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Anomalies in the Dosing of Diltiazem

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Summary: From early research, investigators understood that the dose of diltiazem required for the treatment of hypertension (commonly 360 mg/day) was greater than that required for the treatment of angina (commonly 240 mg/day). Nonetheless, studies of recent prescribing practices show that the 240 and 180 mg capsule strengths constitute more than 70% of the diltiazem prescriptions for hypertension. Physicians became accustomed to the lower antianginal doses of diltiazem for 7 years before a hypertension indication was approved. Subsequently, these dosing levels were reinforced by the production of once-a-day formulations with highest capsule strengths of 240 mg and 300 mg. These strengths were dictated by the sheer bulk of the formulations, which limited how much diltiazem could be inserted into the #00 capsule, the largest capsule that can be comfortably administered. An examination of the combined data from the six randomized, blinded, and placebo-controlled trials submitted to the FDA for the original new drug applications of the three formulations of diltiazem available in the United States shows a clear linear dose–response relationship between diltiazem dose and blood pressure lowering through the 480–540 mg/day range. It also demonstrates that the 90–120 mg/day range is the "no-effect dose." These conclusions are supported by a MEDLINE review of all other studies of multilevel dosing of higher dose levels of diltiazem. The data support the conclusion that diltiazem is generally underdosed, but when properly dosed may be the single most potent antihypertensive overall.

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Introduction

Diltiazem has been a major antianginal and antihypertensive drug in the United States since its introduction in 1982, following 6 years of development and clinical trials.[1] It is unique among either antihypertensive or antianginal drugs in that three independent pharmaceutical manufacturers have gone through the new drug application (NDA) process to gain United States Food and Drug Administration (FDA) approval for separate formulations of diltiazem, and three other pharmaceutical firms market generic forms of diltiazem in the United States. As a result, few other drugs have been studied as intensively in such a systematic way.

Strangely, after being studied and used in the United States for two decades, diltiazem continues to be misunderstood and misdosed by physicians. From research studies leading to the FDA approval of diltiazem in 1982[2–7] for angina and in 1989 for hypertension,[8–17] investigators understood that the dose of diltiazem required for the treatment of hypertension was greater than that required for the treatment of angina. While 240 mg/day was the most common dose leading to angina control, investigators also understood that they might achieve further control of drug-resistant angina using doses of 360 mg/day[2,6,7,18–20] even in the presence of beta blockade[21] and, in some cases, 480 mg/day.[22] In contrast to the most common antianginal dose of 240 mg/day, the most common dose of diltiazem for the treatment of hypertension in early studies was 360 mg/day (required by 85% of patients for complete control).[10]

Since diltiazem is generally recognized as a drug with a low side-effect profile,[1] it seems unlikely that it would be underdosed because of fear of adverse effects. In a large comparative study with other major antihypertensives and placebo, only subjects receiving hydrochlorothiazide had fewer withdrawals due to side effects, while placebo had more.[23] It appears that the reason diltiazem is underdosed is related to an unusual

combination of factors that have shaped physician attitudes. The purpose of this review is to examine the historic reasons that explain anomalies in the dosing of diltiazem and examine the evidence that forms the basis for its proper dosing.

Background

Seven years after diltiazem was approved for use in the treatment of angina, it was approved for use in hypertension. During this period of time, physicians became accustomed to the lower doses successfully used in the treatment of angina, most often 180–240 mg/day. Subsequently, it was difficult to adjust this learned behavior to the new requirements of dosing for hypertension. In addition, this behavior was reinforced by circumstances of the subsequent development of diltiazem.

The first once-daily formulation of diltiazem (Cardizem® CD, Hoechst Marion Roussel, Kansas City, Mo., USA) was developed in the years prior to 1992. A feature of this formulation was the bulk of the excipient. As a result, only 300 mg of this formulation would fit into a #00 capsule, which is the largest size capsule that can be taken effectively by patients. This dose was 60 mg less than the dose that had previously been shown to be required for complete blood pressure control in the majority of moderately hypertensive patients.[10] Nonetheless, size constraints made it the highest dose available and this, in turn, led physicians to believe that greater doses should not be given. With the introduction of the second once-daily formulation of diltiazem (Dilacor XR®, Watson Laboratories, Inc., Corona, Calif., USA) in 1992, there was again a volume problem. This formulation took the form of 60 mg tablets placed in a capsule. Because only four tablets could fit into the #00 capsule, the maximum single capsule dose for this formulation of diltiazem was 240 mg. Again, the underlying implication was that higher doses should not be given. It was not until 1996 that the third once-daily formulation of diltiazem (Tiazac®, Forest Pharmaceuticals, Div. of Forest Laboratories, Inc., St. Louis, Mo., USA), which used a less bulky formulation, became available in a 360 mg dose in a smaller capsule (#0) and in 1999 in a 420 mg dose form, which again reached the volume limit of the largest capsule (#00).

Thus, it is easy to understand that physicians who for years had been comfortable with the 180–240 mg antianginal dose of diltiazem would be unlikely to use higher doses properly for the treatment of hypertension when the highest single dose marketed (usually an indication of the highest safe or effective dose) was 240–300 mg.

Current Prescribing Patterns

Recent data (from 1998) on the prescribing patterns of physicians[24] show that prescriptions of diltiazem for the treatment of hypertension are most frequently for the 240 mg capsule (43.3%), next most frequently for the 180 mg capsule (28.7%), with 9.8% for the 120 mg capsule, and only a total of 4.0% for the 360 mg and higher quantities. Many physicians hesitate at doses > 300 mg/day, become nervous at doses of 360–480 mg/day, and would not consider 540 mg/day (personal experience of the author). *The Physicians' Desk Reference* (PDR), the commonly used source of dosing information,[25] represents FDA-approved indications and states that 180–240 mg/day is the usual starting dose for diltiazem and that titration up to 540 mg/day may be carried out.[26] Thus, there is a wide discrepancy between the dosing levels used by physicians and those that have been found to be appropriate by both the regulatory and scientific communities. Although these differences are surprising, they appear to be explained by the history above.

The consequence of underdosing is an appearance that diltiazem is not particularly effective in moderate hypertension and especially not effective in patients with higher levels of hypertension. This is despite the demonstration that diltiazem is very effective in those with higher levels of blood pressure.[27] Because of these problems, it is important to review the evidence for the proper dosing of this widely used drug.

Clinical Trials

Many studies (Tables I and II) have confirmed the dose–response relationship of diltiazem dose to blood pressure reduction, but among them there are differences in subject populations and inclusion criteria, differences in methods, and small- to medium-size study populations. In contrast, data submitted for the NDA approval of a drug for a specific indication are usually similar among studies even if different pharmaceutical companies submit the data; this is due to the standardized requirements of the FDA. For FDA approval for a hypertension indication, two pivotal studies are usually submitted, one that is a fixed-dose comparison and one that is a forced-dose titration. This was the case for the three separate once-a-day formulations of diltiazem. Thus, NDAs for diltiazem included a total of three fixed-dose and three forced-dose titration studies, all of ample size.

Although the various formulations of diltiazem have a number of pharmacokinetic differences,[28–30] no one has demonstrated clearly important differences in clinical use. Because of the regulatory conditions under which they were carried out, these NDA studies also had similar and clinically relevant inclusion and exclusion criteria, and all the data were harvested under monitored conditions that satisfy regulatory criteria. To confirm the findings of a dose–response relationship, it seemed appropriate to combine the results of these six similar trials (a total of 956 subjects). Five of the six studies have been published separately.[12–15,31] These studies are referred to as the six pivotal studies (submitted to the FDA as NDA 20-062 for Cardizem® CD, NDA 20-092 for Dilacor XR®, and NDA 20-401 for Tiazac®).

Each of the six pivotal studies included hypertensive patients whose untreated supine diastolic blood pressure (SuDBP) was required to be similar on two separate visits and to fall between 95 and 110–114 mmHg supine. Subjects with conditions that would make them poor candidates to receive

TABLE I Multidose diltiazem studies in the 360–540 mg/day range in hypertensive subjects using monotherapy or in combination with hydrochlorothiazide[a]

Trial (Ref. No.)	Dose range mg/day	Result
Pool (1986) (10)	120, 240, 360	A dose titration study. To achieve a 10% reduction in DBP, 360 mg/day was required in 85% of patients
Hedner (1990) (9)	120, 240, 360	A forced-titration study in which progressive increases in response rate were seen with the greatest increment at the 360 mg/day dose
Burris (1990) (8)	DTZ 120, 180, 240, 360; HCTZ 12.5, 25, 50	Multifactorial design study with DTZ and HCTZ showing statistically significant linear reductions (both individual and combination) with increasing dose
Pool (1990) (11)	120, 240, 270, 360	A combination of three studies involving one fixed dose and two titration trials (total of 260 subjects) showed a dose response with 120 mg/day as the ineffective dose
Djian (1990) (35)	240, 300, 360	A dose–response study in which 300 and 360 mg of diltiazem lowered DBP equally and both significantly greater than 240 mg
Massie (1992) (12)	120, 240, 360	A dose titration study with a progressive increase in responders with increasing dose
Felicetta (1992) (13)	90, 180, 360, 540	A fixed-dose study in which a linear dose response was seen with changes in DBP and SBP for trough and peak measurements
Whelton (1992) (14)	120, 240, 360, 480	A fixed-dose study with a significant linear trend across all treatments
Woehler (1992) (15)	180, 360, 540	A forced-dose titration study showing a progressive decline in DBP and progressive increase in responders (41, 59, 65%) with increasing dose
Graney (1992) (17)	120, 180, 240, 360, 480, 540	A combination of two trials, a fixed-dose and forced escalation trial showing an incremental blood pressure reduction and an increase in the percentage of responders with increasing dose
Weir (1992) (16)	DTZ 120, 180, 240; HCTZ 12.5, 25	A forced-dosing multiple-therapy study that demonstrated a dose–response relationship for the combination therapy
Materson (1993) (23)	120, 240, 360	A dose-titration trial comparing six antihypertensives in monotherapy. To lower DBP to < 90 mmHg required a dose of 120 mg in 31%, 240 mg in 33%, and 360 in 36% of responders
Fiddes (1994) (36)	240, 480	An increase in dose from 240 to 480 mg/day increased the number of responders
Materson (1995) (37)	120, 240, 360	When used as second monotherapy after failure of another antihypertensive, lowering DBP to < 90 mmHg required a dose of 120 mg in 16%, 240 mg in 31%, and 360 in 53% of responders
Ollivier (1995) (38)	200, 300, 400	A dose-titration study in which 300 and 400 mg produced more responders than 200 mg/day
Lacourciere (1995) (31)	120, 240, 360, 540	A forced-titration study in which a significant incremental dose–response effect was observed for both systolic and diastolic blood pressure
Nilsson (1996) (39)	240, 300, 360, 420	A fixed-dose study with a linear dose–response and an increase in responders at each dose level. Response rates were 29.1% for placebo, and 54.7, 55.6, 59.0, and 63.2% for each of the doses, respectively

[a] Results of a MEDLINE search using hypertension, dose–response, and the doses 360, 480, and 540 mg.
The reports of five of the six (one remains unpublished) pivotal studies are in bold print.
Abbreviations: DTZ = diltiazem,; HCTZ = hydrochlorothiazide, DBP = diastolic blood pressure, SBP = systolic blood pressure.

diltiazem in a clinical situation were excluded, for example, poor hepatorenal function, advanced heart block, recent myocardial infarction, and congestive heart failure. Subjects could not have secondary forms of hypertension nor take drugs affecting blood pressure.

Taken together, these six studies included daily diltiazem doses of 90, 120, 180, 240, 360, 480, and 540 mg/day. Successful treatment was defined as a response to monotherapy with diltiazem with a reduction of SuDBP at the end of the study and at the end of a 24-h dosing period to < 90 mmHg on

TABLE II Multidose diltiazem studies with doses ≥ 360 mg/day in subjects with angina using monotherapy or in combination with propranolol[a]

Trial (Ref. No.)	Dose range mg/day	Result
Lindenberg (1983) (6)	120, 240, 360	Treadmill time was significantly enhanced by increasing dose
Thadani (1994) (22)	60, 120, 240, 360, 480	A significant linear dose trend ($p = 0.004$) was present across the treatment groups for the primary endpoint—time to exercise termination
Weiner (1986) (18)	240, 360	An increase from 240 to 360 mg/day reduced the frequency of weekly anginal but not treadmill time
Bala Subramanian (1983) (2)	180, 270, 360	Mean exercise time increased significantly with increasing dose from 180 to 270 mg/day and to 360 mg/day
Cutler (1995) (40)	120, 240, 480	Increasing doses significantly improved total exercise time, anginal attacks, nitroglycerin use, and silent ischemic events although the improvement from 240 to 480 mg/day was modest
Go (1984) (20)	120, 240, 360	Progressive increase in exercise time with increasing dose
Humen (1986) (21)	240 and 360, in addition to propranolol	In the presence of full beta-receptor blockade with propranolol, the addition of diltiazem 360 mg/day significantly increased exercise time compared with the addition of diltiazem 240 mg/day
Logan (1988) (41)	180, 270, 360	In elderly subjects over age 71, exercise duration was improved by 180 to 270 mg/day, but not further at 360 mg/day

[a] Results of a MEDLINE search using angina, dose–response, and the doses 360 and 480 mg.

the one hand, or to < 90 mmHg or a fall in SuDBP of at least 10 mmHg on the other hand. The distribution of responders and nonresponders at each group of doses for the six pivotal studies is shown in Table III. Two conclusions are evident from these data. First, it is clear that the 90–120 mg/day dose level is the no-effect dose for the treatment of hypertension. Second, Figure 1 shows that the response at each dose level demonstrates a linear dose–response relationship that could actually extend beyond 540 mg/day. The review by the FDA of the original NDA submission for a once-a-day formulation of diltiazem supported both of these conclusions and went on to suggest that further studies of the therapeutic effects of 720 and 1040 mg/day should be considered.[32] While these higher dose levels have never been tested in systemic hypertensive patients, the efficacy and safety of dose levels up to 540 mg/day have been demonstrated, and doses in the 720 mg/day range have been administered successfully to patients with pulmonary hypertension.[33]

Similarly, the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents (VA Trial) also showed a linear dose–response relationship for diltiazem used as monotherapy, both as a first agent and as a second single agent following the failure of another class of antihypertensive

TABLE III Responders versus nonresponders with respect to supine diastolic blood pressure goals in the six pivotal trials

	Responders/nonresponders	
Dose	< 90 mmHg	< 90 mmHg or ≥ 10 mmHg fall
Placebo	30/103	35/98
90–120 mg	48/178	62/164
180–240 mg	104/209	132/181
360 mg	125/184	165/144
480–540 mg	125/125	161/89

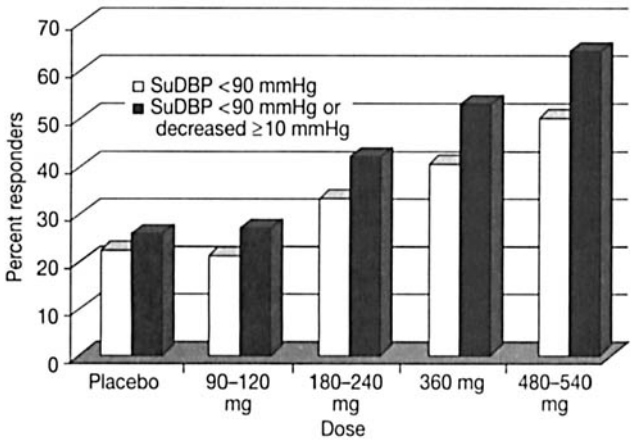

FIG. 1 Percent of subjects who were responders at each dose or range of dosing levels based on a lowering of supine diastolic blood pressure (SuDBP) to < 90 mmHg (clear bars), or a lowering of SuDBP to < 90 mmHg, or a decrease in SuDBP of ≥ 10 mmHg (stippled bars).

agents. However, the response rate of the VA Trial[23] was somewhat greater than that of the six pivotal studies. This difference is likely due to a difference in the demographics of the VA Trial in which 48% of the population was black, 58% was ≥60 years of age, and 26% was both older and black. In the six pivotal studies, the average age was in the low 50s and, where stated, the percent black population was on the order of 20%. Elderly and black populations are known to be more responsive to the antihypertensive effects of diltiazem.[1]

In hypertension studies in the 1980s, the response rate (DBP<90 mmHg) in the specialist hypertension clinics in Britain was on the order of 57%; in a New York City private practice clinic, only 41% had achieved <95 mmHg; and in controlled clinical trials, response rates in the 50–60% range were among the best.[34]

In the VA Trial,[23] in which inclusion required a DBP>95 mmHg, subjects received either placebo, atenolol, captopril, clonidine, diltiazem, hydrochlorothiazide, or prazosin. Response rates to a DBP<90 mmHg ran from 33% for placebo to 54, 56, and 57% for captopril, prazosin, and hydrochlorothiazide, respectively, to 65% each for atenolol and clonidine, and to 75% for diltiazem, which was the most effective overall.

Single-drug treatment for hypertension, which is the recommended approach following nonpharmacologic therapy, is going to be successful in 55–75% of individuals no matter which class of drugs is chosen. Among all the classes of drugs or individual drugs thus far studied, diltiazem has been most effective overall. This result, of course, assumes proper dosing. Among the studies of once-daily diltiazem formulations, none have evaluated the efficacy of twice-daily (b.i.d.) dosing. Despite lack of data, b.i.d. dosing might be considered at dose levels >420 mg/day, a level at which more than one capsule would be required.

Thus, diltiazem, which has been perceived as a weak antihypertensive agent reserved for subjects with mild to moderate hypertension, appears not to be such an agent. Indeed, the extent of blood pressure reduction achieved by diltiazem, both systolic and diastolic, may be greater in subjects with higher baseline blood pressures than in those with only moderately elevated pressure.[27]

Conclusion

It is clear that a linear dose–response can be found whether diltiazem is used in a normal hypertensive population or with a predominantly black and elderly population; or whether diltiazem is used as primary treatment or after prior failed therapy. The data derived from the six pivotal studies, as well as the many other trials in both hypertensive and anginal populations (Tables I and II) clearly show that (1) the most common dose of diltiazem that achieves efficacy in subjects with angina is in the 180–240 mg/day range; (2) that doses of 360 mg/day or even 480 mg/day may improve efficacy in some subjects with angina; (3) that the antihypertensive dose of diltiazem is distinctly higher than that for angina, with the most common dose achieving efficacy being 360 mg/day; (4) that antihypertensive doses as high as 480 and 540 mg/day may be appropriately required in a number of subjects; and (5) that physicians routinely use subtherapeutic doses of diltiazem for reasons that may be explained by the history of the development of this very useful drug.

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