

Drug-Drug and Drug-Transporter Interactions as Obstacles for Absorption

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Presented at ACCP

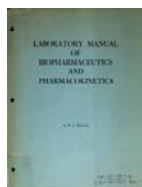
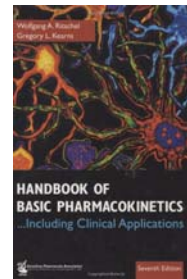
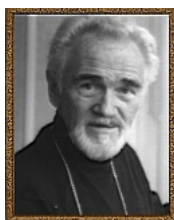
Monday, September 23, 2013
Symposium VIII, ACCP

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Honoring the Memory of Dr. W.A. Ritschel



"All that live must die, passing through nature to eternity".
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Learning Objectives:

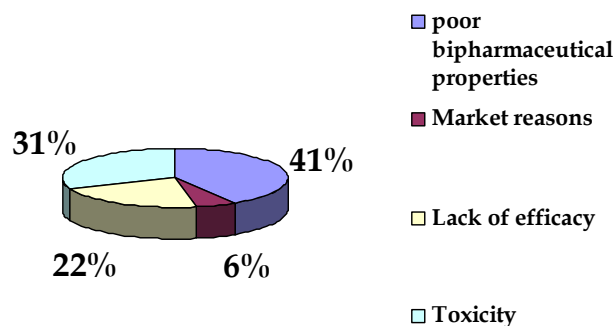
- Comprehend conditions in which the desired outcomes of pharmacotherapy are not achieved;
- Identify methods to develop and test effective drugs for oral administration;
- Describe the conditions and the mechanisms behind a therapeutic failure;
- Recognize problems and prevent therapeutic and R&D failure.

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Reasons for compounds failing during development



Modern Drug Discovery, January/February 1999

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Why it is important to maximize oral bioavailability: Five Reasons

1. To most effectively control plasma concentration, safety, and pharmacological effect
2. Low bioavailability increases variability*
3. To avoid side effects due to products of first-pass metabolism
4. To predict the outcome of therapy (e.g., oral vs. iv ; acute vs. chronic treatment)
5. Most cost-efficient use of drug substance

* variability in drug concentration and response may cause unexpected toxicities or drug-drug interactions.

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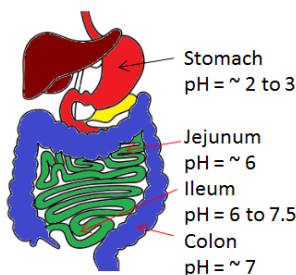
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Physiological Constraints: GI environment

Small Intestine Solution

Volume ~ 500ml
pH ~ 4-7.5
HCO₃⁻, Mucus
Maltase-Lactase-Sucrase-Lipase-Nuclease
Carboxy and Amino peptidase
Fats-Fatty Acids, Lecithin
Bile salts
Transit time ~ 3-4 hr
Surface tension low
Permeability high



Gastric Solution

Volume ~ 300ml
pH = 1-3
Water
HCl, Na⁺, K⁺
PO₄⁻³, SO₄⁻²
HCO₃⁻, Mucus
Pepsin, Protein
Residence time- variable
0.25 - 5 hours
Surface tension < water
Permeability low

Complex Colonic Micro and Macro Environment

Permeability- Drug dependent
Transit time 1 to >24 h
Redox potential -400mv
Bacteria(cfu/g), 1x10¹²
pH ~ 7
Fluid~ 187mL(total), 13mL(free)
Length = 1.66 m
Surface area = 3 m²

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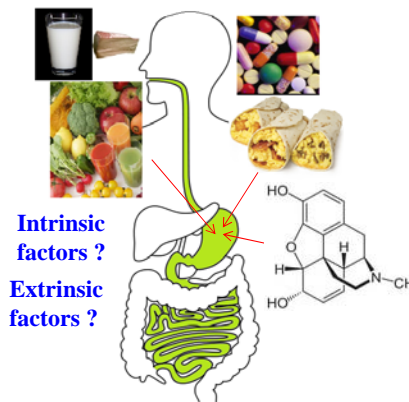
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Drug-Drug and Drug-Transporter Interactions as Obstacles for Absorption

Drug transporters affecting absorption and bioavailability contribute to variability in drug concentration and response:

The Human Genome Project has identified more than 400 transporters that belong to one of two superfamilies: ATP-binding cassette "ABC" (most efflux transporters) or solute carrier "SLC" (most uptake transporters).

1. Efflux (excretion to bile):
P-gp & BCRP
2. Excretion to intestinal lumen: (P-gp, MDR1, ABCB1)



Focus of introduction: Modified release formulations (sustained release or extended release products) and drug combinations.

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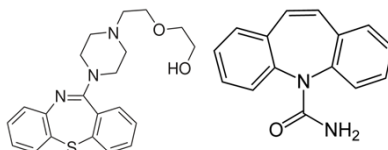
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Biopharmaceutical Considerations in development of Drug Delivery systems

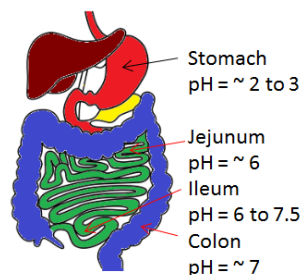
Drug properties:
Solubility
Dissolution,
MW & Shape,
Lipophilicity,
Ionization,
Permeability

Formulation:

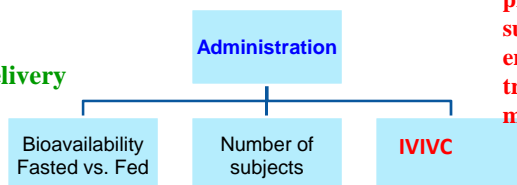
API dose,
Excipients,
Special additives,
Stability,
Unit dose
Type of Delivery System



Quetiapine fumarate and Carbamazepine; Bioavailability of both drugs > 80%; Quetiapine is highly permeable while Carbamazepine is slowly and variably absorbed.



Regional variations:
pH, fluid volume,
surface area, Gut wall enzymes, transporters, transit time, micro flora etc.



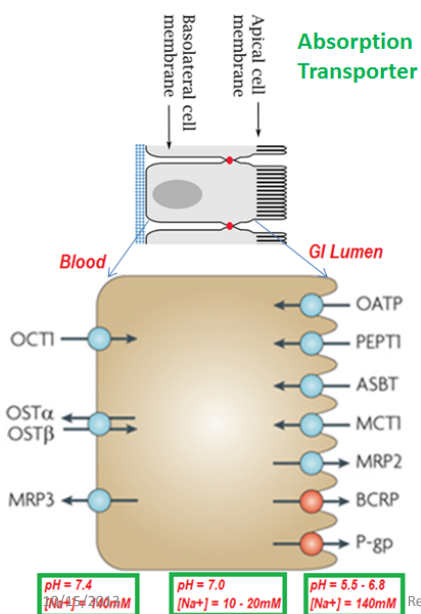
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Fassihi 2011, AAPS Annual Meeting Washington DC.

Absorption of drugs via clinically important transporters in the GI tract that should be considered for evaluation during drug development



- Organic anion transporting polypeptide (OATP) family; peptide transporter 1; solute-carriers (PEPT1; SLC15A1)
- Ileal apical sodium/bile acid co-transporter (ASBT; SLC10A2)
- Monocarboxylic acid transporter (MCT1; SLC16A1)
- The apical ATP-dependent efflux pumps include multidrug resistance protein (MRP2; ABCC2); breast cancer resistance protein (BCRP; ABCG2); and P-glycoprotein (P-gp; MDR1, ABCB1)
- The basolateral membrane of intestinal epithelia contains organic cation transporter 1 (OCT1; SLC22A1); heteromeric organic solute transporter (OSTα-OSTβ); and MRP3 (ABCC3).

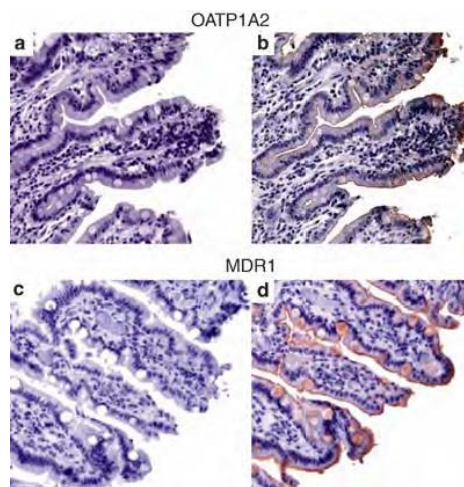
Adapted from: Giacomini et al., (2010) Nat Rev Drug Discov. 9(3):215-236

International Transporter Consortium (ITC) was formed in 2007 to further the understanding of drug transporters in therapeutic and adverse drug effects.

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Immunohistochemical staining of OATP1A2 and P-gp in human duodenal sections

- OATP1A2 expression is co-localized with P-gp on the brush border membrane of human enterocytes
- Glaeser H. et al. (2007) Clin Pharmacol Ther. 81(3); 362-370



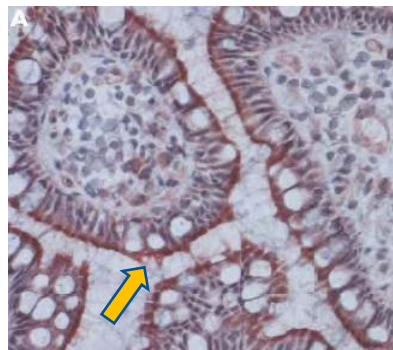
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Apical sodium-dependent bile acid transporter (ASBT; SLC10A2) is highly expressed in the ileum

- Substantial contribution to the enterohepatic circulation of bile acids
- Expressed in the ileum, cecum and kidney
- Mutations in ASBT gene result in bile acid mal-absorption and congenital diarrhea
- Inhibition of ASBT results in changes in cholesterol and bile acid homeostasis



Immuno-reactive ASBT in human ileal slices

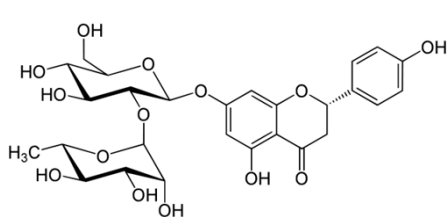
Adapted from: Hruzet et al., Gut 2006; 55:395-402

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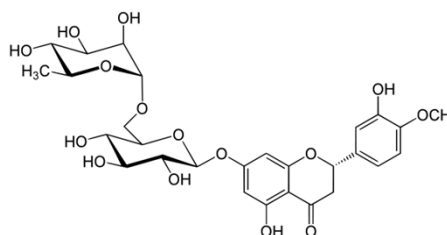
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Components of fruit juices that may inhibit transporter-mediated intestinal absorption



Naringin



Hesperidin

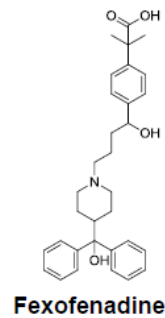
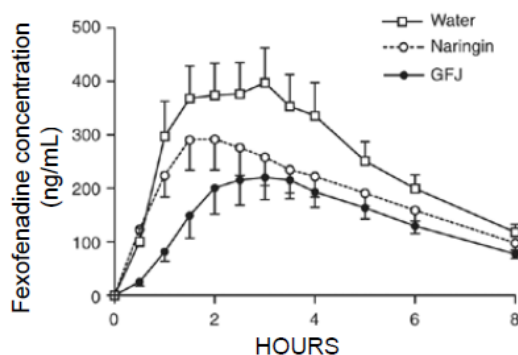
Flavonone glycosides (flavonoids) in citrus juices are believed to be the ingredients responsible for altering the bioavailability of selected drugs (with more examples emerging) due to the inhibition of uptake processes in the intestine or metabolizing enzymes.

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Effect of grape fruit juice or naringin on the oral bioavailability of fexofenadine

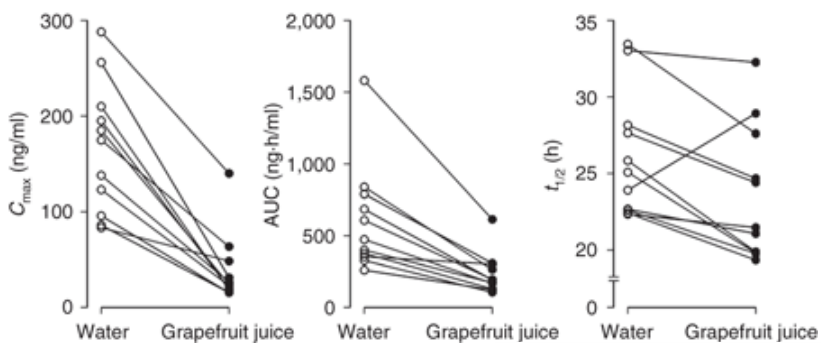


- Grapefruit juice reduced fexofenadine systemic exposure and C_{max}
- The effect was transient in nature likely involving a competitive inhibition mechanism
- Naringin administration had an effect similar to that observed with Grapefruit juice.

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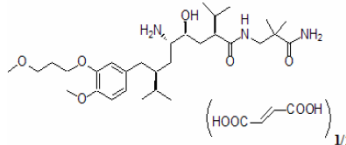
Adapted from Bailey et al. Clin Pharm Ther. 81(4); 495-502 (2007) Reza Fassihi Ph.D. 13

Individual C_{max} , AUC and $t_{1/2}$ of Aliskiren in humans



Hypertension ; F= 2.5%

- Low permeability, P-gp substrate
- Low absorption in humans and animals
- Variable exposure in humans
- Decrease in exposure seen when given with grapefruit juice
- Decreased exposure maybe due to the inhibition of an uptake transporter in the intestine

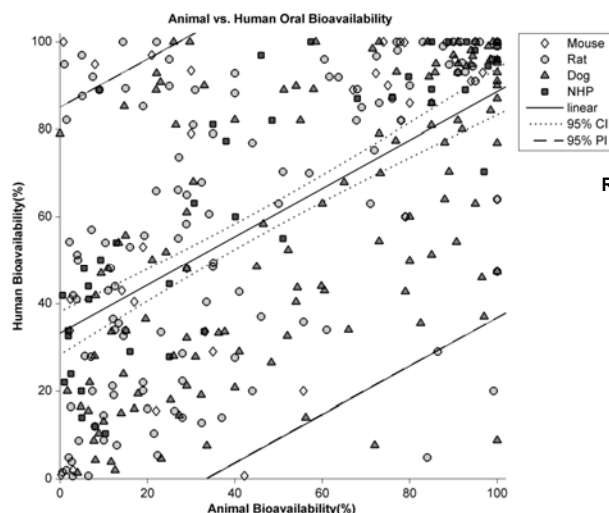


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Tapaninen et al., Clin. Pharm Therap;2010

Oral Bioavailability: Human vs. Animal



A confidence interval (CI) is ideal for quantifying the degree of uncertainty around common parameters of interest such as the center of a sampled population, or its spread.
PI = Prediction Interval

(Data From: Simcyp)

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Methods for Studying Absorption

➤ Examples include:

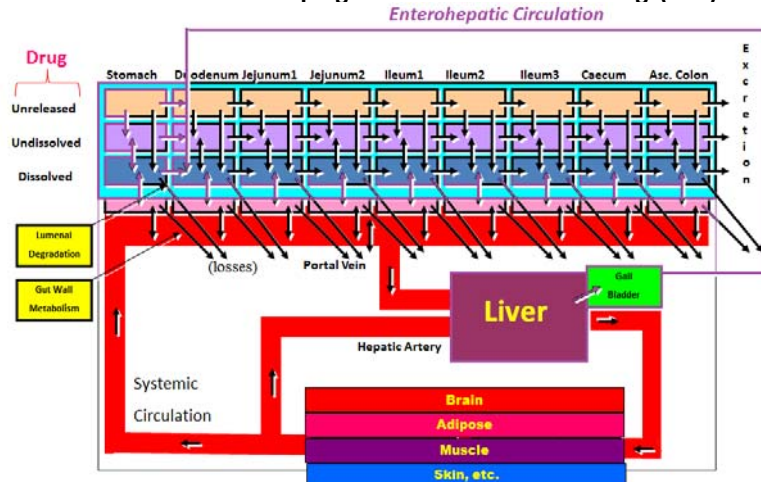
- Cell/membrane models,
- Intact organ/in vivo models;
- Modeling/imaging tools for dynamic studies,
- Enzyme/transporter interplay and
- Mechanistic Approaches
 - GastroPlus™ (ACAT) Advanced Compartmental Absorption and Transit
 - Simcyp's ADAM model(Advanced Dissolution, Absorption & Metabolism)

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Advanced Compartmental Absorption and Transit (ACAT) Model (GastroPlus™)
GastroPlus™ is a valuable in silico tool for simulation of GI bioavailability and IVIVC studies directed at developing formulations of some drugs(BCS)



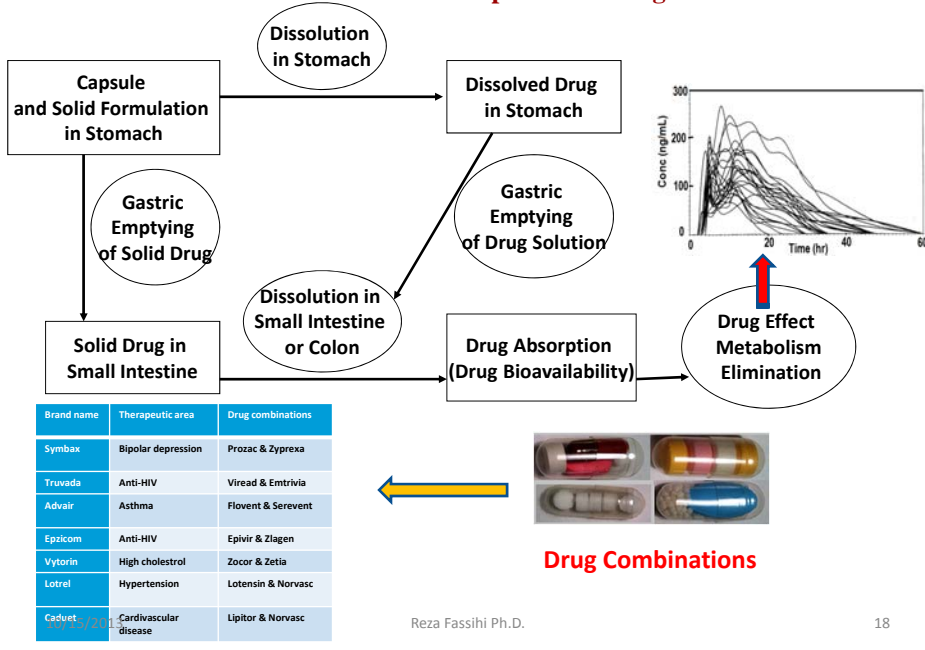
Typically: Simulate drug release profiles within the range of e.g. 5min up to 10 h for 100%.
 Use Virtual Trials—Bioequivalence Testing

For more details on (ACAT) see Yu et al. "Advanced Drug Delivery Reviews 19 (1996) 359-376".

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Simplified Process of Drug Absorption After Per-Oral Administration: Dissolution/Absorption and Drug Combinations

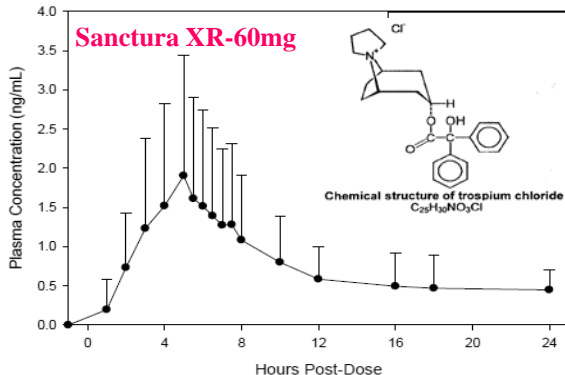


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Individual variability in addition to food effect Coated pellets in capsules

Indicated for urge incontinence
(antispasmodic, antimuscarinic agent).



F = 9.6 % (range 4.0 – 16.1%)
Administration of SANCTURA XR® capsules immediately after a high (50%) fat-content meal reduced the oral bioavailability of trospium chloride by 35% for $AUC_{(0-Tlast)}$ and by 60% for C_{max} .

Mean (\pm SD) Pharmacokinetic Parameter Estimates for a Single 60 mg Oral Dose of SANCTURA XR® in Healthy Volunteers

TREATMENT	AUC(0-24) (NG•H/ML)	C _{MAX} (NG/ML)	T _{MAX} ^A (H)	T _{1/2} ^B (H)
SANCTURA XR® 60 mg	18.0 \pm 13.4	2.0 \pm 1.5	5.0 (3.0-7.5)	36 \pm 22

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Predicting Drug-Drug Interactions

- By understanding which enzymes or transporters may be involved in the ADME process and the potential for a drug to be a **substrate, inhibitor, or inducer** of that process, we can predict the potential for drug interactions.

In Vitro models/Tools



The integration of *in vitro* and *in vivo* (both animal and human) data can identify the role of transporters in drug-drug interactions.

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Examples of Transporter-Mediated Drug-Drug Interactions

Interacting Drug	Affected Drug	Result	Changes in Substrate Plasma AUC
Quinidine	Digoxin	Digoxin Exposure 1.7-fold ↑	P-glycoprotein (P-gp, MDR1) Inhibition
Rifampin	Digoxin	Digoxin Exposure 30% ↓	P-gp Induction
Dronedaronone	Digoxin	Digoxin Exposure 2.6-fold ↑	P-gp Inhibition
Probenecid	Cephadrine	Cephadrine Exposure 3.6-fold ↑	Organic Anion Transporter (OAT) Inhibition
Cimetidine	Metformin	Metformin Exposure 1.4-fold ↑	Organic Cation Transporter (OCT) Inhibition
Cyclosporine	Rosuvastatin	Rosuvastatin Exposure 7-fold ↑	Organic Anion Transporting Polypeptide (OATP) Inhibition & Breast Cancer Resistance Protein (BCRP) Inhibition
Lopinavir/ Ritonavir	Rosuvastatin	Rosuvastatin Exposure 2-fold ↑	OATP Inhibition

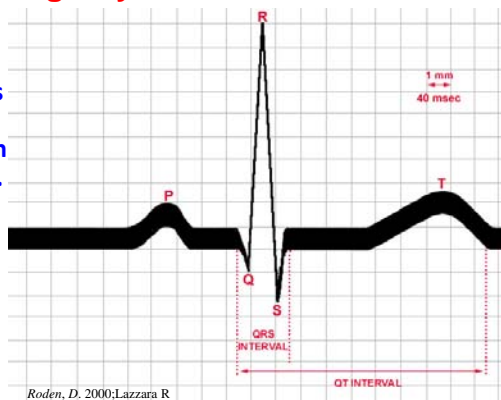
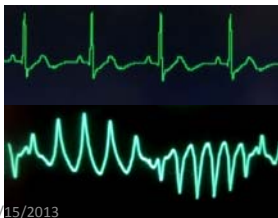
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Drug-Induced QT Interval Prolongation and Torsades de Pointes :Drug-Phytochemical Interaction

- This ECG showing normal sinus rhythm and a classic example of torsades de pointes, which is French for "twisting of the points", occurring in association with terfenadine (Seldane) use.
- The QRS complexes during this rhythm tend to show a series of "points up" followed by "points down".



Rodén, D. 2000;Lazzara R

- Torsades de pointes (ventricular tachycardia) due to medication

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Drugs Withdrawn for TdP (Drug-Phytochemical Interaction)

<u>Drug</u>	<u>Class</u>	<u>Date Withdrawn</u>
*Terfenadine	Antihistamine	Feb 1998
Sertindole	Antipsychotic	Dec 1998
Astemizole	Antihistamine	Jun 1999
*Grepafloxacin (Raxar)	Antibiotic	Warning lable
Cisapride	GI Prokinetic	July 2000

*Grapefruit juice (contains furanocoumarin derivatives) can increase plasma concentration of terfenadine.

* Contraindicated in patients with history of increase in the QT_c

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Alteration of Gastrointestinal Absorption Interactions that involve a change in drug absorption from the GI tract are of variable importance

- Alteration of pH
- Complexation and adsorption: Drug-Drug interactions
 - Antacids markedly reduce the absorption of fluoroquinolone derivatives (e.g., ciprofloxacin), probably as a result of the metal ions complexing with the drug. Antacids should not be used simultaneously or <2 h (or preferably, an even longer period) after ciprofloxacin
- Alteration of motility
 - By increasing GI motility, metoclopramide may hasten the passage of drugs through the GI tract, resulting in decreased absorption
 - By decreasing GI motility, anticholinergics may either reduce absorption by retarding dissolution and slowing gastric emptying, or increase absorption by keeping a drug for a longer period of time in the area of optimal absorption.
- Effect of food
 - Food has been reported to decrease the absorption of many therapeutic agents including astemizole, captopril, and penicillamine and some antibiotics.
- CYP enzyme inhibition and P-gp / Selected efflux & uptake transporters in the gut wall can cause changes in absorption and adverse reactions.

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Summary

- ✓ Nutrient and uptake transporters in the gastrointestinal tract (e.g. OATP1A2 and ASBT) may participate in the transport of xenobiotics (e.g. fexofenadine, aliskiren etc.)
- ✓ Inhibition of such processes can represent a mechanism underlying drug-drug, or drug-diet interactions.
- ✓ A better understanding of uptake transport activity is needed to evaluate the role played by such processes in influencing the pharmacokinetics of new drug candidates

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Conclusion

Understanding absorption transporters and their interactions with drug(s) and Phytochemicals provides a mechanistic approach to:

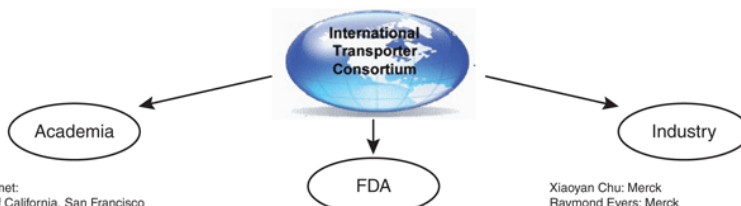
- Explain variability in bioavailability
- Provide insight into PK/PD relationship, and safety in clinical trials and application
- Identify patients at risk of developing adverse events associated with the drug in question or at risk when drug combinations are used
- Help in decision making to improve the use of medications (i.e. **Right drug; Right dose; Right time; for the Right patient**).

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Expert members of the International Transporter Consortium (ITC)
Clinical Pharmacology & Therapeutics (2010) 87 1, 32–36



Leslie Z. Benet:
University of California, San Francisco
Kim L.R. Brouwer:
University of North Carolina at Chapel Hill

Kathleen M. Giacomini:
University of California, San Francisco*
Toshihisa Ishikawa: RIKEN Yokohama Institute*
Dietrich Keppler: German Cancer Research Center
Richard B. Kim: University of Western Ontario
Mikko Niemi: University of Helsinki
Yuichi Sugiyama: University of Tokyo
Peter. W. Swaan: University of Maryland
Stephen H. Wright: University of Arizona

Shiew Mei Huang:
Food and Drug Administration*
Lei Zhuang:
Food and Drug Administration

Xiaoyan Chu: Merck
Raymond Evers: Merck
Volker Fischer: Abbott
Kathleen M. Hillgren: Lilly Research Laboratories
Keith A. Hoffmaster: Novartis
Caroline A. Lee: Pfizer
Joseph W. Poll: GlaxoSmithKline
Donald J. Tweedie:
Boehringer Ingelheim Pharmaceuticals*
Joseph A. Ware: Genentech
Maciej Zamek-Gliszczynski:
Lilly Research Laboratories

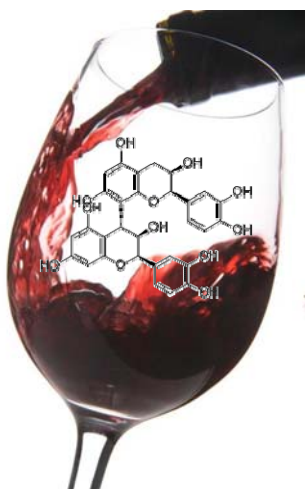
The key transporters, P-glycoprotein (P-gp, ABCB1); breast cancer resistance protein (BCRP); organic anion transporters (OAT1 and OAT3); organic cation transporter (OCT2); and organic anion transporting polypeptides (OATP1B1 and OATP1B3), identified by ITC were selected based on evidence in the literature demonstrating that the transporters play a role in governing drug absorption and disposition and in mediating clinical DDIs.

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What is *Man*, when you come to think upon him, but a minutely set, ingenious machine for turning, with infinite artfulness, the red wine of Shiraz into urine? "Isak Dineson".



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