Clinical guidelines on the application of buprenorphine in
the treatment of painful neuropathies and pain syndromes
in special patient populations

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BUPRENORPHINE (BUP):
AN UNIQUE OPIOID ...
Buprenorphine (BUP): basic considerations

• Interaction with different opioid receptors
  - Mu-opioid receptor agonist
  - Delta-receptor antagonist
    • Norbuprenorphine acts as an agonist
    • Potentiating central analgesic effect
  - Kappa antagonist
    • Spinal dynorphine (kappa R agonist) increases during opioid administration
    • Less 'opioid-like' side effects
  - ORL-1-receptor agonism
    • Neuropathic pain

• Reside in the periphery, the dorsal root ganglion, the spinal cord, and in supraspinal regions associated with pain modulation
  – Distinctly different from μ-opioid
• Activate pain inhibitory pathways in the central nervous system
• Inflammatory state necessary?
  – Induces δ-opioid receptors to migrate to the surface of neuronal cells
    • Accessible to δ-opioid agonists
  – δ-agonists relief inflammatory pain and malignant bone pain

Need for δ-opioid receptor activity?

• The δ-receptor-selective drugs may possess potential clinical benefits compared with the μ-opioid receptor drugs, including:
  – Greater relief of neuropathic pain (Dickenson, 1997)
  – Reduced respiratory depression (Cheng et al., 1993)
  – Less constipation (Sheldon et al., 1990)
  – Minimal potential for the development of physical dependence (Cowan et al., 1988)
    • + anti-depressant-like effect …?
Kappa-opioid-receptor (KOP)

- “clinical” agonists for KOP display much side-effects
  - But: neuroprotective effects!
  - Do not cause respiratory depression
- KOP agonists display anti-opioid action
  - analgesia by endo/exo MOP agonists
  - KOP receptors within nucleus raphe magnus
  - Antagonists analgesic potency of μ-agonists

ORL-1 Opioid Receptor (NOP)

- N/OFQ has pronociceptive, anti-analgesic effect when applied supraspinally whilst spinally N/OFQ causes analgesia at high doses; low doses lead to hyperalgesia
- N/OFQ anti-opioid effect is caused by NOP receptor localization on, and inhibition of, primary cells of the NRM, analogous to the KOP receptor pathway
  - Endogenous N/OFQ act to set threshold to pain
    - NOP receptor antagonists shown to induce long lasting analgesia with similar efficacy to morphine
  - NOP receptor antagonists possible novel analgesics or maybe used as an adjuvant to reduce the amount of classical opioid drug required to produce analgesia

BUP interaction with ORL-1-R

- Interaction of BUP and metabolites with the ORL-1 receptor is complicated
  - Activation of receptor centrally in the brain produces anti-analgesic effects in animals, but at the spinal level in the same models the effect is anti-nociception
  - Central effect at the ORL-1 receptor dampens the dopaminergic reward system
    - Beneficial effects of the use of buprenorphine in the treatment of opioid abuse as well as multidrug abuse
  - ORL-1 activation slows the onset of opioid tolerance
    - Tolerance is less with chronic buprenorphine use than with other primary mu receptor agonists
**BUP: clinical considerations - versatility**

- Different routes of administration!
  - Spinal
  - Epidural
  - Intravenous (bolus)
  - Transdermal
  - Sublingual
  - Oral

**UNIQUE OPIOID WITH DISTINCT CLINICAL PROPERTIES …**

… BUT OFTEN MISUNDERSTOOD

**Special patients populations to consider**

- Neuropathic pain syndromes
- Cancer pain
- Intensive care unit (analgesedation)
  - Opioid-induced hyperalgesia (OIH)
- Post-traumatic/post-surgical painful syndromes
  - Acute analgesia
  - Chronic conditions
NEUROPATHIC PAIN

International guidelines: BUP?

Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update

Robert M. Devorin, PhD; Allic R. O'Connor, MD; Joon A. Ahn, MD; Raal Bakon, MD; Maria C. Favaloro, PhD; Joseph J. Heagle, MD; Joel L. Kent, MD; Elliott J. Krane, MD; Alvin Z. Levy, MD; Robert M. Levy, MD; Sean C. Mackey, MD; Philips John Mayer, DC, PhD; Christian Marrow, RN, PhD; Stephen N. Rall, MD; Andrew S. C. Rees, MB, MS; FICA; Kenneth E. Schmid, MD; Brett Stover, MD; Steven Stover, DO; Raul-Delillo Trejo, Dr. Med; Dennis C. Tsuk, PhD; Gary A. Wallis, PhD; and Christopher H. Wells, MB

NICE: update on Neuropathic Pain (2013)
Value of buprenorphine in neuropathic pain
Omote et al. (1995)

- 2 patients suffering from post-amputation phantom limb
  - Intrathecal administration of buprenorphine
  - BUP produced complete and long-lasting relief
    - single intrathecal injection of 0.1 to 0.2 mg
    - resulted in a complete analgesia lasting for 3 days
    - all phantom sensations were completely abolished
    - significant increase in temperature of the lower part of the body following buprenorphine
      - sympathetic inhibitory effects or by effects on the spinal thermoregulatory system?

Analgesic effect of BUP in neuropathic pain
Zenz et al. (1992)

- Long-term oral opioid therapy in chronic non cancer related pain (n = 100)
  - 53 of whom suffered from neuropathic pain
  - Patients received prior opioid treatment without any clear pain-reducing effect were treated with BUP
    - Initial dose: 0.2mg three times a day
      - titrated to full pain reduction
      - or a maximum daily dose of 4.8 mg
  - Half the total patients showed good pain relief (decrease by 50% or more in visual analogue scale)
    - Lower daily BUP doses in patients with neuropathic pain (buprenorphine 1.3mg) than in non-neuropathic pain syndromes (1.6 mg)
Dose-response to BUP of nociceptive and neuropathic postoperative pain in patients following thoracic surgery (1)
Benedetti et al. (1998)

- Distinction between nociceptive postoperative pain (immediately after surgery) and postthoracotomy neuropathic pain (one month after surgery)
- One month after surgery 8 patients complained of shooting and burning pain with paraesthesiae and showed allodynia around the incision,
  - Remaining 13 patients were hypoesthetic, some even showing complete anesthesia
- All patients treated with i.v. buprenorphine in a double-blind randomized design
- Reduction of spontaneous pain symptoms, in both allodynic patients as well as in hypoesthesia
- Despite lower average pain scores one month after surgery (mean VAS = 6.71 immediately after surgery to mean VAS = 7.24 one month later), the ED50 increased after surgery (0.29 postoperatively compared to 0.50 after one month)
  - Neuropathic pain responds to BUP but higher doses of opioid than those which relieve nociceptive pain are necessary

Short- and intermediate-term analgesic efficacy of BUP-TDS in chronic painful neuropathies
Penza et al. (2008)

- Open-label study
- VAS score ≥ 5 under stable analgesic treatment
- The starting dosage of 35 µg/h was increased up to 70.0 µg/h in case of unsatisfactory pain control
  - The primary endpoint was the number of patients achieving at least 30% pain relief at day 42 visit.
- Treatment was considered safe over the study period
- Thirteen patients (40%) achieved > 30% of pain relief at the final day 42 visit
  - Five patients needed dosage of 52.5 µg/h
**BUP Dosing in NeP: clinical considerations**

- Dose related analgesic effect!
  - Higher doses have effect on descending inhibitory control system (DIC)
  - Most studies have looked at low dose either transdermally or sublingually
    - Higher doses now available either alone (Subitex®) or combined with naloxone (Suboxone®, Zubsolv®) for neuropathic pain would be an interesting area to study
  - Better analgesic efficacy of higher doses of BUP-TDS

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**CANCER PAIN**

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**Myths: antagonistic effect on other opioids**

- Difficulty to use BUP with other opioids or to switch from BUP to another opioid due to an antagonistic effect?
  - Clinically not a problem (no antagonistic effect!)
    - Mismatch of animal behavioral studies and clinical effects
  - Many of these older ideas and some conflicting data could be explained after analyzing the differential effects of BUP and its metabolites at the KOP and ORL-1 (NOP) receptors
Two recent trials have confirmed that no conflicts exist between morphine and buprenorphine.

- Patients (21% with cancer) receiving high-dose morphine (>120mg/day) were switched to BUP-TDS because of inadequate analgesia and severe adverse effects.
  - Better pain relief and high dose stability.

- In the second study (Mercandante et al.), iv boluses of morphine were highly effective (a reduction of >33% within 15 minutes) in combating breakthrough pain in 29 cancer patients whose basic analgesic regimen was BUP-TDS.
Buprenorphine TDS in routine clinical practice: multicenter, prospective, non-comparative, non-interventional post-marketing study

Tschirner et al. (2008)

- Chronic moderate to severe cancer pain, or chronic severe non-cancer pain that was insufficiently controlled by non-opioids were prescribed buprenorphine TDS
- Treatment outcomes and side effects were followed up for 3 months
  - Additional analgesia, and adjuvant/supportive treatments were allowed at discretion of physician
- N = 4,030 patients, with a mean age of 62.8 years
  - The vast majority of patients suffered from cancer-related pain (80.7%)
• Mean pain intensity decreased by 73.5% from 62.3 mm at baseline to 16.5 mm after 3 months
  – Most patients rated pain relief as ‘very good’ (41.4%) or ‘good’ (44.5%)
  – Sleep quality also improved. 48.1% of patients needed no additional analgesics during buprenorphine treatment
  – Most patients (96%) rated the BUP-TDS as ‘very easy’ or ‘easy’ to change.
  – At study end, it was planned to continue treatment with BUP TDS in 70.1% of patients

RCT on high dose BUP-TDS in cancer pain
Poulain et al. (2008)
• BUP-TDS (70μg/h) in 289 opioid-tolerant patients with severe cancer pain
  • Patients who were successfully treated with buprenorphine during a 14-day run-in phase were randomised to receive either active medication or placebo patches during the 14-day double-blind phase
    – Rescue medication (SL BUP 0.2mg)
  • Superior efficacy of BUP during the double-blind phase was statistically significant, despite the high placebo effect of the patch
    – Confirmed by secondary parameters such as pain intensity and consumption of rescue medication

BUP: not suitable to obtain rapid analgesia
• Buprenorphine is not useful for breakthrough pain by any route due to slow onset and long offset times
  – Despite high lipid solubility, similar to that of fentanyl, the onset time to effect and offset time are both prolonged
    • IV: onset time is 10–30 min (for fentanyl about 4 min), time to peak effect 70–100 min and duration 6–8 h
    • Despite high lipid solubility similar to fentanyl, it takes a long time after entering the CNS for buprenorphine to occupy receptors in brain tissue (biophase distribution) which means that receptor exposure is slow and long
POST-TRAUMATIC
(SURGICAL) PAIN

Post-traumatic/Post-surgical Pain

• Acute analgesia
  – Effective when given IV, IM, buccally, and sublingually but slow onset time reduces its usefulness for acute pain
    • onset time is similar with all modes of administration
      – due to the brain biophase effect
  – Epidural use has been described but onset time is not better since there will also be a biophase effect at the spinal level as well
  – Epidural use as an adjunct to other analgesics and started pre or during surgery/trauma would not be affected by the slow onset time
    • Thoracic injuries (rib fractures)

BUP as a perineural additive

• As adjunct BUP significantly ↑↑ duration of nerve blocks
  – At variety of anatomical sites
  – With a variety of local anesthetics
BUP as a perineural additive (2)

- Blocks voltage-gated Na\(^+\) channels via the local anesthetic binding site
  - Potent inhibitor of α-subunit of voltage-gated Na\(^+\) channels
  - Tonic block is concentration-dependent
  - Pronounced state-dependency with high-affinity block of inactivated channels
  - Much higher blocking potency than lidocaine
    - Even stronger than bupivacaine
    - High lipophilicity (octanol:water partition ration 2,000-100,000)
  - Relevance to preventive effect of BUP on development of hyperalgesia!

Other opioids?

- OR-independent inhibition of Na\(^+\) channels by other opioids
  - Meperidine (ratio of 39)
    - Comparable to lidocaine
  - Nav1.2 state-dependent block by sufentanil, fentanyl and tramadol
  - Morphine?
• Chronic conditions

  – Evidence from studies with BUP-TDS indicates that this is relatively safe and effective

  – BUP has been recommended in the population with a history of drug abuse and/or when risk of tolerance

    • Effect at the ORL-1 receptor dampens the brain reward system and the activity of buprenorphine at this class of receptors provides some evidence that there is less abuse potential

    • Slow onset/offset times make it less likely to be abused (little immediate “kick/high”)

ICU

Analgesia in ICU: practical problems

• Critically ill patients are often uncomfortable because of pain, anxiety, mechanical ventilation, …

• Discomfort is treated with continuous sedation, usually in combination with an opioid (intravenously)
  – Associated with prolonged mechanical ventilation and a longer stay
    • Shift from deep to light sedation is recommended
    • Analgesia-based sedation protocols are as effective as conventional hypnotic-based sedation protocols but that the required dose of hypnotic drug is reduced
    • Prolonged administration of opioids induces hyperalgesia
Analgesedation: a paradigm shift in sedation

- Hypnosis
- Analgesia
- ± Muscle Relaxation

Current practice parameters in ICU

- Morphine is cheap and longer acting than synthetic agents but more inclined to accumulate
  - Renal and hepatic impairment
- Fentanyl short-acting but risk of accumulation when given as a continuous infusion
  - Altered pharmacokinetics in critically ill
    - Different volumes of distribution
    - Different elimination half-lives
- Deleriogenic effects
- Immunosuppressive effects
- Chest-wall rigidity
- Gastric dysmotility

New approaches to analgo-sedation

- Opioids
  - Methadone
  - Buprenorphine: BUP-TDS combined with iv opioids
- Local anaesthetics: topical, iv and/or perineurally
- NMDA-antagonists
  - Ketamine
- Alpha-2 adrenergic agonists
  - Dexmedetomidine
- Nitrous oxide and oxygen
- (Micro-current) electrotherapy
Conclusion

- BUP has some unique basic and clinical properties
- Not useful for rapid analgesia (break-through pain)
- Very suitable for prolonged administration
  - "Opioid-resistant" pain conditions
  - Prevention of opioid-induced hyperalgesia
  - Prevention of tolerance (dose-escalation)
  - Peri-neural (additive) administration
- Need for high-quality clinical studies