Pharmacogenetics and clinical opioid efficacy

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Variation in opioid dose

Variation in effects from different opioids

Genetic variability?

- Laboratory and animal studies
- Human experimental pain
- MRI / PET studies
- Opioid maintenance studies
- Clinical analgesic efficacy
<table>
<thead>
<tr>
<th>Preclinical studies</th>
<th>Clinical studies</th>
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<tbody>
<tr>
<td>- Healthy volunteers</td>
<td>- Cancer disease</td>
</tr>
<tr>
<td>- Experimental pain</td>
<td>- Co-morbidity</td>
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<tr>
<td>- Opioid naïve</td>
<td>- Long-term opioid treatment</td>
</tr>
<tr>
<td>- No/little co-medication</td>
<td>- Extensive co-medication</td>
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</tbody>
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Increase the understanding of the relevant biological mechanisms

Does it matter in the real world of patients treatment
Question 1
Biological pathways

Genetic Disposition and Patient-reported Quality of Life Outcomes
Rochester, MN, February 26 – 28, 2009
Question 1
Biological pathways

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Question 2
Known genetic association?

Opioid metabolism

Modifying systems/Transport

Receptor interactions
CYP2D6 polymorphism and the use of codeine as an analgesic

Example illustrates distribution in European Caucasians
Morphine metabolism - cancer patients

Morphine is metabolized to its active metabolite M6G by UGT2B7

13 SNPs observed in the UGT2B7 gene

Associations with serum concentrations of morphine, but no differences in clinical outcomes

Holthe, Klepstad et al Pharmacogenetics J 2003
Question 2
Known genetic association?

Receptor interactions
The OPRM1 118A>G polymorphism and morphine consumption in cancer pain

99 Norwegian cancer pain patients

138 Italian cancer pain patients

Average decrease of pain according to patients genotype, after a week of morphine therapy


Campa D et al., 2007, Clin Pharmacol Ther
Clinical studies and the OPRM1 A118G - postoperative pain

Human Opioid Receptor A118G Polymorphism Affects Intravenous Patient-controlled Analgesia Morphine Consumption after Total Abdominal Hysterectomy

Wen-Ying Chou, M.D.,* Cheng-Hsiung Wang, M.D.,† Ping-Hsin Li, M.D.,* Chen-Cheng Liu, M.D.,* Chia-Chii Tseng, M.D.,† Bruno Jawan, M.D.§

Association of µ-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty

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Genetic variability of the µ-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women 1

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Question 2
Known genetic association?

Modifying systems/Transport
Morphine, M6G, methadone, fentanyl, sufentanil and alfentanil are potential substrates for MDR Efflux transporters at the Blood-Brain-Barrier (BBB).
Average decrease of pain according to patients genotype, after a week of morphine therapy.
Clinical studies and the MDR 3435C>T - cancer pain

Baar, Klepstad et al In Prep
**Catechol-O-methyltransferase (COMT)**

- COMT metabolizes catecholamines such as dopamine, adrenaline and noradrenaline.
- Val158Met polymorphism. Met-allele associated with threefold decrease in enzyme activity.
- Met/Met homozygous individuals have:
  - Higher sensory and affective pain ratings
  - Lower levels of endogenous opioids
  - A compensatory increased µ-opioid receptor concentration in various brain regions

Zubieta J-K et al., *Science* 2003; **299**: 1240-1243
The COMT Val158Met polymorphism may influence morphine requirements in cancer pain patients

Rakvåg, Klepstad et al., *Pain* 2005; 116: 73-78
Current status

- Compelling evidence for that genetic variation in CYP2D6, OPRM1 COMT is important for opioid analgesic efficacy
- For other genes (MC1R, IL-6 etc) some observations but inconclusive
- Several potential candidate genes not studied in clinical relevant samples
- Lack of studies about analgesic efficacy for other opioids than morphine and codeine
- Small samples (2 - 250 patients)
Questions 3
What datasets are available

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European Pharmacogenetic Opioid Study

- 2305 patients
- 17 centres, 11 countries
- All patients use an opioid for cancer pain
  - ~1/3 morphine
  - ~1/3 fentanyl
  - ~1/3 oxycodone
  - ~1/10 others
European Pharmacogenetic Opioid Study

• Detailed clinical data
• Detailed data on use of opioid
• Brief pain inventory
• EORTC QoL-C30
• MMSE
• Center specific add-on questionnaires
• Serum concentrations of opioids
• Genetic analyses
European Pharmacogenetic Opioid Study

• Genetic analyses - candidate gene approach
  • Genes established or putative important for opioid pharmacology (i.e. OPRM1, OPRD1, OPRK1, OPRL1, MDR1, COMT, MC1R, ARRB2, STAT6, ADRA2A .......)
  • Genes putative important for adverse effects (i.e HTR2A ....)

• Genetic analyses - explorative approach
  • Pooled DNA of 10 percentiles

• Difficulties in the analyses - yes
Question 4
New studies

Studies on which clinical factors that influence responses to opioids

Computer adaptiv testing of symptoms

Predict opioid dose (and perhaps which opioid)

Studies on which genetic factors that influence responses to opioids

Analyses of selected SNPs

Genetic Disposition and Patient-reported Quality of Life Outcomes
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Is this fiction?

www.warfarindosing.org
An example of the practical use of clinical and genetic data