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Issues in drug metabolism of major antihypertensive drugs: β-blockers, calcium channel antagonists and angiotensin receptor blockers

Christian Höcht[†], Facundo Martín Bertera, Marcos Alejandro Mayer & Carlos Alberto Taira

[†]*Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Cátedra de Farmacología, Junín 956, (C1113AAD) Buenos Aires, Argentina*

Several first-line antihypertensive drugs, including calcium channel blockers, β-adrenergic blockers and angiotensin receptor blockers, undergo metabolism through different CYP isoforms. As a consequence of CYP-dependent metabolism, wide interindividual variability of plasma concentrations of antihypertensive drugs has been found in clinical practice compromising blood pressure lowering response and clinical outcomes. Several factors, including aging, hepatic impairment, drug interactions, conditions affecting hepatic blood supply and polymorphisms, contribute to changes in oral and systemic clearance affecting drug exposure during antihypertensive therapy and cardiovascular response. Considering that the degree of blood pressure reduction is related to antihypertensive drug plasma concentrations, a greater knowledge of the sources of pharmacokinetic variability of hepatically eliminated antihypertensive drugs and the applicability of an individualized approach in hypertension management by means of pharmacokinetic/pharmacodynamic modeling and pharmacogenetic testing could enhance blood pressure lowering response to pharmacological therapy. The aim of the present review is to discuss the relevance of drug metabolism in the treatment of hypertension.

Keywords: angiotensin receptor blockers, β-blockers, calcium channel blockers, CYP, drug metabolism, genetic polymorphism, stereoselectivity

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1. Introduction

Antihypertensive therapy has two drawbacks which limit the efficacy of the therapeutic approach to hypertension in terms of reducing cardiovascular mortality. First, although a wide range of approved antihypertensive agents with different mechanisms of action is available, only a third of treated hypertensive patients achieve optimal blood pressure control [1,2]. Another weakness of antihypertensive therapy is the failure in finding the optimal dosages of antihypertensive drugs [3]. It has been an almost universal experience with some antihypertensive drugs, including thiazide diuretics and β-blockers (BBs), that the doses used in established practice are significantly higher than the dose regimens recommended when the drugs were first introduced, generating an unnecessary high exposure to antihypertensive drugs [3].

Better understanding of pharmacokinetic properties of antihypertensive drugs and their relationship with blood pressure lowering effect could enhance clinical efficacy of hypertension treatment [4]. A large number of comparative randomized trials have demonstrated that for similar blood pressure reductions, differences in the incidence

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of cardiovascular morbidity and mortality between antihypertensive drug classes are small [5]. Thus, these findings support the notion that the clinical benefit of antihypertensive drugs depends largely on their blood pressure lowering effect [5]. Increasing evidence suggests the existence of a good correlation between plasma drug concentrations of antihypertensive agents and their blood pressure lowering effect [4]. Therefore, knowledge of pharmacokinetic properties and factors involved in drug metabolism of antihypertensive drugs may contribute to improving clinical outcomes of hypertension therapy.

Surprisingly, the impact of drug metabolism and pharmacokinetic properties on antihypertensive response has been largely ignored in clinical practice. Although many antihypertensive drugs show large intersubject variability in their bioavailability and body disposition, this fact has not been considered as a reason of high variability on drug response [6,7].

Several antihypertensive drugs, including BBs, calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs), undergo hepatic metabolism, mainly through CYP isoenzymes [8] and are subject to large interindividual variability due to differential expression and activity of these enzymes. In addition, antihypertensive agents exhibit stereoselective pharmacokinetic properties and/or generate active metabolites, which further contribute to drug response variability. Considering these aspects, the aim of the present review is to discuss the relevance of drug metabolism in the treatment of hypertension.

2. Determinants of antihypertensive drug metabolism

2.1 Pathways involved in drug metabolism of antihypertensive agents

Several antihypertensive drugs are subject to biotransformation after their administration (**Table 1**). In the case of angiotensin converting enzyme inhibitors (ACEIs), these agents are prodrugs which release the active moiety by hydrolysis through esterases mainly in the liver, plasma and intestinal wall [9]. The primary route of elimination of the active metabolites of ACEIs is the kidney and, therefore, conditions with reduced renal function, such as renal failure and heart failure, prolong drug excretion [9]. As CYP is not involved in drug metabolism of ACEIs, drug biotransformation is not an important source of interindividual variability of antihypertensive response to these agents.

Aliskiren is a novel oral antihypertensive agent that exerts its blood pressure lowering effect by direct inhibition of renin [10]. Although *in vitro* experiments found that CYP3A4 is the major isoenzyme involved in aliskiren biotransformation, only a small proportion of the administered dose is eliminated by hepatic metabolism. Therefore, hepatic metabolism plays a minor role in aliskiren systemic elimination [10].

Conversely, BBs have different pharmacokinetic properties that are of clinical importance [11]. Although some BBs, such as atenolol and nadolol, are eliminated unchanged in the urine, most drugs of this therapeutic group undergo hepatic metabolism, mainly by CYP2D6. Therefore, several factors that influence activity and hepatic content of CYP2D6, such as age, race, cigarette smoking, concomitant drug therapy and genetic polymorphism, influence pharmacokinetics of BBs and contribute to drug response variability [11]. For instance, steady-state plasma concentrations of metoprolol varied 17-fold (from 20 to 341 ng/ml) in essential hypertensive patients affecting its bradycardic response [12]. The existence of stereoselective pharmacokinetics and generation of active metabolites for some BBs contribute to the complexity of hepatic metabolism of BBs [11,13].

Hepatic metabolism is also involved in systemic and oral clearance, defined as clearance/oral bioavailability, of CCBs. All drugs included in this therapeutic group are subject to high interindividual variability, considering the fact that they are extensively metabolized by means of CYP3A, an isoenzyme with considerable variation in expression and activity [14]. Active metabolites emerge from oxidation of some CCBs, including verapamil and diltiazem, contributing to cardiovascular response. As described for BBs, some CCBs also exhibit stereoselective metabolism [15], affecting both the enzymes involved and rate of drug biotransformation.

In the case of ARBs, hepatic metabolism also influences concentrations at the steady-state and pharmacological response. Although pharmacokinetic properties of different agents of this therapeutic group are drug-dependent, different isoforms of the CYP, especially CYP2C9, are involved in drug metabolism of most ARBs [8,16]. As activity and expression of CYP2C9 is regulated by genetic and other factors [17], wide interindividual variability exists in drug elimination of ARBs that are substrate of this isoform, including irbesartan, losartan and candesartan.

In the next sections, the most relevant aspects of hepatic metabolism of BBs, CCBs and ARBs are discussed.

2.2 Hepatic extraction of antihypertensive drugs

In order to understand the factors that modify antihypertensive drugs metabolism, hepatic extraction must be considered. As hepatic clearance (CL_H) is the volume of blood from which drug is removed completely by the liver per unit of time, it depends both on hepatic blood flow (Q_H) and the hepatic extraction ratio (E_H) (Equation 1) [18]. In addition, E_H is influenced by different physiological parameters, including Q_H, unbound fraction (f_u) and intrinsic clearance (CL_{in}). CL_{in} represents the efficiency of the liver in removing drugs from circulation [18].

$$CL_H = Q_H * E_H \quad (1)$$

$$CL_H = Q_H * \frac{f_u * CL_{in}}{QH + f_u * CL_{in}} \quad (2)$$

Table 1. Metabolic aspects of selected antihypertensive drugs.

Antihypertensive drug	Hepatic extraction	Metabolic pathway	Active metabolite	Stereoselective pharmacokinetics
Calcium channel blockers				
Amlodipine	Low	CYP 3A4, CYP3A5	No	Yes
Diltiazem	High	CYP 3A4, CYP3A5	Deacetyldiltiazem	Yes
Felodipine	High	CYP 3A4	No	Yes
Isradipine	High	CYP3A4	No	Yes
Nicardipine	High	CYP 3A4	No	Yes
Nifedipine	High	CYP 3A4	No	No
Nimodipine	High	CYP 3A4	No	Yes
Nisoldipine	High	CYP 3A4	No	Yes
Verapamil	High	CYP3A4, CYP3A5	Norverapamil	Yes
β-*Blockers*				
Acebutolol	High	CYP2D6	Diacetolol	Yes
Bisoprolol	Low	CYP2D6	No	Yes
Carvedilol	High	CYP2D6, CYP1A2, CYP3A4, CYP2C9, UGT2B7, UGT1A1, UGT2B4	M2, M4 and M5	Yes
Metoprolol	Intermediate	CYP2D6	No	Yes
Nebivolol	High	CYP 2D6, CYP3A4	Hydroxilated nebivolol	Yes
Propranolol	High	CYP2D6, CYP2C19, CYP1A2, UGT1A9, UGT1A10	4-Hidroxypropranolol	Yes
Angiotensin receptor blockers				
Candesartan	High	Esterase	CV-11974 (candesartan)	No
Eprosartan	High	UGT	No	No
Irbesartan	Low	CYP 2C9, CYP 3A4, CYP1A2, UGT	No	No
Losartan	High	CYP 2C9, CYP 3A4, CYP 1A2	5-carboxylic acid (E-3174)	No
Olmesartan medoxomil	High	Esterase	RNH-6270 (deesterified olmesartan)	No
Telmisartan	Intermediate	UGT	No	No
Valsartan	High	CYP 2C9	No	No

UGT: Uridine diphosphate-glucuronosyltransferase.

According to CL_{in} values, drug substances can be categorized as flow limited (EH > 0.7) and capacity limited (E_H < 0.3) drugs. Flow limited drugs show high total intrinsic clearance, and, therefore, Q_H is numerically insignificant with regard to $f_u * CL_{in}$ in Equation 2. As a consequence, systemic hepatic clearance of flow limited drugs depends on Q_H rather than CL_{in} or f_u. Nevertheless, as oral clearance of flow limited drugs is also influenced by CL_{in}, moderate changes in hepatic enzyme activity could produce alterations in drug bioavailability of flow limited drugs after oral administration [18].

Conversely, hepatic clearance of drugs with low CL_{in}, named capacity limited drugs, is influenced mainly by changes in content and activity of hepatic enzyme. In addition, drugs with E_H < 0.3 and high plasma protein binding (fu < 0.1), displacement of drugs from plasma protein also affect the rate of hepatic metabolism (**Table 2**) [18].

Finally, hepatic metabolism of antihypertensive drugs with intermediate CL_{in} is influenced both by changes in hepatic blood flow and in concentration and activity of liver enzyme (**Table 2**).

2.3 Stereoselective metabolism of antihypertensive drugs

BBs and CCBs contain chiral centers and are administered as racemate. As interaction of two enantiomers with macromolecules, such as enzymes or receptors, is three dimensional [19], S- and R-enantiomers of BBs and CCBs display different pharmacokinetic and pharmacodynamic properties [13,15]. For instance, only the S-enantiomer of BBs possesses β-blocking activity, whereas the R-enantiomer is inactive [13]. In the case of carvedilol, both R-and S-enantiomer also show α_1-adrenergic blocking activity [20].

Nevertheless, enantioselectivity also influences drug metabolism of some BBs and CCBs and could have therapeutic implications. Stereoselectivity in drug metabolism of antihypertensive drugs is a result of preference of metabolizing

Table 2. Determinants of hepatic clearance of antihypertensive drugs.

	Hepatic extraction	Hepatic clearance	Examples
Flow limited metabolism	> 0.7	$CL \cong Q_H$	Carvedilol Nebivolol Propranolol Verapamil Diltiazem Felodipine
Capacity limited metabolism and low protein binding (fu > 0.1)	< 0.3	$CL \cong CLin$	Bisoprolol
Capacity limited metabolism and high protein binding (fu < 0.1)	< 0.3	$CL \cong CLin * f_u$	Amlodipine Irbesartan
Intermediate metabolism	0.3 – 0.7	$CL_H = Q_H * \frac{f_u * CL_{in}}{QH + f_u * CL_{in}}$	Metoprolol Telmisartan

enzymes for one enantiomer over the other. In addition, enantioselectivity could also influence the degree of hepatic first pass and bioavailability or rate of metabolism. **Table 3** highlights stereoselective aspects of drug metabolism of BBs and CCBs.

Racemic carvedilol represents one of the most meaningful examples of stereoselective drug metabolism. Carvedilol is both metabolized by oxidation through CYP2D6, CYP1A2, CYP3A4 and CYP2C9 and by glucuronidation by means of UGT2B7. Both glucuronidation and oxidation of carvedilol through CYP2D6 and CYP1A2 show preference for S-enantiomer with regard to R-carvedilol and, therefore, systemic clearance of S-enantiomer is significantly higher than its antipode [21-23]. Stereoselective pharmacokinetics also influences bioavailability of carvedilol enantiomers, showing R-carvedilol a twofold higher oral disposition with regard to S-enantiomer. Interestingly, stereoselective first pass of carvedilol disappears in patients with liver cirrhosis [24]. Stereoselectivity of carvedilol metabolism has a great impact on drug levels and therapeutic response. For instance, coadministration of carvedilol with amiodarone greatly enhances S-carvedilol concentrations without effect on R-enantiomer levels, increasing also the S:R ratio. Therefore, β-blocking activity of carvedilol could be increased in patients under treatment with amiodarone [25].

Nebivolol also exhibits both stereoselective pharmacokinetic and pharmacodynamic properties. Whilst β-blocking activity has been attributed to D-nebivolol, L-nebivolol exerts vasodilatation by an endothelial-dependent mechanism [26]. In addition, oral disposition of nebivolol is influenced by enantioselectivity of drug metabolism by CYP2D6, considering that peak and trough plasma concentrations of D-nebivolol were greater than the L-enantiomer after single and multiple administrations [26]. As previously reviewed by Mehvar and Brocks [13], enantioselective metabolism is also observed for other BBs, such as metoprolol and propranolol.

Verapamil also possesses pharmacodynamic and pharmacokinetic enantioselective properties. Pharmacological actions of S-verapamil are 10-fold greater with regard to R-enantiomer [27]. Although both enantiomers of verapamil are metabolized by CYP3A4, CYP3A5 and CYP2C, drug metabolism shows stereoselectivity for S-verapamil. Presystemic first-pass metabolism of verapamil is also enantioselective considering that the S:R ratio is significantly greater after intravenous application compared with oral administration [28].

For dihydropyridine (DHP) CCBs, with the exception of the achiral nifedipine, S-enantiomer showed greater vasodilatory activity with regard to its antipode [15]. In addition, stereoselective pharmacokinetics were also described for DHPs, considering that S-enantiomer concentrations of amlodipine, nivaldipine, nitrendipine, felodipine, manidipine and benidipine were significantly greater than the antipode after oral administration due to stereoselective metabolism of R-enantiomer [15,29]. Conversely, for nimodipine, less active enantiomer R-nimodipine achieved higher concentrations with respect to S-nimodipine [15].

2.4 Role of active metabolites on the antihypertensive response

As shown in **Table 1**, hepatic metabolism generates active metabolites for a large number of antihypertensive drugs. Contribution of active metabolites on the pharmacological activity of the parent drug varies among different antihypertensive agents. As mentioned above, for most ACEIs, cardiovascular effects depend totally on the generation of active metabolites. Active metabolites also significantly contribute to the blood pressure lowering response to some ARBs, including losartan and candesartan [16]. Losartan is converted by P450 oxidation to E-3174, which exhibits insurmountable antagonism at AT1 receptor and 10- to 40-fold higher potency compared to losartan [16]. Therefore, antihypertensive response to losartan is attributable to its active metabolite. Candesartan cilexetil and olmesartan medoxomil are prodrugs that completely release their active metabolites, CV-11974 and olmesartan, by activity of intestinal esterases [30,31].

Table 3. Stereoselective properties of antihypertensive drugs.

Drugs	Stereoselective pharmacodynamics		Stereoselective pharmacokinetics	
	Pharmacological effect	Relationship between enantiomers	Pharmacokinetic property	Relationship between enantiomers
β-Blockers				
Metoprolol	β Blockade	S > R (500:1)	Drug metabolism through CYP2D6	R > S (ratio: 1.5)
Nebivolol	β Blockade	D > L	Drug metabolism through CYP2D6	L > D
	Vasodilatory action	L > D		
Carvedilol	β Blockade	S > R (100:1)	Hepatic first pass	S > R
	α Blockade	S = R	Drug metabolism through CYP2D6 and CYP1A2	S > R
			Drug metabolism through UGT	S > R
Propranolol	β Blockade	S > R (100:1)	Drug metabolism through CYP2D6	R > S
			Drug metabolism through UGT	UGT1A9 (S > R) UGT1A10 (R > S)
Calcium channel blockers				
Verapamil	Blockade of L-type calcium channels	S > R (20:1)	Hepatic first pass	R > S
			Drug metabolism through CYP3A4	R > S
			Drug metabolism through CYP3A5	R > S
Dihydropiridines (amlodipine, amlodipine, nivaldipine, nitrendipine, felodipine, manidipine and benidipine)	Blockade of L-type calcium channels	S > R	Drug metabolism through CYP3A4	R > S
Nimodipine	Blockade of L-type calcium channels	S > R	Drug metabolism through CYP3A4	S > R

UGT: Uridine diphosphate-glucuronosyltransferase.

Among CCBs, active metabolites are generated during verapamil and diltiazem metabolism. For instance, diltiazem is converted into three active metabolites, including N-desmethyldiltiazem, desacetyldiltiazem and desmethyldesacetyldiltiazem. As these metabolites show longer half-life compared with the parent drug, they accumulate during chronic administration [32]. Considering that vasodilatory potency of active metabolites is about 20 – 50% of diltiazem, it is expected that these metabolites contribute in the pharmacological response of this CCB [32]. Verapamil is also biotransformed to its active metabolite, norverapamil [33], although contribution of this metabolite on cardiovascular response of the parent drug is uncertain.

In the case of BBs, although propranolol, metoprolol and carvedilol are metabolized to products with pharmacological activity, it seems that these metabolites have no clinical implications [34]. Conversely, generation of active metabolites seems to be important for nebivolol. Nebivolol is converted to its hydroxyl metabolite by CYP2D6 activity. Evidence supporting the role of active metabolite of nebivolol on the blood pressure response comes from pharmacogenetic studies, which found that antihypertensive response to nebivolol is not affected in poor metabolizers (PMs) compared to extensive metabolizers (EMs) [35]. It is suggested that the lower concentration of unchanged nebivolol concentrations in EMs appears to be compensated by substantial formation of active hydroxy metabolites [35].

3. Factors that influence antihypertensive drug metabolism

3.1 Effect of aging on antihypertensive drug metabolism

As prevalence of hypertension increases with aging, knowledge of the impact of age on antihypertensive drug metabolism is clinically relevant. Hepatic mass and content of Phase I pathway enzymes as well as hepatic blood flow are reduced with age, affecting predominantly drug metabolism of antihypertensive drugs with high hepatic extraction [36]. Bioavailability of irbesartan [37], valsartan [38] and E-3174 [39], the active metabolite of losartan, is slightly increased in elderly hypertensive subjects with regard to young adults without clinical significance. Therefore, dose adjustment is not necessary in elderly hypertensive patients treated with ARBs.

Conversely, most CCBs are highly extracted by the liver and, therefore, changes in hepatic mass and blood flow induced by aging may greatly impact bioavailability of these antihypertensive agents. For instance, plasma concentrations

of verapamil [40], diltiazem [41], nimodipine [42], felodipine [43] and nisoldipine [44] are significantly increased in the elderly with respect to young patients. In contrast, pharmacokinetics of amlodipine, a CCB with low hepatic extraction, is not affected by aging [45]. Considering the impact of aging on drug metabolism of many CCBs, dose adjustment is recommended in elderly subjects in order to avoid hypotension [46].

In the case of BBs, as drug elimination pathways are variable among different agents of this therapeutic group, the impact of aging on pharmacokinetics depends on individual drugs. Atenolol and nadolol, which are eliminated mainly by glomerular filtration, are accumulated in elderly hypertensive patients as a consequence of reduced renal function [11]. The effect of aging on BBs undergoing hepatic metabolism depends on intrinsic clearance of the drug. At a theoretical point of view, pharmacokinetics of β-adrenergic agents with high presystemic hepatic metabolism, including metoprolol, propranolol and carvedilol, would be greatly affected in elderly hypertensive patients, requiring a reduction in initial dosing. For instance, plasma levels of propranolol are three to fourfold higher in elderly patients compared with young subjects [47]. Consequently, BBs need to be dosed according to the patient's renal or hepatic function in elderly hypertensive patients [46].

3.2 Effect of cardiovascular disease on antihypertensive drug metabolism

Comorbility of heart failure in hypertensive patients is frequent in clinical practice and, therefore, it is essential to take into account the impact of a reduced ventricular function on metabolism and pharmacokinetics of antihypertensive drugs, especially ARBs and BBs. As hepatic blood flow is reduced in patients with congestive heart failure, metabolism of highly extracted antihypertensive drugs might be reduced requiring lower dosage.

Carvedilol is frequently used in the treatment of heart failure and its metabolism is affected in this cardiovascular disease. Oral clearance of R- and S-carvedilol in heart failure patients were only 29.0 and 25.2% than that reported in healthy volunteers [48]. As a matter of fact, recommended carvedilol dosage in patients with heart failure is lower than dosing of carvedilol in hypertension. To the best of our knowledge, pharmacokinetics of metoprolol, bisoprolol and nebivolol in patients with cardiac failure was not compared with regard to subjects with normal ventricular function. A reduction in systemic clearance of bisoprolol is expected in patients with reduced renal function associated with cardiac failure, considering that this BB is eliminated equally by renal excretion of unchanged drug and by metabolism to inactive products.

In the case of ARBs, pharmacokinetics of irbesartan [49], losartan and its active metabolites [39] are not affected in chronic heart failure. Therefore, dosage adjustment of ARBs is not required in this special population.

3.3 Effects of vascular actions of antihypertensive drugs on hepatic clearance

A peculiarity of drug metabolism of antihypertensive drugs is the fact that vascular actions of these drugs could influence hepatic clearance resulting in nonlinear pharmacokinetic properties. Dose dependency on hepatic drug metabolism is restricted to antihypertensive drugs with high hepatic extraction. For instance, we found an increase in hepatic metabolism of verapamil [50] and diltiazem [51,52] with dose increments. We also found an increase of the estimated diltiazem systemic clearance with dosing in spontaneously hypertensive rats [51] and in an experimental model of hypertension induced by aortic coarctation [52]. As hepatic metabolic rate of diltiazem depends on hepatic blood flow, an increase of diltiazem dose could produce a greater hepatic perfusion due to vasodilatation, enhancing drug biotransformation [51,52].

In contrast, higher plasma concentrations of BBs results in enhancement of drug bioavailability due to reduced hepatic clearance because of reductions in hepatic blood flow [11]. In other words, during long-term treatment with propranolol and metoprolol, negative chronotropic and inotropic response are increased resulting in lower cardiac output and consequently reduced hepatic clearance of these drugs with high hepatic extraction [11].

3.4 Effect of hepatic impairment on antihypertensive drug pharmacokinetics

Considering that many antihypertensive drugs undergo extensive hepatic metabolism, liver impairment may significantly alter drug pharmacokinetics requiring dose adjustment. However, the impact of liver function on hepatic clearance of antihypertensive drugs depends on intrinsic clearance of the antihypertensive agent and the type of liver disease. Hepatic cirrhosis is frequently associated with portal-systemic shunting, which may substantially decrease the presystemic elimination of antihypertensive drugs with high intrinsic clearance following oral administration [18]. Therefore, plasma levels of high extracted antihypertensive agents would be greatly increased due to a significant increase in the extent of absorption and a reduction in their systemic clearance.

For instance, oral bioavailability of carvedilol, metoprolol and propranolol, three BBs with high hepatic extraction, is ~ 4.4-, 1.7- and 1.7-fold greater in patients with liver cirrhosis compared with those with normal hepatic function [18]. Moreover, cirrhosis increased oral disposition of many CCBs, including verapamil, nisoldipine, nifedipine, felodipine and diltiazem [18]. Although amlodipine shows low intrinsic clearance, its hepatic metabolism is also greatly reduced in patients with cirrhosis [53].

Mild and moderate hepatic impairment seems to have little impact on pharmacokinetics of ARBs, especially irbesartan [54] and candesartan [55]. In contrast, drug elimination of valsartan [56], eprosartan [57], telmisartan [58] and the active metabolite E 3174 [39] are significantly reduced in hepatically impaired subjects.

3.5 Influence of enzyme polymorphism on antihypertensive drug metabolism

Several CYP isoforms involved in antihypertensive drug metabolism, including CYP2C9, CYP2D6 and CYP3A5, exhibit polymorphic variants, which greatly affect enzymatic activity and, therefore, the rate of drug metabolism [59]. The PM phenotype, as a consequence of the expression of an aberrant enzyme, shows reduced ability to eliminate certain antihypertensive drugs compared with EM patients, requiring mainly dose reduction. The impact of polymorphism of metabolizing enzymes on pharmacokinetic and pharmacodynamic properties of antihypertensive drugs is highlighted in **Table 4**.

Enantioselective disposition of nebivolol is highly influenced by CYP2D6 phenotypes [26]. PM patients showed steady-state plasma concentrations of D- and L-nebivolol 10- and 15-fold greater than EMs. However, differences in nebivolol pharmacokinetics related to CYP2D6 phenotype are not clinically meaningful, considering that chronic administration of nebivolol produced similar efficacy and tolerability in hypertensive patients either characterized as PMs or EMs [26].

Conversely, CYP2D6 genotype influenced both metoprolol plasma concentrations and their cardiovascular effects. Ultrarapid metabolism of metoprolol due to CYP2D6 gene duplication is associated with reduced drug disposition and absence of therapeutic effect with appearance of ventricular rhythm disturbance [60,61]. In contrast, PM patients show greater metoprolol concentrations and an exaggerated bradycardic response. Moreover, CYP2D6 polymorphism also influences degree of adverse effect to metoprolol. Wuttke *et al.* [62] found a fivefold higher risk for development of adverse reactions to metoprolol in PM patients compared with EM subjects. Moreover, CYP2D6 PMs have a fourfold increase in the risk of bradycardia compared with EMs [63]. In addition, a prospective longitudinal study found that metoprolol evoked significantly greater reductions in diastolic blood pressure and mean arterial pressure in PMs than in EMs [64]. Taking into account these results, Ismail and Teh proposed the role of pharmacogenetic testing in the design of a more individualized metoprolol dosage regimen [65].

In contrast to metoprolol, CYP2D6 phenotype does not affect disposition of bisoprolol and the extent of its β-adrenergic inhibition [66]. This finding could be explained by the fact that only a small percentage of the oral dose of bisoprolol undergoes hepatic metabolism [66].

Although carvedilol also undergoes hepatic metabolism, different enzymes are involved in drug clearance, including CYP2D6, CYP2C9, CYP2C19, CYP3A5, UGT1A1 and UGT2B7. Different reports [67,68] have demonstrated that variability in carvedilol plasma levels can be explained, at least in part, by the presence of UGT1A1, UGT2B7 and CYP2D6 polymorphism. On the other hand, effect of CYP2D6 polymorphism on carvedilol metabolism is stereospecific. Although hepatic clearance of R-enantiomer is greatly reduced in PM as compared with EM, elimination half-life of S-carvedilol is not significantly affected [13,69].

More recently, CYP3A5 genotype has been associated to variability on plasma levels of CCBs and their cardiovascular response. Patients carrying at least one CYP3A5*1 allele expressed this isoform that is involved in drug metabolism of CCBs [70]. For instance, CYP3A5 expressers showed a twofold higher oral clearance of R- and S-verapamil compared with non-expressers. Reduced disposition of verapamil in CYP3A5 expressers was associated with a reduced pharmacological response evidenced by a lower PR-interval prolongation and higher diastolic blood pressure [71].

Conversely, CYP3A5 polymorphism seems to have no impact or opposite effect on pharmacokinetics of other CCBs. For instance, oral clearance of amlodipine is enhanced in CYP3A5*3/*3 carriers, which did not express this isoenzyme, with respect to CYP3A5 expressers (CYP3A5*1) [72]. However, increased disposition of amlodipine observed in CYP3A5*1 carriers was not associated with changes in the hemodynamic response to this CCB [72]. In the case of felodipine [73], nifedipine [74] and diltiazem [75], CYP3A5 polymorphism has only a minor effect on pharmacokinetics and metabolism.

As discussed previously, CYP2C9 has a major role in drug metabolism of ARBs, and, therefore, polymorphism on this isoenzyme may influence both drug pharmacokinetics and cardiovascular response. Conversion of losartan to its active metabolite is mediated by CYP2C9 and explained the fact that patients carrying deleterious alleles of CYP2C9 (e.g., CYP2C9*30) showed a diminished response to the antihypertensive effects of losartan [76]. In addition, presence of CYP2C9*3 alleles is associated with reduced hepatic clearance of irbesartan [77] and candesartan [78] with a possible enhancement of the hypotensive effect.

3.6 Impact of antihypertensive drug metabolism on drug interactions

Success of antihypertensive therapy could be affected by administration of concomitant drugs leading to pharmacokinetic and pharmacodynamic mediated drug interactions (**Table 5**). Considering the fact that many antihypertensive agents are eliminated through hepatic metabolism, risk of drug interactions with concomitantly administered drugs is relative high. However, only few clinically relevant drug interactions with this therapeutic class have been described. Low interaction potential of antihypertensive drugs could be explained by the fact that several blood pressure lowering agents have relative large therapeutic window, and thereby changes in drug concentrations are rarely associated with significantly changes in drug response.

Regarding drug interactions of specific antihypertensive classes, BBs and ARBs have few pharmacokinetic drug interactions of clinical relevance [8]. Most ARBs undergo hepatic biotransformation through CYP2C9, and, therefore, inhibition of this pathway can modify their pharmacokinetic

Table 4. Influence of genetic polymorphism of metabolizing enzymes on pharmacokinetics and pharmacodynamics of antihypertensive drugs.

Drug	Enzyme with allelic variant	Impact on pharmacokinetics	Impact on pharmacodynamics
β-Blockers			
Carvedilol	CYP2D6	Reduced clearance of R-carvedilol (CYP2D6*10)	Not established
	UGT1A1	Low ability of glucuronidation	
	UGT2B7	Reduced clearance of carvedilol (UGT2B7*3)	
Propranolol	CYP2D6	Higher concentrations of S-propranolol (CYP2D6*10)	Absence of changes in dose response relationship
	CYP2C9	Reduced conversion to naphthoxylactic acid	
Metoprolol	CYP2D6	3- To 10-fold increase in metoprolol plasma concentrations in PM	Enhanced blood pressure reduction Greater risk of bradychardia and adverse drug reactions
Nebivolol	CYP2D6	23-Fold increase of nebivolol plasma concentrations in PM	Absence of changes in cardiovascular response
Calcium channel blockers			
Amlodipine	CYP3A5	Increased disposition of amlodipine (CYP3A5*1)	Absence of changes in cardiovascular response
Verapamil	CYP3A5	Reduced disposition of verapamil (CYP3A5*1)	Reduced pharmacological response
Angiotensin receptor blockers			
Losartan	CYP2C9	Reduced conversion to active metabolite E-3174 (CYP2C9*30)	Reduced antihypertensive effect
Candesartan	CYP2C9	Reduced oral clearance of candesartan (CYP2C9*1/*3)	Possible increase in antihypertensive response
Irbesartan	CYP2C9	Higher irbesartan plasma concentrations (CYP2C9*3)	Absence of changes in antihypertensive response

PM: Poor metabolizer; UGT: Uridine diphosphate-glucuronosyltransferase.

properties and cardiovascular response. In the case of irbesartan and losartan, CYP1A2 and CYP3A4 are also involved in drug metabolism. Coadministration of antifungal fluconazole, a potent CYP2C9 and CYP3A4 inhibitor, only slightly increases plasma levels of irbesartan without clinical relevance [8]. Fluconazole and phenytoin also reduce hepatic metabolism of losartan [8]. As losartan is converted to its active metabolite E 3174 through CYP2C9 activity, a reduction in antihypertensive drug response is expected in patients concomitantly treated with fluconazole or phenytoin [8]. However, to date, the clinical relevance of these interactions is unclear.

Regarding, β-adrenergic agents, although a significant pharmacokinetic interaction has been described between metoprolol and some selective serotonin reuptake inhibitors due to strong inhibition of CYP2D6 [79], the clinical relevance of this interaction is unclear. Recently, Goryachkina *et al.* [80] have found that inhibition of metoprolol metabolism by paroxetine was not associated with serious adverse effects in acute myocardial infarction.

Conversely, as CCBs are mainly metabolized through CYP3A isoenzymes and some agents within this therapeutic class, that is, verapamil and diltiazem, strongly inhibit this metabolic pathway, several important drug interactions have been described for CCBs. As discussed previously, oral clearance of drugs with high first pass effect is influenced by intrinsic clearance. Therefore, inhibition of hepatic and intestinal enzyme activity could produce alterations in drug bioavailability enhancing cardiovascular effects and increasing the risk of bradycardia or postural hypotension. Impact of concomitant ingestion of grapefruit juice on bioavailability of different CCBs has been reviewed by Ohnishi *et al.* [81]. It is a well-known fact that grapefruit juice enhances plasma concentration of drugs metabolized due to irreversible inhibition of CYP3A4 located in the small intestine. Drug interaction between grapefruit juice and CCBs is highly influenced by the bioavailability of the antihypertensive drug. Whilst bioavailability of CCBs with high first pass effect, including nisoldipine, nimodipine and felodipine, was greatly increased by grapefruit juice, the effect on pharmacokinetics of CCBs with intermediate disposition, such as diltiazem, nifedipine and amlodipine, was minimal [81].

In contrast to grapefruit juice, other CYP3A4 inhibitors, such as erythromycin and HIV protease inhibitors not only inhibit this metabolic pathway in small intestine but also in the liver, affecting both the bioavailability and systemic clearance. Therefore, these drugs can increase plasma concentration of all CCBs, independently of their first pass effect [8]. Moreover, it is also important to mention that interactions between CCBs and CYP3A4 inhibitors have a great influence

Table 5. Clinical significant drug interactions with major antihypertensive drugs.

Antihypertensive group/drug	Interacting drug	Mechanism of interaction	Clinical consequence
β-Blockers	Diltiazem, verapamil	Pharmacodynamic	Potential for bradycardia or heart block
	Clonidine	Pharmacodynamic	Rebound hypertension following withdrawal of clonidine
	Theophylline	Pharmacodynamic	Attenuation of bronchodilatation
	NSAIDs	Pharmacodynamic	Reduction of antihypertensive response
	Insulin, hypoglycemic agents	Pharmacodynamic	Risk of prolonged hypoglycemia
Hepatically eliminated β-blockers	Barbiturates	Pharmacokinetic	Reduction of antihypertensive response
	Rifampicin	Pharmacokinetic	Reduction of antihypertensive response
	Selective serotonin reuptake inhibitors	Pharmacokinetic	Increase in pharmacological response, risk of bradycardia
Calcium channel antagonist	Azole antifungal, grapefruit juice, erythromycin, HIV protease inhibitors	Pharmacokinetic	Increase in plasma concentration and antihypertensive response
	barbiturates, phenytoin	Pharmacokinetic	Decrease in plasma concentration and antihypertensive response
Verapamil, diltiazem	β-Blockers	Pharmacodynamic	Potential for bradycardia or heart block
	Digoxin	Pharmacokinetic	Risk of digitalis toxicity
	Carbamazepine, cyclosporine, tacrolimus, simvastatin, lovastatin, atorvastatin, benzodiazepines	Pharmacokinetic	Increase in plasma concentrations of concomitant drug and risk of specific toxicity
Angiotensin receptor blockers	NSAIDs	Pharmacodynamic	Reduction of antihypertensive response
	Potassium-sparing diuretics	Pharmacodynamic	Risk of hyperpotassemia
	Lithium	Pharmacokinetic	Lithium toxicity due to increase in lithium levels
Losartan	Fluconazole, phenytoin	Pharmacokinetic	Reduced antihypertensive efficacy
	Rifampicin, phenobarbital	Pharmacokinetic	Reduced antihypertensive efficacy

Data from Baxter K, editor, Stockley's Drug Interactions 8. [CD-ROM]. London: Pharmaceutical Press; 2008.

in clinical outcomes. A recent report has found that concomitant treatment with a CYP3A4 inhibitor and a CCB increases the risk of adverse drug reactions by 53% compared with CCB monotherapy [82].

It is also important to mention that verapamil and diltiazem greatly affect pharmacokinetics of concomitantly drugs, which are eliminated by CYP3A4-dependent metabolism, including carbamazepine, cyclosporine, tacrolimus, simvastatin, lovastatin, atorvastatin and several benzodiazepines [8]. The high impact of verapamil and diltiazem CYP3A4 inhibition on pharmacokinetics of substrate of this isoform could be explained by the fact that both CCBs generate inactivation of the enzyme [83]. Mechanism-based inhibition of CYP3A4 is produced both by the parent drug and metabolites of verapamil and diltiazem, and involves the inactivation of the enzyme through the formation of metabolic intermediates that bind tightly and irreversibly to the enzyme [83]. Considering these facts, metabolic drug–drug interactions involving mechanism-based inactivation of CYP3A4 showed high clinical relevance, because the reduction in metabolic clearance of substrates can be more severe and long-lasting than reversible inhibition [83].

4. Conclusions

Hepatic metabolism through CYP pathways plays an important role in pharmacokinetics of many first-line antihypertensive drugs, that is, BBs, CCBs and ARBs. As dosage of these agents are not individualized during clinical practice, wide interindividual variability in drug levels has been described for hepatically metabolized antihypertensive drugs with possible clinical relevance. Age, hepatic impairment, drug interactions, conditions affecting hepatic blood supply and polymorphisms contribute to changes in oral and systemic clearance affecting drug exposure during antihypertensive therapy and cardiovascular response.

5. Expert opinion

As mentioned above, influence of pharmacokinetic properties and plasma levels of antihypertensive drugs on their cardiovascular response has been largely ignored as a possible explanation to interindividual variability in clinical practice. Traditionally, it was thought that first-line antihypertensive drugs have a wide therapeutic window and, therefore, only

large changes in plasma levels would impact negatively in pharmacological response. On the other hand, early belief of the absence of a clear relationship between antihypertensive drug plasma concentrations and blood pressure lowering effect could also explain the lack of recognition of the importance of pharmacokinetic variability on therapeutic outcomes. Nevertheless, in the last years several authors have reinforced the role of optimizing pharmacokinetics and pharmacokinetic/pharmacodynamic (PK/PD) modeling as a tool to increase clinical efficacy of antihypertensive therapy [4,6].

It is a well-known fact that only a third of treated hypertensive patients achieve control of their blood pressure values. In addition, only a small improvement in the percentage of hypertensive patients with optimal therapeutic response has been found in the last years. Despite intensive research, the control rate of hypertension slightly increased from 26.1% between 1988 and 1994 to 35.1% between 1999 and 2004 [84].

As recognized by Meredith [6], plasma concentrations of antihypertensive drugs are probably the most important determinant of response. To date, a large body of evidence has found an excellent correlation between antihypertensive drug plasma levels and their blood pressure lowering effect by means of PK/PD modeling [4]. Taking together, evaluation of the factors involved in pharmacokinetic variability of antihypertensive agents may be a powerful tool for optimization of drug therapy in hypertension.

Pharmacokinetic optimization of antihypertensive therapy is not only important to improve normalization of blood pressure values but also to reduce adverse effects associated with high plasma levels. As previously mentioned, pharmacogenetic studies have found an increase in the report of adverse drug reactions in PMs with regard to EMs. The side effect of antihypertensive medication has been acknowledged as a reason for lack of adherence to pharmacological management and poor control of blood pressure [85]. Therefore, pharmacogenetic testing could be an interesting approach to improve antihypertensive drug therapy with specific agents, such as metoprolol and verapamil.

On the other hand, as the magnitude of blood pressure reduction in response to drug therapy is clearly related to plasma concentrations of antihypertensive drugs, it is probable that an important proportion of patients taking an agent with large interindividual pharmacokinetic variability be under treatment with a suboptimal dosage regimen. To describe the importance of interindividual pharmacokinetic variability in blood pressure lowering response, we describe two examples. Baek *et al.* [86] have found that, after a single dose administration, antihypertensive drug response to carvedilol varies from absence of blood pressure effect to maximal response in a range of drug concentrations of ~ 8 – 48 ng/ml. Variability of carvedilol plasma concentrations detected in clinical practice is greater than this range.

In another example, Donnelly *et al.* [87] studied PK/PD relationship of verapamil and nifedipine by means of PK/PD modeling. After applying a linear pharmacodynamic model, the authors found that antihypertensive response of nifedipine and verapamil increases in 0.48 and 0.13 mmHg, respectively, for each increment in 1 ng/ml of plasma concentrations of the corresponding CCBs [87]. In other words, in the case of nifedipine, a change in its plasma concentration of 20 ng/ml will translate in a modification of the blood pressure lowering response of 10 mmHg. Considering that mortality from ischemic heart disease and stroke doubles every increment in 20 and 10 mmHg of systolic and diastolic blood pressure [88], respectively, changes in antihypertensive response associated with interindividual variability of plasma levels are highly relevant.

Taking together, in our opinion, a greater knowledge of the sources of pharmacokinetic variability of hepatically eliminated antihypertensive drugs and the applicability of an individualized approach in hypertension management could enhance blood pressure lowering response to pharmacological therapy. In the next years, PK/PD modeling and pharmacogenetic testing may become powerful tools for better understanding and predicting individual antihypertensive drug effects. PK/PD modeling may significantly improve therapy of hypertension by establishing the optimal antihypertensive drug and its dose schedule in each hypertensive patient. In addition, pharmacogenetic testing allows early detection of patients with abnormal hepatic clearance of selected antihypertensive drugs, preventing the appearance of therapeutic failure or adverse drug reactions associated with pharmacological treatment.

Declaration of interest

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Affiliation

Christian Höcht[†1,2] PhD,
Facundo Martín Bertera[1],
Marcos Alejandro Mayer[1,2] &
Carlos Alberto Taira[1,2]
[†]Author for correspondence
[1]Universidad de Buenos Aires,
Facultad de Farmacia y Bioquímica,
Cátedra de Farmacología, Junín 956,
(C1113AAD) Buenos Aires,
Argentina
Tel: +54 11 4964 8265; Fax: +54 11 4508 3645;
E-mail: chocht@ffyb.uba.ar
[2]Universidad de Buenos Aires,
Instituto de Fisiopatología y Bioquímica Clínica,
Junín 956,
(C1113AAD) Buenos Aires,
Argentina