Clinical Pharmacology of Alpha-1 Blockers
Improving Drug-profile through Novel Formulations

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Introduction

The clinical management of chronic diseases, including hypertension, involves sustained control of risk-factors over a prolonged duration. In such conditions, pharmacotherapy plays an essential role, towards ensuring long-term clinical protection. Certain perspectives of drug therapy may have critical influence on patient outcomes. For example, the mode of administration of a drug may have a direct impact on the efficacy, tolerability, and medication compliance. However, some of these perspectives may not be appropriately or adequately recognised.

Prazosin is one such molecule, which has been extensively used in the management of hypertension, for nearly 4 decades. Owing to α-1 selective adrenergic receptor blockade, prazosin and its congeners are associated with favourable metabolic profile and minimal adverse effects. The α-1 blockers, including prazosin, terazosin and doxazosin, differ mainly in terms of their elimination half-lives, with that of prazosin being the shortest. However, the older formulations of these drugs were associated with quite a few clinical challenges, owing to their pharmacokinetic characteristics.

Challenges with Earlier Formulations of Prazosin and Congeners

An important limitation of the earlier standard formulation of prazosin was a short half life, resulting in a very short duration of action.¹⁻³ This necessitated twice- or thrice-a-day dosing, to maintain effective control. Need for repetitive dosing affects the patient’s medication compliance, which may result in inconsistent blood pressure control. Also, repetitive dosing, by itself, leads to fluctuating plasma concentrations of the drug at steady state. Plasma level fluctuations at steady state, may further lead to inconsistent blood pressure control.

The initial formulations of α blockers, including prazosin, doxazosin and terazosin, were associated with first-order kinetics. This is characterised by a rapid absorption of the drug, resulting in attainment of peak concentrations in the plasma. Rapid exposure to higher drug concentrations, may explain the possibility of first-dose effect, observed commonly with this formulation. First-dose effect is an important determinant of the tolerability of α-blockers. The risk of hypotension and syncope were serious concerns, apart from other symptomatic adverse effects, which necessitated multiple-step dose titration of the drugs.²⁻³

Following rapid absorption, a constant decline is observed in the plasma levels, owing to drug metabolism. Around the end of dosing interval, a trough concentration is reached, which may be low enough to result in a possible loss of efficacy. Possible loss of efficacy, during the dosing interval, is of critical significance in the management of hypertension. This is because a smoother control of blood pressure results in better clinical outcomes. A high peak-trough ratio observed with the conventional formulations, reflect the fluctuations of plasma concentrations during the dosing interval. Such fluctuations may lead to inconsistent control of blood pressure, and dose-related adverse effects.

Controlled Release Formulations

The controlled release formulations,
like sustained release formulations and osmotically controlled drug delivery systems, including the gastro-intestinal therapeutic system (GITS) or osmotic release oral system (OROS), have been instrumental in improving the clinical profile of α-1 blockers. The GITS formulations of prazosin or doxazosin have been such successful attempts, addressing some of the pharmacokinetic challenges, encountered with the initial formulations.3-6 The mechanism of action of the GITS formulations, and the clinical pharmacokinetics are described, considering the case of prazosin GITS.

### Prazosin GITS formulation

GITS formulation involves a unique push-pull mechanism that ensures drug delivery at a constant rate (Figure 1). A prazosin GITS tablet is a 2-compartment tablet, covered with a rigid, non-expandable, non-biodegradable, semi-permeable membrane. The semi-permeable membrane allows water, but not any of the tablet’s core components, to pass through. One compartment contains the drug - prazosin, while the other contains an osmotic polymer. The 2 compartments are separated by a flexible, impermeable diaphragm. A fine hole (0.1-0.4 mm) is drilled into the drug compartment by means of a laser beam.2 When such a tablet is swallowed, fluid from the gastro-intestinal tract enters both these compartments through the semi-permeable membrane. In the drug compartment, this helps form a suspension of prazosin. At the same time, the osmotic substance in the other compartment absorbs water, expands, and pushes the diaphragm towards the drug compartment. As a result, prazosin is gradually delivered into the GI tract through the laser-drilled orifice.2,3 The drug’s release rate can be controlled by varying the amount of drug in the tablet, and membrane thickness. Stenosis of the gastrointestinal tract or chronic diarrhoea may influence the therapeutic effect.

### Pharmacokinetics of Prazosin GITS Formulation

In a study on 24 healthy volunteers, the bioavailability of prazosin GITS was observed to be 60% relative to the older prazosin formulations.2 In individuals receiving prazosin GITS formulation, the drug was detectable in the plasma well beyond 24 hours. Importantly, absorption was slow, without an observable peak; the peak-trough ratio was minimal, indicating minimal fluctuations in plasma concentrations during the dosing interval.

In a study on healthy volunteers, prazosin GITS formulations were compared to the traditional formulations (immediate release or sustained release).8 With the traditional formulations, peak levels of plasma concentrations were observed within 4 hours of administration; with the GITS formulations, no peak levels were observed, and plasma concentrations were detectable only after 3-4 hours (lag time during first dose). The plasma concentrations remained virtually constant for nearly 24 hours post-dosing, with the GITS formulations. On evaluation in mild hypertension as a monotherapy or in moderate hypertension in combination, an excellent tolerability profile was observed with the GITS formulations, whereas first-dose hypotension was observed on several occasions with the traditional formulations.3 With the GITS formulation, bioavailability is not influenced by morning versus evening administration or by concurrent food ingestion; there have been no observations of dose-dumping, either in the presence or absence of food.9

With the GITS formulation, minimal fluctuation in plasma concentration at steady state ensures smoother
control of blood pressure throughout dosing interval, and minimises adverse effects.

These properties are indicative of a possible benefit in terms of reduction in first-dose hypotension and syncope, and smoother control of blood pressure throughout the dosing interval of 24 hours. Slower rate of drug release reasonably leads to gradual blockade of α1-receptors, allowing better adaptation of circulatory system to the haemodynamic alterations. Apart from this, a smooth control of blood pressure may ensure reduction in blood pressure variability, a significant determinant of clinical outcomes in terms of stroke, cardiac, vascular and renal morbidity and mortality. Therefore, a smooth control of blood pressure may ensure reduction in blood pressure variability, a significant determinant of clinical outcomes in terms of stroke, cardiac, vascular and renal morbidity and mortality.7,12

**Tolerability and efficacy of GITS formulations**

In a pivotal clinical trial on 205 patients, to evaluate the tolerability and efficacy of prazosin GITS, increasing doses of prazosin GITS (2.5 mg, 10 mg, 20 mg) were associated with greater reductions in systolic and diastolic blood pressure. Both the 10 mg and 20 mg doses resulted in statistically significant reductions in systolic as well as diastolic blood pressure, compared to placebo. Significant proportion of patients was able to achieve the target blood pressure level at these doses of prazosin GITS. Study results indicated good 24-hour control of blood pressure with once-a-day dose of prazosin GITS, throughout the study period of 4 weeks. Out of a total of 220 patients included for safety analysis (166 receiving prazosin GITS and 54 receiving placebo), there was no significant difference in the incidence of adverse events, between the prazosin GITS and placebo groups. Most of the reported adverse events were of mild to moderate severity. Similarly, in patients maintained on background diuretic therapy, similar trends of antihypertensive efficacy and tolerability were observed with prazosin GITS.3

Substantial evidence has also emerged from the post-marketing studies of prazosin GITS. In an open-label study in 13,381 hypertensive patients (with baseline diastolic blood pressure of 96-114 mmHg), treatment with prazosin GITS was observed over a 12-week period. Prazosin GITS was initiated at a dose of 2.5 mg, which was increased if the patient’s diastolic BP remained above 90 mmHg. Average dose used in the study was 4.5 mg/day. Significant reductions were observed following prazosin GITS administration, in both systolic and diastolic blood pressure levels, with 88% of the patients achieving target levels at week 12. 94% of patients responded to prazosin GITS, with a fall of diastolic blood pressure levels of at least 10 mmHg over a 12 week period. Fall in blood pressure was gradual and sustained.5

In this large scale analysis, prazosin GITS formulation was well tolerated by 89% of patients. In 8% of patients, the undesirable effects were attributable to prazosin. Importantly, hypotension was observed in only 0.7% of patients; syncope was not observed in any patient following first dose of prazosin GITS.5 With the older formulations of prazosin capsule, the observed incidence of postural hypotension was 1-4%, and of syncope was nearly 1%. In view of these observations, the GITS formulation of prazosin has demonstrated a significantly improved tolerability profile. With the GITS formulation, the most commonly observed undesirable effects included vertigo (3%) followed by dizziness, headache, asthenia, oedema and nausea in about 1-2% of the patients. The older formulation (prazosin capsule) was associated with a higher incidence of adverse events, including dizziness (10.3%), headache (7.8%), drowsiness (7.6%), lack of energy (6.9%), weakness (6.5%), palpitations (5.3%), and nausea (4.9%). The GITS formulation was well tolerated by individuals in all the age-groups. Importantly, a distinct advantage possible with the GITS formulation is the absence of dose-dependent increase in risk of these side effects, which is not the case with the standard formulation. The dose of GITS formulation could be altered without influencing the risk of side effects.5

The study also demonstrated favourable metabolic profile of prazosin in the GITS formulation. This was apparent in terms of significant reductions in total cholesterol, triglycerides and blood glucose. There was a modest but significant increase in the HDL cholesterol levels. Besides this, prazosin GITS therapy resulted in normalisation of these parameters, and in the serum potassium or creatinine levels, in a significant number of patients with baseline abnormalities. Thus, the formulation appeared to have a beneficial impact on the overall cardiovascular risk, beyond blood pressure control.

Overall, from the clinical pharmacology perspective, the GITS formulation of prazosin represents significant advancements over the standard formulations, in terms of improving the tolerability profile, maintaining smoother control of blood pressure, offering better prospects of patient compliance owing to once-a-day dosing, while preserving the pleiotropic metabolic benefits of the drug.

A study evaluated the efficacy, safety and tolerability of doxazosin GITS formulation compared to the standard formulation. According to the observations, equivalent blood pressure control was observed with the GITS and standard formulations, with no overall difference in efficacy or safety. With the GITS formulation, effective control was achieved without any dose-titration, unlike the standard formulation. Another study compared the efficacy and safety of doxazosin GITS relative to standard doxazosin, in patients with mild to moderate hypertension. In this study, blood pressure reductions were comparable with equivalent doses (4 mg) of the two formulations. However, compared to standard formulations, the GITS formulation was associated with a significantly
greater reduction in night-time ambulatory blood pressure and mean blood pressure. Although the tolerability and adverse event profile was comparable between the groups, no dose titration was required with the GITS formulation, resulting in more rapid blood pressure control.\textsuperscript{7} This is a clearly recognised benefit of the GITS formulation.

Many small Indian studies have evaluated the tolerability, safety and efficacy profile of prazosin GITS in hypertension.\textsuperscript{14-17} A study evaluated the efficacy and tolerability of prazosin GITS compared to enalapril over 24 weeks of therapy.\textsuperscript{14} The mean fall in the systolic and diastolic blood pressure, throughout the study period (from baseline to all the study time points), was equivalent in the prazosin GITS and enalapril groups. Prazosin GITS was associated with consistent beneficial effect on some of the lipid parameters, whereas enalapril was associated with variable effect. Adverse events related to the drug, were observed in 4.5% of patients receiving prazosin GITS, compared to 15.4% of patients receiving enalapril.\textsuperscript{14} Beneficial effect on serum lipid parameters were also observed with prazosin GITS, when compared to atenolol.\textsuperscript{15}

Different α-blockers have demonstrated a protective effect in terms of decreased platelet activity and aggregation. Prazosin GITS has demonstrated significant inhibition of platelet aggregation at trough levels, an effect not observed with atenolol, nifedipine SR, and enalapril.\textsuperscript{16} In another study, doxazosin decreased platelet activity in patients of metabolic syndrome, whereas amlodipine did not demonstrate this effect.\textsuperscript{19} Increased platelet aggregation is an important phenomenon observed in essential hypertension, which may also cause vascular complications. Antiplatelet activity observed with α-blockers, has clinical relevance in the management of essential hypertension.

**Summary**

Clinical pharmacology is an essential consideration in chronic therapies, and may play a significant role in modifying the pharmacological characteristics of drug formulations. Improvement in drug formulations may ensure their safe and effective use over a period of time. This has been particularly observed with α-1 adrenergic blockers in hypertension management. Advancements in formulations like prazosin GITS, have resulted in improvement in tolerability profile and smoother, more effective blood pressure control, which reasonably translate into improvement in patient compliance and better clinical outcomes.

**References**

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