Drug-Drug Interactions

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Limitations of clinical trials

- Short study period
- Small sample size
- Control environments, e.g. simple regimen
- DDIs are difficult to find

Definition of drug-drug interactions

- The phenomenon that occurs when the effects or pharmacokinetics of a drug are altered by prior administration or coadministration of a second drug.

Prevalence and consequence of potential drug-drug interactions

- 27 to 37% of potential DDIs in general prescriptions
- About 100,000 deaths result from adverse drug reactions (ADRs) each year in the USA
- Among ADRs, the 6% to 10% are related with DDIs

Major factors of potential DDIs

- Age
- Polypharmacy

References:

1. Costa AJ. Potential drug interactions in an ambulatory geriatric population. *Fam Pract* 1991;8:234-6.
2. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *Jama* 2003;289:1652-8.
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5. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. *Br J Clin Pharmacol* 2004;57:121-6.
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7. Kohler GI, Bode-Boger SM, Busse R, Hoopmann M, Welte T, Boger RH. Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. *Int J Clin Pharmacol Ther* 2000;38:504-13.
8. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use. A study of community-dwelling persons 65 years of age and older. *Ann Intern Med* 1992;117:634-40.
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Mechanisms of Drug Interactions

- Pharmacokinetics
- Pharmacodynamics

Pharmacokinetic

- Altered Absorption
  - Ciprofloxacin and di- or trivalent cations
- Altered Distribution
  - Protein binding
    - Albumin and phenytoin
  - Receptor binding
    - Quinidine displaces digoxin
- Altered Metabolism
  - Grapefruit Juice and Amlodipine
  - Cimetidine and Lovastatin
- Altered Excretion
  - Methotrexate and NSAIDs

Major metabolisms and Risk of Potential DDI

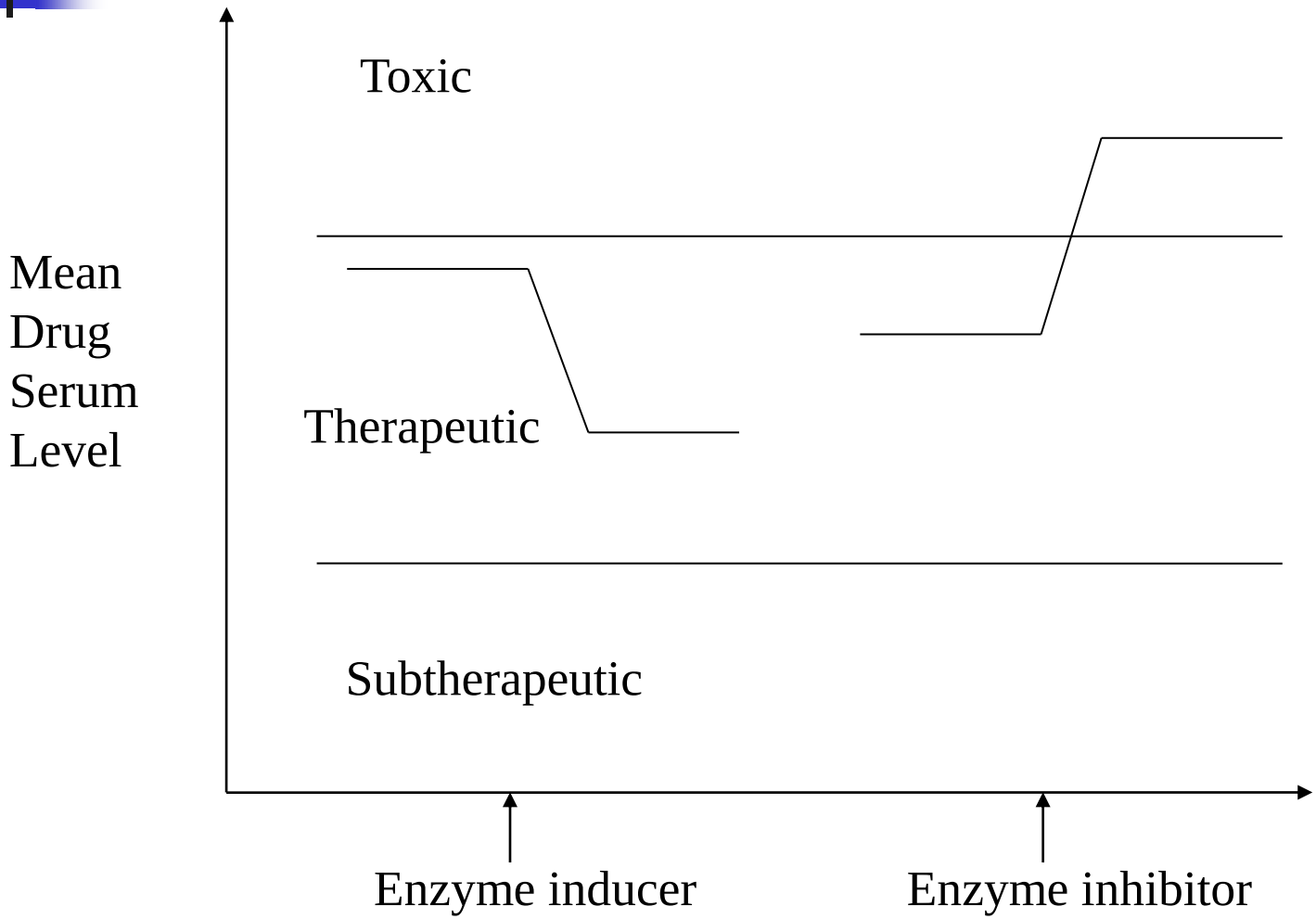
- Most of antihypertensive drugs are metabolized from the cytochrome P450 enzyme systems
- That Individual variability in the metabolizing capacity of cytochrome P450 enzymes, is the most clinically important types of pharmacokinetic DDIs and will result in the higher risks of potential DDIs

References:

1. Delafuente JC. Understanding and preventing drug interactions in elderly patients. *Crit Rev Oncol Hematol* 2003;48:133-43.
2. Flockhart DA, Tanus-Santos JE. Implications of cytochrome P450 interactions when prescribing medication for hypertension. *Arch Intern Med* 2002;162:405-12.
3. Katoh M, Nakajima M, Shimada N, Yamazaki H, Yokoi T. Inhibition of human cytochrome P450 enzymes by 1,4-dihydropyridine calcium antagonists: prediction of in vivo drug-drug interactions. *Eur J Clin Pharmacol* 2000;55:843-52.
4. Anderson JR, Nawarskas JJ. Cardiovascular drug-drug interactions. *Cardiol Clin* 2001;19:215-34.

Mean drug blood level response to an enzyme inducer or enzyme inhibitor

(Ref: Tatro DS. Drug interaction facts. 2009 ed. St. Louis: Facts and Comparisons.)



Pharmacodynamic

- One drug induces a change in a patient's response to a drug without altering the object drug's pharmacokinetics
  - Digoxin and potassium-wasting diuretics

Significance rating

(Different references may have different ratings)

- Onset
  - Rapid---within 24 hours
  - Delayed---days to weeks
- Severity
  - Major---life-threatening or permanent damage
  - Moderate---deterioration of patient's status
  - Minor---bothersome or little effect
- Documentation
  - Established---proven to occur in well-controlled studies
  - Probable---very likely, but not proven clinically
  - Suspected---may occur; some good data, but needs more study
  - Possible---could occur, but data are very limited
  - Unlikely---doubtful; no good evidence of a clinical effect

The classification of DDIs pairs

Significance Rating#	Severity*	Documentation**
1	Major	Suspected or >
2	Moderate	Suspected or >
3	Minor	Suspected or >
4	Major/Moderate	Possible
	Minor	Possible
5	Any	Unlikely

#1: is a severe and well-documented interaction; #5: is an interaction of no more than unlikely or possible documentation; *Major: life-threatening or permanent damage; Moderate: deterioration of patient's status; Minor: bothersome or little effect; **Established: proven to occur in well-controlled studies; Probable: very likely, but not proven clinically; Suspected: may occur, some good data, needs more study; Possible: could occur, but data are very limited; Unlikely: doubtful, no good evidence of an altered clinical effect

Reference: Tatro DS. Drug interaction facts. 2002 ed. St. Louis: Facts and Comparisons; 2002.

Variability in patient response

- Age
- Genetics
- disease states
- alcohol consumption
- Smoking
- Diet
- environmental factors

- particularly susceptible patients
  - elderly patients
  - patients with acute illness
  - patients with unstable diseases
  - drug treatment-dependent patients
  - patients with renal or hepatic disease
  - patients with multiple prescribing physicians

Structure of the Anatomical Therapeutic Chemical (ATC) Classification System

- 1st level —
  Anatomical main group, 14 main groups
- 2nd level —
  Pharmacological/therapeutic subgroup
- 3rd and 4th levels —
  Chemical/pharmacological/therapeutic subgroups
- 5th level —
  Chemical substance

例：**Acyclovir眼藥膏之ATC為S01AD03，**
Acyclovir口服及注射藥之ATC為J05AB01。

Ref: WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment.

Examples: Cardiovascular drugs with Significance 1 of potential DDIs those should be avoided use

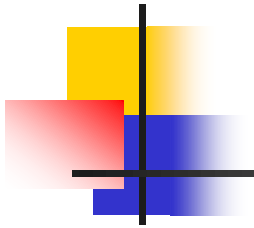
Drug pairs of potential DDIs		Drug pairs of potential DDIs	
Drug A	Drug B	Drug A	Drug B
Antiarrhythmics	Cisapride	Nitrates	Sildenafil
Amiodarone		Amyl nitrite,	
Disopyramide		Isosorbide dinitrate	
Flecainide		Isosorbide mononitrate	
Procainamide		Nitroglycerin	
Quinidine			
Propafenone			
Sotalol			

Examples: Cardiovascular drugs with Significance 1 of potential DDIs those doses should be adjusted

Drug pairs of potential DDIs		Drug pairs of potential DDIs	
Drug A	Drug B	Drug A	Drug B
Anticoagulants Warfarin Diuretics Furosemide	Amiodarone Digoxin	Anticoagulants Warfarin	Azol antifungal agents Fluconazole Itraconazole Ketoconazole Miconazole

結論

- 臨床上發現有藥品交互作用時之考量重點
  - 評估風險效益
  - 是否有代用藥品
  - 是否具臨床重要性之等級
  - 是否可調整劑量
  - 是否可錯開時間服用
- 除了藥品交互作用外，臨床上也要注意藥品與食物的交互作用



Thanks for your attention