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Influence of a single dose of 20 mg tadalafil, a phosphodiesterase 5 inhibitor, on ambulatory blood pressure in subjects with hypertension

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Aims
To test the non-inferiority of a single dose of tadalafil 20 mg compared with placebo with respect to 26-h mean ambulatory systolic and diastolic blood pressure in treated and untreated hypertensive subjects.

Methods
A multicentre, randomized, double-blind, placebo-controlled crossover study in 114 subjects with hypertension (36 subjects on no therapy with daytime mean ambulatory blood pressure ≥140/85 mmHg; 38 subjects on two to four classes of antihypertensive agents with daytime mean ambulatory blood pressure ≥140/85 mmHg and 40 subjects on two to four classes of antihypertensive agents with ambulatory blood pressure <140/85 mmHg).

Results
Overall tadalafil reduced mean ambulatory blood pressure monitor systolic and diastolic blood pressure by 4.8 mmHg [95% confidence interval (CI) 3.7, 5.9; $P < 0.01$] and 2.9 mmHg (95% CI 1.9, 3.6; $P < 0.01$), respectively, compared with placebo. In hypertensive subjects with uncontrolled blood pressure on two to four classes of antihypertensive agents ($n = 36$) tadalafil reduced mean ABPM systolic and diastolic blood pressure by 7.5 mmHg (95% CI 5.4, 9.6; $P < 0.01$) and 4.3 mmHg (95% CI 6.1, 8.9; $P < 0.01$) compared with placebo.

Conclusions
In patients with uncontrolled hypertension on multiple agents the addition of tadalafil 20 mg lowered mean 26-h blood pressure.

Introduction

Although hypertension itself is asymptomatic, it is often associated with severe erectile dysfunction (ED) [1]. This link can be partially explained by the recognized association between traditional vascular risk factors and ED [2, 3]. In the USA, for example, approximately 36% and 20% of men in their 5th decade have hypertension and ED, respectively, while both these figures increase to over 60% by the age of 70 years [4–6].

With the global increase in life expectancy, obesity rates and the associated vascular disease, one can foresee a burgeoning health burden from both hypertension and ED [7, 8]. Addressing these linked vascular disorders with a single agent is a novel yet logical approach,

particularly when considering that antihypertensive drug treatment has often been implicated as a cause of ED.

Sildenafil citrate, the first agent in the class of phosphodiesterase-5 (PDE_5) inhibitors to receive regulatory approval, has been shown to have mild transient peripheral vasodilatory and hypotensive effects [9], in addition to its beneficial effects in the penile vasculature. In contrast with sildenafil and its half-life of 4 h, tadalafil, a newer PDE_5 inhibitor, has a 17.5-h half-life and the potential to provide prolonged pharmacotherapeutic benefits in subjects with both hypertension and ED. Tadalafil has been proven to be efficacious in the treatment of ED in patients with a variety of clinical conditions, including hypertension [10]. In addition, its effect on ED when taken as an alternate day therapy has been assessed [11].

Various data from studies in both normotensive and hypertensive subjects available at the time of the study design suggested a significant but small antihypertensive effect when tadalafil was taken alone and an additive effect with other monotherapies for hypertension. Significant additive office blood pressure (BP)-lowering effects of between 6 and 8 mmHg systolic and 4–5 mmHg diastolic BP have been demonstrated with tadalafil 10 mg in conjunction with metoprolol (25–200 mg) and bendrofluazide (2.5 mg) and with 20 mg tadalafil and angiotensin II receptor antagonists when compared with placebo [12].

Studies using both sildenafil and tadalafil have suggested that there is a shallow dose–response curve for haemodynamic effects. However, the effect of 20 mg tadalafil in hypertensive subjects on multiple antihypertensive therapies and in hypertensive subjects on no antihypertensive therapy had not been tested in a large study assessing ambulatory blood pressure.

Methods

This study was conducted by the Scottish Hypertension Academic Research Collaboration (SHARC) at three centres. Local ethics committees approved the study, which was designed to test the hypothesis that in hypertensive subjects the effect on BP of tadalafil 20 mg was no different from that of placebo. The study was conducted in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. All subjects gave written voluntary informed consent and continued on their usual medication throughout the study.

Outcomes

The primary and secondary outcomes were changes from screening in ambulatory blood pressure monitor (ABPM) mean systolic (SBP) and diastolic BP (DBP), respectively.

Participants

Subjects were recruited from outpatient clinics at the three affiliated hospitals. Exclusion criteria included active substance abuse, major organ disease (apart from drug treatment for diabetes mellitus, acid indigestion, osteoarthritis, hypercholesterolaemia or anxiety/depression), nitrate use or PDE_5 inhibitor allergy.

Subjects ≥18 years of age with normal laboratory test and ECG results (apart from left ventricular hypertrophy) were randomized into the double-blind, placebo-controlled, crossover phase if their screening mean daytime ABPM BP fulfilled one of the following group criteria:

- ≤175/105 but ≥140/85 mmHg
  - ✧ on no therapy for at least 1 week Group A
  - ✧ on two to four classes of antihypertensive agents Group B

  or
- <140/85 mmHg on two to four classes of antihypertensive agents Group C.

Interventions

Screening Subjects ingested no grapefruit-containing products and 2 units (1 unit =a drink with 10 ml of ethanol/ethyl alcohol) or less of alcohol per day from 1 week before randomization until the study end. Subjects attended fasted for an initial full medical examination and laboratory indices (ECG, haematology, biochemistry and urinalysis). An ABPM device was then fitted and subjects completed a standardized breakfast within 30 min and consumed only water during a 6-h period of observation for hourly monitoring of vital signs. Smoking was not allowed during this time. Subjects returned the following day for ABPM removal, 26 h after fitting.

Crossover study The procedure for treatment periods 1 and 2 was identical to that during the screening period. Subjects were dosed with either tadalafil 20 mg or placebo 30 min after ABPM fitting. On day 2 subjects returned for removal of the monitor, inquiry about adverse events and blood sampling for electrolytes.

Blood pressure

Manual BP. A trained nurse measured blood pressure in the seated position in the dominant arm according to British Hypertension Society guidelines with a well-calibrated mercury sphygmomanometer [13].

ABPM. Between 08.00 and 10.00 h, an ABPM (Spacelabs 90207, Issaquah, WA, USA) was fitted on the nondominant arm and then calibrated using five manual BP readings via a T-piece. The ABPM device was programmed to record for 26 h with 15-min measurement intervals, apart from 22.00–08.00 h when the interval was 30 min. Upon return of the ABPM, data were downloaded via a modem link to Biomedical Systems Corporation (Brussels, Belgium) for blinded analysis. The screening mean daytime BP results were faxed back to the study centre for categorization of subjects into Group A, B or C. On treatment results were analysed at the end of the study.

Clinically significant blood pressure changes Changes from baseline in systolic and diastolic BP of >30 or >20 mmHg, or an absolute value of <85 or <45 mmHg, respectively, were considered clinically significant. These values, based upon values for normotensive subjects [12], were specifically required by the regulatory authorities (Food and Drug Administration) with regard to previous haemodynamic interaction studies with tadalafil [14].

Adverse event monitoring Subjects were asked to keep a study diary recording the time and details of daily activities, medication taking and adverse events. Subjects were also questioned about adverse events at study visits.

Sample size

For each population a non-inferiority hypothesis with a limit of non-inferiority of 4 mmHg was tested. Using this criterion and assuming a within-subject standard deviation for maximum post-baseline difference in ambulatory mean SBP of 7.77 mmHg, a population size of 36 subjects per group provided 90% power to declare non-inferiority.

Randomization and blinding

Eli Lilly and Company Ltd (Windlesham, UK) entered anonymized subjects into a stratified randomization after assigning each a kit number, kits containing matching tadalafil 20 mg and matching placebo having previously been allocated to each study site. The randomization code remained unbroken throughout the study.

Statistics

Two distinct analyses were performed

1 For each group, the change from the screening in both 26-h ambulatory BP was calculated for each time point post dose. Least squares (LS) means, mean differences and the upper 95% confidence interval (CI) for differences were calculated using a mixed effects model where the period and treatment were fixed effects and the subject was a random effect. Non-inferiority was confirmed if the upper 95% CI was <4 mmHg.
2 The change from the screening mean 26 h ambulatory BP was calculated for periods 1 and 2. These data were analysed using repeated measures ANOVA (SPSS v 11.5; SPSS Inc., Chicago, IL, USA) with change in mean 26 h ABPM BP as the dependent variable, screening mean SBP as a covariate and antihypertensive treatment as a between-subject factor.

Results

Study subjects

A total of 114 caucasian subjects were randomized (112 completed; 41 females, 71 males): 36 subjects in population A, 38 subjects in population B and 40 subjects in population C. Two subjects in population B were withdrawn following dosing in treatment period 1 due to protocol violations (administration of five classes of antihypertensive medication and change of antihypertensive medication during the study). Both subjects were dosed in treatment period 1 (one received 20 mg tadalafil and one received placebo). Available data for all subjects were included in the safety and pharmacodynamic evaluations (Tables 1 and 2).

Table 1
Subject demographics, mean (SD)

Group	A	B	C
Age, years	53 (10)	57 (10)	57 (10)
Weight, kg	85 (15)	87 (17)	87 (16)
Height, cm	170 (9)	170 (10)	167 (11)
Body mass index, kg m^{-2}	29 (4)	29 (4)	31 (5)
Number	36	38	40
Male	26	25	22
Female	10	13	18
LVH	3	7	7
HC (no. on treatment)	6 (4)	16 (10)	10 (7)
DM	2	2	4

LVH, Left ventricular hypertrophy from ECG or echocardiography; HC, hypercholesterolaemia; DM, diabetes mellitus.

Blood pressure

An initial analysis using least squares means demonstrated that tadalafil-induced changes from screening BP were non-inferior to placebo only for DBP in Group A and for SBP in Group C. All other BP differences failed non-inferiority testing (Table 3).

The secondary analysis using ANOVA demonstrated statistically significant 26-h ambulatory BP changes for Groups A, B and C (see below). An analysis of 24-h ambulatory data revealed results similar to the 26-h monitoring analysis.

Table 2
Concomitant antihypertensive therapy for Groups B and C

Drug	Antihypertensive therapy Group B	Group C
ACE-inhibitors	15 (39)	11 (28)
Angiotensin II antagonist	13 (34)	13 (32)
β-Blocker	22 (58)	18 (45)
Calcium antagonist	16 (42)	19 (47)
Thiazide	29 (76)	29 (73)
Loop diuretic	3 (8)	1 (2.5)
Doxazosin	7 (18)	4 (10)
Spironolactone	1 (2.6)	1 (2.5)
Moxonidine	2 (6)	0

n *(%); ACE, angiotensin converting enzyme.*

Group A (uncontrolled hypertension on no drug therapy) Mean changes from baseline 26-h ambulatory mean SBP and DBP on tadalafil compared with placebo were −3.9 mmHg (95% CI 2.2, 5.6; $P < 0.01$) and −2.2 mmHg (95% CI 0.6, 3.8; $P < 0.01$), respectively.

Group B (uncontrolled hypertension on two to four classes of antihypertensive) Mean changes from baseline 26-h ambulatory mean SBP and DBP on tadalafil compared with placebo were −7.5 mmHg (95% CI 5.4, 9.6; $P < 0.01$) and −4.3 mmHg (95% CI 2.9, 5.6; $P < 0.01$), respectively.

Group C (controlled hypertension on two to four classes of antihypertensive) Mean changes from baseline 26-h ambulatory mean SBP and DBP on tadalafil compared with placebo were −3.3 mmHg (95% CI 1.5, 5; $P < 0.01$) and −2.8 mmHg (95% CI 1.5, 4; $P < 0.01$), respectively.

In addition changes in SBP and DBP for all subjects combined were significant when compared with ANOVA (Table 4).

Mean daytime and night time data are shown in Table 5.

Clinically significant BP changes

More subjects experienced clinically significant decreases in ambulatory systolic and diastolic BP following administration of tadalafil compared with placebo, but this was statistically significant only for Group

Table 3
Summary results for each of the groups for the change from the screening in ambulatory blood pressure (mmHg) calculated for each time point post dose and analysed by least squares means

Group 26-h screening blood pressure			A 144/90	B 144/86	C 127/77
SBP	Change from screening	Tadalafil	–7.2 (3–22)	–11.2 (0–22)	–5.7 (3–13)
		Placebo	–3.2 (8–11)	–3.8 (5–17)	–2.4 (6–11)
	Tadalafil–placebo LSM		–4.9 [8.1]	–8.3 [13.6]	–1 [3.6]
DBP	Change from screening	Tadalafil	–5.1 (1–19)	–7.6 (1–14)	–3.8 (7–7)
		Placebo	–2.9 (5–13)	–3.3 (6–19)	–0.9 (6–19)
	Tadalafil–placebo LSM		–0.8 [3.1]	–6.0 [8.7]	–4.1 [6.3]
HR	Change from screening	Tadalafil	3	1	2
		Placebo	–1	–2	0

Data are mean (range); [upper 95% CI]; LSM, least squares means; SBP, systolic blood pressure; DBP diastolic blood pressure; HR, heart rate.

Table 4
Summary of blood pressure (mmHg) results for the whole group (A + B + C)

n = 112	Screening	Tadalafil	Screening-tadalafil	Placebo	Screening-placebo	*P*-value
SBP	137 (135, 140)	129 (127, 131)	–7.9 (6.7, 9.1)	134 (132, 137)	–3.1 (1.8, 4.3)	<0.01 –
DBP	84 (82, 85)	78 (77, 80)	–5.4 (4.6, 6.2)	82 (80, 83)	–2.3 (1.3, 3.2)	<0.01 –
HR	68	69	1	67	–1	NS

Data are mean (95% CI); SBP, systolic blood pressure; DBP diastolic blood pressure; HR, heart rate; data analysed using ANOVA (SPSS v 11.5) with change from screening in mean 26-h ambulatory blood pressure monitor BP as the dependant variable, screening mean SBP as a covariate and antihypertensive treatment as a between-subject factor.

Table 5
Mean day time and night time peak and trough ambulatory blood pressure data per treatment group

			Day time		Night time	
			Tadalafil 20 mg	Placebo	Tadalafil 20 mg	Placebo
Group A	SBP	Peak	173 (168, 177)	177 (173, 182)	150 (145, 154)	152 (147, 156)
		Trough	117 (114, 120)	120 (116, 123)	102 (99, 106)	107 (103, 111)
	DBP	Peak	110 (108, 112)	113 (110, 115)	92 (90, 95)	96 (93, 99)
		Trough	69 (67, 72)	72 (69, 74)	56 (54, 58)	61 (58, 63)
Group B	SBP	Peak	166 (163, 170)	178 (172, 184)	150 (145, 155)	156 (151, 161)
		Trough	109 (106, 112)	117 (114, 121)	102 (98, 105)	108 (104, 112)
	DBP	Peak	104 (101, 107)	109 (106, 112)	91 (88, 95)	93 (90, 97)
		Trough	61 (59, 64)	67 (64, 70)	53 (51, 56)	58 (56, 61)
Group C	SBP	Peak	153 (150, 156)	159 (156, 163)	132 (128, 135)	134 (131, 137)
		Trough	101 (98, 103)	104 (102, 106)	95 (92, 98)	96 (94, 98)
	DBP	Peak	94 (92, 97)	98 (96, 101)	82 (79, 85)	84 (81, 87)
		Trough	56 (54, 58)	59 (57, 62)	51 (48, 53)	53 (51, 55)

mmHg (95% CI); day time 08.00–20.00 h; night time 20.00–08.00 h.

B ($P = 0.041$). No decreases in BP were associated with hypotensive symptoms (Table 6).

Tolerability

The total number of adverse events that were thought to be drug related was 120 and 30 for tadalafil and placebo, respectively. Of the adverse events attributable to tadalafil, 33% were mild, 53% were moderate and 14% were severe. There was a similar distribution of adverse event severity for placebo (30%; 50%; 20%) No serious adverse events were reported (Table 7).

The adverse events reported (listed in order of frequency observed in the study), namely headache, dyspepsia, back pain, myalgia and flushing were consistent with the data sheet on tadalafil. In total, 65 of the 114 subjects were adverse event free after tadalafil dosing and 96 subjects were adverse event free on placebo only. Thus, 57% of subjects experienced no adverse events after tadalafil dosing and the figure for placebo was 84%. Of the total headache incidents reported following tadalafil, 42% were mild, 53% moderate and 5% severe. Of the total myalgia incidents reported following tadalafil, 16% were mild, 56% moderate and 28% severe. Of the total back pain incidents reported following tadalafil, 13% were mild, 50% moderate and 37% severe. Adverse events either resolved spontane-

ously or responded to paracetamol or other simple analgesia as required.

Discussion

This study has proved that a single dose of tadalafil 20 mg results in a significant BP reduction in subjects with hypertension. These BP-lowering effects are in keeping with other interaction studies in both hypertensive and coronary artery disease subjects [12, 15]. Taken as a whole, these effects are clinically important as systolic BP is recognized to be the major risk predictor in hypertension [16, 17] and is generally unsatisfactorily managed, with only small proportions of patients reaching target BP [18].

Table 6
Numbers of clinically significant decreases in ambulatory blood pressure (BP)

		Number of subjects with a CSD in ambulatory BP		
	Group	A	B	C
SBP	Screening	1 (9)	1 (2)	3 (6)
	Tadalafil	29 (170)	33 (310)	28 (130)
	Placebo	27 (96)	28 (153)	25 (90)
DBP	Screening	2 (4)	1 (3)	7 (17)
	Tadalafil	35 (195)	35 (273)	37 (162)
	Placebo	31 (175)	29 (152)	32 (120)

CSD, Clinically significant decrease; (number of clinically significant decreases); SBP, systolic blood pressure; DBP diastolic blood pressure.

The mechanism responsible for the haemodynamics effect of tadalafil requires clarification. The vasodilatory mechanism is known to interact with both nitrate and α-blocker therapy. PDE_5 inhibitors are contraindicated with nitrates due to the substantial potentiation of hypotensive effects. Tadalafil augments the vasodilatory action of doxazosin by up to 9.8 mmHg and currently may only be used with caution for patients on this drug [19]. Peripheral vasodilation secondary to PDE_5 inhibition is known to occur during periods of augmented nitric oxide drive [20]; despite this, the dose–response at the doses used for ED is shallow. Incremental dosages do not significantly lower blood pressure further in otherwise healthy subjects [9]. The hypotensive action of tadalafil may depend upon a balance between nitric oxide and renin bioavailability in relation to the degree of constriction/dilation of the peripheral circulation. Sildenafil citrate has been shown to increase renin production in normotensive men [21], a possible mechanism limiting its vascular vasodilatory effect. This generates a hypothesis for the limited blood pressure responses seen in the untreated hypertensive subjects in study group A, in which the effects of reflex PDE_5 inhibitor-induced renin secretion (not blocked by drug therapy such as ACE-inhibitors) could limit the blood pressure-lowering effects of tadalafil. In contrast, subjects with uncontrolled hypertension on multiple therapies (Group B) demonstrated the largest blood pressure fall, probably due to the relatively vasoconstricted vasculature in the presence of antihypertensive therapy inhibiting the effects of any reflex renin secretion upon the angiotensin–aldosterone axis. Subjects with controlled BP (Group C) on therapy, on the other hand, tend to be relatively vasodilated [22] and less prone to further BP reduction from PDE_5 inhibition. Unfortunately, we

Table 7
Frequencies of drug-related adverse events by type

	Overall $n = 114$		Group A $n = 36$		Group B $n = 38$		Group C $n = 40$	
	Tadalafil	Placebo	Tadalafil	Placebo	Tadalafil	Placebo	Tadalafil	Placebo
Headache	23 (41)	4 (6)	25 (12)	3 (1)	21 (16)	8 (4)	23 (13)	3 (1)
Myalgia	10 (18)	2 (3)	14 (9)	0	11 (7)	0	5 (2)	5 (3)
Back pain	11 (16)	0	8 (3)	0	11 (6)	0	13 (7)	0
Flushing	7 (9)	0	8 (1)	0	5 (3)	0	8 (3)	0
Dyspepsia	4 (8)	0	3 (1)	0	3 (1)	0	8 (6)	0

Percentage of subjects with adverse event (number of adverse events).

did not measure renin values during this study to confirm this hypothesis.

The use of tadalafil and other PDE-5 inhibitors in subjects at risk of cardiovascular disease has to date not been associated with adverse effects on cardiovascular morbidity or mortality [15, 23]. Data from clinical trials performed in the general population of men with ED, including those with cardiovascular disease, show that the incidence of cardiovascular adverse events is not increased in men taking tadalafil or sildenafil and is similar to that observed in the general population of men with ED [11, 22]. Additionally, the myocardial infarction rate across 29 double-blind and open-label tadalafil clinical trials in patients with ED was 0.43 per 100 patient years in tadalafil-treated patients compared with 0.6 per 100 patient years in placebo-treated patients [15], while in a meta-analysis, sildenafil citrate was found to have a favourable effect on mortality [24].

One question that remains unanswered is whether the antihypertensive effects of tadalafil persist at the dosages and frequency of use in ED subjects. Certainly, tolerability is not a problem with chronic use for ED [25]. One of the remaining challenges for modern therapeutics is the maintenance of a good quality of life when treating hypertensive patients. This study has demonstrated that tadalafil may be useful in reducing some of the excess risk attributable to BP in uncontrolled hypertension, with little reduction in quality of life. Indeed, men with resistant hypertension are more likely to have severe ED and may have an improved quality of life on tadalafil. Patients on antihypertensive therapy often implicate drug therapy as a major contributor to ED, whilst clinicians implicate risk factors. The ideal antihypertensive drug should have a neutral or positive effect on erectile function. Tadalafil could fulfil such a role. This, however, was a single dosing study and at present little is known of its blood pressure effects when taken chronically in hypertensive subjects, although in healthy subjects it has been shown to reduce SBP by 2.79 mmHg compared with 0.63 mmHg by placebo when taken over 26 weeks at the 20-mg dose [15]. Additionally, the side-effect profile in the present study may not be insignificant for the average patient with hypertension. Tadalafil is, however, well tolerated when used chronically in the ED setting [26]. Patients with both hypertension and ED may be more inclined to tolerate side-effects in lieu of improved erectile function. It is also possible that tolerance to side-effects may occur [27].

We have demonstrated an incremental antihypertensive effect of a single dose of tadalafil in uncontrolled hypertensive subjects. An additional mortality and morbidity benefit may be brought about by the chronic use of tadalafil in subjects with both ED and uncontrolled hypertension and, more specifically, in diabetic subjects who are at increased cardiovascular risk [28], more likely to suffer severe ED [29] and require more aggressive blood pressure-lowering therapy than the general hypertensive population [13, 30].

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