Clinical Pharmacokinetics of Prazosin – 1985

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Summary

Prazosin is a selective α₁-adrenoceptor antagonist which is useful alone or in combination for the treatment of hypertension and heart failure. Unlike many other antihypertensive drugs, the action of prazosin appears to be closely related to its concentration in plasma or whole blood. Prazosin is variably absorbed, is subject to first-pass metabolism, and is eliminated almost entirely as metabolites of much lower hypotensive activity than the parent drug. Prazosin is highly bound to plasma and tissue proteins.

The influences of renal, hepatic and cardiac disease on the disposition of prazosin are reviewed, as are the effects of pregnancy and ageing. The optimum use of prazosin in clinical practice depends on an understanding of the pharmacokinetic properties of the drug.

Prazosin (fig. 1) is a quinazoline derivative used widely in the treatment of hypertension and congestive cardiac failure. It is now recognised to be a selective specific competitive antagonist of α₁-adrenoceptors; antagonism of post-junctional α₁-receptors on vascular smooth muscle of arterioles and veins appears to be the basis of the cardiovascular actions of this drug in clinical practice. Prazosin does not possess significant effects on β-receptors or α₂-receptors, and although it has direct vasodilator activity at high concentrations, this is unlikely to contribute to its therapeutic action.

Prazosin is largely free of toxic or major symptomatic side effects, with the exception of postural hypotension and syncpe after first doses or large dose increments. Unlike several other antihypertensive drugs such as the thiazide diuretics and reserpine, there appears to be a close relationship between plasma concentrations of prazosin and the pharmacological effect, at least after the first doses. In addition, the antihypertensive dose-response relationship is steeper than that observed with thiazide diuretics or β-blockers. Thus, changes in the disposition of prazosin, which is subject to first-pass metabolism, are likely to be of relevance in clinical practice and an understanding of the clinical pharmacokinetics of prazosin is an important guide to optimising therapy.

The pharmacokinetic properties of prazosin in humans and the possible relationship between plasma concentrations and pharmacodynamic effects have been the subject of a considerable number of studies, the validity of which has been dependent upon the development of reproducible, sensitive and specific drug assays (Dynon et al., 1980; Twomey and Hobbs, 1978; Yee et al., 1979). However, the relatively restricted availability of an intravenous formulation of prazosin has limited the
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interpretation and analysis of many of the published pharmacokinetic studies.

1. Fundamental Pharmacokinetic Properties

1.1 Absorption and Bioavailability

Orally administered prazosin is rapidly absorbed from the gastrointestinal tract, but there is marked variation between individuals in the peak plasma or whole blood drug concentrations attained and in the time to reach peak concentrations. This variability in absorption is dependent on the formulation of the drug administered. Systemic availability after oral dosing is influenced by the degree of first-pass metabolism and the patient's age. Although there may be some differences in the rate of absorption of different pharmaceutical formulations of prazosin (tablet, capsule or solution), the extent of absorption, as reflected by the area under the plasma concentration-time curve (AUC), appears to be similar for all formulations studied (Hobbs et al., 1978, Jaillon, 1980). The rate and extent of absorption is not significantly influenced by the presence of food (Verbesselt et al., 1976) as the AUCs in the fasting state, after breakfast and after lunch were found to be identical.

Time to peak concentrations following administration of the oral tablet or capsule formulation occurred between 1 and 3 hours (Hobbs et al., 1978). These authors reported peak concentrations of 35.9 ± 17.3 ng/ml in 24 patients taking 5mg capsules, while Wood et al. (1976) reported peaks of 23 ± 10.3 ng/ml in 10 patients taking 5mg tablets. Following administration of 2mg tablets, Verbesselt et al. (1976) reported peaks of 23.01 ± 10.5 ng/ml, while Bateman et al. (1979) reported peaks of 5.6 ± 13.3 ng/ml using 1mg tablets in 6 subjects. In other studies, Hobbs et al. (1978) observed a peak concentration of 58.2 ± 16.8 ng/ml using a 5mg water-alcohol solution in 21 subjects, while Baughman et al. (1979) observed a peak concentration of 50.9 ± 24.7 ng/ml in 5 subjects taking a 5mg capsule of prazosin.

The absolute bioavailability of prazosin in humans ranges from 43.5% to 69.3%, with a mean of 56.9% in normal subjects (Bateman et al., 1979) [table I] and 63% in hypertensive patients (Grahnen et al., 1981) [table II]. In elderly subjects, Rubin et al. (1981) observed a significant reduction in bioavailability (48% vs 68% in younger subjects). Grahnen et al. (1981) found that prazosin exhibits first-order kinetics with a linear relationship between daily dose and steady-state plasma concentrations in hypertensives while Silke et al. (1981) made a similar observation in patients with congestive heart failure.

Bateman et al. (1979) determined the hepatic extraction of prazosin in humans as 27% following intravenous administration; however, the observed bioavailability was 56.9% compared with the theoretical value of 73% predicted from the extraction ratio. Rubin et al. (1979) made similar observations in the dog where they noted that with an hepatic extraction of 47% the absolute bioavailability was 38%. To account for these differences a number of factors have been suggested and these include poor absorption, metabolism by microorganisms in the gut, or enzymatic metabolism in the gut wall itself (Jaillon, 1980).

1.2 Distribution

The limited availability of intravenous prazosin has hampered study of the volume of distribution. However, the published data are in good agreement. Rubin et al. (1981) calculated a mean value of 0.63 L/kg in normotensive subjects, while in hypertensives, mean values of 0.57 ± 0.09 L/kg (Grahnen et al., 1981), 0.51 ± 0.06 L/kg (Chau et al., 1980), and 0.54 ± 0.06 L/kg (Flouvat et al., 1978) have been reported.