Pharmacological Tolerance to α_1-Adrenergic Receptor Antagonism Mediated by Terazosin in Humans

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Abstract

Chronic administration of α_1-receptor antagonists is associated with loss of clinical efficacy, especially in congestive heart failure, although the mechanism is uncertain. To evaluate changes in venous α_1-adrenoceptor responsiveness during chronic α_1-adrenoceptor blockade, dose-response curves to phenylephrine and angiotensin II were constructed in 10 healthy subjects before, during, and after administration of terazosin 1 mg orally for 28 d. Terazosin initially shifted the dose-response curve of phenylephrine to the right, with a significant increase in ED_{50} for phenylephrine from a control value of 102 to 759 ng/min on day 1 of terazosin ($P < 0.001$). However, by day 28, the dose-response curve had shifted back towards baseline with an ED_{50} of 112 ng/min. After discontinuing terazosin, the ED_{50} for phenylephrine remained near the baseline value, indicating no evidence of supersensitivity to phenylephrine. There was no change in responsiveness to angiotensin II during the course of treatment with terazosin. Plasma terazosin concentrations were stable throughout the period of drug administration. The mean K_d of terazosin was estimated as 11±15 nM in the first few days of treatment. This study demonstrates that pharmacological tolerance to the α_1-adrenoceptor blocking action of terazosin occurs in man and may be responsible for loss in efficacy with chronic therapy. (*J. Clin. Invest.* 1992. 90:1763–1768.) Key words: hand vein • desensitization • α_1-adrenoceptor blockade

Introduction

Selective blockade of α_1-adrenoceptors has been shown to be beneficial in the treatment of a variety of diseases including hypertension and congestive heart failure, especially in patients whose condition is complicated by bronchial asthma, hyperlipidemia, diabetes mellitus, or Raynaud's disease (1–5) or who have benign prostatic hypertrophy (6–8). However, one major problem with the clinical efficacy of α_1-adrenergic receptor antagonists is that tolerance to the therapeutic effect develops during chronic drug administration, especially in congestive heart failure (9–13). Many mechanisms to account for tolerance to α_1-receptor antagonists have been suggested, including alterations in α_1-receptor responsiveness (14–16), increased sodium retention in the vascular wall leading to increased vascular smooth muscle stiffness and interstitial edema (16–18), compensatory neuroendocrine mechanisms manifested as increased activity of the sympathetic nervous system and the renin–angiotensin–aldosterone system (19–24), advancing disease (25, 26), and altered production of vasodilator factors (27).

General mechanisms of tolerance to drugs can be classified as those that involve alterations in pharmacokinetics or those that are due to changes in pharmacodynamic responses to drugs with time. Tolerance resulting from pharmacokinetic changes can be caused by increased clearance of a drug with time, thus reducing the concentration of drug at its site of action. Changes in drug receptors have frequently been implicated as an explanation for pharmacodynamic alterations in responsiveness with time. For example, β-adrenergic agonists promote β-receptor downregulation, diminishing the effects of this class of drugs with time (28). The mechanism for tolerance to α_1-adrenoceptor antagonists is not clear despite several studies addressing it. Studies in man (16) and animals (14) relied on systemic infusions of agonists. These studies, which demonstrated tolerance in vivo, could not exclude the possibility that tolerance was due to activation of homeostatic reflexes as a result of the changes in blood pressure (29). In vitro studies in animals using a variety of vascular preparations and radioligand techniques have shown changes in α_1-receptor number and responsiveness; however, such studies may not directly reflect similar responsiveness in man. We have previously shown that by using a linear variable differential transducer (LVDT)[1] to measure the vascular responses of smooth muscle in the human hand vein in vivo it is possible to directly measure effects of systemically administered vasoactive drugs (30). In addition, this technique, referred to as dorsal hand-vein compliance, permits the construction of full dose-response curves from which the maximum response (E_{max}) and the ED_{50} (dose producing half-maximal response, which is an index of potency) are derived and is not affected by systemic reflexes.

Terazosin is an α_1-selective antagonist and, like prazosin, is a quinazoline derivative. Its hemodynamic effects are predominantly due to selective peripheral α_1-adrenoceptor antagonism in man (3, 4, 6, 31–33).

In this study, we used terazosin in normotensive subjects to determine whether there are changes in vascular α_1-adrenoceptor-dependent and -independent responsiveness during chronic α_1-receptor blockade. In addition, after withdrawal of chronic terazosin administration we looked for the presence of hypersensitivity to phenylephrine or angiotensin II.

Methods

10 subjects (6 males and 4 females) took part in this study. Their mean age was 29±6 yr (range 22–40), and their weight was 70±15 kg (range

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1. *Abbreviations used in this paper:* ANOVA, analysis of variance; CI, confidence interval; E_{max}, maximum response; LVDT, linear variable differential transducer.

56–92). They were all healthy as determined by a battery of routine biochemical and hematological tests, electrocardiogram, and physical examination. Each subject gave an informed written consent before taking part in the study, which was approved by the Stanford Administrative Panel on Human Subjects in Medical Research. None of the subjects was taking any drugs at the time of the study. All were nonsmokers and refrained from caffeine-containing foods for ≥ 12 h before each study. Exclusion criteria included a history of any significant disease state, illicit drug use or alcoholism, and the chronic use of any medication, including over-the-counter preparations.

Study design. Each subject was studied on eight different days. On each occasion, dose–response curves to phenylephrine (21–6,775 ng/min) and angiotensin II (2–460 ng/min) were constructed, using the dorsal hand-vein technique. The order of phenylephrine and angiotensin II infusions was randomized but the sequence was the same in each subject throughout the study. A washout period of ≥ 40 min, during which normal saline was infused continuously, separated the two dose–response curves.

Two baseline dose–response curves to phenylephrine and angiotensin II were constructed before terazosin administration was begun. The first dose of terazosin, 1 mg orally with 200 ml of water, was given to each subject and they were requested to remain in the supine position for the next 5 h as a precaution against profound hypotension and syncope occasionally associated with the first dose of α_1-adrenoceptor antagonists. 2 h after the administration of the first dose of terazosin, dose–response curves to phenylephrine and angiotensin II were repeated. The subjects subsequently took terazosin 1 mg daily for 28 d. Dose–response curves to phenylephrine and angiotensin II were repeated on the 4th, 25th, and 28th days of terazosin administration, and then on the 3rd and 7th days after stopping terazosin. All the dose–response curves during terazosin administration were constructed within 2 h of taking the dose on the study day. Compliance was determined using the Medication Event Monitoring System device (Aprex Corp., Fremont, CA) (34), as well as by pill count. Blood samples for estimation of plasma concentrations of terazosin were obtained before and at the end of the dose–response evaluations on each study day. The samples were centrifuged and the plasma stored at −70°C until they were assayed.

Dorsal hand-vein technique. The dorsal hand-vein technique was used to quantitate responsiveness of the dorsal hand vein to vasoactive drugs. This technique was previously modified by Aellig (35) and has been used in our laboratory for the study of both systemically administered (30) and locally infused drugs (36). The dosages of the locally infused drugs are very small, usually 1/1,000th to 1/60th of the usual clinical dose, thus avoiding potentially confounding systemic hemodynamic effects. Complete dose–response curves are generated by administering sequentially increasing concentrations of drugs. From the curves obtained, the comparative indices of E_{max} and sensitivity (ED_{50}) are obtained.

Each subject was studied in the supine position with one arm placed on a padded support at an angle of 30° from the horizontal to allow for complete emptying of the veins. A suitable vein was chosen on the dorsum of the hand and a 23-gauge needle inserted. Normal saline infusion was started at a rate of 0.37 ml/min using a Harvard infusion pump. The tripod holding an LVDT (Schaevitz Engineering, Pennsauken, NJ) was mounted on the back of the hand with the central aperture of the LVDT centered over the vein under investigation at a distance of 10 mm proximal to the tip of the needle. The central aperture of the LVDT contains a freely movable core. The signal output from the LVDT is directly proportional to the vertical movement of the core and is recorded on a strip-chart recorder and measured. Recordings of the position of the core situated over the top of the vein were made both before and after inflation of a sphygmomanometer cuff on the arm to 40 mmHg. The difference between the two positions of the core gives a measure of the diameter changes of the vein at a given congestion pressure. Baseline recordings were obtained during normal saline infusion after ~ 30 min to allow for equilibration of the vein from the initial vasoconstriction induced by the insertion of the needle. Responses to each concentration of the drug were recorded after infusing for ≥ 5 min. Preliminary studies indicated that this time was adequate for the maximum effect to appear for that concentration. Blood pressure and heart rate were regularly monitored in the opposite arm throughout the study. There was no change in blood pressure or heart rate with phenylephrine or angiotensin II. The temperature of the room was maintained at ~ 72°F during the study period.

Data analysis. For the dose–response curves, the peak height obtained during normal saline infusion at the beginning of the study was considered as 100% relaxation, whereas the baseline with the cuff deflated was considered 100% venoconstriction. Venoconstriction produced by phenylephrine and angiotensin II were expressed as percentages of the baseline response during saline infusion. Phenylephrine and angiotensin II dose–response curves in individual subjects were fitted to a four-parameter logistic equation using the ALLFIT program (37). This approach provides an objective measure of E_{max} and ED_{50}. The ED_{50} values were log transformed since log values are normally distributed (38).

The dose ratios were calculated as ED_{50} for agonist in presence of terazosin/ED_{50} for agonist at baseline. The dose ratio is used to quantitate the shift in the dose–response curve for a competitive antagonist, such as terazosin. An estimate of the K_d for terazosin in this study can be made using the equation $(DR - 1) \times K_d$ = [terazosin concentration] (39), where DR is the dose ratio and [terazosin] is the concentration of terazosin.

Plasma terazosin was assayed by HPLC (40). The mean of the concentration of terazosin in the two samples taken during each dose–response evaluation was used as the estimate of terazosin plasma concentration during that dose–response curve and used for estimation of K_ds.

Statistical analysis was by means of the repeated measures analysis of variance (ANOVA) for the comparison of E_{max}, log ED_{50}, and dose ratios. Posthoc analysis was performed using Duncan's multiple comparison procedure with $\alpha = 0.05$. Linear regression analysis was used to evaluate the relationship between responsiveness to phenylephrine and angiotensin II in individual subjects following the administration of terazosin. The results are expressed as mean±standard deviation.

Results

Terazosin was well tolerated by all the subjects and compliance, estimated using the medication event monitoring system device, was 100% for ingesting the drug on a daily basis and 68% for ingesting the drug within 1 h of prescribed time. Terazosin is rapidly absorbed (41) and steady state concentrations were achieved almost immediately without any evidence of drug accumulation in these subjects. The mean serum terazosin concentrations on all days of active treatment were similar and are shown in Table I.

The two separate baseline phenylephrine dose–response studies had similar mean log ED_{50} values: 2.02±0.63 (104.7 ng/min) for the first baseline study and 2.00±0.62 (100 ng/min) for the second baseline study, indicating that the technique was reproducible. On study day 1 of terazosin administration, there was a shift to the right of the dose–response curve with a significant increase in the mean log ED_{50} of phenylephrine to 2.88±0.82 (758.6 ng/min) ($P < 0.001$) (95% confidence interval [CI] [0.192, 1.372]) (Table II). The results on day 4 of terazosin were similar to day 1, with a mean log ED_{50} of 2.76±0.32 (575.4 ng/min). Therefore, this dose of terazosin caused a 5–7-fold shift to the right in the phenylephrine dose–response curve. The mean K_d for terazosin was 11.2±15.3 nM in the first few days of administration of terazosin; this compares with a K_d for terazosin of 3±0.3 nM, determined using membrane homogenate from rat liver (33).

*Table I. Terazosin Concentrations from 10 Subjects Treated with Terazosin 1 mg/d for 28 d**

Study day	Terazosin concentration
	nM
Day 1	27.2±4.1
Day 4	29.6±9.3
Day 25	26.3±10.4
Day 28	30.2±13.7

* Mean±SD. Statistical analysis by repeated measures ANOVA did not show any difference in day-to-day concentrations in individual subjects, suggesting that steady state was achieved early and there is no evidence for drug accumulation on chronic dosing.

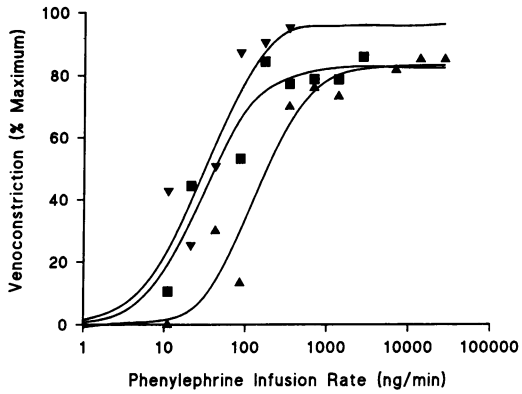

Figure 1. Dose-response curves constructed from infusion of phenylephrine into the dorsal hand vein of a representative subject treated with terazosin, 1 mg/d for 28 d. Baseline ■ —— ■ refers to the curve constructed before institution of terazosin; ▲ —— ▲ refers to the curve constructed after the first dose of terazosin; and ▼ —— ▼ refers to the curve constructed after 28 d of terazosin administration. Terazosin, 1 mg given orally, caused a significant shift to the right in the dose-response curve to phenylephrine during the early days of administration but by day 28 the dose-response curve had shifted back to baseline.

However, by study days 25 and 28 of terazosin administration, the dose-response curve had shifted back towards the baseline, with mean log ED_{50} values of 2.23±0.32 (169.8 ng/min) and 2.05±0.61 (112.2 ng/min) (P = 0.11; 95% CI [−0.585, 0.149] and P = 0.43; 95% CI [−0.463, 0.397]), respectively (Table II). On days 3 and 7 after discontinuation of terazosin, there was no difference in the log ED_{50} for phenylephrine compared with baseline values (Table II), suggesting that there was no hyperresponsiveness to α_1-adrenoceptor stimulation after abrupt cessation of terazosin. There was no significant change in the slope of the phenylephrine dose-response curves during the course of the study. Dose-response curves for each of the study days from a typical individual subject are shown in Fig. 1.

Infusion of angiotensin II produced highly variable results. In two subjects on certain study days there was a lack of a dose-response relationship between the dose of angiotensin II administered and the amount of venoconstriction produced and these data were not used in the subsequent analysis. For the remaining eight subjects, there was no significant change in the mean log ED_{50} for angiotensin II between the baseline; terazosin dosing days 1, 4, 25, and 28 of terazosin administration; or days 3 and 7 after discontinuation of terazosin (P = 0.653 by ANOVA; 95% CI [−0.798, 0.902]) (Table III). Dose-response curves from a representative subject are shown in Fig. II.

In an effort to exclude a nonspecific loss in vasoconstriction accounting for the change in the ED_{50} values for phenylephrine during the course of terazosin administration, we looked for a correlation between those subjects who demonstrated a de-

Table II. Log ED_{50} Values Derived from Dose-Response Curves from Phenylephrine Infusion

Subject	Baseline	Day 1	Day 4	Day 25	Day 28	Post day 3	Post day 7
1	0.85	1.84	2.63	1.89	1.59	2.15	1.86
2	1.23	2.17	2.19	1.29	1.47	1.25	1.47
3	1.84	2.29	3.17	2.06	1.81	1.61	1.65
4	2.18	3.29	2.84	1.79	3.24	1.41	2.90
5	2.78	2.98	2.77	2.73	2.01	2.57	1.88
6	2.64	4.43	3.17	1.96	2.16	2.31	2.80
7	2.48	3.33	2.71	2.74	2.35	2.48	1.98
8	1.86	3.35	2.69	2.32	1.43	1.95	1.33
9	2.24	2.35	2.35	2.96	2.80	2.17	2.10
10	2.03	2.25	3.06	2.57	1.60	2.35	2.10
Mean log ED_{50}	2.01±0.61	2.88±0.82*	2.76±0.32*	2.23±0.53‡	2.05±0.61§	2.05±0.60‡	2.01±0.51§
ED_{50} (ng/min)	102.3	758.6	575.4	169.8	112.2	112.2	102.3

Log ED_{50} values and mean log ED_{50} values (±SD) derived from dose-response curves constructed from infusion of phenylephrine into dorsal hand veins of subjects treated with terazosin 1 mg/d. The baseline value represents the mean value of 2 study days before initiation of terazosin. Days 1, 4, 25, and 28 refer to study days during active drug therapy. Post days 3 and 7 refer to study days after the completion of terazosin therapy. The antilog of the geometric means of the ED_{50} values for phenylephrine are also indicated, for clarity.

* $P < 0.01$ compared with baseline.

‡ $P < 0.05$ compared with study day 1.

§ $P < 0.01$ compared with study day 1.

Table III. Log ED_{50} Values Derived from Dose-Response Curves from Angiotensin II Infusion

Subject	Baseline	Day 1	Day 4	Day 25	Day 28	Post day 3	Post day 7
1	1.14	1.46	2.41	1.46	—	2.06	—
2	0.67	1.99	1.05	0.84	0.74	0.66	0.94
3	2.00	1.52	1.02	1.32	—	0.98	0.44
4	2.29	0.99	2.02	—	—	0.75	—
5	1.94	—	—	—	—	—	—
6	1.53	—	0.88	1.07	0.86	1.37	1.08
7	0.97	1.35	1.23	1.39	0.51	2.08	0.76
8	1.89	—	0.91	0.51	1.30	0.25	1.23
9	1.43	0.88	0.74	1.28	0.79	1.23	0.84
10	0.91	—	1.10	1.11	—	2.27	—
Mean log ED_{50}	1.48±0.54	1.37±0.40	1.26±0.57	1.12±0.32	0.84±0.29	1.29±0.71	0.88±0.27
ED_{50} (ng/min)	30.2	23.4	18.2	13.2	6.9	19.5	7.6

Log ED_{50} values and mean log ED_{50} values (±SD) derived from dose-response curves constructed from infusion of angiotensin II into dorsal hand veins of subjects treated with terazosin 1 mg/d. The baseline value represents the mean value of 2 study days before initiation of terazosin therapy. Days 1, 4, 25, and 28 refer to study days during active drug therapy. Post days 3 and 7 refer to study days after the completion of terazosin therapy. Study days in which no value appears are days in which the infusion of angiotensin II produced such inconsistent results that no satisfactory dose-response curve could be generated.

crease in the log ED_{50} late in the study for the phenylephrine infusion and those subjects who had a tendency to demonstrate a decrease in the log ED_{50} for angiotensin II infusion. A correlation analysis of the late/early log ED_{50} ratio for phenylephrine infusion versus the late/early log ED_{50} ratio for angiotensin II infusion was not significant ($r = 0.496$, $P = 0.212$).

Discussion

Systemically administered terazosin caused a marked parallel shift to the right of the dose–response curve to phenylephrine during the first several days of administration of the drug. These data are compatible with competitive antagonism, with a K_d for terazosin of ~ 11 nM. However, this shift in sensitivity to phenylephrine was lost by 25 d of continuous terazosin administration while the plasma concentrations of the drug remained unchanged. This observation of a decrease in responsiveness over time in the presence of similar drug concentrations is strong evidence for tolerance to the α_1-blocking property of terazosin in the hand vein since terazosin did not appear to alter responsiveness to angiotensin II.

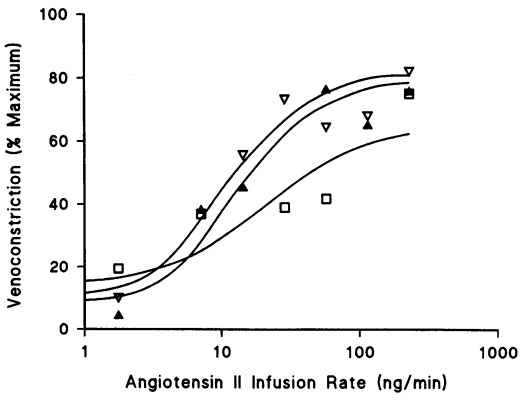

Figure 2. Dose–response curves constructed from infusion of angiotensin II into the dorsal hand vein of a representative subject. Baseline □ —— □ refers to the dose–response curve generated before the initiation of terazosin therapy; ▲ —— ▲ refers to the curve constructed after the first dose of terazosin; and ▽ —— ▽ refers to the curve constructed after 28 d of terazosin administration. There was no change in the responsiveness to angiotensin II after administration of terazosin.

There are several possible mechanisms that could explain the loss in terazosin's α_1-blocking activity. These include (*a*) a decrease in affinity of α-adrenergic receptors for terazosin (i.e., an increase in the K_d for terazosin), (*b*) an increase in the potency of phenylephrine in causing smooth muscle contraction, or (*c*) a change in the concentration of terazosin at α_1-adrenoceptors.

Terazosin is a competitive α_1-adrenoceptor antagonist (4, 31). The mean K_d of terazosin in individual subjects during the early few days of treatment was 11 nM. If the explanation for the loss in α_1-receptor antagonism was due to a loss in affinity of α_1-receptors for terazosin, then this dose–ratio equation can be used to calculate the putative new K_d for terazosin after continuous therapy. With a mean dose ratio of 1.3 (the antilog of the mean log dose ratio) obtained after 28 d of terazosin treatment, the terazosin's K_d would have to increase by ~ 12-fold to account for the change in dose ratio. Although it has been shown that stimulation of α_1-adrenoceptors can lead to posttranslational changes (i.e., phosphorylation) (42), there are no data that have demonstrated molecular changes in α_1-receptors induced by antagonists. In rabbits given the related α_1-adrenergic antagonist prazosin for 28 d, Hamilton and Reid (14) did not detect any changes in the dissociation constant for prazosin in the spleen, heart, forebrain, or hindbrain. Consequently, although a change in α_1-receptor affinity for terazosin could hypothetically explain the results of our study, there are no molecular or laboratory animal data on which to base such a conclusion.

An adaptive increase in the sensitivity of the vascular α_1-adrenoceptors to phenylephrine over time with prolonged administration of terazosin could also explain our results. It has been shown that prolonged treatment with the nonselective

β-adrenoceptor antagonist propranolol results in an increase of β-adrenoceptors on circulating human white blood cells and enhanced responsiveness to β-adrenoceptor agonists (43, 44). After administration of prazosin, an increase in α_1-adrenoceptor–binding sites in the heart of normotensive rats has been reported after 21 d (45). However, in rabbits, prolonged administration of prazosin does not change expression of α_1-receptor number in a variety of peripheral tissues (14). Bevan et al. (46) have shown that α-adrenoceptor–mediated sensitivity to norepinephrine in the smooth muscle from a variety of arterial preparations in the rabbit is linearly related to the agonist affinity. It is possible that prolonged α_1-adrenoceptor antagonism with terazosin increased the number of α_1-adrenoceptors in the veins, thus resulting in an enhanced responsiveness to phenylephrine.

This possible enhanced sensitivity to phenylephrine could result from increased expression of α_1-adrenoceptors induced by terazosin, or other postreceptor changes in the pathway from activation of the α_1-receptors to induction of smooth muscle contraction. In the setting of chronic administration of β-receptor antagonists, increased expression of β-receptors leads to enhanced sensitivity to β-agonists 3–7 d after abruptly discontinuing therapy with the antagonist. We were unable to detect enhanced sensitivity to phenylephrine 3 d after discontinuing terazosin, which has an elimination half-life of 12 h (47). This does not exclude the possibility of enhanced sensitivity to phenylephrine after discontinuing treatment with terazosin, especially if this adaptation were rapidly reversible when this drug was discontinued. Plasma concentrations of terazosin were unmeasurably low 3 d after discontinuing the administration of terazosin. It is possible that there might have been a difference in response if we had tested for the phenylephrine sensitivity earlier than 3 d. Our choice of 3 d was based on the published pharmacokinetics of terazosin and β-adrenoceptor antagonist withdrawal studies, which generally found maximal sensitivity at $\sim$ 3 d. During administration of α_1-adrenoceptor antagonists, increases in circulating concentrations of vasoconstrictors such as norepinephrine (19, 20, 48–50) or angiotensin II (22) have been found previously in humans; such changes could augment responsiveness to phenylephrine. However, there was no change in responsiveness to angiotensin II during therapy with terazosin; this result tends to argue against a generalized increase in vascular smooth muscle sensitivity associated with enhanced sensitivity to phenylephrine. However, the angiotensin II data were highly variable, and there is a possibility that a nonspecific change could have been missed because of inadequate power. A power calculation using the standard deviation derived from the baseline studies (51) indicates that, given the number of subjects in this study and the variability in our data, we had an 80% chance of detecting a difference of 50% between means in log ED_{50} for angiotensin II with $\alpha = 0.05$ ($\beta = 0.2$).

A reduction in drug concentration due to altered clearance could also result in a reduction in the α_1-adrenoceptor–blocking effect of terazosin. However, in this study, terazosin concentrations were virtually identical on all study days. Consequently, it is very unlikely that concentrations of terazosin at α_1-receptor sites changed during the course of treatment with the drug. Similar plasma concentrations of terazosin have been observed by other investigators after the administration of the same dose of terazosin (41, 47).

Elliott et al. (52) used systemic infusions of phenylephrine to evaluate vascular α_1-adrenoceptor responsiveness. In their study, a modest but significant loss of arterial α_1-adrenoceptor blockade occurred at the end of the first week of treatment, which then remained stable during chronic treatment with prazosin for 3 mo. In hypertension, arterial responsiveness is of major significance whereas, in congestive heart failure, responsiveness of the capacitance vessels (veins) is of considerable importance. The study of Elliott et al., in conjunction with this study, suggest that loss of α_1-blockade occurs in both arterial and venous vascular beds but may be more marked in the latter. In view of the large effect observed in this study, tolerance in veins could be very important and extrapolation of these findings to congestive heart failure must be done cautiously. In an earlier study, we (30) administered prazosin to hypertensive patients and evaluated α_1-adrenoceptor responsiveness using the dorsal hand-vein compliance technique after 6 wk of treatment with prazosin. In this study, α_1-adrenoceptor antagonism was substantial with a significant increase in ED_{50} for phenylephrine after treatment with a constant dose of prazosin for up to 4 wk. Whether the result of this earlier study differs from our current study is not clear since α_1-receptor blockade was not evaluated earlier in the course of treatment with prazosin. Our findings with terazosin suggest that there may be differences between prazosin and terazosin in the way they interact with α_1-adrenoceptors, with prazosin having a greater affinity for the postjunctional α_1-adrenoceptors.

In this study, we have shown that tolerance develops to the α_1-adrenoceptor–blocking activity of terazosin in man, manifested as an increased sensitivity to phenylephrine but not to angiotensin II. The exact mechanism of this tolerance is not clear but the most likely possibilities relate to alterations in receptor or postreceptor events. The simplest hypothesis to explain these findings is an increase in the expression of vascular α_1-adrenoceptors. This increase in receptor number or affinity could result in an increase in sensitivity to an α_1-receptor agonist; this general mechanism would be similar to observations after treatment with 6-hydroxydopamine (53) or the increased responsiveness to β-receptor agonists after abrupt discontinuation of chronic propranolol administration (44). Compatible with this hypothesis, Awan et al. (9) have shown that tolerance to prazosin can be reversed by increasing the dose of prazosin or by introducing a drug-free interval during treatment.

True pharmacological tolerance to α_1-adrenoceptor blockade by terazosin occurs in man. The molecular mechanism of this phenomenon and its implications for the clinical use of these agents in humans need further study.

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