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Doxazosin Gastrointestinal Therapeutic System

A Review of its Use in Benign Prostatic Hyperplasia

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Data Selection

Sources: Medical literature published in any language since 1980 on doxazosin, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were 'doxazosin' and ('GITS' or 'gastrointestinal therapeutic system'). EMBASE search terms were 'doxazosin' and ('GITS' or 'gastrointestinal therapeutic system'). AdisBase search terms were 'doxazosin' and ('GITS' or 'gastrointestinal therapeutic system'). Searches were last updated 14 June 2005.

Selection: Studies in patients with benign prostatic hyperplasia who received doxazosin GITS. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Doxazosin GITS, benign prostatic hyperplasia, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Doxazosin, a well established treatment in patients with bothersome lower urinary tract symptoms from benign prostatic hyperplasia (BPH), is available in a new controlled-release formulation, doxazosin gastrointestinal therapeutic system (GITS).

Doxazosin GITS (Cardura® XL, Cardular® PP Uro, Diblocin® PP Uro) has an altered pharmacokinetic profile, which allows a higher initial dosage to be used than with the standard formulation and less titration steps to reach a clinically effective dosage. In two large, double-blind, randomised studies (one was placebo-controlled) in patients with BPH, doxazosin GITS (4–8mg once daily) was as effective as the standard formulation (2–8mg once daily), and both were more effective than placebo, after 13 weeks' treatment in improving symptom scores, health-related quality of life (HR-QOL), and maximum urinary flow rate (Qmax).

Doxazosin GITS was at least as well tolerated as the standard formulation of doxazosin in clinical studies in patients with BPH.

Pharmacological Properties

Doxazosin is a quinazoline derivative, which selectively inhibits α_1-adrenoceptors in the smooth muscle of the prostate and bladder neck, resulting in a decrease in resistance to urinary flow in patients with BPH. In the GITS formulation of doxazosin, water is 'pulled' into the tablet by osmotically active excipients in a nondrug layer, which expands and 'pushes' doxazosin suspension out through a laser-drilled orifice at a constant rate. Doxazosin GITS has a lower, and prolonged time to, peak doxazosin concentration than obtained with the standard formulation, and the peak-trough plasma doxazosin concentration ratio is reduced.

Therapeutic Efficacy

In two large, double-blind, randomised trials in patients with symptomatic BPH (n = 1475), doxazosin GITS 4–8 mg once daily was as effective as standard doxazosin 2–8 mg once daily, and both were more effective than placebo (in one study) at improving lower urinary tract symptoms and Qmax after 13 weeks' treatment.

Mean total International Prostate Symptom Score was reduced from baseline by 43–47% at the final visit with both formulations, whereas in placebo recipients there was a 34% reduction ($p < 0.001$). Similarly, Qmax improved by 22–26% from baseline with either doxazosin formulation, compared with a 9% improvement with placebo ($p < 0.001$). Although statistical equivalence for these outcomes was demonstrated (in a combined analysis) after 13 weeks, it appeared that doxazosin GITS exerted its effects earlier (after 3 weeks' treatment) than the standard formulation, probably reflecting the higher starting dosage.

Several secondary outcomes in these studies (the effect on HR-QOL, target efficacy response rates, sexual dysfunction, and investigator's overall assessment) supported the conclusion that doxazosin GITS and standard doxazosin have similar efficacy in patients with BPH.

Tolerability

Doxazosin GITS was generally well tolerated in two large, double-blind, randomised trials in patients with BPH (n = 1473). A lower incidence of all-cause adverse events and treatment discontinuations occurred with doxazosin GITS than with standard doxazosin, although the treatment-emergent rates were similar between both formulations and placebo.

The most common treatment-emergent adverse events were headache (5–6%) and dizziness (2–9%). An episode of syncope occurred in only 1 of 666 patients receiving doxazosin GITS. Other serious adverse events were an episode of slurred speech and unsteadiness in the doxazosin GITS group, and an episode of chest pain in a patient receiving standard doxazosin.

1. Introduction

Benign prostatic hyperplasia (BPH), characterised histologically by prostatic stromal and epithelial hyperplasia, is a frequent cause of bothersome lower urinary tract symptoms in men.[1] Lower urinary tract symptoms, such as urinary frequency, nocturia, reduced urinary flow and intermittency, and a sensation of incomplete bladder emptying, affect about 40% of men after the age of 60 years.[2] It is estimated that about 35% of men who reach the age of 50 years will require some form of treatment of BPH in their lifetime.[3]

In addition to prostatic enlargement, which may cause an anatomical bladder outlet obstruction, a dynamic component appears to exist, with sympathetic α_1-adrenoceptor stimulation increasing smooth muscle tone in the prostate and bladder neck.[1] Doxazosin, originally used to treat hypertension, is a well established, safe and effective α_1-adrenoceptor selective antagonist that is used in BPH once daily to improve clinical symptoms.[1,3,4]

Use of doxazosin, in its standard formulation, however, requires a multiple-step titration regimen in order to minimise the risk of a first-dose hypotensive effect.[3-5] A new formulation, doxazosin gastrointestinal therapeutic system (doxazosin GITS; Cardura® XL, Cardular® PP Uro, Diblocin® PP Uro)[1] has been developed to change the pharmacokinetic profile of doxazosin and more precisely control the drug delivery rate, allowing a higher and more clinically effective initial dose and a simplified titration regimen.[5,6] This article reviews the pharmacology and clinical profile of doxazosin GITS in patients with symptomatic BPH.

2. Pharmacodynamic Properties

The pharmacological properties of doxazosin have been reviewed previously in *Drugs*.[4] Briefly, it is a quinazoline derivative, which selectively inhibits α_1-adrenoceptors in the smooth muscle of the proximal urethra, bladder base and prostate.[4] Blockade of the α_1-adrenoceptors reduces smooth muscle tone in these structures and decreases resistance to urinary flow.[4]

Doxazosin is non-subtype-specific and may exert some additional beneficial effects on lower urinary tract symptoms via CNS pathways.[7] In contrast, tamsulosin, a non-quinazoline derivative and an inhibitor of the α_{1A}-adrenoceptor, may have its effect more in the prostate, where it is the major receptor subtype, than in the central nervous system.[7]

In addition to improving urinary flow in patients with BPH, doxazosin decreases total peripheral resistance and mean arterial pressure, and has a favourable effect on the serum lipid profile, in patients with mild-to-moderate hypertension.[4] Although the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)[8] did not specifically address the use of doxazosin in patients with concomitant BPH, or in combination with other antihypertensive drugs, findings from the study have

1 The use of trade names is for product identification purposes only and does not imply endorsement.

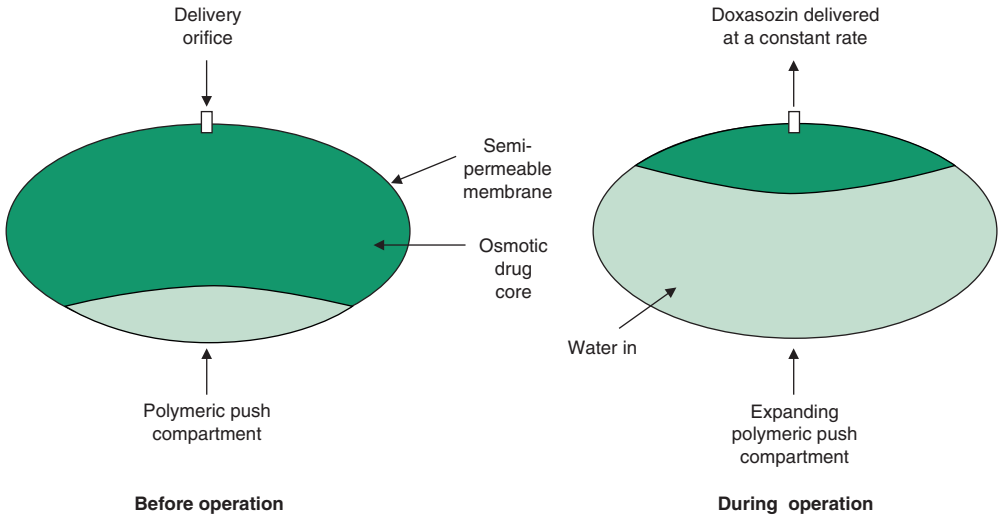

Fig. 1. Doxazosin gastrointestinal therapeutic system is a push-pull osmotically activated, controlled-release formulation. Water is absorbed at a constant rate as the tablet passes through the gastrointestinal tract. The polymeric 'push' compartment expands at a controlled rate, pushing against the drug layer so that the doxazosin suspension is released through the delivery orifice at a constant rate.

led to a reduction in use of this drug in hypertension.[9]

3. Pharmacokinetic Properties

The pharmacokinetic profile of standard doxazosin has been reviewed previously in *Drugs*.[4] This section summarises pharmacokinetic results for doxazosin GITS from two *in vitro* studies[10] (release-rate profile) and from four clinical pharmacology studies,[10] some of which used standard doxazosin as a comparator. Additionally, some pharmacokinetic parameters reported only for standard doxazosin are included.[4,6]

3.1 Absorption and Distribution

Doxazosin GITS uses 'push-pull' osmotically activated technology (figure 1).[5] A polymeric 'push' compartment is juxtaposed to an osmotic doxazosin core, surrounded by a semi-permeable cellulose membrane, with a laser-drilled delivery orifice on the drug side. In the gastrointestinal tract, water is drawn in at a constant rate and expands the 'push' layer, causing the doxazosin suspension to be released at the same rate (for 12–16 hours) as water enters the system. The tablet is eliminated intact in the faeces.

Doxazosin GITS produced similar release rates *in vitro* in conditions designed to mimic the variable pH and motility conditions in the gastrointestinal tract.[10] Similar release rates occurred at pHs of 1.2 (artificial gastric fluid) and 7.5 (artificial intestinal fluid) and were independent of the stirring rate.

Doxazosin GITS is less rapidly absorbed and has a lower peak plasma concentration (C_{max}) than the standard formulation in steady-state conditions (table I); trough plasma concentrations are similar between the two formulations.[10] In a randomised, crossover study in 31 healthy men, C_{max} was 11.3 ng/mL after 8.2 hours with doxazosin GITS 4 mg/day and 28 ng/mL after 9.1 hours after administration of doxazosin GITS 8 mg/day. In contrast, corresponding C_{max} values were 2- to 3-fold higher with standard doxazosin and were reached within 4 hours (table I; $p < 0.05$).

Additionally, the area under the concentration-time curve (AUC) with doxazosin GITS was reduced compared with that of standard doxazosin.[10] Values for AUC at steady state with doxazosin GITS were between 50% and 60% of those obtained with the standard formulation (table I; $p < 0.05$). The

peak-trough fluctuation index with doxazosin GITS 4 or 8 mg/day was 41% and 38% of that with the standard formulation (table I; $p < 0.05$).

The bioavailability of doxazosin GITS 4 and 8mg dose in the multiple-dose crossover study, relative to standard doxazosin, was 54% and 59%, respectively.[10] Doxazosin is 98–99% protein-bound in plasma and has a volume of distribution of 0.97–1.69 L/kg.[4] Other studies reported by Chung et al.[10] show minimal impact on the pharmacokinetic parameters of doxazosin GITS of age, gender, or whether the patient is fasted or fed. Additionally, bioequivalence was demonstrated between the dose strengths of two doxazosin GITS 4mg tablets and one doxazosin GITS 8mg tablet.[10]

3.2 Metabolism and Elimination

Doxazosin is extensively metabolised by the liver, primarily by *O*-demethylation and hydroxylation,[4] with <5% of the drug excreted unchanged in the faeces.[6] Elimination via the kidneys is low, with 9% of a radioactive dose being recovered in the urine.[11] Total body clearance of doxazosin has been reported as 83–140 mL/min.[4] In the crossover study in 31 healthy men, the elimination half-life was similar between doxazosin GITS and the standard formulation (18.6 vs 20.5 hours; table I).

No data are available on the effect of hepatic impairment on the pharmacokinetic profile of doxazosin GITS or the standard formulation. No adverse drug interactions are reported.[6]

4. Therapeutic Efficacy

The efficacy of doxazosin GITS 4–8mg once daily in patients with symptomatic BPH has been compared with that of the standard formulation (standard doxazosin; 2–8mg once daily) in two large double-blind, randomised trials of 13 weeks' duration; a placebo-controlled study conducted in Scandinavia (n = 795 randomised)[12] and a non-placebo-controlled study conducted in Europe, Canada and South Africa (n = 680).[13] A combined analysis of these studies has also been published.[14] Finally, a small double-blind, randomised, 8-week crossover trial (n = 52) has compared the efficacy of doxazosin GITS 4–8mg once daily with that of tamsulosin 0.4–0.8mg once daily in patients with BPH.[15]

Patients (mean age ≈64 years) in all studies were required to have a maximum urinary flow rate (Qmax) of between 5 and 15 mL/s (in a total voided volume of ≥150 mL) [mean ≈10–11 mL/s at baseline] and a total International Prostate Symptom Score (IPSS) of ≥12 units (mean ≈16–18 units).[13-15] The IPSS, validated for use in BPH, consists of seven questions about lower urinary tract symptoms (each on a 0 [never] to 5 [almost always] scale) and one health-related quality of life (HR-QOL) question (0 [excellent] to 6 [very poor] scale).

Exclusion criteria included known or suspected malignancy, previous prostate surgery or microwave thermotherapy, presence of a prostatic stent, or balloon dilatation performed within the previous 6 months.[12,13,15]

Table I. Comparative pharmacokinetics of doxazosin gastrointestinal therapeutic system (Dox-GITS) and standard doxazosin formulation (Dox-S) at steady state. Results from an open-label, randomised, crossover study in 31 healthy men[10]

Parameter	Dox-GITS		Dox-S	
	4mg	8mg	4mg	8mg
Relative bioavailability (%)	54.1	58.6	100	100
C_{max} (ng/mL)	11.3	28.0	29.3*	66.8*
t_{max} (h)	8.2	9.1	3.7*	3.9*
C_{min} (ng/mL)	6.4	17.8	7.4	19.0
AUC_τ (ng • h/mL)	201	504	379*	878*
Peak-trough FI	0.60	0.52	1.47*	1.37*
$t_{½\beta}$ (h)		18.6		20.5

AUC_τ = area under the plasma concentration-time curve for the dosage interval (τ); **C_{max}** = peak plasma concentration; **C_{min}** = minimum plasma concentration; **FI** = fluctuation index; **$t_{½\beta}$** = terminal half-life; **t_{max}** = time to C_{max}; * $p < 0.05$ vs equivalent dosage of Dox-GITS.

Following a 2-week single-blind placebo run-in phase, patients randomised to receive doxazosin GITS commenced at a dosage of 4 mg/day, which was increased to 8 mg/day after 4 weeks in the crossover trial,[15] or after ≥7 weeks in the two large trials,[12,13] in patients who had not achieved a reduction in total IPSS of ≥30% and an increase in Qmax of ≥3 mL/s. The initial dosage of doxazosin standard was 1 mg/day, then 2 mg/day (after 1 week), then, in nonresponders, 4 mg/day (after 3 weeks) up to 8 mg/day (after 7 weeks).[12,13] Tamsulosin was commenced at 0.4 mg/day and increased to 0.8 mg/day after 4 weeks in nonresponders.[15]

The primary endpoints in each study were the mean change from baseline at the final visit in the total IPSS score and Qmax (for the per-protocol analysis population in the two large trials[12,13] and in the intent-to-treat population in one of these trials[12] and in the crossover study[15]).

Secondary endpoints (all in the intent-to-treat population) in the studies comparing the two doxazosin formulations included the mean changes in individual IPSS (including HR-QOL) scores and in urinary flow rate, the investigator's overall efficacy assessment, and the proportion of patients achieving target efficacy responses.[12,13] Additionally, in one study,[13] the effect of treatment on sexual function was assessed using the International Index of Erectile Function (IIEF) questionnaire.

4.1 Compared with Standard Doxazosin and Placebo

Doxazosin GITS was as effective as standard doxazosin,[12,13] and both formulations were more effective than placebo,[12] at improving total IPSS and Qmax after 13 weeks (primary endpoints) in two large, randomised double-blind studies in patients with BPH. Improvements in secondary endpoints supported these findings (reported here mainly from the combined analysis).[14]

The final mean dosages in the two trials were 6.1 and 6.2 mg/day for doxazosin GITS and 5.7 and 6.0 mg/day for the standard formulation.[12,13] The majority of randomised patients (57%) in either doxazosin group were receiving maximal (i.e. 8 mg/day) treatment at study end.[14]

4.1.1 Effect on International Prostate Symptom Score

Doxazosin GITS or standard doxazosin reduced total IPSS by 7.9–8.4 units after 13 weeks' treatment in both studies[12,13] (table II); both formulations were more effective than placebo (treatment difference 2.0 or 2.4 units; $p < 0.001$) in the placebo-controlled study (table II).[12]

In a combined analysis of these studies, the least-squares adjusted mean change from baseline in the total IPSS after 13 weeks was −7.9 (≈45% improvement; n = 640), −8.0 (≈45%; n = 624) and −5.8 (≈34%; n = 151) units in recipients of doxazosin GITS, standard doxazosin and placebo, respectively.[14] Statistical therapeutic equivalence was demonstrated between the two doxazosin formulations.[14]

Doxazosin GITS, with fewer titration steps, appeared to have an earlier onset of full therapeutic effect than the standard formulation. After 3 weeks' treatment, there was a statistically significant difference between the two formulations in the total IPSS score in favour of doxazosin GITS ($p = 0.042$; actual values not reported).[14]

Doxazosin GITS and standard doxazosin reduced the majority (5 of 7) of individual scores in the IPSS to a significantly ($p < 0.05$) greater extent than placebo after 13 weeks' treatment.[12]

4.1.2 Effect on Urinary Flow

Both doxazosin GITS and standard doxazosin increased Qmax by a similar amount (2.2–2.7 mL/s) after 13 weeks in both studies (table II).[12,13] Both formulations were more effective than placebo (0.8 mL/s; $p < 0.001$) in the placebo-controlled study (table II).[12]

Statistical therapeutic equivalence between doxazosin GITS and standard doxazosin was demonstrated in a combined analysis of these studies.[14] After 13 weeks, the mean least-squares adjusted change from baseline in Qmax was 2.8, 2.6 and 1.1 mL/s in patients receiving doxazosin GITS (n = 622), standard doxazosin (n = 617) and placebo (n = 151), respectively.[14]

Table II. Efficacy of doxazosin gastrointestinal therapeutic system (Dox-GITS) in patients (pts) with benign prostatic hyperplasia. Primary endpoint results (mean values) from randomised trials comparing Dox-GITS with standard formulation doxazosin (Dox-S), placebo (PL) or tamsulosin (Tam)

Study	Study design (duration)[a]	Treatment (no. of randomised pts)	Final mean dosage (mg/day)[b]	Total IPSS		Qmax (mL/s)	
				change from baseline at final visit[c] (no. of evaluable pts)	% improvement	change from baseline at final visit[c] (no. of evaluable pts)	% improvement
Andersen et al.[12]	r, db, dd, pg, mc (13wk)[d]	Dox-GITS (317)	6.2	−8.0**† (310)	45	2.6**† (300)	24
		Dox-S (322)	5.7	−8.4**† (311)	47	2.2**† (303)	22
		PL (156)		−6.0** (151)	34	0.8* (151)	9
Gratzke and Kirby[13]	r, db, pg, mc (13wk)[d]	Dox-GITS (350)	6.1	−8.1** (330)	≈44	2.7** (322)	≈26
		Dox-S (330)	6.0	−7.9** (313)	≈43	2.7** (314)	≈25
Kirby[15]	r, db, co (8wk)[e]	Dox-GITS (52)	6.3	−8.0**‡	≈49	2.6**	≈25
		Tam (52)	0.67[f]	−6.4**	≈40	1.7**	17

a Duration of db phase(s); each study also included 2-wk PL run-in and washout (before run-in[12,13] or prior to co[15]) phases.

b Dox-GITS commenced at 4mg od, then increased to 8mg od after 4wk[15] or from 7wk[12,13] if target efficacy response (30% reduction in IPSS score and an increase in Qmax of ≥3 mL/s) not achieved. Dox-S commenced at 1mg od, increased to 2mg od after 1wk (all pts), and then increased to 4mg od after 3wk and 8mg od after 7wk if target efficacy response achieved.[12,13]

c Least-squares adjusted.

d Results expressed for the per-protocol population.

e Results expressed for the intent-to-treat population (n = 47); 1 withdrawal in PL run-in phase, 4 withdrawals in first db phase (1 Dox-GITS and 3 Tam) prior to co.

f Tam commenced at 0.4mg od, then increased to 0.8mg od after 4wk if target efficacy response achieved.

co = crossover; **db** = double-blind; **dd** = double-dummy; **IPSS** = International Prostate Symptom Score; **mc** = multicentre; **od** = once daily; **pg** = parallel-group; **Qmax** = maximum urinary flow rate; **r** = randomised. * $p < 0.01$, ** $p \leq 0.001$ vs baseline; † $p < 0.001$ vs PL; ‡ $p < 0.05$ vs Tam.

Doxazosin GITS appeared to increase Qmax earlier (after 3 weeks) in the combined analysis than standard doxazosin ($p < 0.05$).[14]

Finally, the mean urinary flow rate increased by a similar extent after 13 weeks from baseline (5.1–5.5 mL/s) with doxazosin GITS or standard doxazosin (1.3 and 1.2 mL/s vs 0.6 mL/s with placebo).[14]

4.1.3 Response Rates

Doxazosin GITS and the standard formulation appeared to produce similar response rates in target efficacy measures. The majority of patients (≈71% in the combined analysis) receiving either doxazosin formulation achieved a ≥30% reduction in total IPSS by study end (figure 2a).[14] Furthermore, a similar proportion of patients receiving either doxazosin formulation achieved an increase in Qmax of ≥3 mL/s at the final visit (37% or 40% vs 21% placebo) [figure 2b].[14]

A combined endpoint of a ≥30% reduction in total IPSS score and a ≥3 mL/s increase in Qmax was achieved in 32%, 30% and 14% of doxazosin GITS, standard doxazosin or placebo recipients, respectively (figure 2c).[14]

Finally, similar proportions of patients receiving either doxazosin formulation were considered by the investigators to have had an excellent or good efficacy response (61% or 62%), or a poor response (12% or 13%), to 13 weeks' treatment.[14] In contrast, 38% and 31% of placebo recipients achieved an excellent/good or a poor response.[14]

4.1.4 Effect on Health-Related Quality of Life and Sexual Function

Doxazosin GITS and standard doxazosin produced a similar improvement from baseline in the IPSS quality-of-life question after 13 weeks' treatment in both studies.[12,13] In the combined analysis,[14] the mean score decreased (i.e. improved) from 3.7 to 2.3 units in doxazosin GITS recipients, from 3.6 to 2.3 units in standard doxazosin recipients and from 3.5 to 2.6 units in placebo recipients ($p < 0.05$ vs either doxazosin formulation[12]).

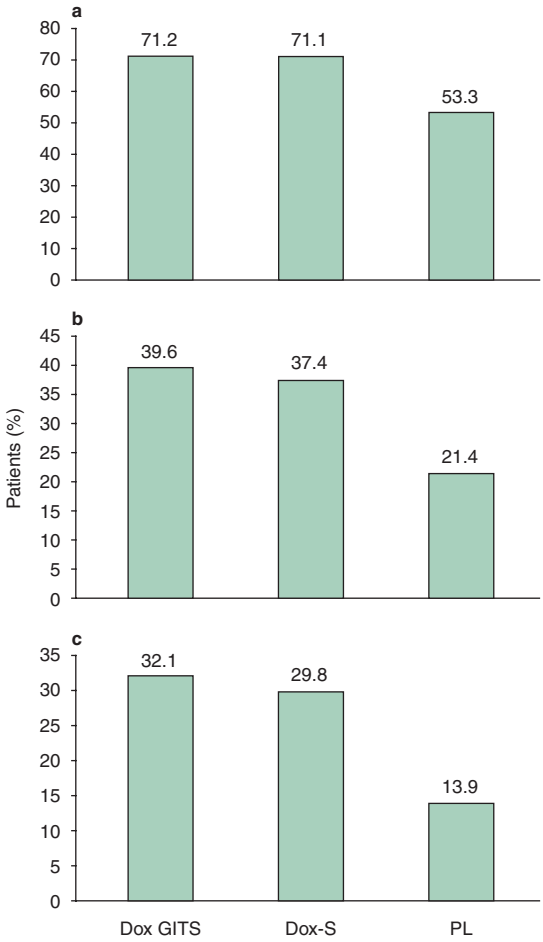

Fig. 2. Efficacy response rates achieved with doxazosin gastrointestinal therapeutic system (Dox-GITS) compared with standard doxazosin formulation (Dox-S) and placebo (PL) in patients with benign prostatic hyperplasia. In a combined analysis[14] of two double-blind, randomised studies,[12,13] patients received Dox-GITS 4 or 8 mg/day (mean final dosage 6.3 mg/day; n = 666), Dox-S 2–8 mg/day (6.0 mg/day; n = 651) or PL (n = 156) for 13 weeks. Bars show the proportion of patients at study end achieving target responses of (**a**) a ≥30% reduction in total International Prostate Symptom Score (IPSS) from baseline; (**b**) a ≥3 mL/s increase in maximum urinary flow (Qmax); and (**c**) both a ≥30% reduction in IPSS and a ≥3 mL/s increase in Qmax from baseline.[14] Statistical analyses were not reported.

In patients (≈50%) with some sexual dysfunction at baseline in the non-placebo-controlled study, doxazosin GITS was as effective as standard doxazosin at improving scores in each domain of the IIEF questionnaire after 13 weeks' treatment (both $p < 0.05$).[13] Furthermore, each component variable of the IIEF improved significantly from baseline with doxazosin GITS ($p < 0.01$) and all but one ('erections hard enough for penetration') with standard doxazosin ($p < 0.05$).

4.2 Compared with Tamsulosin

Doxazosin GITS (mean final dosage 6.3 mg/day) reduced total IPSS by a significantly greater extent than tamsulosin (0.67 mg/day) [−8.0 vs −6.4 units; $p < 0.05$] after 8 weeks in a small (n = 52) randomised, double-blind crossover trial in patients with BPH (table II).[15] No significant between-group effect was demonstrated for Qmax (table II).[15]

In a *post hoc* analysis,[16] a significant difference after 8 weeks (pre-crossover), in favour of doxazosin GITS (n = 23) compared with tamsulosin (n = 22), was also demonstrated in the total IPSS score ($p < 0.05$) and the irritative symptoms IPSS subscore ($p < 0.01$), but not in the obstructive symptoms subscore. In another *post hoc* analysis,[16] after the first 4 weeks of treatment (i.e. prior to dose titration; n = 47) doxazosin GITS 4 mg/day improved the obstructive symptoms subscore (but not the total score or irritative subscore) by a significantly greater extent than tamsulosin 0.4 mg/day ($p < 0.05$).

5. Tolerability

Doxazosin GITS was generally well tolerated in two large double-blind randomised trials in patients with BPH.[12,13] Adverse events were generally mild-to-moderate in severity. This section reviews results from a combined analysis (n = 1473) of the safety data from these studies.[14]

Recipients of doxazosin GITS 4–8 mg/day (n = 666) or placebo (n = 156), compared with standard doxazosin 2–8 mg/day (n = 651), experienced a lower incidence of all-cause adverse events (41.4% and 39.1% vs 53.6%; both $p < 0.001$) and treatment discontinuation due to all-cause adverse events (5.7% and 2.6% vs 7.2%; both $p < 0.001$); no statistically significant differences were demonstrated between doxazosin GITS and placebo in either measure.[14]

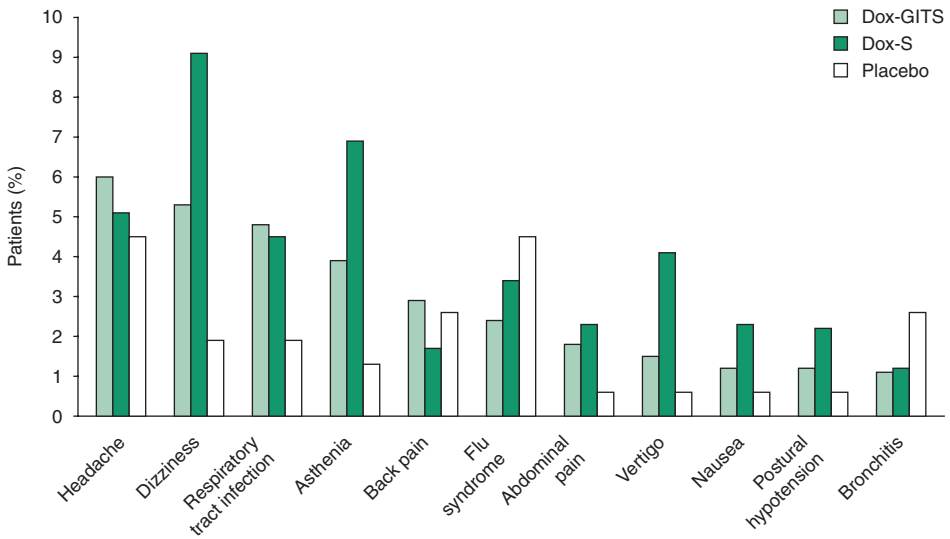

Fig. 3. Tolerability profile of doxazosin gastrointestinal therapeutic system (Dox-GITS) in patients with benign prostatic hyperplasia. In two large, double-blind, randomised studies, patients received Dox-GITS 4–8mg, standard doxazosin (Dox-S) 2–8mg or placebo once daily for 13 weeks.[12,13] Bars show the proportions of patients experiencing the most common treatment-emergent adverse events during the studies (combined analysis; n = 1473).[14]

Individual treatment-emergent adverse events occurred at similar rates in all treatment groups, with headache (5–6%) and dizziness (2–9%) being among the most common (figure 3).[14] Overall, treatment-emergent adverse events occurred in 16.1%, 25.3% and 7.7% of patients receiving doxazosin GITS, standard doxazosin or placebo, respectively; the discontinuation rates due to these events were 3.3%, 4.8% and 0.6%.

Three treatment-related serious adverse events were reported (an episode of syncope and an episode of slurred speech and unsteadiness in the doxazosin GITS group, and an episode of chest pain in a patient receiving standard doxazosin).[14] There were no treatment-related deaths.

No between-group differences occurred in the rates of clinically significant laboratory abnormalities (2.6–5.1%), with the most common events being raised serum eosinophil and potassium levels.[14]

Clinically significant decreases from baseline in sitting systolic and diastolic blood pressure occurred with either doxazosin formulation in patients who were hypertensive at baseline (−9.4/−6.8mm Hg with doxazosin GITS, −7.4/−6.1mm Hg with standard doxazosin and −3.9/−5.0mm Hg with placebo).[14] In normotensive patients, there were no inappropriate changes in blood pressure following administration of either doxazosin formulation.

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Dosage and Administration

Doxazosin GITS, like standard doxazosin, is indicated for the treatment of urinary outflow obstruction and symptoms associated with BPH.[6] The drug is also indicated as monotherapy or as a component of combination therapy for hypertension.[6]

The starting dosage of doxazosin GITS in BPH is 4mg once daily (higher than that of the standard formulation; 1mg once daily), which should be continued for at least 4 weeks for optimal response. The dosage may then be increased to 8mg once daily (the maximum recommended dosage), depending on response. The drug can be administered with or without food.

No dosage adjustment is required in patients with renal impairment; caution is required, however, when administering doxazosin GITS to patients with hepatic impairment.[6]

Caution is also required in patients with hypertension and/or BPH on diuretic therapy.[17] If the diuretic is replaced directly with doxazosin (as in ALLHAT)[8] latent heart failure may be manifested. Instead, the dosage of diuretic could be reduced, but not stopped, when doxazosin is started, and then blood pressure and symptoms of heart failure controlled over the following weeks.[17]

7. Place of Doxazosin GITS in the Management of Benign Prostatic Hyperplasia

Severity of lower urinary tract symptoms, and their impact on HR-QOL, are major factors in deciding whether to treat BPH.[1,18] Many patients with mild symptoms (typically IPSS total score ≤7 units), or those with moderate-to-severe symptoms (≥8 units) but who are not bothered by them, can be managed by watchful waiting.[1,2,18] For those with bothersome symptoms, but otherwise uncomplicated BPH, medical therapies, while not as efficacious as surgical approaches, are generally adequate at improving symptoms, HR-QOL and decreasing bladder outlet obstruction, and have less serious adverse events.[1,2,18]

The use of α_1-adrenoceptor antagonists, such as doxazosin and terazosin, for the treatment of symptomatic BPH has increased over the last 10–15 years and all are considered to have similar efficacy.[1,18] However, the possible hypotensive effect of the first doses requires multiple-step titration regimens.[5] With the standard doxazosin formulation, for example, an initial dose of 1 mg/day is carefully doubled (up to 4–8 mg/day) until optimal symptom relief and improvement is reached.

Doxazosin GITS, a controlled-release formulation of doxazosin, was designed to allow for a higher initial dosage (4mg once daily), a dosage more likely to be clinically effective, to be administered to patients with BPH, thus simplifying the titration regimen.[5,17] By reducing the doxazosin plasma concentration peak-to-trough ratio, and allowing a lower C_{max} and a prolonged time to reach C_{max} the risk of a hypotensive event at this increased dosage is considered to be reduced.[5]

In two large, double-blind, randomised trials,[12,13] one of which was placebo-controlled,[12] doxazosin GITS 4–8 mg/day was as effective as standard doxazosin 2–8 mg/day, and both were superior to placebo, in improving symptoms and Qmax after 13 weeks' treatment (section 4). This was supported by similar results with both formulations of doxazosin for the secondary outcomes in these studies, including the proportion of patients achieving target response rates, the investigator's assessment of efficacy, the effect on HR-QOL, and the improvement in sexual dysfunction (section 4).

In a combined analysis of the two large, randomised trials, doxazosin GITS appeared to exert its effect earlier than the standard formulation, with a statistically significant between-group difference in both total IPSS score and Qmax at 3 weeks (section 4). This difference probably reflected the fact that a higher initial dosage had been used with doxazosin GITS; after 3 weeks no significant between-group differences were detected for these parameters.[12,13]

Comparisons between doxazosin GITS and other medical therapies, other than standard doxazosin, are limited and further studies are required. In a small crossover study, doxazosin GITS reduced symptom scores, but not Qmax, by a significantly greater extent than the α_{1A}-adrenoceptor antagonist tamsulosin (section 4.2).[15] There are no published studies evaluating doxazosin GITS in combination with other medical therapies, such as the 5α-reductase inhibitor finasteride.

Doxazosin GITS was generally well tolerated in large, randomised studies in patients with BPH (section 5).[12,13] Compared with the standard formulation, there was no difference in the types and rates of treatment-emergent adverse events. Only one patient of 666 receiving doxazosin GITS experienced an episode of syncope.[14]

In conclusion, doxazosin GITS, a new controlled-release formulation of a well established

treatment in patients with bothersome lower urinary tract symptoms from BPH, was as effective as the standard formulation of doxazosin and both were more effective than placebo in improving symptom scores, HR-QOL, and Qmax after 13 weeks' treatment in two large, double-blind, randomised studies. Doxazosin GITS has an altered pharmacokinetic profile, which allows a higher initial dosage to be used than with the standard formulation and less titration steps before a clinically effective dosage is reached. Doxazosin GITS was at least as well tolerated as the standard formulation in clinical studies in patients with BPH.

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