Opioids: Effects on Human Performance and Behavior

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Opioids

- Used to refer to a group of drugs that are opium- or morphine-like in their properties
- Includes natural and synthetic drugs
- Drugs which are used primarily as analgesics
Papaver somniferum
Opium
Why more than morphine?

- Improve analgesia
- Reduce side effects
- WWII time period - synthesis of demerol and methadone
- 1950s – Nalorphine
- 1960s-1970s - Discovery of opioid receptors
Mu Receptors

- Pharmacological effects:
  - Analgesia (supraspinal)
  - Respiratory depression
  - Miosis
  - Euphoria
  - Decreased GI activity
  - Drowsiness
  - Nausea
  - Hypo/hyperthermia
  - Increased addiction potential
  - Mental clouding

- Two types:
  - $\mu_1$ pain modulation
  - $\mu_2$ respiratory depression
Kappa receptors

- Described as G\(_i\) protein linked to Calcium channels

- Pharmacological effects:
  - Analgesia
  - Diuresis
  - Sedation
  - Dysphoria
  - Mild respiratory depression
  - Miosis
  - Lower addiction potential
Delta receptors

- Not well described
- Endogenous ligand binding appears to predominate

Pharmacological effects:
- Analgesia
- Dysphoria
- Delusions
- Hallucinations
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGN</td>
<td>None</td>
</tr>
<tr>
<td>Vertical Nystagmus</td>
<td>None</td>
</tr>
<tr>
<td>Lack Of Convergence</td>
<td>None</td>
</tr>
<tr>
<td>Pupil Size</td>
<td>Constricted</td>
</tr>
<tr>
<td>Reaction to Light</td>
<td>Little or None Visible</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>Down</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Down</td>
</tr>
<tr>
<td>Temperature</td>
<td>Down</td>
</tr>
<tr>
<td>Muscle Tone</td>
<td>Flaccid</td>
</tr>
</tbody>
</table>
# Narcotic Analgesics Category

<table>
<thead>
<tr>
<th>General Signs</th>
<th>Drug Effects:</th>
<th>Common Methods:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>Heroin:</td>
<td>Injected</td>
</tr>
<tr>
<td>Depressed reflexes</td>
<td>4 – 6 hours</td>
<td>Oral</td>
</tr>
<tr>
<td>Low, raspy, slow speech</td>
<td>Methadone:</td>
<td>Smoked</td>
</tr>
<tr>
<td>Fresh puncture marks</td>
<td>Up to 24 hours</td>
<td>Snorted</td>
</tr>
<tr>
<td>Track injection marks</td>
<td>Others: vary</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constricted pupils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowered pulse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Miosis
Morphine

- Serum half life average 3 h
- 20-40% bioavailable orally
- Up to 87% of a dose is excreted in urine with 75% present as morphine-3-glucuronide
Morphine

- 10-80 mg doses peak serum concentration = 0.052-0.256 mg/l
- 15 patients on intrathecal morphine daily dose schedules
  - No blood morphine level over 0.020 mg/l
  - Urine levels exceeded 300 ng/ml cut-off
Epidemiological Studies

- Bjorneboe et al 1987
  - 1446 apprehended drivers; 445 drug tests; 26 positive for morphine

- Poklis et al 1987
  - 137 DUlD cases; 3 positive for morphine

- Stoduto et al 1993
  - 854 auto injury victims; 5% morphine present
Morphine

Kerr et al. (1991)
- IV maintained steady state serum concentrations of 0.02, 0.04, 0.08 mg/l
- Evaluated maintenance of isometric force, verbal comprehension, and memory

Impaired recall of information and impaired ability to maintain low consistent force
Morphine

  - Numerous studies with both IV and oral
  - Psychomotor performance
    - Maddox-wing, DSST, eye-hand coordination, and auditory reaction times
  - Physiological endpoints
    - Heart rate, B.P., Respiration rate, and miosis
- Mild or no effect on cognition or psychomotor performance tests measured
Morphine

- Meijler 2000
  - cancer patients
  - 209 mg morphine daily for three months
  - evaluated for thinking ability, alertness, concentration, reaction speed and divided attention
  - performance did not differ significantly from the control group
WA DRE cases - morphine only

- 15 single drug cases; 12 with full DRE data
- Blood morphine concentration
  Average = 0.04 mg/L (<0.01 - 0.09 mg/L)
- 9 admitted Heroin Use
  - 5 polydrug 0.08 - 0.21 mg/L
  - 4 single drug <0.01 - 0.06 mg/L
Morphine Concentrations Compared

- **WA DRE Cases**
  - Morphine only cases: <0.01 - 0.09 mg/L
  - 9 Heroin Use: <0.01 - 0.21 mg/L

- **Meissner et al 2002**
  - 27 drivers free: 0.028-0.093 mg/L, total: 0.230-1.451 mg/L

- **Samyn et al 2002**
  - 5 plasma specimens: > 0.020 mg/L

- **Edwards et al SOFT 2002**
  - 9 positive for morphine: 0.01 - 1.9 mg/L
Codeine

- Mixed agonist/antagonist of μ and δ receptors
- Extensively used for mild to moderate pain and as an antitussive
- Dosage ranges from 15-60 mg with daily dosages from 60-240 mg
Codeine

- 10-20% of an oral dose is excreted in the urine within 24 h
- 95% of a single dose eliminated in 48h
- 3d after use only morphine present in the urine
**Codeine**

- Serum half life approximately 3 h

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time after dose</th>
<th>Peak Serum mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg (oral)</td>
<td>1 h</td>
<td>0.126</td>
</tr>
<tr>
<td>60 mg (oral)</td>
<td>1 h</td>
<td>0.11</td>
</tr>
<tr>
<td>65 mg (IM)</td>
<td>1 h</td>
<td>0.264</td>
</tr>
<tr>
<td>100 mg (oral)</td>
<td>1.5h</td>
<td>0.105</td>
</tr>
<tr>
<td>120 mg (oral)</td>
<td>1 h</td>
<td>0.256</td>
</tr>
</tbody>
</table>
Codeine - Epidemiological Data

- Bjorneboe 1987 - Norway apprehended drivers
  - 15 out of 445  3.4%
- Jonasson 2000 - Sweden DUID cases
  - 388 out of 4896  7.9%
- Leville 1983 - injured elderly drivers
  - relative risk = 1.8; codeine most common opioid prescribed
- Poklis 1987 - DUID cases
  - 2 out of 137  1.5%
Codeine - Laboratory Studies

- Bradley and Nicholson (1986)
  - 30, 60, 90 mg oral dose
  - Linear decrease in performance on visuo-motor coordination
  - No modification of saccadic and smooth eye movement as with other morphine-like drugs

- Evans and Witt (1966)
  - 32 mg oral at varying altitude
  - DSST - mixed result
Codeine - Laboratory Studies

- Heishman et al. (1998)
  - 0, 60, 120 mg oral
  - Modified DRE evaluations
  - Best indicators - decreased sum of pupillary diameter and decreased rebound dilation of pupils.

- Linnoila and Hakkinen (1974)
  - Driving simulator with alcohol combination
  - Increased risk for collision.
Hydrocodone

Hydromorphone
Hydromorphone/Hydrocodone

- µ agonists
  - HYC - analgesic and antitussive
    - Typical dosages 5-10mg three times per day
  - HYM - post-operative pain and cancer pain
  - 1.5-2 mg hydromorphone equianalgesic to 10 mg morphine
  - Average terminal $t_{1/2}$ 2.4-3 h IV, 4.1 oral, 3.8 rectal
Hydromorphone

- Peak plasma concentrations

<table>
<thead>
<tr>
<th>Dose (IV) µg/kg</th>
<th>mg/L plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.008</td>
</tr>
<tr>
<td>20</td>
<td>0.014</td>
</tr>
<tr>
<td>40</td>
<td>0.022</td>
</tr>
</tbody>
</table>
Hydromorphone

- Steady-state concentrations in cancer patients
  - Avg dose = 48 mg
  - Range = 6 - 216 mg
  - Controlled-release = 0.018 mg/L
  - Immediate-release = 0.020 mg/L
Hydrocodone metabolism

- $O$-demethylated to hydromorphone
  - CYP2D6 involved
    - HYM concentration varies greater than 5-fold
    - Increased excretion of unchanged HYC in poor metabolizers
  - Peak plasma HYM concentrations occur 1-2 h after dose of HYC

- N-demethylated to norhydrocodone

- C6-keto reduction also occurs
Hydromorphone metabolism

- Hydromorphone excreted as glucuronide conjugate (35%)
- Majority of the dose is excreted in 24 h
- Undetectable in 8h (unconjugated) and 48 h (conjugated)
Hydromorphone

- McCaul et al (1983) 2, 4 or 6 mg IV. Miosis and respiratory rate depression proportional to dose.
  - Miosis: mean 6.3 mm prior to dosing
    - 2 mg dose decrease of 2.2 mm
    - 6 mg dose decrease of 3.7 mm
  - Respiration Rate: decreased 2 h post injection
Hydromorphone

- Hill and Zacny (2000)
  - Single dose of 0.33 to 1.3 mg/70kg IV.
  - Miosis and respiratory rate depression proportional to dose.
  - DSST impaired at highest dose
  - No impairment to reaction time, eye-hand coordination, logical reasoning, or memory
  - Less impairing than benzos & other sedative drugs
Hydromorphone

- Walker and Zacny (1999)
  - cumulative-dosing
  - 0.33, 0.65, and 1.3 mg/70 kg IV
  - 1 hour between doses
  - Significantly increased sedation
  - Dose-proportional miosis
  - Dose-proportional impairment on psychomotor tasks
Hydromorphone/Hydrocodone

**case data**

- **WA**
  - 0 out of 1068

- **DiGregario (2001)**
  - 1 out of 619 DUID cases
  - HYC 0.225 mg/L

- **CO (‘92-’94) (urine)**
  - 25 out of 1194 (DRE cases)
  - 0.02 - 0.6 mg/L; avg 0.06 mg/L

- **VA (2001)**
  - 54 out of 999 DUI/DUID
* = Chiral Center
(R,S)-methadone = d,l methadone
(R)-methadone = l methadone = levomethadone
(S)-methadone = d methadone
Methadone

- Long-acting μ-agonist
- Used for analgesia and replacement therapy
- Approximately equipotent to morphine
- Supplied as the hydrochloride salt of the racemic mixture
Methadone

- 50 mg or less has proven fatal
- As much as 180 mg/day in methadone programs
- Up to 780 mg/day in rare instances
- With regard to preventing consumption of illegal opioids
  - 0.250 mg/l (r)-methadone
  - 0.400 mg/l (r,s)-methadone
Methadone

- 41-99% bioavailable orally
- Terminal half life
  - R- 37 h (30-59), S- 28h (18-41)
- Pharmacokinetics are stereoselective
Methadone Metabolism

- Metabolized extensively by P450 enzymes
- 9 metabolites have been identified
- 2 minor pharmacologically active
  - methadol & normethadol
- Primary pathway is to EDDP and EMDP
- Unchanged methadone 5-50% of dose in 24 h urine
- EDDP - 3 -25% of a dose
# Methadone

- **Peak serum concentrations**

<table>
<thead>
<tr>
<th>Dose</th>
<th>mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg oral</td>
<td>0.075</td>
</tr>
<tr>
<td>100-120 mg oral</td>
<td>0.86</td>
</tr>
<tr>
<td>100-200 mg chronic oral</td>
<td>0.83</td>
</tr>
<tr>
<td>10 mg IV</td>
<td>0.50</td>
</tr>
<tr>
<td>Chronic</td>
<td>0.57-1.06</td>
</tr>
</tbody>
</table>
Methadone - Epidemiology

- No difference in traffic violation rate
- No difference in accident rate
- Infrequent in fatal drivers - 0.1%
- Infrequent in DUID (Colorado) - 1.1%
- Slovenia - 462 cases; 6 years
  - 5th most frequent in traffic accidents - 17.2%
  - 3rd most common in suspected drivers - 19.2%
Methadone - Laboratory

  - Attention and perception tasks were impaired in methadone maintenance patients.
  - Better explained by sociodemographic factors.
  - Determine fitness to drive individually.

  - Performed significantly poorer on all of the neuropsychological measures.
  - Implications of heroin use.
Methadone - Driving

- Dittert et al (1999)
  - Looked at driving ability of methadone patients
  - Only 6 out of 28 had sufficient driving skills
  - No significant correlation with patient’s age or dose
  - Therapeutic methadone dose
  - Traffic related performance
  - Methadone group had lower results on almost all variables
  - 2/3 urine positive for other drugs
  - “Methadone only” = Control group
  - Driving ability depends on other drugs taken and personality.
Methadone - WA

- DRE cases:
  - Polydrug use - 30/34
    - Other opioids, CNS Depressants, Cannabis
  - Driving Behavior
    - causing driver 2/3 in single drug cases
- Blood Levels
  - 0.11 - 0.20 mg/L single drug cases
  - 0.04 - 0.36 mg/L
  - (15 mg = 0.075 mg/L 100-120 mg = 0.86 mg/L)
Oxycodone

- Semisynthetic
- Derived from thebaine
- μ agonist
- Available for use since 1915
- Equipotent to morphine
- Prescribed for pain that requires longer treatment
Oxycodone

- Tablets, capsules, and liquid formulations
- 2.25 - 5 mg oxycodone/dose
- Many contain aspirin, phenacetin, or caffeine
1996 OxyContin a controlled-release formulation in 10, 20, 40 mg tablets with 80 and 160 mg tablets introduced in 1997 and 2000
Oxycodone

- 60% - 87% oral bioavailability; $C_{\text{max}}$ 1-1.5 h
- Controlled-release two phase absorption
  - Rapid phase = $t_{1/2\text{abs}} = 37 \text{ min}$ 38% of dose
  - Slow phase = $t_{1/2\text{abs}} = 6.2 \text{ h} = 62\%$ of dose
- 61% bioavailability rectally
- Half life 4-6 h
Oxycodone

- Metabolized in liver through $n$-and $O$-demethylation, 6-ketoreduction, and conjugation with glucuronic acid
  - $O$-demethylation by cytochrome P450 2D6 produces oxymorphone; Potency 10X morphine
  - $N$-demethylation produces noroxycodone
- 8-14% excreted unconjugated
**Oxycodone - Single Dose**

- Plasma concentrations

<table>
<thead>
<tr>
<th>Dose</th>
<th>mg/L peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 mg oral</td>
<td>0.009 - 0.037</td>
</tr>
<tr>
<td>20 mg controlled release</td>
<td>0.0186</td>
</tr>
<tr>
<td>20 mg immediate release</td>
<td>0.0416</td>
</tr>
<tr>
<td>0.14 mg/kg IM</td>
<td>0.034</td>
</tr>
<tr>
<td>0.28 mg/kg oral</td>
<td>0.038</td>
</tr>
</tbody>
</table>
Oxycodone - Laboratory

- Heiskanen et al. (1998)
  - 20 mg controlled-release to 10 subjects
  - Psychomotor tests - MW, DSST, & CFF
  - Pupil size measured
  - Peak plasma at 2.25 h = 0.0204 mg/L
  - Pupil size and MW correlated with plasma level
    - Marked drowsiness and impairment on CFF
Oxycodone - Laboratory

- Poyhia et al 1992
  - 19.6 mg/70 kg
  - MW, DSST, CFF, pupil size, & self-eval of sedation
  - Decremental effects on all measures
  - Maximal miosis at 1 h
  - Impairment on CFF and sedation for 5 h
Saarialho-Kere et al 1986

- 0.13 mg/kg IM tested 1.5, 3 and 4.5 h
- MW, DSST, CFF, choice reaction time, tracking, & divided attention
- Effects on performance peaked at 1.5 h
- Prolonged reaction time, impaired vigilance, attention, and body balance
- Subjects self assessment - impaired 3h after dosing
- Mean plasma: 0.010 mg/l at 45 min, 0.022 at 1.5 and 0.011 at 3 h
Oxycodone and DUID

- WA - 1 case (out of 1068 subset)
  - 0.12 mg/L (also + for codeine and cyclobenzaprine)

- VA - 29 cases
  - 0.01 - 0.50 mg/L
  - driving on the wrong side of the road, falling asleep, unresponsive, extremely unsteady, slurred speech, etc.
Summary of Effects

- Some indications of impairment and increased risk of collision.
- Miosis and reduced pupillary reaction to light evident in both controlled studies and in DRE assessments.
- Depressed respiration rates consistent.
- Environmental/personality modulation of effect.
- Individuals may adapt under long term dosage.
Summary of Effects

- Metabolism via CYP2D6 polymorphisms may alter effect due to differential production of active metabolites.
- Numerous reports of improved performance, possibly due to decreased distraction and anxiety.
- Multiple drug use a significant issue particularly with methadone. Leading to an increased impairment potential.
Conclusion

- Impairment cannot be determined by quantitative blood toxicology alone.
- Paired with the observations of a DRE, a determination of impairment can be made.