Clinical Pharmacokinetics of β-Adrenoceptor Antagonists
An Update

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Summary

The β-adrenoceptor antagonists have been widely used clinically for over 20 years and their pharmacokinetics have been more thoroughly investigated than any other group of drugs. Their various lipid solubilities are associated with differences in absorption, distribution and excretion. All are adequately absorbed, and some like atenolol, sotalol and nadolol which are poorly lipid-soluble are excreted unchanged in the urine, accumulating in renal failure but cleared normally in liver disease. The more lipid-soluble drugs are
subject to variable metabolism in the liver, which may be influenced by age, phenotype, environment, disease and other drugs, leading to more variable plasma concentrations. Their clearance is reduced in liver disease but is generally unchanged in renal dysfunction.

All the \( \beta \)-adrenoceptor antagonists reduce cardiac output and this may reduce hepatic clearance of highly extracted drugs. In addition, the metabolised drugs compete with other drugs for enzymatic biotransformation and the potential for interaction is great, but because of the high therapeutic index of \( \beta \)-adrenoceptor antagonists, any unexpected clinical effects are more likely to be due to changes in the kinetics of the other drug.

Because satisfactory plasma concentration effect relationships have been difficult to establish for most clinical indications, and little dose-related toxicity is seen, plasma \( \beta \)-adrenoceptor antagonist concentration measurement is usually unnecessary.

The investigation of the clinical pharmacokinetics of the \( \beta \)-adrenoceptor antagonists has added greatly to our theoretical and practical knowledge of pharmacokinetics and made some contribution to their better clinical use.

Since their introduction to clinical practice 20 years ago, the \( \beta \)-adrenoceptor antagonists have become established for the treatment of angina, hypertension, cardiac arrhythmias, anxiety, thyrotoxicosis, migraine and glaucoma (McDevitt 1979). It is 10 years since the clinical pharmacokinetics of these drugs were reviewed in this journal (Johnson & Regardh 1976). In the intervening period several new drugs have been introduced or are at an advanced stage of development, and many studies made of their pharmacokinetics.

Along with the new data there have been conceptual changes, including a greater awareness of the principles of pharmacokinetics in clinical practice, and of their limitations. Developments include sustained release preparations; improved assay methods; and a greater knowledge of protein binding to \( \alpha \)-acid glycoprotein, stereoselective metabolism and oxidative genetic polymorphism.

This review summarises the current knowledge of the clinical pharmacokinetics of the commonly used \( \beta \)-adrenoceptor antagonists with the emphasis on their clinical relevance (discussed in section 5). Because of the enormous literature on the subject the references quoted are necessarily selected to be comprehensive rather than exhaustive.

1. **Physicochemistry**

All the familiar \( \beta \)-adrenoceptor antagonists, and many that are currently in development, are weak bases (table I), and are slightly soluble in water (Johnsson & Regardh 1976). With pKa values of approximately 9.5 they exist predominantly in the ionised form in the acid of the stomach and the slightly alkaline contents of the small intestine (Johnsson and Regardh 1976). All have at least 1 asymmetric carbon atom in the side chain and, except for timolol and penbutolol, which are the S enantiomers, are used clinically as a racemic mixture.

With the exception of metabolism, the pharmacokinetic behaviour of drugs depends more on their lipophilic and electronic properties than on their steric characteristics (Hinderling et al. 1984). The great variability in the lipophilicity of \( \beta \)-adrenoceptor antagonists (table I) accounts for some of the differences in their absorption, distribution and excretion.

2. **Basic Pharmacokinetics**

2.1 **Absorption**

The major determinants of the absorption of a drug are either properties of the drug administered (formulation, lipid solubility, pKa, molecular size) or of the subject (gastric and intestinal motility, absorptive area of the small intestine) [Parsons 1977; Prescott 1977]. All \( \beta \)-adrenoceptor antagonists (table I) are fairly rapidly absorbed from the gastrointestinal tract, with a time to maximum