CHAPTER-III

PHARMACOKINETIC DRUG INTERACTIONS

BY

Prof. C. Ramasamy,
Head, Dept of Pharmacy Practice
SRM College of Pharmacy,
SRM University
<table>
<thead>
<tr>
<th>DRUG</th>
<th>CATEGORY</th>
<th>REASON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>antihistamine</td>
<td>serious metabolic drug intxns</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>analgesic</td>
<td>hepatotoxicity</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>anorectic</td>
<td>cardiovascular tox</td>
</tr>
<tr>
<td>Felbamate</td>
<td>anticonvulsant</td>
<td>aplastic anemia</td>
</tr>
<tr>
<td>Flosequinan</td>
<td>vasodilator</td>
<td>increased mortality</td>
</tr>
<tr>
<td>Grepaflozin</td>
<td>antibiotic</td>
<td>proarrhythmic</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>Ca channel blocker</td>
<td>serious drug intxns</td>
</tr>
<tr>
<td>Temaflozin</td>
<td>antibiotic</td>
<td>severe ADR</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>antihistamine</td>
<td>serious drug intxn</td>
</tr>
<tr>
<td>Travaflozin</td>
<td>antibiotic</td>
<td>hepatotoxicity</td>
</tr>
</tbody>
</table>

I. GENERAL CONSIDERATIONS

A. CONCEPT OF A THERAPEUTIC WINDOW

- Toxicity Desired
- Probability of Response
- Log Concentration
- Desired
- Toxicity
# B. EPIDEMIOLOGICAL CONSIDERATIONS

## HOSPITALIZED PATIENTS EXPERIENCING AN ADVERSE REACTION

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>% Pts with Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives</td>
<td>12</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>11</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>6</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>4</td>
</tr>
<tr>
<td>Antiinflammatory</td>
<td>3</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3</td>
</tr>
<tr>
<td>Analgesics</td>
<td>2</td>
</tr>
</tbody>
</table>

### B. EPIDEMIOLOGICAL CONSIDERATIONS

**Effect of the Number of Drugs a Patient Receives on the Frequency of Adverse Drug Reactions**

<table>
<thead>
<tr>
<th>Number</th>
<th>Antihypertensives</th>
<th>Anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>6-10</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>11-15</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>16-20</td>
<td>23</td>
<td>18</td>
</tr>
</tbody>
</table>

### B. EPIDEMIOLOGICAL CONSIDERATIONS

**Prospective study of 237 patients treated with warfarin analyzed for determination of whether or not a drug interaction occurred with concurrent chloral hydrate**

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients who received chloral hydrate during warfarin therapy</td>
<td>237</td>
</tr>
<tr>
<td>Those patients who received chloral hydrate for at least 3 consecutive days</td>
<td>69</td>
</tr>
<tr>
<td>Impossible to evaluate (unstable/change therapy)</td>
<td>28</td>
</tr>
<tr>
<td>Potentiation of anticoagulant action</td>
<td>22</td>
</tr>
<tr>
<td>No observable interaction</td>
<td>19</td>
</tr>
</tbody>
</table>

C. TYPE OF INTERACTION

**Unidirectional**

A $\rightarrow$ B

**Bidirectional**

A $\leftrightarrow$ B
D. CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION

Complexation/Chelation

Example: antacids + tetracycline

Impact: tetracycline complexes with divalent cations forming an insoluble complex
D. CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION

Complexation/Chelation

Altered GI Transit

Example: anticholinergics + acetaminophen

Impact: delay in absorption of acetaminophen
D. CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION

Complexation/Chelation

Altered GI Transit

Altered Gastric pH

Example: H-2 blockers + ketoconazole

Impact: dissolution of ketoconazole is decreased, resulting in reduced absorption
D. CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM

Induction of Metabolism

Example: phenobarbital + warfarin

Impact: phenobarbital increases the metabolism of warfarin, resulting in reduced anticoagulation
D. CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION

ALTERATIONS IN HEPATIC METABOLISM

Induction of Metabolism

Inhibition of Metabolism

**Example: cimetidine + theophylline**

**Impact:** Cimetidine reduces the clearance of theophylline causing an increase in adverse effects
D. CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE

Increase in Renal Blood Flow

Example: hydralazine + digoxin

Impact: hydralazine increases the renal clearance of digoxin
D. CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE

Increase in Renal Blood Flow
Inhibition of Active Tubular Secretion

Example: probenecid + penicillin

Impact: probenecid prolongs the half-life of penicillin, allowing single dose therapy
D. CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE

Increase in Renal Blood Flow
Inhibition of Active Tubular Secretion
Alterations in Tubular Reabsorption

**Example:** antacids + aspirin

**Impact:** antacids reduce the tubular reabsorption of salicylate via an increase in urine pH
D. CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE
ALTERATIONS IN PLASMA PROTEIN BINDING

Example: phenytoin + valproic acid

Impact: protein binding of valproic acid is reduced and total Css decreased
II. ALTERATIONS IN ABSORPTION

A. Mediated by binding or chelation of drug in the gastrointestinal tract

\[
\text{carbidopa} \\
\text{L-dopa}
\]
Effect of ferrous sulfate (325 mg) on plasma levodopa and carbidopa concentrations after ingestion of Sinemet (100/25) in patients with Parkinson's disease. Concentrations shown are mean values without (triangles) and with (circles) ferrous sulfate administration simultaneously. Adapted from Campbell NRC et al: *Br J clin Pharmacol* 30:599-605, 1990
COMPOUNDS DEMONSTRATED TO BIND WITH IRON

ACETAMINOPHEN
AMPICILLIN
CAPTOPRIL
CARBIDOPA
CIPROFLOXACIN
ETHAMBUTOL
FOLIC ACID
INDOMETHACIN
LEVODOPA
METHYLDOPA
MINOXIDIL
NALIDIXIC ACID
NORFLOXACIN
PENICILLAMINE
RIFAMPIN
TETRACYCLINE
THYROXINE
SALICYLIC ACID
B. Mediated by alterations in gastric emptying or gastrointestinal transit

Effect of food on gastric residence time (GRT) of the Heidelberg capsule administered to healthy male (circles) and female (squares).

Effect of sumatriptan on acetaminophen absorption in patients with migraines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APAP alone</th>
<th>with Sumatriptan</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>36.3 (10.9)</td>
<td>18.3 (6.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hr)</td>
<td>1.4 (0.4)</td>
<td>2.7 (1.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>2.3 (0.7)</td>
<td>3.0 (1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>$\text{AUC}_{0-1.5}$</td>
<td>26.9 (9.5)</td>
<td>11.8 (3.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>$\text{AUC}_{0-3}$</td>
<td>62.3 (14)</td>
<td>33.1 (12.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>$\text{AUC}_{0-8}$</td>
<td>109 (37)</td>
<td>78.8 (31.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

III. ALTERATIONS IN DRUG METABOLISM

A. Induction

\[
CL_H = \frac{Q_H f_{ub} CL_{u int}}{Q_H + f_{ub} CL_{u int}}
\]

\[
AUC_O = \frac{F \times Dose}{f_{ub} CL_{u int}}
\]
Figure 1. Mean Plasma Quinidine Concentrations in the Four Subjects Who Received Oral Quinidine Sulfate, 6 mg per Kilogram, before (Control) and after Oral Rifampin, 500 mg Daily for Seven Days.
From: Rowland M, Tozer TN. Ibid. p. 282.
B. Inhibition

Effect of cimetidine on the clearance on diazepam (D), desmethyldiazepam (DZD), chlordiazepoxide (CZD) and oxazepam (OXM). CZD values are x10, while OXM values are 1/10. Data from: Somogyi A, Gugler R: Drug interactions with cimetidine. Clin Pharmacokinet 7:23, 1982.
Figure 2  Impact of ritonavir on the pharmacokinetics of saquinavir. Shown are plasma concentration-time profiles in human subjects (mean ± standard error of the mean) for oral saquinavir at 400 mg alone (closed circles), 400 mg of saquinavir plus 600 mg of ritonavir (open circles), and 600 mg of ritonavir alone (open squares). (Reprinted from Reference 52, with permission.)
### FACTORS WHICH ALTER HEPATIC BLOOD FLOW

<table>
<thead>
<tr>
<th>Increased Flow</th>
<th>Decreased Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Glucagon</td>
<td>• Propranolol</td>
</tr>
<tr>
<td>• Isoproterenol</td>
<td>• Norepinephrine</td>
</tr>
<tr>
<td>• Phentolamine</td>
<td>• Anesthetics</td>
</tr>
<tr>
<td>• Phenobarbital</td>
<td>• Labetalol</td>
</tr>
<tr>
<td>• PGE</td>
<td>• Upright posture</td>
</tr>
<tr>
<td>• Supine posture</td>
<td>• Hypovolemia</td>
</tr>
<tr>
<td>• High-protein meal</td>
<td>• CHF</td>
</tr>
<tr>
<td>• Viral hepatitis</td>
<td>• cirrhosis</td>
</tr>
</tbody>
</table>
**Effect of changing posture on liver blood flow and lidocaine clearance**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Supine</th>
<th>Sitting/tilted</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_H$ (mL/min)</td>
<td>1100 (167)</td>
<td>765 (106)</td>
</tr>
<tr>
<td>$CL$ (mL/min)</td>
<td>602 (101)</td>
<td>475 (109)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)
Fig 1. Mean ± SD recombinant tissue factor pathway inhibitor [rTFPI] concentration profiles. rTFPI was infused concomitantly with sorbitol from t = 0 to 240 minutes. During one infusion the subjects remained resting (open circles); during the other infusion (solid circles) at 180 minutes the subjects exercised for 30 minutes. The continuous lines represent the average fitted curves based on the individual empirical Bayes estimates provided by NONMEM.
V. ALTERATIONS IN RENAL CLEARANCE

A. Renal Blood Flow

B. Active Tubular Secretion

Fig. 12–7. The plasma concentration (on left), and hence the area under the curve, for amoxicillin is increased when 500 milligrams are administered orally in solution to fasting subjects in the absence (○) and presence (●) of probenicid (1 gram, 12 hours and then 1 hour before the antibiotic). The effect is due to probenicid decreasing the renal clearance of amoxicillin (on right), its primary route of elimination. (One mg/liter = 2.7 micromolar.) (Data from Staniforth, D.H., Jackson, D., Clarke, H.L., and Horton, R.: Amoxicillin/clavulanic acid: The effect of probenecid. J. Antimicrob. Chemother., 12: 273–275, 1983.)
VI. ALTERATIONS IN PROTEIN BINDING

Fig. 17-3. The valproate-phenytoin interaction involves displacement only. Although plasma protein binding of phenytoin is decreased when sodium valproate is administered chronically to a group of patients stabilized on phenytoin, with a resultant fall in the steady-state plasma phenytoin concentration, there was no substantial change in the unbound phenytoin concentration. These observations are consistent with a displacement interaction of phenytoin by valproic acid. Note that the degree of phenytoin displacement depends on the dose of sodium valproate. Of the 25 patients stabilized on phenytoin, 11 received 900 milligrams sodium valproate per day; 9 received a 1350-milligram daily dose; and some received both. (One mg/liter = 4.0 micromolar.) (Taken from Mattson, R.H., Cramer, J.A., Williamson, P.D., Novelty, R.A.: Valproic acid in epilepsy: Clinical and pharmacological effects. Ann. Neurol., 3: 20–25, 1978.)

Fig. 17-5. Warfarin-phenylbutazone interaction. A subject received 10 milligrams warfarin orally each day and 100 milligrams phenylbutazone three times a day on days 13 to 22. As the phenylbutazone concentration rose, bound warfarin was displaced and the plasma warfarin concentration fell. The sustained elevation in the unbound warfarin during phenylbutazone administration implies inhibition of warfarin elimination. (Phenybutazone: One mg/liter = 3.2 micromolar; warfarin: One mg/liter = 3.3 micromolar.) (Modified from Schary, W.L., Lewis, R.J., and Rowland, M.: Warfarin-Phenylbutazone interaction in man: A long term multiple-dose study. Res. Commun. Chem. Pathol. Pharmacol., 10:663–672, 1973.)

Reproduced from: Rowland M, Tozer TN. Ibid, p. 280
Fig. 17–4. When constantly infused, the unbound concentration of a drug with a low extraction ratio remains virtually unchanged if a displacer with a long half-life, relative to the drug, is either infused or withdrawn. The change in plasma drug concentration reflects the displacement.