



Health
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Therapeutic Products Directorate

Health Products and Food Branch

Direction des produits thérapeutiques

Direction générale des produits
de santé et des aliments



Hepatic Safety

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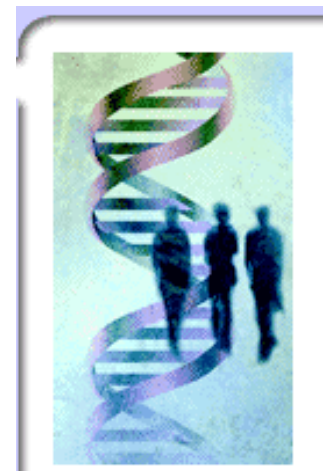
Presentation to
Critical Markers of Disease
May 17, 2010



Drug-induced Liver Injury (DILI)

- All chemicals (xenobiotics) have risk;
some more so than others
- Variability – in disease, drug and population: one size does not fit all!

“.....that no two individuals are exactly alike chemically.....”
Garrod, A. 1902.



Liver Injury

adapted from Assis and Navarro 2009

Encompasses a wide range of pathology and presentation from asymptomatic elevations of enzymes to serious dysfunction

Mechanisms of hepatic injury (Lee 2003) include:

- Disruption of intracellular calcium homeostasis (membrane)
- Disruption of actin filaments (canaliculus)
- Covalent binding leading to nonfunctioning adducts (endoplasmic reticulum)
- Immune-mediated (Target immunogens, vesicular release)
- Apoptotic pathways leading to programmed cell death
- Loss of mitochondrial function (mitochondrion)



DILI Injury Patterns

Lucena MI, et al. 2008

- **Cholestatic – 2 subtypes:** ↓ bile (salt) flow, ↑ alkaline phosphatase (AP) and gamma-glutamyl transpeptidase (GGT).
- **Hepatocellular:** most serious type of life-threatening reaction; ↑ alanine (ALT1 isoform) and aspartate (AST) aminotransferase. Rapid onset may impair liver capacity to function
- **Mixed**
- **Hypersensitivity/immunologic**
- **Mitochondrial**



Assessment of Causality

No specific means of diagnosis, treatment or prevention (early ID & withdrawal)

- Drug exposure precedes symptoms or lab abnormalities; latency can vary greatly
- Other causes excluded
- Injury often improves with withdrawal; rechallenge may create more serious response (e.g. immunologic)



Levels of Severity

Senior JR, Clin Pharm Therap, 2009

5. Death/Tx
4. Acute liver failure
3. Serious, sick, hospitalized
2. Detectable, slight functional loss
1. Just enzyme elevations, most adapt
0. Tolerate exposure – no ADR



Serious: Common Terminology Criteria for Adverse Events v4.0, May 28, 2009

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental **Activities of Daily Living (ADL)***.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death



Hy's Law

- three criteria must be met; have been “modified” or taken to mean:
- i) **injury**: maintained elevation of $>3xULN$ ALT or AST serum activity; and
- ii) **function**: $>2xULN$ TB (**1 of many**) without $>2 xULN$ ALP (or other clinical marker, such as $>1.5xULN$ INR, if the change is clinically significant in the absence of obstruction); and
- iii) **clinical verification**: effect is product-induced and not disease-induced injury.

Variance - Inter-relationships

Intrinsic (genetic/ physiological): gender, race, polymorphisms, genetic disease, age, organ/tissue function, clinical status – disease state, pregnancy

Extrinsic (environmental): ambulatory status, climate, sunlight, culture (adherence, education – awareness), socio-economic (nutrition), diet, alcohol, smoking, stress, pre-systemic and systemic exposure to ↑ multiple products (incl. foods, NHPs) and other xenobiotics (load), single or repeated dosing (pattern of use)



“Environment often trumps genetics. Even if you’ve been dealt a bad hand of genes, it’s not a life sentence for most people,” Hegele as quoted to delegates at the Canadian Cardiovascular Congress, Edmonton, Alberta (Globe and Mail, Oct 2009)

Predictable & Not



- **Predictable, type A:** by the known pharmacokinetic (PK) or pharmacodynamic (PD) properties of the stimulus; dose-related
- **Idiosyncratic, type B:** not predicted *a priori* by the known PK or PD, low frequency individualistic response to a stimulus, confounded by :
 - **Complex-trait response with two or more susceptibility factors:**
 - **Individual variation** - intrinsic and extrinsic factors
 - **ADME Promiscuity Factors** - xenobiotic enzymes, receptors, & transporters are unlike their classical forms
 - **Interactions** - foods, NHPs, drugs & other xenobiotics

ADME

[Andrade et al.](#) Curr Drug Metab 2009. DeGorter and Kim; Nies et al. Hepatology. 2009

- Major pathways:
 - **metabolic activation**: > 20 enzymes; CYP450 CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5; CES
 - **metabolic detoxification**: NAT2, GSTM1, GSTT1, SULT, UGT1A1, UGT1A3, UGT1A9 and UGT2B7
 - ***transport**: important rate-limiting step in drug clearance and response; Major Facilitator Superfamily (MFS), ATP-binding Cassette Superfamily (ABC); more than just P-glycoprotein
 - ***nuclear regulators**: farnesoid X-receptor (FXR), liver X-receptor (LXR), pregnane X-receptor (PXR) and peroxisome proliferator-activated receptor-alpha (PPAR-alpha) among others
- Localization may be cell & tissue dependant
- Immune pathways may not be independent from ADME



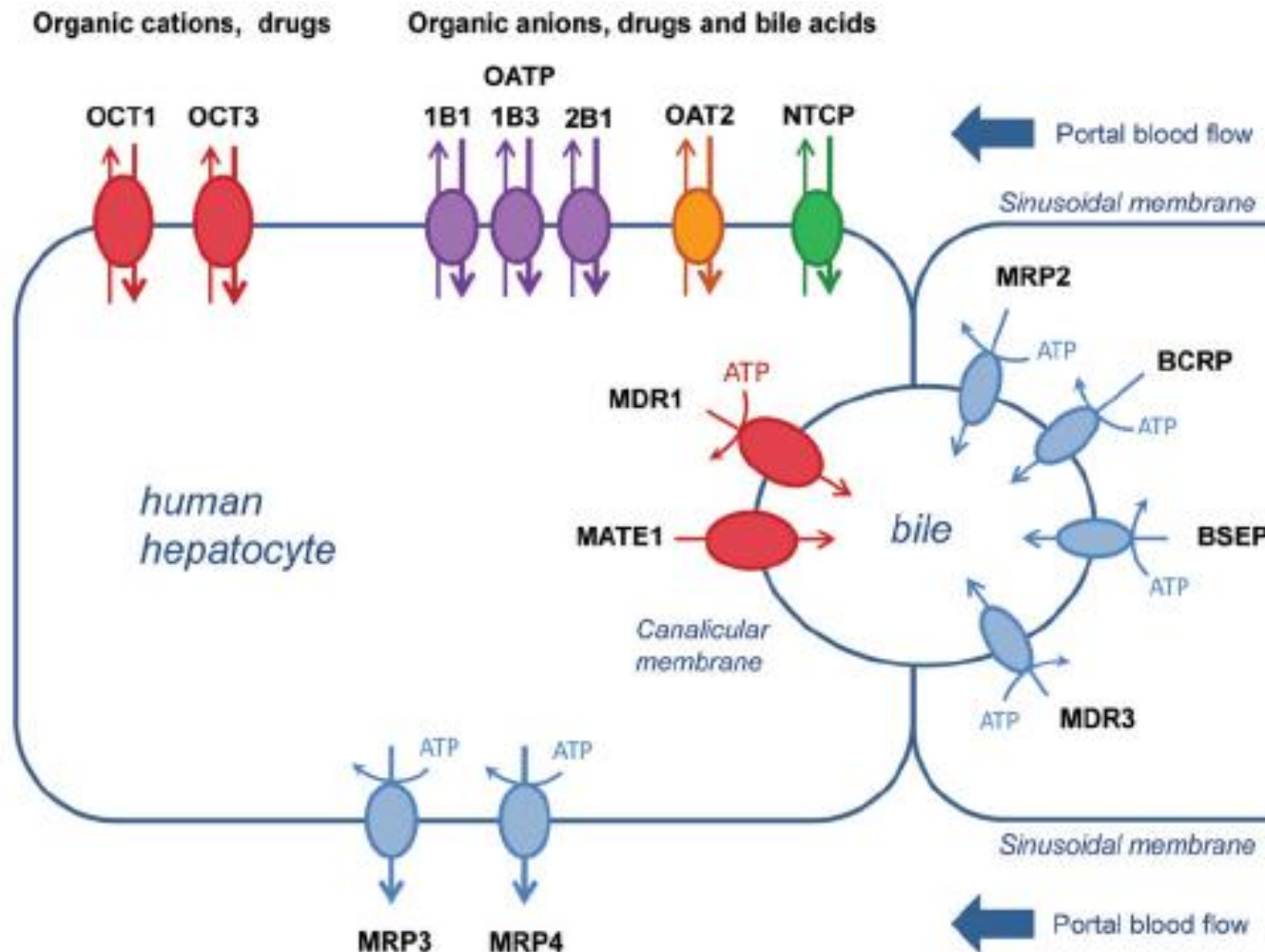


Fig. 1. Transporters expressed in the human hepatocyte. The cation uptake transporters OCT1 and OCT3 and the cation efflux transporters MATE1 and MDR1 are colored red. The anion uptake transporters OATPs, OAT2, and NTCP are purple, orange, and green, respectively. Transporters colored blue are efflux transporters of the ATP-binding cassette superfamily. Abbreviations: ATP, adenosine triphosphate; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; MATE1, multidrug and toxin extrusion 1; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; NTCP, sodium-dependent taurocholate cotransporting polypeptide; OAT2, organic anion transporter 2; OATP, organic anion transporting polypeptide; OCT, organic cation transporter.

Equivocal Genotype

Nebert DW, Tox Appl Pharmacol. 207:S34-42, 2007

- Genocopy – same SNP, different trait (outcome);
- Phenocopy – different SNPs, same trait;
- Penetrance – proportion with same SNP and trait if <100%;
- Non-penetrance – failure of trait when SNP present;
- Expressivity – var. in expression, degree, severity of trait;
- Epistasis – interaction ≥ 2 genes, dominance of another;
- Epigenetics – not classical Mendelian genetics;
- Dynamic genome;
- Gene-gene interactions;
- Molecular or meiotic drive;
- Gene conversion or silencing; and
- 19 others

all can override the importance of any one SNP and its association with a trait



Clinical Trials Inclusion Criteria and Monitoring - DRAFT

Healthy subject - product dependent (conservative approach)

- **not suspected:** ALT1 and AST $<2xULN$, and TB $<ULN$ at entry, subject awareness, monitored more frequently (every 2 to 4 wk) for 3 mo, then bimonthly unless systemic exposure is extremely low
- **known or suspected:** ALT1 and AST $<1.5xULN$ and TB $<ULN$ at entry, \uparrow monitoring, studies of the effects of different doses and durations may be warranted
- **products to treat liver disease:** assess individually, no obvious arbitrary entry levels

Patient (if part of the target population for the product)

- **known liver metastases:** clinical judgement is acceptable
- **mild hepatic impairment** (ALT1 $<3xULN$ and TB $<1.5xULN$): inclusion in some trials is prudent
- **seriously ill:** may be included, inclusion should be based on the risk profile and potential benefit



Clinical Trial Guidance (draft)

- Withdrawal: a conservative approach (any serum ALT $>3xULN$ or $>1.5xULN$ TB; repeated within 3 to 7 days for ALT, AST, AP and TB):

TPD

- serum AT $>5xULN$ with no change in TB > 2 weeks, a worsening of clinical symptoms, or the product meets Hy's Law

FDA

- ALT or AST $>8xULN$
- ALT or AST $>5xULN$ for > 2 weeks
- ALT or AST $>3xULN$ and (TB $>2xULN$ (Hy's) or INR >1.5)
- ALT or AST $>3xULN$ with worsening of clinical symptoms

Screen

- matched control samples: plasma and urine for [drug and metabolite], and WBCs/tissue for genomic (SNPs & expression)
- evaluate for ALL xenobiotic, intrinsic and extrinsic factors



Ambiguities - Needs

- more accurate harmonized disease diagnoses & descriptions
- validated risk algorithms (SNP; cell, serum, tissue biomarker; assessment tools; etc.)
- may require multiple markers to demonstrate biologic plausibility rather than spurious association in multi-allelic response
 - single [gene-based] testing: cannot identify global signalling, pathways or networks
 - locus heterogeneity: except for null genes, 1 SNP \neq 1 response (think haplotypes)
 - pluralistic approach: genomic (inc. epigenetic), transcriptomic, proteomic, and metabonomic (drug & biological)
- large, statistically valid, multi-centered, multi-ethnic (intrinsic), multi-factorial studies with broadened monitoring are required, not sanitized PGx studies.





**All substances are
poisons:**

**There is none which is
not a poison.**

**The right dose
differentiates a poison
and a remedy.**

Paracelsus (1493-1541)

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