Clinical Aspects of Drug Metabolism

Authors
Paul Skett, Suzanne Chorleton, Neil Kitteringham, and Gavin McLellan

Distributor
pharma-CAL-ogy, British Pharmacological Society,
16 Angel Gate, City Road, London, EC1V 2SG. United Kingdom. Tel: 44-(0)20-7417-0382. Fax: 44-(0)20-7417-0114. E-mail: cal@bps.ac.uk.

Software type
Macromedia Authorware

Subject area
Clinical relevance of drug metabolism

Intended audience
Undergraduates

Cost
£25.00 UKHE and £250.00 others

Hardware specifications
Stand-alone, networked and intra/internet delivery on Windows 3.1, '95, '98 or NT platforms.

License details
Full site for multi-users

Documentation
Tutor’s notes and software installation guidelines

This software program is divided into three sections (a) Introduction (b) Important factors which are responsible for variability in human drug metabolism and (c) Summary

Introduction
The stated aim of this program is to illustrate clinical relevance of drug metabolism. It mentions that this program is to be used in conjunction with other programs on drug metabolism: ‘Induction and Inhibition of Drug Metabolism’, ‘Pharmacogenetics’ and ‘Drug Metabolism’. However it does not include any reference to the topics of ‘Drug Absorption’ and ‘Drug Excretion’. These have equal relevance to drug metabolism as far as the bioavailability of a drug is concerned and hence the clinical consequences. It needs to be made clear that in the clinical context, drug metabolism is usually viewed together with absorption, distribution and excretion with cross references to packages (if available) which cover these topics.

This section also covers factors which have been shown to affect drug metabolism in experimental animals and the significance of these factors in man. These are covered under the headings of Species difference, Strain difference, Disease, Gender, Environmental factors (including drugs) & physiological conditions, Diet, Genetically determined enzyme activity and Age.

In some cases, specific examples of drugs used clinically are given. Where specific drug names e.g. phenylbutazone and isoniazid are given as examples, some text (with ‘hot’ links) is needed to explain the therapeutic class of drugs cited as examples. Similarly a ‘hot’ link (such as that which has been included for definition of Dibucaine number under genetically determined factors) is also needed with text defining ‘fast acetylators’ and ‘slow acetylators’ with an explanation of how this is seen in a clinical situation in different populations treated with isoniazid and the significance on effectiveness of isoniazid in treating TB.

Under the ‘Diet’ section a definition (with ‘hot link) is needed for pyrolysis products, vitamins and carbohydrates. In the ‘Age’ section a graphic representation of examples of chloramphenicol metabolism in neonates and commonly used benzodiazepine metabolism in the elderly would be useful. Clarification is also needed for the point that it is the ‘biological age’ (in terms of liver and kidney function) that has significance in drug metabolism rather than the ‘chronological age’ of an individual.

Important factors responsible for variability in drug metabolism in humans
This section is divided into three sections (a) Genetic polymorphism (b) Induction/Inhibition and (c) Disease.
(a) Genetic polymorphism This section is further subdivided into:

**Contribution of affected pathway to overall elimination of drug:** An example of a drug used clinically would be useful here. There is also a need to link the likelihood of toxic effects of a drug due to genetic polymorphism to the section on 'The therapeutic index of the drug'. Under examples of genetic polymorphism definitions (with 'hot' links) are needed for 'fast metabolisers', 'slow metabolisers', 'poor metabolisers', 'extensive metabolisers' and 'phenotypes'. Differences in definition of 'poor' and 'slow' metabolisers and 'fast' and 'extensive' metabolisers is not covered.

**The therapeutic index of the drug:** The concept is covered well by using graphs and animation using general terms 'Drug A' and 'Drug B'. A specific example of a drug used clinically would be useful.

(b) Induction/Inhibition

The title of section 'Induction/Inhibition' is confusing as drug metabolism is also 'slowed down' or 'speeded up' as a consequence of genetic polymorphism or disease. Perhaps a more appropriate title for this section would be 'Environmental Factors'.

This section covers environmental factors (drugs, alcohol, and diet) and leads on to explain how these factors affect drug metabolism via either 'Induction' of 'Inhibition' of cytochrome P450 enzymes in the liver.

**Induction:** this subsection is further subdivided into 'drugs' 'polycyclic aromatic hydrocarbons' and 'ethanol' (the term 'alcohol' is used under section on Inhibition).

The section on 'drugs' covers 'Induction of drug metabolism of another drug' and 'Autoinduction'. The section on 'drug metabolism of another drug' covers the principles of induction and gives the example of interaction between the cardiac glycoside, digitoxin, and carbamazepine. Digitoxin is little used now, so another example of induction of metabolism may be more appropriate. This section needs clarification in that when two interacting drugs are used together in a clinical situation, appropriate management usually consists of careful monitoring and adjustment of dosage. The section on 'autoinduction' covers general principles and cites carbamazepine and diazepam as examples.

The subsection on 'polycyclic aromatic hydrocarbons' (definition with 'hot' link needed) is further subdivided into 'barbecued foods' and 'cigarette smoke'. The effect of barbecued food (meat) on metabolism of the drug phenacetin and the effect of cigarette smoke on theophylline concentrations is covered very well with the appropriate explanations and 'hot' links.

The section on 'ethanol' covers 'acute exposure' and 'chronic exposure'. The section covers the concepts well with appropriate and creative use of graphics and animation.

**Inhibition:** this subsection is further subdivided into 'drugs', 'alcohol' and 'diet'. The section on 'drugs' covers 'competitive inhibition' and 'non-competitive inhibition'. The 'Competitive Inhibition' section includes the example of inhibition of terfenadine metabolism by ketoconazole. It may be worth adding that terfenadine was withdrawn from the market because of the possibility of toxic effects due to interaction with other commonly used drugs. The 'Non-competitive Inhibition' section includes the example of the interaction between cimetidine and diazepam. Perhaps a graphical representation would be useful here.
The section on ‘alcohol’ covers the effects of ‘acute’ and ‘chronic’ exposure on liver enzymes. The section on diet covers the effects of grapefruit juice on the bioavailability (measured as ‘area under the curve’) of the calcium channel blocker, felodipine. However there is no mention of the possible reasons for increased bioavailability of felodipine - these being the flavenoid (naringin) or sesquiterpenoid components of fruit juice which can inhibit the activity of cytochrome P450 isoform CYP3A4 in the liver.

(c) Disease
This section is subdivided into ‘liver disease’, ‘infections’ and ‘hormonal disorders’

The section on liver disease covers the effects cirrhosis and ‘alcoholic’ liver well with appropriate use of ‘hot’ links and animation. The section on infections demonstrates the effect of infection with malaria. The section on hormonal disorders covers the involvement of the hormones from the pituitary gland, the pancreas and the thyroid gland. The section on thyroid disorders is represented very well.

Summary
In the summary of the program it would be helpful to give some indication of the frequency with which the different factors affecting drug metabolism are implicated in consequences of clinical significance. Inclusion of a short discussion of clinical consequences of interference with normal drug metabolism profile e.g. necessity of adjusting dosage, avoidance of environmental factors such as grapefruit juice would also be helpful.

The program provides a basic introduction to factors which can affect drug metabolism in man. The potential of the electronic medium has not been fully exploited therefore the program does not offer the fullest advantage over reading a textbook. The multiple-choice questions could be more challenging. A little more thought needs to be given to the ‘learning activity’ aspect of the content. However the program's appeal could be vastly improved with addition of appropriate definitions with ‘hot’ links to the earlier part of the program along the lines of the section on Induction under subsection ‘polycyclic aromatic hydrocarbons’. The program would then better serve to provide a multidimensional perspective to the topic of clinical aspects of drug metabolism.

(****Maximum)
Ease of installation  *****
Ease of use  *****
Quality of interface/navigation  ****
Quality of content/visual appearance  ****
Clarity of learning objectives  ****
Accuracy of content  *****
Value to teacher  ****

Anjana Patel
Independent Pharmaceutical Consultant, Harrow, Middlesex, UK

N.B. Please note that this program is now undergoing extensive rewrite for both content and technical upgrading.