ORAL OXYCODONE FOR ACUTE PAIN SERVICE IN POSTOPERATIVE PAIN MANAGEMENT

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INTRODUCTION

- Pain is a likely outcome of any surgical procedure
- In several countries the use of oxycodone has surpassed morphine in post-operative pain management

- Oxycodone is a strong opioid
  - Acts at mu- and kappa-opioid receptors
  - Greater analgesic potency to morphine

- Prolonged-release form of oxycodone
  - Fast onset of analgesia
  - Control pain for 12 hours

- It has relevant points of difference from other opioids and as such may be a suitable alternative to morphine
INTRODUCTION

- Visceral pain can be difficult to treat with classical μ-opioid agonists
  - Oxycodone has different effects compared to morphine
  - Clinical observations have shown that oxycodone may be superior to morphine

- In a study, 24 healthy subjects were randomised to treatment with either morphine (30 mg), oxycodone (15 mg) or placebo in a crossover study
  - The experimental pain model involved multi-modal (mechanical, thermal and electrical) pain tests in the skin, muscles and viscera

- Morphine and oxycodone were equipotent in pain modulation of the skin and muscles
- Oxycodone had superior analgesic effect to both morphine and placebo on the mechanical \((P < 0.001)\) and thermal \((P < 0.001)\) stimulations of the oesophagus \textit{ie visceral pain}
OXYCODONE$^{1,2}$

- Semi-synthetic derivative of a morphine alkaloid, thebaine
- Full opioid receptor agonist activity on mu, kappa and delta receptors
- The clinical efficacy of oxycodone is similar to morphine, with a ratio of 1/1.5–2 for the treatment of cancer pain
- Up to 87% oral bioavailability
- Plasma protein binding is 45%

OXYCODONE

After oral administration of immediate release, analgesic effect may occur within 10-15 minutes and last 3-6 hours
- Extended release commences after 1 hour and lasts 12 h

- There is no differences between immediate and slow-release oxycodone, except half-life is 3–4 h, and 12 h, (1/2 of morphine)

- Stable plasma levels are reached within 24 h (2–7 days for morphine)

- Most of the drug is metabolised in the liver, while the rest is excreted by the kidney along with its metabolites
  - The two main metabolites are oxymorphone — which is also a very potent analgesic — and noroxycodone, a weak analgesic

- Oxycodone metabolism is more predictable than morphine, therefore titration is easier
OXYCODONE ANALGESIC EFFICACY

Cancer pain

- Citron 1998
- Bruera 1998
- Hagen 1997
- Mucci-LoRusso 1998

OA pain

- Roth 2000
- Zautra 2005
- McCroskery 2000
- Markenson 2005

Neuropathic pain

- Riley 2008
- Heiskanen 1997
- Biancofiore 2006

Post-herpetic neuralgia

- Watson 1998
- Sindrup 1999

Diabetic neuropathy

- Hanna 2008
- Watson 2003
- Gimbel 2003

Post-operative pain

- Curtis 1999
- Sunshine 1996
- Ginsberg 2003
- Cheville 2001
- De Beer 2005
- Wirz 2005

OA=osteoarthritis
OPIOIDS PLACE IN PAIN MANAGEMENT

- Patients with moderate-severe pain\(^1,2\)

- Other conservative methods of analgesia have been tried and failed\(^1\)

- Pain is having a significant impact on the patient’s quality of life\(^1,3\)

- There is no psychological contraindication, drug-seeking behaviour or history of prescription medicine, illicit drug or alcohol misuse.\(^1\)

WHO ANALGESIC LADDER

Key concepts to effective pain management:

By mouth:
- If possible, the analgesic should be given by mouth

By the clock:
- Analgesics should be given at fixed time intervals and the dose should be titrated according to the patient’s pain.
- The next dose should be given before the previous dose has fully worn off

For the individual:
- The choice and dosage of the analgesics should be tailored to the patient

By the ladder:
- Stepped approach to the use of analgesics
WHO ANALGESIC LADDER
May 2013 (GENERALLY FOR NOCICEPTIVE PAIN)

- Non- opioids (paracetamol, NSAID’s, COX-2)

- Persistent pain or increasing pain
  - Weak opioids (codeine, tramadol, buprenorphine, tapendatol)
    for mild-moderate pain
    +/- non opioids +/- adjuvants (TCA, AED)

- Persistent pain or increasing pain
  - Strong opioids (oxycodone, Targin, morphine, fentanyl, hydromorphone)
    for moderate-severe pain
    +/- non opioids +/- adjuvants

- Supervised

Symptoms

Severe

Mild

Supervised
OPIOID-RELATED SIDE EFFECTS

- **Common**
  - Constipation, nausea, anorexia
  - Sedation, dizziness, cognitive impairment
  - Postural hypotension
  - Pruritus, dry mouth, miosis

- **Less common**
  - Hormonal effects – reduced testosterone / oestrogen
  - Immunosuppression
  - Opioid-induced hyperalgesia
  - Respiratory depression

OPIOID-INDUCED CONSTIPATION (OIC)

- OIC is common and experienced by 40–95% of opioid-treated patients and typically continues for the duration of opioid therapy.\(^1\)\(^-\)\(^3\)

OIC COMPROMISES PAIN MANAGEMENT\(^4\)\(^-\)\(^6\)

- OIC is one of the most common reasons chronic, moderate to severe pain patients avoid using opioids.\(^5\)\(^,\)\(^7\)

- 1 in 3 patients with chronic pain* reduce or skip opioid doses specifically to facilitate a bowel movement.\(^5\)

\*taking laxatives and daily oral opioids

OPIOID-INDUCED BOWEL DYSFUNCTION (OIBD) and OIC SYMPTOMS\textsuperscript{1,2}

- Anorexia
- Bloating
- Nausea, vomiting
- Abdominal distension
- Flatulence
- Abdominal pain

MECHANISM OF OIC

The primary cause of OIC is activation of opioid receptors in the gut\(^1\)–\(^3\)

Normal bowel function requires co-ordinated motility, mucosal transport and defaecation reflexes

Opioid receptors lie within the enteric nervous system of the GI wall

Gastrointestinal wall

Gastrointestinal lumen

Epithelium

Opioid molecule, binding to enteric opioid receptors to exert local effects

OIC=opioid-induced constipation.
PATHOGENESIS OF CHRONIC CONSTIPATION

PRIMARY CONSTIPATION

- Functional constipation (low fibre and fluid intake)\textsuperscript{1,3,4}
- Idiopathic (includes irritable bowel disease)\textsuperscript{1,2,4}

SECONDARY CONSTIPATION

- Iatrogenic → opioids, \textit{Ca}^{2+} channel blockers, anti-cholinergics, TCA’s, antacids \textsuperscript{1–3}
- Metabolic & endocrine disorders → diabetes, thyroid disease, \textsuperscript{1–3}
- Psychological → depression\textsuperscript{2}
- Neurologic and myopathic disorder → Parkinson’s disease, multiple sclerosis, stroke\textsuperscript{1–3}
- Structural obstruction → colon cancer, stricture, anal fissures and stenosis\textsuperscript{1–3}

CURRENT THERAPIES DO NOT ADDRESS THE CAUSE OF OIC\textsuperscript{1–3}

- Recommending laxatives for opioid-treated patients is considered best practice, however laxatives:
  - fail to address the underlying cause of OIC\textsuperscript{1,2}
  - are commonly associated with side effects\textsuperscript{1,3}
  - add to treatment costs for patients\textsuperscript{4}

- OIC often persists despite laxative use\textsuperscript{1,3}

What is required is the blocking of opioid action at receptors in the gut, to prevent or reverse OIC \textsuperscript{4,5}

TARGIN® TABLETS (APRIL 2011)
OXYCODONE + NALOXONE

TARGIN® TABLETS 12-HOURLY CONTROLLED RELEASE

OXYCODONE
Opioid agonist with central action

NALOXONE
Opioid antagonist that acts locally in the gut

TARGIN® TABLETS EFFECTIVELY RELIEVE MODERATE TO SEVERE CHRONIC PAIN

TARGIN® TABLETS HELP PREVENT OIC

NALOXONE

- Synthetic congener of oxymorphone\(^1\)
- Pure antagonist at opioid receptors\(^2\)
- Parenterally administered naloxone is used to reverse effects of opioids\(^1\)
- Metabolised extensively in the liver\(^1\) during 1\(^{st}\) pass metabolism
- Less than 2\% oral bioavailability\(^1\)

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Oxycodone preferentially binds to enteric opioid receptors, preventing oxycodone binding.

Opioid receptors within the enteric nervous system of the GI wall

Epithelium

Intestinal wall

Gastrointestinal lumen

TARGIN® TABLETS
INITIATION and TITRATION

Opioid therapy should only be used as part of a multimodal pain management plan

USUAL STARTING DOSE
- Patients uncontrolled on weaker opioids
- 10/5 mg TARGIN® tablet 12-hourly

12-hourly oral dosing
- TARGIN® tablets must be swallowed whole and must not be broken, chewed or crushed
- Titrate cautiously, to achieve pain relief and functional improvement, and to minimise the risk of adverse events

1. TARGIN® tablets Product Information. April 2011.
TARGIN® TABLETS
INITIATION and TITRATION

50% STARTING DOSE IN:¹
- Patients with mild hepatic impairment
  Bil to 45, Alb to 28, INR 2.3
- Patients with renal impairment
  Clcr < 60mL/min
- Debilitated elderly patients

MAXIMUM RECOMMENDED DOSE¹
- A maximum recommended dose exists due to limited exposure of patients receiving doses beyond 40/20 mg 12-hourly
- If longer-term treatment is anticipated, careful and regular assessment and monitoring is required to establish the clinical need for ongoing opioid treatment

¹ TARGIN® tablets Product Information. April 2011.
TARGIN® TABLETS
BREAKTHROUGH or INCIDENT PAIN

- Reassess non-pharmacological treatment adjuncts such as pacing and coping techniques, physical exercise and TENS

**OxyNorm® capsules**

5-10 mg q4hr

- If clinically necessary, treat with oxycodone IR (OxyNorm / Endone) rescue medication

- If more than two doses of rescue medication are required per day re-assess the patient and, if appropriate, adjust the dosage of TARGIN® tablets

- If incident pain can be predicted, consider rescue medication prior to activity causing pain

- If pain persists, consider neuropathic component to pain

CONTRAINDICATIONS (similar to OXYCONTIN):

- Moderate to severe hepatic impairment
  - Bil >45, Alb <28 and INR >2.3
- Patients with moderate to severe renal impairment
  - Clcr <40mL/min
- Severe respiratory depression
- Pregnancy and lactation

Please review Product Information for complete details of Adverse Reactions, Contraindications and Precautions.
SINGLE DOSE
MEAN OXYCODONE PLASMA CONCENTRATIONS

EFFECTIVE LONGER-TERM ANALGESIA

The majority of patients remained on a TARGIN® tablets dose that was comparable with the dose they received during the double-blind phase.

Mean oxycodone dose:
- 35.6 mg/day at week 2
- 40.9 mg/day for weeks 1-52

Mean Brief Pain Inventory score (NRS 0-10)

- Baseline
- 1 week
- 3 months
- 6 months
- 9 months
- 12 months

Mean pain scores stable over 12 months (379 patients)

TARGIN® TABLETS
CLINICAL TRIAL SUMMARY

ANALGESIC EFFICACY
- Analgesic efficacy equivalent to oxycodone CR\(^1,2\)
- Mean pain scores remained low and stable throughout the 12-month extension with minimal dose escalations\(^3\)

BOWEL BENEFITS
- Significant improvements in OIC were apparent after only 1 week\(^2\)
- Significant improvements in OIC were maintained for the 12-week study period\(^2\) compared with oxycodone CR\(^2\)
- Improvements in OIC were maintained throughout the 12-month extension study\(^3\)
- Fewer patients required laxatives compared with oxycodone CR\(^2\)

MR JR

- 76 yo carpenter
  - Now manager at carpentry firm
  - Also likes working in garden
- 5 year history of right knee pain
- Maximum dose paracetamol/codeine (30 mg)
  - NSAID for breakthrough pain
- Has regular physiotherapy
  - Home-based exercise programme
  - Heat packs
**POST – OP MANAGEMENT**

- **Right Total Knee Replacement**

- **Day 1 – 3 (Anaesthetist)**
  - Patient Controlled Analgesia (PCA) - Morphine IV
  - Paracetamol IV or orally regularly
  - Celecoxib 200mg daily for 3 days

- **Day 4 - 6 (Orthopaedic Surgeon)**
  - Paracetamol 2 tablets every 4 hours regularly
  - Oxycodone 5-10 mg every 4 hours as required
  - Pain assessment NRS 8/10 = moderate to severe pain
  - Knee Flexion 60 degrees

NRS = Numerical rating scale
REHAB MANAGEMENT

- Day 7 - Transferred to Rehab
  - Targin 10/5 mg twice a day
  - Paracetamol 2 tablets every 4 hours regularly
  - Oxycodone 5-10 mg as required (2-4 times a day)
  - Movicol 2 sachets twice a day
  - Coloxyl with Senna 2 tablets twice a day

- Pain assessment NRS 8/10 = moderate to severe pain
  - Knee Flexion 60 degrees

- Commence Hydrotherapy and Physiotherapy
Day 9
- Targin increased to 20/10 mg twice a day
- Paracetamol 2 tablets every 4 hours regularly
- Meloxicam 15 mg daily
- Oxycodone 5-10 mg every 4 hours as required (reduced to once a day)
- Coloxyl with Senna reduced to 2 at night and Movicol ceased
- Pain assessment NRS 2/10 and Knee flexion 90 degrees

Day 12
- Discharged home walking with 1 stick
- Targin reduced to 10/5 twice a day
- Pain 2/10 and Knee flexion 100 degrees
Mr EM

- 56 year old man

- L2-4 Lumbar laminectomy and Rhizotomy
  - Back pain resolved
  - Right leg sharp shooting pain resolved
  - Pregabalin 150 mg twice a day pre-op

- Developed LEFT FOOTDROP post-op
  - Secondary to neuropraxia from dural traction
  - Left leg pain 5/10
  - Oxycodone 10 mg twice a day

- Transferred to Rehab Day 3
  - Walking FASF
REHAB MANAGEMENT

Day 4
- Targin 10mg twice a day
- Reduced Pregabalin to 75 mg twice a day
- Regular Paracetomol 2 tablets twice a day
- Pain Free
- Hydrotherapy
- DICTUS BAND for footdrop

Day 7
- Targin reduced to 5/2.5 mg twice a day
- Ceased Pregabalin
- Walking with 1 stick
CONCLUSION

- Pain is a likely outcome of any surgical procedure
- In several countries the use of oxycodone has surpassed morphine in post-operative pain management

- Oxycodone is a strong opioid
  - Acts at mu- and kappa-opioid receptors
  - Greater analgesic potency to morphine

- Prolonged-release form of oxycodone
  - Fast onset of analgesia
  - Control pain for 12 hours

- It has relevant points of difference from other opioids and as such may be a suitable alternative to morphine
Opioids can be an important component of a multimodal pain management plan\(^1\)

Pharmacokinetic properties of oxycodone in TARGIN\(^\circledR\) tablets are bioequivalent to oxycodone CR tablets\(^6,7\)

Oxycodone in TARGIN\(^\circledR\) tablets is bioequivalent to oxycodone CR tablets\(^3\)

Effective in patients with chronic moderate - severe osteoarthritis, back, neuropathic and cancer pain\(^5-7\)

SUMMARY

- TARGIN® tablets offer a specific mode of action in PAIN MANAGEMENT to help prevent OIC

- There are many causes of constipation: one of these is opioid-induced constipation (OIC), which is common and can be debilitating

- OIC can have a significant impact on health-related QoL

- Laxatives fail to address the underlying cause of OIC

- When administered orally, naloxone undergoes extensive first-pass metabolism resulting in negligible (<2%) systemic bioavailability

THANK YOU
TYPES OF PAIN

Nociceptive pain

Mixed pain
(Both types of pain co-exist in many conditions)

Neuropathic pain
**NOCICEPTIVE PAIN**

- A sensory and emotional experience that occurs when specific peripheral sensory neurons (nociceptors) respond to noxious stimuli

- Painful region is typically localised at the site of injury
  - Throbbing, aching or stiffness
  - Aggravated by movement

- Usually time-limited and resolves when damaged tissue heals (e.g. bone fractures, burns and bruises)

- Can be chronic (e.g. osteoarthritis)

- Responds to conventional analgesics
NEUROPATHIC PAIN

- Pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system

- Pain often described as shooting, electric shock-like, burning – commonly associated with tingling or numbness

- Pain occurs in the neurological territory of the affected structure (nerve, root, spinal cord, brain) – typically distant from the site of injury

- Commonly a chronic condition (e.g. Post-herpetic neuralgia, post-stroke pain), but can occur with acute nerve injury (e.g. spinal cord injury, sciatica or surgery)

- Responds poorly to conventional analgesics
PAIN SCALES

- Subjective experience - rely on self reporting

- Verbal Rating Scale
  - no pain, mild, moderate and severe (0-3)

- Visual Analogue Score
  - 10cm line from “no pain” to “worst pain”
Carbamazepine (NNT to obtain 50% relief - 1.7)
Valproate, Phenytoin, Gabapentin, Lamotrigine, Topiramate, Oxcarbazepine
Pregabalin, Levetiracetam, Tiagabine
Lacosamide (Vimpat), Zonisamide
Clonazepam

Amitriptyline, Nortriptyline, Imipramine
Duloxetine

Opioids – Tramadol, Buprenorphine, Oxycodone (Targin), Tapentadol, Morphine, Fentanyl, Hydromorphone

Baclofen, Mexilitene, Clonidine
Capsaicin cream, Lignocaine 5% Dermal patch

N-methyl-D-aspartate (NMDA) blockers – Ketamine, Memantine
Botulinum Toxin
Vitamin B12