Zopiclone: A Third Generation of Hypnotics

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Many years ago now the benzodiazepines began to replace the barbiturates, but, when we think about this change and remember that the barbiturates were probably being used in unnecessarily high doses, the therapeutic advantage of the benzodiazepines may not have been so great as it appeared at the time. The major advance was that of increased safety in overdosage. Initially, the benzodiazepines were used in relatively high doses, and so they may not have provided the most favourable balance possible between efficacy on one hand and adverse effects on the other. It has only been over the past few years that the advantage of lower doses of hypnotics has been widely appreciated, and this has been accompanied by the development of drugs with rapid rates of elimination.

It is the rapidly eliminated hypnotics which we may now call the 'Third Generation'; within this group there are several drugs, and their mean elimination half-lives differ. The different half-lives may well have discrete clinical indications. They include the triazolobenzodiazepines and the imidazobenzodiazepines and a new chemical group – the cyclo-pyrrolones – of which zopiclone (Imovane®), the subject of this symposium, is an example. Their advantage is that daily ingestion will not lead to accumulation. However, though a rapidly eliminated drug is unlikely to accumulate with appropriate daily dosage, it does not necessarily mean that its duration of action is short enough to avoid a residual effect. Many pharmacokinetic factors determine persistence of activity of an hypnotic, and these include the distribution phase which influences markedly the initial fall in plasma level.

Nowadays, an hypnotic which has a favourable balance between efficacy on one hand and persistence of activity on the other, and which is without adverse effects on sleep either during administration or on withdrawal, is sought. In this context many of the currently available benzodiazepines when used appropriately have proved themselves in clinical practice, but there are certain aspects of their activity which have recently become

2

Nicholson

of some concern. An hypnotic with a metabolic pathway free of any serious interaction with alcohol and other drugs – in the same way that the metabolic pathway of lorazepam appears to be free of interaction with cimetidine – would be an advantage, and it would also be useful if dependency, which may or may not be a problem with the benzodiazepines, could be avoided. However, the question also arises whether a drug with a new chemical structure retains the advantages of established hypnotics.