Questions and Exercises for Chapter 13

Group Discussion/ Private research

In the 1960s and 70s it was shown that certain drugs, for example phenylbutazone, can modify the distribution of other drugs (e.g. warfarin) between bound and unbound forms in plasma, and that drugs such as phenobarbital can accelerate the metabolism of some drugs, notably warfarin, thereby reducing the plasma concentration. Both of these interactions can, in some circumstances, lead to the same clinical result. Tease these multiple effects apart, and show how the same clinical result can occur.

Short Answer Questions

1. Drug B was suspected of interacting with drug A, to reduce the efficacy of the latter. A test dose of drug A was administered orally and the AUC determined from the plasma concentration– time data. Drug B was administered for three weeks and the test with drug A was repeated. The AUC was reduced after treatment with drug B showing that oral clearance (CLoral) of A had increased. It was concluded that B was an enzyme inducer. Discuss.

2. Paracetamol (acetaminophen) is considered to be a safe and efficacious analgesic and antipyretic drug when used appropriately. However, overdoses may result in hepatotoxicity, which if untreated may be fatal. Briefly explain the mechanism of this toxicity and outline the measures that can be taken when treating an overdosed patient.

Multiple Choice Questions (Answer TRUE or FALSE)

1. Drug interactions:
   (a) should always be avoided whenever possible
   (b) are described as homergic when the interacting drugs have the same effect
   (c) include displacement of a drug from its protein binding sites
   (d) are most important for drugs with low a therapeutic index
   (e) include the interaction between ethanol and benzodiazepines

2. Clinically useful interactions include:
   (a) the use of epinephrine to prolong the duration of action of local anaesthetics
   (b) carbidopa to reduce the peripheral metabolism of levodopa
   (c) cimetidine to reduce the renal excretion of metformin
   (d) probenecid to reduce the nephrotoxicity of cidofovir
   (e) erythromycin to increase the oral bioavailability of terfenadine

3. With regard to enzyme induction :
   (a) it is irreversible
   (b) it is prevented by administration of actinomycin D
   (c) it is used to treat paracetamol poisoning
   (d) cimetidine is a potent inducer of microsomal enzymes
   (e) clozapine doses my need to be increased when patients give up smoking

4. Ketoconazole:
   (a) absorption is increased by lowering gastric pH
   (b) absorption is increased by food
(c) inhibits CYP 3A4
(d) decreases the bioavailability of terfenadine
(e) reduces the anticoagulant effect of warfarin

5. The following may be useful antidotes for the toxicity indicated:
   (a) phenacetin (acetophenetidin) – methaemoglobinaemia
   (b) ethanol – ethylene glycol poisoning
   (c) fomepizole – intoxication with ethanol
   (d) reduced glutathione (GSH) – paracetamol overdose
   (e) sodium bicarbonate – aspirin overdose

Calculation

1. The bacteriostatic activities of trimethoprim and sulfamethoxazole were tested against *bacillus subtilis* ATTC 6633 (Zani F, Incerti M, Ferretti R, Vicini P. Hybrid molecules between benzenesulfonamides and active antimicrobial benzo[d]isothiazol-3-ones. *Eur J Med Chem* 2009; 44: 2741-7). Having established the minimum inhibitory concentration (MIC) for each drug, the drugs were tested in combination and the concentrations expressed as the factional of the MIC – the fractional inhibitory concentration (FIC):

<table>
<thead>
<tr>
<th>Compound</th>
<th>Fractional inhibitory concentration (FIC)</th>
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<tbody>
<tr>
<td>Trimethoprim</td>
<td>0.015 0.061 0.124 0.248 1.000</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>1.000 0.050 0.246 0.126 0.063</td>
</tr>
</tbody>
</table>

Construct an isobologram and comment on the effect of using the drugs in combination.