drug kinetics & genomics: relevant in ICU?

Yoanna Skrobik MD FRCP(c)
drug kinetics & genomics: relevant in ICU?

Yoanna Skrobik MD FRCP(c)

And do we really care?
Conflicts of interest

- Member, SCCM Pain, Agitation and Delirium guidelines writing committee
- Investigator initiated research funding, Hospira
- Academic chair, Université de Montréal
Academic chair

Astellas
Merck
Pfizer
Baxter
Hospira
Otsuka
Novartis
Lilly
Pharmacokinetics, pharmacogenomics and drug-drug interactions related to the administration of sedatives in the critically ill

- Introduction: why you should care as an ICU caregiver
- Pharmacokinetics and some examples (relevant to sedatives in the ICU)
- The evidence we have with regard to sedatives and opioids in the ICU (alone, and in combination with other drugs)
- Some thoughts on putting it all together
Pharmacokinetics, pharmacogenomics and drug-drug interactions related to the administration of sedatives in the critically ill

Introduction: why you should care
why we should care (introduction)

• More medications are administered in ICU than on most hospital wards

• ICU and its pharmacy expenditures often approach 20% of a hospital’s and pharmacy’s respective budgets

• These costs are increased when adverse events (AEs) occur

• Adverse drug reactions (ADRs) occur in 6.7% of hospitalized patients, and twice as commonly in the critically ill

• Sedatives and opiate analgesics are routinely administered in ICU patients, and rank among the top 6 medication categories responsible for ADRs in critical care
Touching briefly on the notion of pharmacogenomic variability

Philip Empey, Critical Care Med. 38 S106-116 2010
N. Pinto & E. Dolan, Current drug metabolism 12 2011 p. 487
Historical background

- In the 1950s, a case describing prolonged apnea after the administration of succinyl-choline (butyrylcholinesterase)
- Several subsequent studies
- 20 to 95 % of kinetic or dynamic pharmacotherapeutic is genetic
In the literature
Cytochrome P450

Figure 1–4. The proportion of drugs metabolized by the major cytochrome P450 enzymes.
Some examples

CYP 450 3A4/5: midazolam, fentanyl

CYP 450 2D6: haloperidol, codeine, oxycodone, and tramadol

CYP 2C19: propofol
Figure 3. Pharmacogenetics of CYP2D6.

Urinary metabolic ratios of debrisoquin to its metabolite, 4-hydroxydebrisoquin, are shown for 1011 Swedish subjects. The Cutoff box indicates the cut-off point between subjects with poor metabolism as a result of decreased or absent CYP2D6 activity and subjects with extensive metabolism. Modified
CYP2D6

Figure 4. Pharmacogenetics of Nortriptyline.
Mean plasma concentrations of nortriptyline after a single 25-mg oral dose are shown in subjects with 0, 1, 2, 3, or 13 functional CYP2D6 genes. Modified from Dalén et al. with the permission of the publisher.
Pharmacokinetics, dynamics and genetics

- Is it relevant to ICU patients?
Drug-drug interactions

Effect of voriconazole and fluconazole on the pharmacokinetics of intravenous fentanyl

Teijo I. Saari · Kari Laine · Mikko Neuvonen · Pertti J. Neuvonen · Klaus T. Olkkola

Fig. 1 Mean plasma ± standard deviation concentrations of fentanyl (solid line) and norfentanyl (dashed line) in 12 healthy volunteers after an intravenous dose of 5 μg/kg of fentanyl without pretreatment (control) or following pretreatment with oral voriconazole or oral fluconazole. Voriconazole was given 400 mg twice on the first day and 200 mg twice on the second day. Fluconazole was given 400 mg once on the first day and 200 mg once on the second day.
Pharmacokinetics and pharmacogenomics

Figure 1. Metabolic Pathways of Codeine Biotransformation.
The conversion of codeine into norcodeine by CYP3A4 and into codeine-6-glucuronide by glucuronidation usually represents 80 percent of codeine clearance, and conversion of codeine into morphine by CYP2D6 represents only 10 percent of codeine clearance (blue arrows). Morphine is further metabolized into morphine-6-glucuronide and into morphine-3-glucuronide. Morphine and morphine-6-glucuronide have opioid activity (blue arrows). Glucuronides are eliminated by the kidney and are thus susceptible to accumulation in cases of acute renal failure. The patient (red arrows) had ultrarapid CYP2D6 metabolism, inhibition of CYP3A4 as a result of treatment with clarithromycin and voriconazole, and glucuronide accumulation due to acute renal failure. Red arrows with dotted lines indicate low levels of drug conversion or elimination, green arrows with dotted lines indicate low levels of brain penetration, and thick arrows indicate high levels.
Have I convinced you that you should care?

and now for some ICU data
The Effect of Critical Illness on the Pharmacokinetics and Dose-Response Relationship of Midazolam
### Results

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled – no.</td>
<td>9</td>
</tr>
<tr>
<td>Age – mean +/- SD (range)</td>
<td>56.3 +/- 11 (33-72)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Co-morbidities on admission – no.</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>1</td>
</tr>
<tr>
<td>CKD</td>
<td>1</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>1</td>
</tr>
<tr>
<td>Chronic benzodiazepine use</td>
<td>0</td>
</tr>
<tr>
<td>Chronic ethanol use</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>2</td>
</tr>
<tr>
<td>Condition on study enrollment</td>
<td></td>
</tr>
<tr>
<td>APACHE II – mean +/- SD (range)</td>
<td>24 +/- 10 (7-43)</td>
</tr>
<tr>
<td>Acute kidney injury – no.</td>
<td>4</td>
</tr>
<tr>
<td>GCS – mean +/- SD (range)</td>
<td>7 +/- 2 (3-14)</td>
</tr>
<tr>
<td>GCS &lt; 8 – no. (%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Study details – mean +/- SD (range)</td>
<td></td>
</tr>
<tr>
<td>Days in study</td>
<td>8.8 +/- 3.9 (3-14)</td>
</tr>
<tr>
<td>Days on MDZ infusion</td>
<td>4.8 +/- 3.1 (1-11)</td>
</tr>
<tr>
<td>Days in study off infusion</td>
<td>4.0 +/- 2.9 (0-10)</td>
</tr>
<tr>
<td>Days with GCS &lt; 8</td>
<td>3.8 +/- 4.0 (0-12)</td>
</tr>
<tr>
<td>GCS &lt; 8 during study – no. (%)</td>
<td>7/9 (78%)</td>
</tr>
</tbody>
</table>

---

Table 1: Patient Characteristics and Study Details

**Variable**

- Patients enrolled – no.
- Age – mean +/- SD (range)
- Male sex – no. (%)
- Co-morbidities on admission – no.
- Condition on study enrollment
- Study details – mean +/- SD (range)

**Notes:**

- CHF: Congestive Heart Failure
- CKD: Chronic Kidney Disease
- APACHE II: Acute Physiology and Chronic Health Evaluation II
- GCS: Glasgow Coma Scale
- MDZ: Midazolam
**Results**

## Midazolam PK

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Study Patients</th>
<th>Healthy Controls†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean +/- SD</td>
<td>Range</td>
</tr>
<tr>
<td>$\text{CL}_{ss}$ (mL/min)</td>
<td>418 +/- 324</td>
<td>31-1157</td>
</tr>
<tr>
<td>$T_{\frac{1}{2}}$ (h)</td>
<td>16.0 +/- 9.6</td>
<td>2.3-34.9</td>
</tr>
</tbody>
</table>

Table 3: Pharmacokinetic Parameters in Study Participants and Healthy Controls
Results

Midazolam Clearance

Figure 1: Observed intra- and intersubject variability in midazolam clearance at steady-state.
Results

Midazolam Elimination Half-life

Figure 2: Variability in terminal half-life of midazolam among study patients.
Results

Figure 3: Average clearance at steady state (Css), vs. Terminal Half-life.

Spearman’s rho = -0.786, (p=0.036)
Pharmacodynamic Midazolam characteristics:

It’s About Time

- Highly lipid soluble
- α-OH midazolam metabolite
- CYP3A4 activity decreased in critical illness
- Substantial CYP3A4 variability
Pharmacodynamic Midazolam characteristics: It’s About Time

Pharmacodynamic Midazolam characteristics: It’s About Time

Synergistic sedation with propofol and midazolam in intensive care patients after coronary artery bypass grafting.

Table 5: Comparison of extubation and total recovery time (mean +/- SD)

<table>
<thead>
<tr>
<th></th>
<th>Propofol (n = 25)</th>
<th>Midazolam (n = 25)</th>
<th>Propofol-Midazolam (n = 25)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to extubation (hr)</td>
<td>0.9 ± 0.3</td>
<td>2.3 ± 0.8</td>
<td>1.2 ± 0.6</td>
<td>.01</td>
</tr>
<tr>
<td>Total recovery time (hr)</td>
<td>1.3 ± 0.5</td>
<td>3.8 ± 1.8</td>
<td>1.6 ± 0.8</td>
<td>.01</td>
</tr>
<tr>
<td>Capacity for autonomous</td>
<td>2.8 ± 2.5</td>
<td>6.3 ± 4.3</td>
<td>3.3 ± 1.9</td>
<td>.01</td>
</tr>
<tr>
<td>physiotherapeutic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>program (hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drainage extraction (hr)</td>
<td>35.3 ± 4.2</td>
<td>38.2 ± 6.2</td>
<td>36.7 ± 3.9</td>
<td>.06</td>
</tr>
<tr>
<td>Able to sit down (hr)</td>
<td>38.3 ± 5.3</td>
<td>40.2 ± 7.0</td>
<td>38.8 ± 6.1</td>
<td>.09</td>
</tr>
</tbody>
</table>

*Reflects differences between the second column and the other two columns.
Determination of midazolam and its metabolite as a probe for cytochrome P450 3A4 phenotype by liquid chromatography–mass spectrometry

Hideko Kanazawa a,*, Akiko Okada a, Eri Igarashi a, Megumu Higaki b, Takako Miyabe c, Tadashi Sano c, Ryouhei Nishimura c

a Department of Physical Chemistry, Kyoritsu College of Pharmacy, 1-5-30 Sihbako-en, Minato-ku, Tokyo 105-8512, Japan
b Institute of Medical Science, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kanagawa 216-8512, Japan
c Faculty of Agriculture, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Abstract

This study demonstrated the analysis of midazolam and its metabolites by liquid chromatography–mass spectrometry (LC–MS) with a sonic spray ionization (SSI) interface. The analytical column was a YMC-Pak Pro C18 (50 mm × 2.0 mm i.d.) using 10 mM ammonium acetate (pH 4.8)–methanol (1:1) at a flow rate of 0.2 ml min⁻¹. The drift voltage was 100 V. The sampling aperture was heated at 110°C and the shield temperature was 230°C. The lower limits for the detection of midazolam and 1’-hydroxymidazolam were 26.3 and 112.76 pg injected, respectively. The calibration curves for midazolam and 1’-hydroxymidazolam were linear in the range of 0.1–5 μg ml⁻¹. Within-day relative standard deviations was less than 7%. The method was applied to the determination of midazolam in monkey plasma, and the analysis of midazolam and its metabolites in an in vitro study with recombinant cytochrome P450 3A4. This method is sufficiently sensitive and useful to elucidate the kinetics of midazolam metabolite formation. We also investigated the effect of propofol on the metabolism of midazolam using recombinant CYP3A4. Propofol competitively inhibited the metabolism of midazolam to 1’-hydroxymidazolam by CYP3A4.

Keywords: Sonic spray ionization; Interfaces, LC–MS; Midazolam; Cytochromes; Propofol
Intensive care unit-acquired infection as a side effect of sedation

Saad Nseir¹*, Demosthenes Makris², Daniel Mathieu¹, Alain Durocher¹, Charles-Hugo Marquette³

Figure 1 Potential mechanisms of immunomodulatory effects of sedative agents.

Enhanced by Opioids  Inhibited by Benzodiazepines  Enhanced by Clonidine
Enhanced by Opioid withdrawal  Inhibited by Barbiturates  Inhibited by Clonidine
Enhanced by Opioid withdrawal  Inhibited by Propofol  Inhibited by Dexmedetomidine
Cell receptor = µ, κ, δ = opioid receptors
Point: Should Benzodiazepines be Avoided in Mechanically Ventilated Patients? Yes

Counterpoint: Should Benzodiazepines Be Avoided in Mechanically Ventilated Patients? No
Are Delirium and Iatrogenic Coma linked with Drug Metabolism and Transport?

In adult critical care
Sedatives and opiates are part of routine ICU care
Alteration of consciousness and outcome

- Coma is bad for you
Early Intensive Care Sedation Predicts long-term Mortality in Ventilated Critically Ill Patients


Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the ANZICS Clinical Trials Group.

Figure 4: Kaplan Meier curves for time to extubation and mortality at 180 day

Panel A: Time to extubation was significantly longer amongst patients who were deeply sedated early in ICU compared with those that were not. Median [IQR] 7.7[6.0-8.6] vs 2.4[1.9 - 4.0] days (Log-rank P<0.001).

Panel B: Those who were deeply sedated early (first 48 hours) showed significantly reduced survival (Log-rank P=0.048) compared with patients who were not deeply sedated.
Excessive sedation (and iatrogenic coma) are bad for you.
The role of drug metabolism and membrane transport activities in the development of delirium and coma in the intensive care unit

- Coma presumably associated with administered drug dose
- Drug metabolism status
- Drug transport across the blood brain barrier
- What link with pharmacokinetics or pharmacogenetics?
Dose → Co-Rx; CYP 3A5 → Infl.med. → levels → Co-Rx; CYP 3A5 → Infl.med. → MDR1 (Pgp) → Clinical effect (delirium or coma)
The occurrence of delirium and iatrogenic coma in intensive care may be explained by the dose, metabolism or cellular transport of midazolam and/or fentanyl systemically or within the brain.
Why people develop coma

Critical Care Medicine
Predisposing factors to coma and delirium: Fentanyl and midazolam exposure, CYP3A5, ABCB1 and ABCG2 genetic polymorphisms, and inflammatory factors.
Design:

- Population: consented critically ill med-surg ICU patients
- Inclusion criteria: receiving midazolam, fentanyl or both.
- Exclusion criteria: patients with baseline dementia; patients in whom delirium assessment is not possible.
Methods:

The collected data included:

- Blood sampling (7.5mL) for CYP3A5 & MDR1 genotype.
- Age; hepatic dysfunction; renal failure; BMI; race; gender.
- Drugs which influence CYP3A4/5 or glycoprotein-P activity.
- During fentanyl or midazolam infusions, serum levels on days 1, 2, and 3; then Q 48 hours.
- Patients evaluated at least every 8 hours for:
  - Numerical Rating Scale for pain
  - RASS (The Richmond Agitation–Sedation Scale)
  - Intensive care delirium checklist
administered drugs which influence CYP3A4/5 or glycoprotein-P activity

- **CYP3A4/5 inhibitors**: antibiotics (clarithromycin, erythromycin, telithromycin), antifungals (fluconazole, itraconazole, ketoconazole, metronidazole), cimetidine
- **High-affinity substrates for CYP3A4/5**: amiodarone, calcium channel blockers (diltiazem and verapamil)
- **Intermediate-affinity substrates for CYP3A4/5**: dihydropyridine-type calcium channel blockers (felodipine and nifedipine), statins (atorvastatin, lovastatin, simvastatin), buspirone, cyclosporin, sertraline
- **P-glycoprotein inhibitors**: quinine, quinidine, calcium channel blockers (diltiazem, nifedipine, verapamil), amiodarone, cephalosporins, cyclosporine, neuroleptics ( trifluoperazine, promethazine, fluphenazine, pimozide)
- **P-glycoprotein substrates**: anti-cancer drugs, macrolide antibiotics, domperidone, digoxin, loperamide, methotrexate, morphine, olanzapine, ondansetron, statins
- **Inducers**: carbamazepine, dexamethasone, phenytoin, St. John’s wort (Hypericum), barbiturates
- 100 patients
396 patients éligibles recevant Fentanyl ou Midazolam

296 exclus : 14 moribonds, 27 pas de proche, 59 fentanyl cessé avant consentement, 1 Jéhovah anémique, 67 refus, 13 patients neuro; 2 manqués, 8 refus MD, 104 ss propofol, 1 erreur

100 patients inclus
31 patients fentanyl
2 patients midazolam
67 patients midazolam et fentanyl

1 patient mal documenté

24 coma
49 delirium et coma
14 delirium

77 pts avec prélèvement en 24 heures du coma OU delirium pour médiateurs inflammatoires

13 Patients sans delirium ni coma
<table>
<thead>
<tr>
<th></th>
<th>Coma</th>
<th>Delirium</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>56</td>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>55.4</td>
<td>50.0</td>
<td>51.3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.8 ± 14.6</td>
<td>61.6 ± 14.2</td>
<td>59.4 ± 15.6</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>20.8 ± 7.8</td>
<td>19.9 ± 7.8</td>
<td>19.1 ± 6.1</td>
</tr>
<tr>
<td>BMI</td>
<td>26.8 ± 5.2</td>
<td>27.4 ± 6.4</td>
<td>28.0 ± 8.7</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>41.1</td>
<td>33.9</td>
<td>23.1</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>37.5</td>
<td>30.6</td>
<td>28.2</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>21.4</td>
<td>19.4</td>
<td>10.3</td>
</tr>
<tr>
<td>Renal dysfunction (%)</td>
<td>37.5</td>
<td>35.5</td>
<td>25.6</td>
</tr>
</tbody>
</table>
results
Occurrence of coma not related to administered midazolam or fentanyl doses

Coma occurrence correlated with the co-administration of CYP3A4/5 inhibitors (p=0.0046) when adjusted for doses of fentanyl and midazolam
Coma and plasma levels of fentanyl
Coma and plasma levels of fentanyl
Coma and plasma levels of midazolam
Coma and the effect of CYP3A4/5 inhibitor co-administration
Genetic determinants

<table>
<thead>
<tr>
<th></th>
<th>Coma</th>
<th>Delirium</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP3A5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*1/*1</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>*1/*3</td>
<td>6 (10.9%)</td>
<td>7 (11.7%)</td>
<td>2 (5.1%)</td>
</tr>
<tr>
<td>*3/*3</td>
<td>49 (89.1%)</td>
<td>53 (88.3%)</td>
<td>37 (94.9%)</td>
</tr>
<tr>
<td><strong>MDR1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>15 (27.3%)</td>
<td>14 (23.3%)</td>
<td>12 (30.8%)</td>
</tr>
<tr>
<td>C/T</td>
<td>29 (52.7%)</td>
<td>32 (53.3%)</td>
<td>19 (48.7%)</td>
</tr>
<tr>
<td>T/T</td>
<td>11 (20.0%)</td>
<td>14 (23.3%)</td>
<td>8 (20.5%)</td>
</tr>
</tbody>
</table>
Pharmacokinetic considerations

- Midazolam and fentanyl metabolites
Editorial comment about pharmacogenomic variability in the Quebec population

**Figure 2. Simulated Activities of Cytochromes P-450 CYP3A4 and CYP3A5 in Blacks and Whites.**

The simulated activities of CYP3A4 (black dashed lines) and CYP3A5 (white dashed lines) are shown in blacks (Panel A) and whites (Panel B), assuming a normal distribution and a 10-fold range in activity (shown in arbitrary units) among those expressing functional forms of these enzymes, and further assuming that all patients express CYP3A4, but that only 25 percent of whites and 50 percent of blacks express functional CYP3A5 because of genetic polymorphism. The solid area reflects the combined activity of CYP3A4 and CYP3A5 in the two populations for medications that are metabolized equally by the two enzymes.
In conclusion
In critical care...

Pharmacokinetic and pharmacodynamic research in the intensive care unit: an unmet need.
Thank you