What can we learn from analysis of the toxicokinetic / toxicodynamic relationships in acute poisonings?

Bruno Mégarbane, MD, PhD

Réanimation Médicale et Toxicologique, INSERM U705 - CNRS, UMR 7157, Université Paris 7, Hôpital Lariboisière, Paris, France

Acute poisoning, a dynamic process

Increasing symptoms

Delay

To exposition

Possible death

24 to 72 h

Possible sequellae

Possible outcome

Time

Acute poisoning, a leading cause of hospital admission and mortality in youths.

A poisoning should be considered as severe if:

• Life-threatening symptoms occur, including hemodynamic instability, heart dysrhythmia or conduction disturbances, coma, seizures, respiratory failure or alveolar hypoventilation

• The patient has been exposed to a large amount of toxicant requiring a close monitoring

• The patient is more vulnerable (co-morbidities, elderly or infants)

Epidemiology of acute poisonings

French Society of Critical Care Medicine

Réanimation 2006

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Time
Prognostic value of plasma concentration measurement in the case of injuring toxicants

Acetaminophen poisonings: Prescott normogram
Paraquat poisonings: Proudfoot and Scherrmann normograms

Definitions...
Intoxication: interaction between a toxicant / target cells (biological mechanisms)

Concentration of the target tissue → (G)reversible cellular modifications → Clinical signs and symptoms

Toxicokinetics: Concentration = f (Time)
Toxicodynamics: Effect = f (Dose)
Dynamics: Effect = f (Time)

TK/TD relationship: Effect = f (Time-cource concentration)

PK/PD relationships ... in toxicology
More difficult because:
- The ingested dose and ingestion date are generally unknown
- Measurement of blood concentrations is not routinely performed
- A reversible PD effect is not directly attributable to the toxicant and easily measurable in clinical practice

PK/PD: Data base + Mathematical analysis
Analysis:
- LCHP
- LCMS
- GCMS

PK/PD relationships ... in pharmacology
Fields of application:
- Analgesics
- Hypnotics
- Anticonvulsive drugs
- Cardiovascular
- Steroids
- Antibiotics
- Anticancer drugs

酚K/PD relationships... in toxicology

Severity Blood Conc

Functional toxicant - Injuring toxicant
I- Functional toxicants: Severity factors
II- Injuring toxicants: Prognosis factors

Mégarbane B. Expert Opin Drug Metab Toxicol 2008
The concept of “biophase”

Definition: The virtual compartment containing the receptors that interact with the active compound.

Each active compound should reach its target site to exhibit its effects

- No simple relationship between concentrations in blood and biophase.
- Corresponds to the delay between the occurrence of the effects and evolution of the concentrations.
- The onset of effects depends on:
  - Distribution according to the specificities of the target tissue (anatomy, perfusion, permeability, ...)
  - Metabolism if the ingested compound is inactive.
  - Cellular events (receptor affinity, transduction, post-receptor events, ...)

PK/PD relationships for pralidoxime treatment of OP-related respiratory depression in rats

Concentration = 7.1 mg.L\(^{-1}\) in resorption phase = efficiency

Concentration = 7.3 mg.L\(^{-1}\) in elimination phase = inefficiency

Hypothesis of PK/PD relationships showing clockwise or anticlockwise hysteresis

When connected in chronological order, the manner in which the data points appear allows one to define a hysteresis loop, meaning that the time courses of concentration and effect are out of phase.

Correlation between toxicity and blood concentrations in acute ethanol poisoning

- 0.9 - 2.5 g/l: euphoria - excitation
- 1.8 - 3 g/l: confusion
- 2.5 - 4.5 g/l: stupor, coma
- > 4.5 g/l: respiratory depression, death

Correlation between toxicity and plasma concentrations in acute theophyline poisonings

- 10-20 mg/l (55-110 µmol/l): Therapeutic level
- 20-40 mg/l: Minor toxicity
- 40-100 mg/l: Moderate toxicity
- > 100 mg/l: Severe toxicity
- > 120 mg/l: Risk of convulsions (50%)

Sources of individual variability

PHARMACOKINETICS (A.D.M.E)

GENETIC POLYMORPHISM

PHYSIOLOGY (Age, sex, weight, ...)

OBSERVANCE TOLERANCE

PHARMACODYNAMICS

(Receptors : number and affinity)

PATHEOLOGY

(Bend, liver and cardiac insufficiencies, burnings, ...)

CHRONOBIOLOGY

ENVIRONMENT

EXPOSURE

VARIABILITIES

DIFFERENCES BETWEEN THE ACTIVE CONCENTRATIONS AND THE EFFECTS
Effecting proteins represent the origin of the variability

<table>
<thead>
<tr>
<th>PK (TK)</th>
<th>PD (TD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism enzymes</td>
<td>40%</td>
</tr>
<tr>
<td>Circulating transport proteins</td>
<td>20%</td>
</tr>
<tr>
<td>Membrane transport proteins</td>
<td>30%</td>
</tr>
</tbody>
</table>

Receptors

Signal transducing proteins and other pharmacological targets

750 (368 cloned)

100

a) Number implicated in chemotherapy

Gene polymorphism of CYP 2D6

Rapid Metabolizers (85-90 %)

Metabolic ratio (log)

Slow Metabolizers (7-10 %)

Clinical consequences of gene polymorphism of CYP 2D6

Case report 1 -
Male 62 yrs, Chronic lymph leukemia
Bilateral pneumonia, fever, cough
D1: ceftriaxone + clarithromycine + voriconazole + codeine (25 mg x 3/d)
D4: consciousness impairment (GCS: 6), with myosis
Naloxone 0,4 mg/h: normal consciousness

Biology
Creatinine: 182 µmol/L
Pharmaceutical concentrations:
- Codeine 114 µg/L (N: 13-75)
- Morphine 80 µg/L (N: 1-4)
- G6M 136 µg/L (N: 1-13)

Genotyping:
- CYP2D6 ultra-rapid

Case report 2 -
Normal pregnancy and birth
Postpartum pain:
- Codeine 120 mg/d
- Paracetamol 500 mg/d

D7: sleepness, reduced milk intake
D13: death of the new-born

Autopsy:
- No congenital disease
- Morphine in blood 70 µg/L (N: 10-12)
- Paracetamol in blood: 5.9 µg/L

Maternal genotyping:
- heterozygote CYP2D6*2x2 (ultrarapid)
- UGT2B7*2 (ultrarapid)

Guengerich FP, Mol Interv 2003

Guengerich FP, Mol Interv 2003

Guengerich FP, Mol Interv 2003

Guengerich FP, Mol Interv 2003

Gasche et al NEJM 2004

Koren et al Lancet 2007
Near-fatal tramadol cardiotoxicity in a CYP2D6 ultrarapid metabolizer

- Ultrarapid metabolizer phenotype suggested by tramadol/M1 metabolic ratio
- Heterozygous for duplicated wt allele predictive of CYP2D6 ultrarapid metabolizer phenotype
- Ketoconazole at inhibitory concentration of CYP3A/CYP6 (200 ng/ml)


**Pharmacokinetic Role of Transporters**

From JM Scherrmann - Comprehensive Med Chem 2007

**Common Properties between Enzyme and Transporter Proteins**

- They share common substrates and inhibitors with similar ranges of active concentrations (from µM to mM)
- They share similar regulation pathways from gene to protein expression (induction, repression of genes...)
- They are sensitive to genetic polymorphisms, physiological and disease states
- They follow Michaelis-Menten kinetics like metabolism enzymes

**Steps of the pharmacokinetics**

**Absorption**
- Enterocyte
- Endothelial cell (BBB)
- Hepatocyte

**Distribution**
- Renal epithelium

**Metabolism**
- CYP...
- UGT, SULT, GST, NAT...

**Excretion**
- M-O-R
- M-O-S
- M-O-R

**Two superfamilies involved in drug transport**

- SLC (Solute Linker Carrier) SUPERFAMILY
  - 362 mammalian genes; ≈ 30 drug transporters
  - http://www.slc.ncl.ac.uk/nomenclature
  - INFLUX

- ABC (ATP Binding Cassette) SUPERFAMILY
  - 48 human genes; 9 drug transporters
  - http://nutrigene.4t.com/human abc.htm
  - EFFLUX


**Superfamily of ABC (ATP-Binding Cassette) transporters**

<table>
<thead>
<tr>
<th>Subfamilies</th>
<th>ABCA</th>
<th>ABCB</th>
<th>ABCC</th>
<th>ABCD</th>
<th>ABCE</th>
<th>ABCF</th>
<th>ABCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Members</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Important isoforms for PK</td>
<td>?</td>
<td>ABCB</td>
<td>?</td>
<td>?</td>
<td>ABCG</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

P-gp: P-glycoprotein
MRPs: Multidrug resistance-associated proteins
BCRP: Breast cancer resistance protein

N = 48 in humans, 7 superfamilies
**P-glycoprotein substrates**

**Anticancer agents**
- Doxorubicine
- Vincristine
- Irinotecan
- Paclitaxel
- Inhibiteurs tyrosine kinase...

**Anticoagulants**
- Dabigatran

**Cardiovascular drugs**
- Digoxine
- Quinidine
- Ivabradine

**Antiproteases**
- Indinavir
- Nelfinavir
- Saquinavir

**Anti-diarrheas drugs**
- Loperamide

**Antibiotics**
- Erythromycine...

**Immunosuppressive agents**
- Cyclosporine
- Tacrolimus

**Sedatives**
- Benzodiazepines...

**Antidepressants**
- Amitriptyline

**Others**
- Colchicine
- Phenytoine

**Mechanisms of buprenorphine toxicity**

Central respiratory toxicity

Pharmacological effect

**Modeling of individual TK-TD relationships**

\[
D \to C_e(t), C_p(t) \to C_e(t) \to E(t)
\]

if \( C_e(t) \) and \( E(t) \) simultaneous \( \Rightarrow \) similar \( C_e(t) \) and \( C_p(t) \) kinetics

if \( C_e(t) \) and \( E(t) \) with delay \( \Rightarrow \) different \( C_e(t) \) and \( C_p(t) \) kinetics

- Mono- and multi-compartment modeling
- Kinetics of the effects \( E(t) \) according to the measured concentration \( (C_e, C_p, C_t) \)

**Linear model:**

\[
E = S \cdot C_p + E_0
\]

**Semi-log model:**

\[
E = S \cdot \log C_p + E_0
\]

**E max model:**

\[
E = E_{\text{max}} \cdot \frac{C_e}{E_{C50}} + E_0
\]

**Sigmoidal model:**

\[
E = E_{\text{max}} \cdot \frac{C_e}{C_{E50}} + E_0
\]

**Transporters expressed at the blood–brain barrier**

**Pharmacogenetics of PK effectors for opioids**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Transport</th>
<th>Metabolism</th>
<th>Metabolites</th>
<th>Active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>P-glycoprotein</td>
<td>UGT2B7</td>
<td>MM6G, M3G</td>
<td>yes (M6G)</td>
</tr>
<tr>
<td>Codeine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>P-glycoprotein</td>
<td>CYP3A4</td>
<td>EDDP</td>
<td>no</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>P-glycoprotein</td>
<td>CYP3A4</td>
<td>Norfentanyl</td>
<td>no</td>
</tr>
<tr>
<td>Tramadol</td>
<td>P-glycoprotein</td>
<td>CYP2D6</td>
<td>M1, M2</td>
<td>yes (M1)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>P-glycoprotein</td>
<td>CYP2D6</td>
<td>oxymorphone</td>
<td>yes</td>
</tr>
</tbody>
</table>

**Sigmoidal modeling of individual TK/TD relationships**

**BMI**

**Slope of toxicity**

**Threshold of toxicity**

**EC50**

**Blood concentration of the toxic**
**Description of a TK/TD relationship in drug-related coma**

1 g/l = 21.7 mmol/l

1. Plateau of effects
2. Sigmoid curve
3. Functional toxicant
4. Calculation of $C_{50}$ and Hill coefficient

**Findings suggestive of a drug-drug interaction**

1. Move to the right
2. Lower $C_{50}$

**Findings suggestive of a pharmacodynamic tolerance**

1. Move to the left
2. More elevated $C_{50}$
3. Lower plateau

**TK/TD relationships in acute meprobamate poisonings**

Mégarbane B. Clin Toxicol 2004 (abstract)

**TK/TD relationships in acute phenobarbital poisonings**

Mégarbane B. Clin Toxicol 2005 (abstract)
**Description of the sigmoidal models to represent TK/TD relationships in psychoactive drug poisonings**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Hill coefficients</th>
<th>$C_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>14.9 [5.7-75.9]</td>
<td>61.2 mmol/l [38.9-96.3]</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>10.1 [2.8-49.2]</td>
<td>384 µmol/l [116-772]</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>4.8 [2.5-11.8]</td>
<td>257 µmol/l [160-442]</td>
</tr>
</tbody>
</table>

**Case report**

**TK/TD relationship in GHB intoxication**

- **M**, 26 years
- Ethanol: 36.1 mmol/l
- GHB: 124 mg/l
- Unique consumption

**Therapeutic range**: 25-50 µmol/l

**Hill coefficient**: 9.2

**$E_{50}$**: 189 mg/l

**Modeling of respiratory effects in methadone overdose**

- Hypothesis: Slow CYP 2D6 metabolizer

**Modeling of cardiac toxicity in venlafaxine poisoning**

- Hypothesis: Slow CYP 2D6 metabolizer

**TK/TD variability according to the TD parameter used in flecainide poisonings**

**Insulin self-poisonings: interests of TK-TD relationships to analyze the needs in dextrose infusion**

- Hypothesis: Slow CYP 2D6 metabolizer

**Mégarbane B. Clin Tox 2007 (abstract)

**Mégarbane B. Intensive Care Med 2006**
Chloroquine poisonings: interests of measuring blood concentrations in comparison to plasma concentrations

TK/TD using blood concentrations

TK/TD using plasma concentrations

Chloroquine poisonings: Design of a PK/PD model

Goodness-of-fit plots: population predictions (PRED) versus observations (DV) and population-weighted residuals (WRES) versus predictions

Population-based PK/PD methodology

- Is required when data are derived from studies with different designs and with great numbers of individuals with sparse and unbalanced data.
- Allows estimation of population mean values of PK parameters, their inter-individual and intra-individual variability, as well as residual variability.
- May test the influence of pertinent factors that could explain inter-individual variability including age, use of charcoal, and co-ingestions (CYP metabolism).
- The Bayesian approach allows estimation of individual PK parameters from population parameters and concentrations/effects measured in the patient.
- However, usually requires numerous statistical assumptions (for random and fixed effects distribution), estimation methods (algorithms & approximations), and softwares (NONMEM, PKBUGS/WinBUGS, S-PLUS, and MLwiN).

Chloroquine poisoning: Evaluation of the final PK/PD model

Comparison between the 10th (dash line), 50th (full line), and 90th (dash line) percentile obtained from 1,000 simulations and the observed data (DV, points)
**PK/PD population modelling in chloroquine poisonings**

Mégarbane B. Clin Toxicol 2011

**Chloroquine poisonings:** Simulated probability over time for having an epinephrine infusion rate >3 mg/h

Mégarbane B. Clin Toxicol 2011

**QT prolongation following citalopram poisonings**

Isbister G. BJCP 2005

**Risk reduction in escitalopram-related QT prolongation with charcoal**

Van Gorp F. Br J Clin Pharm 2011

**The effects of decontamination procedures on venlafaxine pharmacodynamics in overdose**

Isbister G. BJCP 2011

**Conclusions**

Is the study of TK/TD relationships interesting in acute poisonings?

- To help establish the positive and differential diagnosis;
- To understand the clinical presentation and evolution of poisoned patients;
- To suggest and identify a mechanism of individual variability in response to a given toxicant;
- To understand the limits and identify the patients that may benefit from any toxicokinetic treatment (ex: GI decontamination);
- To explain the interests of an antidote (if weak therapeutic index) or determine its efficient dose (if weak toxicity slope).