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Duration of Action as an Important Characteristic of Antihypertensive Drugs

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Abstract
A variety of drugs are available for the treatment of hypertension. They have traditionally been characterized by their mode of action, e.g. diuretics, ACE-inhibitors, angiotensin receptor antagonists, calcium channel blockers. Despite marked differences in the mechanisms decreases in blood pressure (BP), their prognostic effects appear to be similar. This has led to the consensus that BP lowering itself is the main mediator of the cardiovascular protection provided by antihypertensive therapy. Duration of action may be another important aspect to characterize antihypertensive drugs. Most of the available medication to be taken once daily will sufficiently lower BP for a 24 hour period. However, non-compliance with antihypertensive therapy may markedly prolong the dosing interval when medication time points are delayed or even missed. In clinical trials with electronic medication monitoring, about 10% of the scheduled doses were omitted on any given day, almost half of those omissions being part of a sequence of several days. In the common scenario of a prolonged dosing interval drugs with prolonged efficacy act as forgiving drugs in the sense that therapeutic coverage is provided in spite of irregular intake. The present review focusses on this important aspect of antihypertensive therapy and points to the fact that besides the thiazide-type diuretic chlorthalidone and the calcium channel blocker amlodipine the direct renin inhibitor aliskiren is also characterized by prolonged efficacy and thus, forgiveness.

Key words: aliskiren – antihypertensive drugs – compliance – duration of action – forgiveness

Introduction

Hypertension is a well established risk factor for cardiovascular and renal disease. While increases in blood pressure (BP) are associated with excess morbidity and mortality, numerous intervention trials have shown that BP lowering with a variety of antihypertensive drugs reduces both morbid events and mortality [1–3]. Interestingly, commonly prescribed antihypertensive drugs, thiazide diuretics, ß-blockers, calcium channel blockers (CCB), ACE-inhibitors (ACEI), angiotensin receptor blockers (ARB) and the more recently introduced direct renin inhibitor (DRI) aliskiren lower BP by different mechanisms of action [1–4].

Thus, diuretics primarily increase renal NaCl and water excretion thereby decreasing extracellular fluid volume. The mechanism(s) translating these volume changes into persistent BP lowering are still incompletely understood [5,6]. The main antihypertensive effect of ß-blockers may be to reduce cardiac output with some agents having additional effects on the peripheral vasculature and on plasma renin activity [7]. CCB reduce vascular tone and, consequently, vascular resistance by blocking calcium influx into smooth muscle cells via so called L-channels [8]. Finally, three groups of agents reduce the activity of the renin angiotensin system (RAS) and, by that mechanism, total peripheral vascular resistance. Even these three latter groups of agents differ markedly with respect to their pharmacologic action. Thus, ACEI slow the conversion of the decapeptide angiotensin I into the octapeptide angiotensin II and at the same time also reduce metabolic breakdown of some peptide hormones such as kinins or substance P. In contrast, ARB interfere with the binding of angiotensin II with its main (type 1) receptor and may, at the same time, enhance stimulation of other (e.g. type 2) angiotensin receptors. Finally, direct renin inhibitors interrupt the RAS further upstream and may thus more completely block this important pressor system [9].

It has been suggested, that the beneficial effect of BP lowering varies depending on the type of drug used. This concept of "effects beyond BP control" has received some support by studies showing that ß-blockers such as atenolol are less effective in reducing strokes than other antihypertensive agents [10]. However, data on the relative efficacy of diuretics, CCB, ACEI and ARB on "hard" morbidity and mortality endpoints have not consistently demonstrated BP independent differences. Thus, there is a growing consensus that these drugs show little if any differences in their potential to protect from the severe consequences of

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hypertension and that BP lowering is all that matters [1–3,11,12]. However, in addition to distinguish antihypertensive drugs by their mode of action some of these agents exhibit marked differences with respect to their duration of action. To date, the heterogeneity with respect to the duration of action of the various antihypertensive agents has received only little attention. This small review raises the question, whether the duration of action of antihypertensive drugs may be of crucial importance for the outcome achieved with a given treatment.

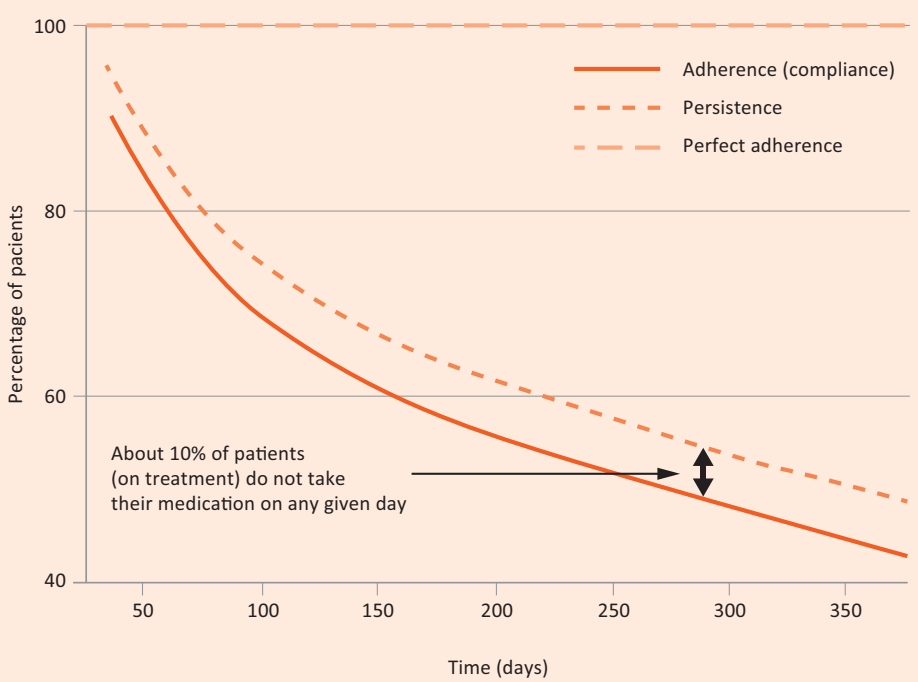
Non adherence with antihypertensive therapy

Despite the availability of a wide range of antihypertensive agents with proven BP-lowering efficacy the achievement of adequate BP control in hypertensive patients remains difficult. In the 2013 heart disease and stroke statistics of the American Heart Association the awareness, treatment and control rates for hypertension are given as 81.5%, 74.9% and 52.5%, respectively [13]. This would imply that about 30% of all treated hypertensives do not reach their BP goal. Available data from other countries indicate that the percentage of treated hypertensive patients reaching their BP goal is usually even lower than those reported for the USA [14]. Among the many factors potentially involved in this problem, patients' adherence with antihypertensive drug therapy (i.e. the extent to which the medication is taken as prescribed) may play a crucial role [1].

The magnitude of non-adherence has recently been demonstrated by Vrijens et al. who reported electronically compiled dosing history data from 21 studies, in which 4,783 patients were treated with once-daily antihypertensive drugs [15]. According to their data, the main problem with non-adherence to antihypertensive drug treatment is non-persistence, which means unauthorized cessation of therapy. In addition, of those remaining on therapy, approximately 10% of patients who are prescribed a once-daily antihypertensive medication miss their doses on any given day [15]. 42% of all missed doses are single-day omissions, 15% are missed doses over two consecutive days and the remaining 43% are omissions in sequences of 3 or more consecutive days [15].

Poor adherence to antihypertensive therapy is a multifactorial problem that affects many treated hypertensive patients and continues to be one of the main causes of unsatisfactory BP control [16–19]. Various approaches for improving adherence have been investigated including reminder strategies as well as patient education and motivation [20–22]. However, the success of these methods has remained difficult to quantify and appears to be rather small [22].

Figure 1. Schematic depiction of the time course of non-persistence and non-adherence to antihypertensive monotherapy [15]



About half of the patients who were prescribed an antihypertensive drug had stopped taking it within one year (non-persistence). On any day, patients who were still on therapy omitted about 10% of the scheduled doses [15].

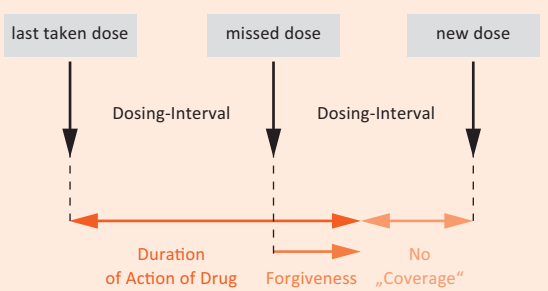
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The "forgiving drug" concept

A once daily antihypertensive medication (usually taken in the morning) has a dosing interval of about 24 hours. If the drug is taken in the evening instead of in the morning the dosing interval is prolonged to 36 hours, missing one dosing time point makes it 48 hours and missing two dosing time points in a row will result in a dosing interval of 72 hours. In the real world, such interruptions in ambulatory patients' dosing for varying lengths of time may occur with an even higher incidence than those described in the setting of clinical trials [15–17].

Most antihypertensive drugs available today exhibit plasma half-lives of 12 hours or less. When the dosing of these drugs is interrupted, their concentrations in plasma will fall below an effective range as a function of the drugs pharmacodynamics and pharmacokinetics and the extent of the prolongation of the dosing interval. In 1996, the concept of "drug forgiveness" was put forward [16]. The main basis for forgiveness is the relationship of a drug's duration of action and the prescribed dosing interval (Figure 1). Forgiveness (F) is thus defined as the difference between a drug's post dosing duration of action (D) minus the prescribed dosing interval (I) (Figure 2) [16].

Figure 2. Concept of therapeutic coverage and drug forgiveness [16]



In the presence of a missed dose, drug forgiveness determines the extent of time with or without "therapeutic coverage" and thus the clinical consequences of irregular drug intake [16].

It should be kept in mind that forgiveness of a given drug may, among other factors, depend on the dose. So in general, one factor associated with higher doses of a given therapeutic is an increase in forgiveness.

Forgiveness in the context of intervention trials

The degree of forgiveness may be a predictor of cardiovascular protective efficacy of a given drug [23]. Thus, the long acting dihydropyridine CCB amlodipine (t ½ 35–50 hours) [24] represents a suitable example of a drug with a high degree of forgiveness and a well-documented cardiovascular risk reduction in several hypertension intervention trials such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [25] or the Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE) [26,27]. The thiazide-type diuretic chlorthalidone (t ½ ~50 hours) is another drug with a long duration of action [28] that performed well in ALLHAT [25], the Hypertension Detection and Follow up Program (HDFP) [29], and the Systolic Hypertension in the Elderly Program (SHEP) [30]. Shorter acting thiazide diuretics such as hydrochlorothiazide and bendroflumethiazide have performed less well in several large scale morbidity and mortality intervention studies in hypertension [31]. As a contrasting example, the short-acting ß-blocker atenolol [32,33] has provided disappointing results in several hypertension intervention studies [34,35]. The high and low degrees of forgiveness of amlodipine and atenolol, respectively, are also supported by studies in which the loss of BP control in patients with hypertension after a simulated missed dose was investigated [36].

It is noteworthy that these results were obtained in randomized controlled trials in which adherence to medication is substantially greater than in clinical practice [17,37]. The advantage of drugs that safely forgive one or more days of interruption of dosing may thus be even greater in real world clinical practice than in controlled clinical trials.

In addition to amlodipine and chlorthalidone, the direct renin inhibitor aliskiren is the third antihypertensive drug with an extended duration of action and thus a high degree of forgiveness.

The direct renin inhibitor aliskiren: a forgiving drug

In addition to ACE-inhibition and angiotensin receptor blockade, renin inhibition represents a promising new option to block the RAS. After many failures to develop a suitable drug with such mechanism of action the orally active nonpeptidic renin inhibitor aliskiren has recently been approved for the treatment of hypertension [4,38]. The ongoing clinical research program with this compound, however, has suffered some disappointments [39]. This is, at least in part, due to the fact that in these studies aliskiren was added on top of an ACE-inhibitor or ARB with the intention to reduce the residual risk of patients on such treatment. However, previous morbidity and mortality studies in patients at high cardiovascular risk or post myocardial infarction had already put doubt on the strategy of double RAS blockade [40,41]. A recent metaanalysis of 33 randomised controlled trials with 68,405 patients has also pointed to the failure of dual RAS blockade as compared with RAS-blocking monotherapy to reduce mortality and to the increased risk of adverse events such as hyperkalemia, hypotension, and renal failure [42].

In addition to its new mechanism of action, aliskiren is characterized by a long duration of action due to its long plasma half-life (t ½) of up to 40 hours [43–45].

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Additional characteristics of aliskiren may contribute to its long efficacy such as the strong tissue binding characteristics, probably to the drug's target molecule, renin [45].

Several clinical studies underline the prolonged efficacy of aliskiren. In one study, approximately 80% of the BP-lowering effect with aliskiren was maintained even after 4 days of stopping active treatment [46]. Similarly, in a double-blind comparator study of aliskiren- and ramipril-based therapy, the BP-lowering effect was more prolonged after discontinuing aliskiren-based as compared to ramipril-based therapy [47]. In a randomized double-blind study, aliskiren demonstrated significant more sustained BP-lowering efficacy after a single missed dose as compared with the ACE inhibitor ramipril and the ARB irbesartan [47]. In yet another double blind study, the BP lowering efficacy of aliskiren was superior to the ARB telmisartan after a single missed dose [36]. Aliskiren also showed a greater and more sustained BP-lowering effect than telmisartan during a 7-day treatment withdrawal [48].

In addition to the effects on BP, the time-dependent efficacy of drugs acting on the RAS after missed doses can also be evaluated by measuring biomarkers such as plasma renin activity (PRA). Aliskiren significantly reduces PRA levels during treatment and this reduction is maintained following cessation of treatment for up to 2 weeks [46,50,51]. In the study cited above with sustained BP lowering of aliskiren even after 1 week treatment cessation persistent suppression of PRA on day 7 of the withdrawal period was also notable [48]. It appears legitimate, therefore, to postulate persistent RAS suppression as the main mechanism by which aliskiren exhibits its sustained BP-lowering effect.

In conclusion, aliskiren, in addition to its new mechanism of action can also be characterized as an agent with a remarkably long duration of action translating into a high degree of forgiveness. Whether these characteristics translate into clinical benefit, remains to be demonstrated.

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Received for publication February 13, 2013
Accepted in revised form March 4, 2013

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byť ohodnotená meraním biomarkera – plazmovej renínovej aktivity (PRA). Aliskirén signifikantne znižuje hodnoty PRA počas terapie a toto zníženie pretrváva až 2 týždne po prerušení liečby [46,50,51]. V predchádzajúcej citovanej štúdii s pretrvávajúcim znížením TK aliskirénom bola zaznamená perzistujúca supresia PRA aj v siedmy deň, týždeň po vysadení terapie [48]. Zdá sa plauzibilné predpokladať, že perzistujúca supresia RAS je hlavným mechanizmom, ktorým aliskirén dosahuje pretrvávajúci efekt na zníženie TK.

Záverom môžeme povedať, že aliskirén, okrem svojho nového mechanizmu účinku, môže byť charakterizovaný ako liek s nezvyčajne dlhým trvaním účinku premietajúcim sa do vysokého stupňa tolerancie. Či sa tieto vlastnosti premietajú aj do klinického benefitu, zostáva predmetom ďalšieho skúmania.

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Doručené do redakcie 13. februára 2013
Prijaté do tlače po recenzii 4. marca 2013

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