Pharmacogenomics and Anesthesia

Maren Kleine-Brueggeney

University Department of Anesthesiology and Pain Therapy, Bern, Switzerland
Nephrectomy: Cumulative analgesic consumption

Tramadol + Dipyprone via PCA

Patient A
56 years, 65 kg

Patient B
61 years, 100 kg

Pain score: 61
2000 mg tramadol

Pain score: 34
1600 mg tramadol

Pain score: 34
1200 mg tramadol

rescue medication
morphine
20 mg
Pharmacogenomics

genetic variants ↔ drug effects
Drug or Toxic Agent?

Meta-analysis about adverse drug reactions (ADRs)

- 2,216,000 serious ADRs (6.7%) per year in the US
- 106,000 fatal ADRs (0.32%) per year in the US

Pain
Placebo effect
Genetic background
Pain related
Drug related
Compliance
Response / Outcome

Sex
Age
Organ function

Genetic background
Drug related

Pharmacokinetics
Pharmacodynamics

Disease
Co-morbidity
Nutrition Life-style

Psychological & Socio-environmental variables
Severity of tissue damage

Co-medication

Adapted from Pharmacogenomics (2010) 11(6):843-864 with permission of Future Medicine Ltd
Pharmacogenomics

Genetic variants ↔ Drug effects

Goal: Prevent therapeutic failure, side effects, toxicity
## Targets of Variable Drug Response

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors</td>
<td>μ-opioid receptor</td>
</tr>
<tr>
<td>Transporter</td>
<td>Transmembrane transporter</td>
</tr>
<tr>
<td></td>
<td>ABCB1/ multi-drug resistance gene</td>
</tr>
<tr>
<td>Metabolizing enzymes</td>
<td>Cytochrome P450 “CYP”</td>
</tr>
</tbody>
</table>
# Impact of CYP2D6 Polymorphisms on Drug Therapy

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants</td>
<td>sedation, cardiotoxicity</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>overdose</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>arrhythmia</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>parkinsonism</td>
</tr>
<tr>
<td>5-HT3-antagonists</td>
<td>nausea, emesis</td>
</tr>
<tr>
<td>Opioids</td>
<td>reduced analgesia, respiratory depression</td>
</tr>
</tbody>
</table>

[http://medicine.iupui.edu/flockhart](http://medicine.iupui.edu/flockhart)
Pharmacogenomics
Metabolism Depends on CYP 450 Enzyme Function

- Drug normal function
- Drug reduced function
- Drug increased function

Adapted from Schwab et al DÄ 2002
Drug Effect Depends on Metabolism

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Active Drug</th>
<th>Overdose</th>
<th>Lack of Effect</th>
</tr>
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<tr>
<td>Poor Metabolism</td>
<td>Active Drug</td>
<td>Overdose</td>
<td>Lack of Effect</td>
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<tr>
<td>Ultrarapid Metabolism</td>
<td>Prodrug</td>
<td>Lack of Effect</td>
<td>Overdose</td>
</tr>
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</table>
No CYP2D6 Metabolism
„Poor Metabolizer“

**Case 1**: 65-y patient, postherpetic neuralgia

amytriptyline (Saroten®) 10 mg/d
side effects: tiredness, dry mouth, constipation, tachycardia
→ Discontinuation of therapy

- amitriptyline: active drug
- CYP2D6: enzyme
- M1-metabolite: inactive
- overdose: side effects
Case 2: 55-y patient, eye surgery (cataract)
postoperative analgesia: codeine + paracetamol
insufficient analgesia, repeat medication
→ no sufficient analgesia
Tramadol

CYP2D6

(+)-M1-Metabolite
(+)-O-Demethyltramadol

(+) - Tramadol

(-) - Tramadol

(+) - O-Demethyltramadol

µ-opioid receptor agonist

Poor metabolizer

5-HT

inhibition of reuptake

5-HT-level ↑

5-HT-Receptor?

Noradrenalin

NA-level ↑

α2-Adreno-receptor
Cumulative Tramadol Consumption

Nonresponse to Tramadol

Plasma Concentrations (+)-O-Demethyltramadol

Tramadol 3 mg/ kg i.v.

CYP2D6 Genotype + Co-Medication

Drug Effect Depends on Metabolism

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<tr>
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<td>Overdose</td>
</tr>
</tbody>
</table>
Ultrarapid Life
Ultrarapid Metabolizer
+ Life 
threatening 
respiratory depression 
after codeine 3x25 mg

Gasche Y et al.
NEJM 2004, 351: 2827-31
Ultrarapid Metabolism and Codeine

  Boy, 13d old, mother codeine 30mg + paracetamol 500mg 2x/d

- Ciszkowski et al. NEJM 2009: Postoperative death
  Boy, 2-y old, 13 kg

- Voronov et al. Paediatr Anaesth 2007: Apnea in a child after oral codeine
  Child 29 months old, North African descent
Antiemetic Treatment and CYP2D6 Genotype

Cancer patients under chemotherapy  n=270

CYP2D6 ultrarapid metabolizers have little effect from
- tropisetron
- ondansetron
- tricyclic antidepressants

Perspective

- Pharmacogenomics has the potential to improve efficacy and safety of drug therapy
- Translate the increasing amount of pharmacogenomic knowledge to clinical practice
- Sufficiently powered studies excluding by chance findings considering different ethnic populations
- Demonstrate superiority to conventional dosing regimes
Lessons from pharmacogenomics

- Consider the influence of the genetic background on drug therapy
- Caution with tramadol and codeine, especially in children and in patients with co-morbidities and certain ethnic backgrounds
- CYP inhibiting co-medications can result in poor CYP metabolism
Frequency of Gene Duplication
CYP2D6*2 x N

Ingelman-Sundberg
Trends Pharmacol Science
1999
μ-opioid receptor

extracellular

cell membrane

intracellular
µ-Opioid Receptor: A 118 G Polymorphism

M6G (morphine-6-glucuronide) and its constrictory effects on pupil size

% Decrease in pupil size

Lötsch et al. Pharmacogenetics 2002, 12:3-9
A118 G Polymorphism + Morphine Consumption

<table>
<thead>
<tr>
<th></th>
<th>Abdominal Hysterectomy</th>
<th>Knee Arthroplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80</td>
<td>120</td>
</tr>
<tr>
<td>118 AA (wt)</td>
<td>37.5 ± 12.2</td>
<td>25.3 ± 15.5</td>
</tr>
<tr>
<td>118 AG</td>
<td>41.6 ± 17.7</td>
<td>25.6 ± 11.7</td>
</tr>
<tr>
<td>118 GG</td>
<td>44.0 ± 13.3</td>
<td>40.4 ± 22.0</td>
</tr>
</tbody>
</table>

Chou et al. *Anesthesiology* 2006, 105: 334
A 118 G Polymorphism and Post-Cesarean Morphine Consumption

spinal anesthesia: bupivacain 10 mg + morphine 0.1 mg; n=585

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<tr>
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<th>Morphine Consumption</th>
<th>PCA</th>
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<tr>
<td>118 AA</td>
<td>271 (46%)</td>
<td>5.94 ± 7.36</td>
</tr>
<tr>
<td>118 AG</td>
<td>234 (40%)</td>
<td>7.97 ± 8.47</td>
</tr>
<tr>
<td>118 GG</td>
<td>80 (14%)</td>
<td>9.38 ± 9.36</td>
</tr>
</tbody>
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p=0.001

CYP2C9 polymorphism + pharmacokinetics of celecoxib

21 volunteers
celecoxib 100 mg
frequency
CYP2C9*3/*3 7%

CYP2C9 and Disposition of (R)-Ibuprofen Enantiomer

Ibuprofen 400 mg p.o.

n=25

Clearance of NSAIDs depending on CYP2C9 Genotype

Letality / year by NSAIDs in the USA

- M. Hodgkin: 1.443
- HNO-Neoplasien: 4.499
- Asthma: 5.434
- Plasmozytom: 10.368
- NSAID (GIT): 16.500
- HIV: 16.516
- Leukämie: 20.313

CYP2D6 Substrates

- **Betablocker**: Metoprolol, Timolol
- **Antiarrhythmics**: Flecainid, Propafenon, Mexiletin
- **Antidepressants**: Amitryptilin, Desipramin, Fluoxetine, Paroxetine, Venlafaxin
- **Neuroleptics**: Chlorpromazin, Haloperidol, Risperidon
- **Opioids**: Tramadol, Codeine
- **Tamoxifen**
- **Ondansetron**
CYP2D6 inhibitors

- Amiodaron
- Cimetidin
- Fluoxetine
- Haloperidol
- Paroxetine
- Ritonavir