Concepts of non-linear pharmacokinetics and KMD

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Disclosure Statement

• Member of several science advisory boards (public and private sector) [non-remunerated] (e.g. ILSI, HESI, Owlstone Medical, Cosmetics Europe LRSS, Swiss Centre for Applied Human Toxicology, MSU Center for Research on Ingredient Safety, A*STAR Food and Chemical Safety Programme Singapore)

• Member/chair of several national and international scientific advisory committees (UK COT, UK COMEAP, JMPR, JECFA, TobReg, ISO TC126 WG10 Intense Smoking Regime)

• I have no financial interests in the subject matter of the session
Risk characterization

Hazard ID
Hazard characterisation

Exposure assessment

Uncertainty factor

HBGV (e.g. ADI)
HBGV = POD/UF

Risk characterisation (Exposure cf HBGV)

MOE = POD/Exposure

MOE = POD/Exposure

HBGV (e.g. ADI)
HBGV = POD/UF
Bioavailability

Solubility

Permeation & pre-systemic metabolism

Yu, 1999

External dose → Bioaccessible dose → Bioavailable dose
Dose-dependency of systemic exposure

<table>
<thead>
<tr>
<th>Species</th>
<th>Durat.</th>
<th>Dose (mg/kg)</th>
<th>Plasma concentration (µg/ml)</th>
<th>AUC(0-24) (µg·h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Gavage</td>
<td>2 Week</td>
<td>500</td>
<td>13.5</td>
<td>9.92</td>
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<tr>
<td></td>
<td></td>
<td>1250</td>
<td>27.6</td>
<td>25.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2500</td>
<td>47.4</td>
<td>40.7</td>
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<tr>
<td>Diet</td>
<td></td>
<td>500</td>
<td>11.5</td>
<td>10.7</td>
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<td>1250</td>
<td>25.9</td>
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<tr>
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<td>2500</td>
<td>50.7</td>
<td>32.4</td>
</tr>
</tbody>
</table>

Fractional absorption independent of dose

Fractional absorption dependent on dose
Absorption, distribution, metabolism, excretion (ADME) determine exposure

- Absorption
- Distribution
- Metabolism
- Excretion
Human drug transporters

Giacomini & Huang (2013)
Xenobiotic biotransformation

- Specificity
- Maximum rate ($V_{\text{max}}$)
- Affinity ($K_m$)

Yeung et al, 2013
Kinetics of metabolism

Rate of metabolism = \( \frac{V_{\text{max}} \times C}{K_m + C} \)

When \( C \ll K_m \)

Rate of metabolism \( \approx \frac{V_{\text{max}} \times C}{K_m} \)

i.e. Rate of metabolism \( \propto C \)

When \( C > K_m \)

Rate of metabolism \( \approx \frac{V_{\text{max}} \times C}{C} \)

i.e. Rate of metabolism \( \rightarrow V_{\text{max}} \)

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From Winter & Tozer, 1986
Normal vs. saturating kinetics

A) Normal kinetics

B) Saturating kinetics

Plasma concentration (µmol/l)

Days

Therapeutic range

Dose (units = µmol/kg)
Effects of furafylline on caffeine kinetics

Furafylline (90 mg p.o.)
Point of departure

Hazard ID
Hazard characterisation

Exposure assessment

Uncertainty factor

HBGV (e.g., ADI)
HBGV = POD/UF

Risk characterisation
(Exposure cf HBGV)

MOE = POD/Exposure

POD

Exposure

Risk characterisation

HBGV

BMDL

BMDU

BMR = 5%

Dose

NOAEL

LOAEL
Major and minor routes of elimination

\[ \text{Cl} = \text{Cl}_R + \text{Cl}_{m1} + \text{Cl}_{m2} + \text{Cl}_{m3} + \text{Cl}_{\text{other}} \]

Propranolol and metoprolol are both cleared > 90% by CYP-dependent oxidation.

Parent
- Metabolite 1
- Metabolite 2
- Metabolite 3
- Renal
- Other

Parent \rightarrow Metabolite 1 \rightarrow Metabolite 1 conj

Plasma conc (ng/ml)

Data from Tucker, Lennard, Wood et al
Acetaminophen hepatotoxicity

Acetaminophen $\rightarrow$ Oxidation of cellular constituents $\rightarrow$ Loss of cellular functions $\rightarrow$ GSH depletion $\rightarrow$ Oxidative damage $\rightarrow$ GSH conjugate $\rightarrow$ Excretion

Acetaminophen $\rightarrow$ GSH-reductase $\rightarrow$ GSH conjugate $\rightarrow$ Excretion

Acetaminophen $\rightarrow$ UGT, SULT $\rightarrow$ Sulphate and glucuronide conjugates

Acetaminophen $\rightarrow$ P450 $\rightarrow$ Protein arylation $\rightarrow$ TOXICITY

Acetaminophen $\rightarrow$ HNCOCH$_3$ $\rightarrow$ OH $\rightarrow$ NCOCH$_3$ $\rightarrow$ NABQI $\rightarrow$ GSH $\rightarrow$ GSSG $\rightarrow$ 2GSH $\rightarrow$ GSH reductase $\rightarrow$ 2GSH $\rightarrow$ GSH $\rightarrow$ GSH conjugate $\rightarrow$ Excretion $\rightarrow$ TOXICITY
GSH depletion and acetaminophen toxicity

Data of Gillette, Mitchell, et al
Quantitative Adverse Outcome Pathway (AOP)

Dose-MIE (KE1)

Exposure

KE1-KE2
KE2-KE3
KE3-AO

ADME/TK
KE1
KE2
KE3
Adverse outcome
Conclusions

• The maximum dose used in toxicity testing is often many orders of magnitude greater than worst-case human exposure

• Limited solubility and/or saturation of processes of absorption, distribution, metabolism and excretion can lead to marked non-linearity between dose and plasma/active-site concentration

• This confounds interpretation of dose-effect relationships and extrapolation to human relevant exposures; hence, substantial over- or under-estimation of risk to exposed populations is possible

• Kinetic considerations are therefore essential in both study design and data interpretation