Factors affecting drug metabolism: internal factors

4.1 Introduction

Many factors affect the rate and pathway of metabolism of drugs, and the major influences can be sub-divided into internal (physiological and pathological) and external (exogenous) factors as indicated below:

Internal: species, genetic (strain), sex, age, hormones, pregnancy, disease.
External: diet, environment.

The internal factors will be discussed in this chapter, and diet and environment in the following chapter. Each of these factors will be examined in turn and their influences on drug metabolism highlighted by the use of examples. It should be remembered that this is not an exhaustive list and that examples of other factors affecting drug metabolism can be found in the literature. It can also be seen that certain categories overlap, such that species, strain, genetic and sex differences in drug metabolism have some common features as do hormonal influences on drug metabolism and sex differences; wherever this occurs the reader will be referred to the other section of possible interest. We begin with a look at the way in which the make-up of the animal in question affects the way in which it metabolizes drugs:
4.2 Species differences

Studies on the various differences in drug metabolism abound in the literature and are variously treated from the point of view of evolutionary development to the effects of these metabolic differences on the toxicity of the compound.

Species differences occur in both phase I and phase II metabolism and can be either quantitative (same metabolic route but differing rates) or qualitative (differing metabolic routes). A few examples of each of these cases are given in Table 4.1.

Table 4.1 The species variation in hexobarbitone metabolism, half-life and sleeping time

<table>
<thead>
<tr>
<th></th>
<th>Sleeping time (mins)</th>
<th>Hexobarbitone half-life (mins)</th>
<th>Hexobarbitone metabolism (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>12 ± 8(^{\dagger})</td>
<td>19 ± 7</td>
<td>16.6</td>
</tr>
<tr>
<td>Rats</td>
<td>90 ± 15</td>
<td>140 ± 54</td>
<td>3.7</td>
</tr>
<tr>
<td>Dog</td>
<td>315 ± 105</td>
<td>260 ± 20</td>
<td>1</td>
</tr>
<tr>
<td>Man</td>
<td>~ 360</td>
<td>~</td>
<td>~</td>
</tr>
</tbody>
</table>

\(^{\dagger}\)mean ± (standard deviation)

(Data from Quinn, G. P. et al. (1958) Biochem. Pharmacol., 1, 152–9. Reprinted with permission of Pergamon Press.)

In this example (Table 4.1) the oxidative metabolism of hexobarbitone is shown to vary widely between species and to be inversely related to the half-life and duration of action of the drug. It should be noted that there is not always a direct relationship between metabolism, half-life and action of a drug. These problems are more extensively discussed in Chapter 7. In this case however, this would seem to indicate that Man metabolizes hexobarbitone at a slower rate than the dog, and that the rate of elimination of the drug from the body is dependent on metabolism of the drug.

Phenol is metabolized by conjugation to glucuronic acid and/or sulfate, and the relative proportion of each metabolite depends on the species studied (Table 4.2).

As can be seen from Figure 4.1, oxyphenbutazone is rapidly metabolized in the dog \((t_{1/2} \sim 30\text{ mins})\) whilst in Man the rate of metabolism is rather slow \((t_{1/2} \sim 3\text{ days})\). This is an extreme example but clearly indicates the possible range of species differences.

The 7-hydroxylation of coumarin is catalysed by human, guinea pig, cat and rabbit liver but not in rat or mouse liver.

The anticoagulant, ethyl biscoumacetate, is rapidly metabolized by rabbit and Man but the resultant metabolites are different (Figure 4.2): the