80mg codeine
- Dihydrocodeine 30mg is equal to 30mg nalbuphine

Kantor 1984
Kay 1988
Beaver W 1978
Bahar M 1985

Dosing

- Usual doses : 10mg IV q3-6 h up to 20mg q3-6 h with a daily maximum of 160mg/day
- Pruritus: 2.5 -5mg (25-50% usual dose)
- Oral doses : 30mg as a single up to 240mg/d
- Reversal of opioid induced respiratory depression-0.1 mg/kg, 0.22mg/kg, 20mg single dose, 2.5mg every 2 minutes
- Elderly and in renal failure- reduce starting dose in half

Possible Uses of Nalbuphine

- As a step II analgesic for cancer pain
- Individuals in shock or unstable cardiovascular physiology, myocardial infarction
- Pediatric balanced analgesia
- Post operative shivering
- Parkinson's disease-L-dopa dyskinesia
- Uremic pruritus and pain in renal failure or hepatic failure

Summary

- Nalbuphine is a mixed 6TM mu, kappa receptor agonist, 7TM mu antagonist
- Utility is greater than morphine for acute pain
- Has the potential of being a primary analgesic in multiple clinical situations
- Has the potential for abuse
- Causes withdrawal symptoms in the opioid tolerant patient