Chapter 7
The Pharmacokinetic Properties of Amlodipine

“In the discovery of secrets and in the investigation of the hidden causes of things, clear proofs are afforded by trustworthy experiments rather than by probable guesses or opinions.”

WILLIAM GILBERT, 1544–1603

Earlier in this monograph mention was made of the fact that the relatively short duration of action of the first generation calcium antagonists was one of the major factors limiting their clinical use, because even with repetitive dosing, large differences between peak and trough plasma levels are encountered (Figure 7.1). Such a difference is undesirable since it makes it unlikely that a stable effect can be achieved over the whole of the dosage interval. In addition, there is another problem that was encountered during the use of the first generation antagonists. This relates to the fact that their rate of metabolism and hence their bioavailability can be affected by the time of day. Take verapamil, for example. Its half-life during the night (midnight until six o’clock in the morning) is significantly longer than during the daylight hours, as is the peak plasma level that is achieved (Jespersen et al., 1989). It was precisely because of these inherent weaknesses that the various slow and sustained release formulations of the prototype drugs (verapamil S.R., diltiazem S.R., felodipine ER and nifedipine GITS and Retard) have been developed.

Fig. 7.1. Comparison of the plasma drug concentration profiles for amlodipine (5 mg daily) (—) and nifedipine (20 mg Retard, twice daily) (---). Note the relatively steady plasma levels obtained for amlodipine, relative to the peak and trough situation which develops for nifedipine. Adapted from Elliott and Meredith, 1991
It is also why the pharmacokinetic profile of amlodipine is of such interest, because with this particular calcium antagonist it is the inherent physicochemical characteristics of the drug which dictates its:

(I) long duration action;
(II) its slow onset and offset of action (Burges, 1991);
(III) its high bioavailability; and
(IV) its slow rate of clearance.

In turn, it is precisely because of these special properties that amlodipine can be used on a once-a-day basis for the treatment of hypertension, angina and other cardiovascular disorders without inducing side-effects due to changing plasma levels or a rapidly developing vasodilator response, and without marked peak and trough variations in plasma levels and hence in efficacy. On the other hand, it does mean that when amlodipine is being used therapeutically, sufficient time must be allowed for the peak response to develop – and this may take days – or even weeks. For example, when Caponnetto and his colleagues (Caponnetto et al., 1991) were investigating the antianginal efficacy of amlodipine, several days were required to reach a nadir with respect to the effectiveness of a particular dose of this antagonist. The same picture emerged when investigators started using amlodipine for the treatment of hypertensives (Chapter 14), in that the drop in blood pressure took some days to develop, and sometimes even weeks to stabilize (Kaplan, 1991).

The clinical significance of the slow onset of the effect of amlodipine is a theme which occurs frequently in the latter chapters of this book, as is its long duration of action and high bioavailability. The present chapter is aimed only at explaining why amlodipine behaves in this way. After all – it is still a dihydropyridine, and yet it is becoming increasingly apparent that its pharmacodynamic and pharmacokinetic properties are quite different from those of the prototype – nifedipine, and many of the other derivatives – including, for example, nitrendipine, and felodipine. Such a task necessarily requires describing amlodipine’s pharmacokinetic profile. Of course, to some extent the slow rate of onset and offset of action of amlodipine can be explained in terms of its slow rate of association with, and dissociation from the binding sites in the Ca^{2+} channel complex described in the last chapter (Chapter 6). This is only part of the explanation, however. Other factors which are involved include:

(I) a slow rate of absorption due to its prolonged hepatic transfer time (Walker et al., 1992);
(II) a relatively slow rate of hepatic metabolism, resulting in an unusually long elimination half-life;
(III) a wide volume of distribution, indicative of widespread tissue binding resulting in an in situ reservoir of the drug; and
(IV) a high bioavailability.