Chapter 18
The Side-Effects of Calcium Antagonist Therapy. Is Amlodipine Different?

“The greater the ignorance, the greater the dogmatism.”
Sir William Osler, Medical Journal of Montreal, 1902

In a utopian world cardiovascular disorders would not exist, and even if they were to appear then the pharmacological agents developed for their control would undoubtedly lack any appreciable side-effects. Unfortunately, and despite its obvious attraction, even the concept or a utopian world is pure fantasy, as is the likelihood of effective therapeutic agents being developed which lack any side-effects. In reality physicians have had to cope with the side-effects of therapeutically useful agents for centuries. Take digitalis for example – its side-effects of nausea, vomiting and diarrhoea were described when the drug was first introduced over two hundred years ago, but its use persists. On a more recent note, the cough caused by the ACE inhibitors is now recognized as being an unwanted and troublesome side-effect of this particular form of therapy [due, probably to raised plasma levels of thromboxane A$_2$, which is a potent bronchoconstrictor (Naomi et al., 1992)], as is the bronchospastic effect of the beta-adrenoceptor antagonists – but, again, these drugs are widely used. In some cases, however, the side-effects – such as skin irritations, lethargy, headache and insomnia – that some therapeutic agents cause are so severe as to be intolerable and result in discontinuation of the planned therapy. Clearly, therefore, the phenomenon of side-effects cannot be ignored and accordingly needs to be considered with respect to the calcium antagonists. As far as this monograph is concerned, the following questions need to be answered:

(I) do the calcium antagonists exhibit unwanted side-effects; and
(II) does the side-effect profile differ according to which particular calcium antagonist is being used? In particular does amlodipine differ in this respect from other vascular selective calcium antagonists?

What Constitutes a Side-Effect?

Before comparing the side-effects of the currently available calcium antagonists, including amlodipine, it may be useful to define precisely what this term denotes. For the present purposes a “side-effect” can be described as a “response which does not form part of the desired response.” The cough-relat-
Table 18.1. Comparison of the effect of hydrochlorothiazide (HCTZ) and amlodipine therapy on plasma cholesterol and triglycerides

<table>
<thead>
<tr>
<th>Lipid parameter</th>
<th>Placebo</th>
<th>HCTZ</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>−2.4</td>
<td>+4.4</td>
<td>−2.2</td>
</tr>
<tr>
<td>Total triglycerides</td>
<td>−1.9</td>
<td>+6.7</td>
<td>−1.9</td>
</tr>
</tbody>
</table>

Results are expressed as percentage change relative to the mean base-line values. + denotes an increase, and − a decrease.
(Adapted from Osterloh, 1989).

ed side-effect of the ACE inhibitors, for example, can hardly be thought of as contributing to the desired blood pressure lowering effect of these drugs. Similarly, the insomnia induced by some of the beta-adrenoceptor antagonists cannot be considered as contributing to their targeted response of lowering blood pressure, relieving angina pectoris or reducing the incidence of mortality following myocardial infarction. Sometimes the side-effects even involve an altered blood plasma biochemical profile – as illustrated by the altered plasma lipid levels which develop during hydrochlorothiazide (HCTZ) therapy (Table 18.1), and the raised plasma noradrenaline levels caused by some calcium antagonists (see Table 18.5, for examples).

In general, it is probably acceptable to describe the side-effects of therapeutically useful agents as responses, which are:

(I) usually unwanted;
(II) do not contribute to the targeted response; and
(III) are dose-dependent.

The Side-Effects of the First Generation Calcium Antagonists (Verapamil, Nifedipine and Diltiazem)

The major side-effects of these drugs are listed in Table 18.2. Two facts emerge from this data:

(I) the side-effects differ from drug to drug. For example, constipation is a major side-effect of verapamil therapy but does not occur with nifedipine; and
(II) ankle oedema occurs in each case and therefore may be regarded as a “class” side-effect, although it is milder in some instances than others (see following section on nifedipine).

Many of the side-effects listed in Table 18.2 – flushing, headache and ankle oedema – are obviously related to the peripheral vasodilator activity of these drugs. The ankle oedema is of particular interest because it is a local phe-