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Drug Interactions with Angiotensin Receptor Blockers: A Comparison with Other Antihypertensives

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Abstract

The ever-increasing introduction of new therapeutic agents means that the potential for drug interactions is likely to escalate. Numerous different classes of drugs are currently used to treat hypertension. The angiotensin receptor blockers offer one of the newest approaches to the management of patients with high blood pressure. Compared with other classes of antihypertensive agents, the angiotensin receptor blockers appear overall to have a low potential for drug interactions, but variations within the class have been detected. Losartan and irbesartan have a greater affinity for cytochrome P450 (CYP) isoenzymes and, thus, are more likely to be implicated in drug interactions. There is pharmacokinetic evidence to suggest that such interactions could have a clinical impact. Candesartan cilexetil, valsartan and eprosartan have variable but generally modest affinity and telmisartan has no affinity for any of the CYP isoenzymes. *In vitro* studies and pharmacokinetic/pharmacodynamic evaluation can provide evidence for some

interactions, but only a relatively small number of drug combinations are usually studied in this way. The absence of any pharmacokinetic evidence of drug interaction, however, should not lead to complacency. Patients should be made aware of possible interactions, especially involving the concurrent use of over-the-counter products, and it may be prudent for all patients receiving antihypertensive treatment to be monitored for possible drug interactions at their regular check-ups. The physician can help by prescribing agents with a low potential for interaction, such as angiotensin receptor blockers.

1. The Impact of Drug Interactions

Failure to respond to treatment is a relatively common phenomenon in the management of hypertensive patients: between about 40–60% of patients receiving a single antihypertensive agent do not achieve target blood pressure.[1,2] Although the most common explanation for inadequate blood pressure control is poor adherence to the dosage regimen, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure identified drug interactions as one of the other possible explanations.[3] To overcome the problem of lack of adequate response in a patient, the prescribing physician may then prescribe alternative, and possibly less well-tolerated, antihypertensive treatment, with an inevitable delay in achieving satisfactory blood pressure control and at increased cost. Awareness of possible interactions, identification of patients at risk, and the prescribing of agents with a low interaction potential may reduce the need to change the initial prescription.

Although hypertension occurs in all age groups, antihypertensive drugs are prescribed extensively to the elderly,[4] who are also likely to be receiving treatment for a variety of other clinical conditions. The number of drugs prescribed, the number of physicians involved in the patient's care, and the presence of greater frailty and comorbidity all increase the likelihood of drug interactions.[5] A review of medical records suggests that about one-third of patients may be prescribed five or more drugs, with women being treated with more drugs than men.[6] The problem may be exacerbated as, in recent years, the availability of non-prescription medication has increased, with some drugs now being reclassified as over-the-counter (OTC) products. Among the elderly, between 1 and 3.4 non-prescribed medications are taken on a regular basis.[7] In addition, patients may use OTC products for the treatment of acute conditions. The perceived innocuousness of these drugs, and their having been taken on a regular basis for a considerable time, results in patients tending to omit any mention of them. Nevertheless, self-medication generates a serious potential for drug interactions.[8] Among 75-year-olds living in the community, because of the varied nature of medications used, the potential for clinically significant drug interactions was identified in about 15% of patients.[9] The possibility of drug interactions may also be enhanced in the elderly, because physiological changes may result in changes in the metabolism and elimination of drugs.[10]

Only a relatively small proportion of physicians document their patients' use of herbal treatments and nutritional supplements.[11] Also, they would rarely question their patient's eating habits and preference for specific foods. Nevertheless, certain herbs, nutritional supplements, foods or beverages can modify drug metabolism and can result in clinical modification of the antihypertensive activity of certain agents and can cause adverse events.[12,13]

2. Management of Hypertensive Patients

When treating the hypertensive patient, it is important to maintain adequate blood pressure control throughout the dosage interval, with 24-hour blood pressure control being essential to reduce the risk of potentially life-threatening cardiovascular events.[14]

At the same time, hypotension must be avoided.[15] The various classes of agents with different modes of action that are used to achieve the target pressures recommended by The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[3] and World Health Organization – International Society of Hypertension[16] include diuretics, α-adrenoceptor antagonists (α-blockers), β-adrenoceptor antagonists (β-blockers), calcium channel antagonists, ACE inhibitors and angiotensin receptor blockers. However, α-blocker use has declined markedly in recent years.

The pharmacokinetic features of the different agents mean that some may be given once daily, whereas others require more frequent administration to achieve adequate blood pressure control at all times of the day and night. The adverse-effect profiles of the different classes of agents also vary. Some adverse effects, whether perceived or real, are often considered by patients to impinge on their quality of life to such an extent that they regard the therapy as unacceptable; patients experiencing these adverse effects are unlikely to be compliant and will remain hypertensive. Examples include incontinence (e.g. diuretics),[17] impotence (e.g. β-blockers, diuretics),[18] headache, flushing and oedema (e.g. calcium channel antagonists)[19] and dry, persistent cough (e.g. ACE inhibitors).[20] Among the most well-tolerated antihypertensive agents are the angiotensin receptor blockers. Placebo-controlled, double-blind studies using different angiotensin receptor blockers have consistently shown that the adverse-effect profiles of the different agents are similar, and that the incidence and the nature of adverse effects are similar to those of placebo.[14] They also have the advantage of once-daily administration.

The potential for drug interactions should also influence the choice of agent. Hypertensive patients often have chronic cardiovascular comorbidity that requires treatment,[21] and resultant cerebrovascular disease can lead to other conditions requiring long-term management, such as epilepsy[22] and depression.[23] Other chronic conditions, not necessarily related to hypertension, may also require regular medication (e.g. ulcers, rheumatoid arthritis, type 2 diabetes mellitus, psychiatric conditions). Elderly patients, in particular, are also highly susceptible to acute conditions, such as bacterial infections (e.g. pneumonia, acute bacterial exacerbations of chronic bronchitis) that require short-duration antibiotic therapy. The occurrence of general aches and pains in the elderly means that they often resort to the use of OTC NSAIDs.[24] Use of concomitant medication for acute conditions may also be common in other age groups, who may be likely to self-prescribe for acute conditions.

The rest of the article will concentrate on the potential of the various angiotensin receptor blockers currently available to interact with other substances, and how the interaction potential of angiotensin receptor blockers compares with that of other commonly prescribed classes of drugs for lowering blood pressure.

3. Nonspecific Antihypertensive Drug Interactions

Some drugs used for other indications may also affect blood pressure (table I). In addition, herbal products may modify blood pressure. If the drug given with the antihypertensive agent also has the effect of lowering blood pressure, there may be a further reduction in blood pressure. In some cases this may be advantageous, but in some patients orthostatic hypotension may lead to dizziness and falls, and necessitate a reduction in the antihypertensive dose. There is also the potential for nocturnal hypotension. In susceptible patients (e.g. the elderly and those with established coronary artery disease,

Table I. Some non-antihypertensive drugs that affect blood pressure

Hypotensive effect	Hypertensive effect
Anaesthetics	Corticosteroids
Antipsychotics	Cyclosporin
Anxiolytics	Feverfew
Dopamine agonists	Ginseng
Garlic	Goldenseal
Nitrates	Hypericum (St John's Wort)
Tricyclic antidepressants	NSAIDs
	Sympathomimetics

Table II. Substrates, inhibitors and inducers of cytochrome P450 (CYP) isoenzymes that metabolise angiotensin receptor blockers

	CYP1A2	CYP2C9	CYP3A4
Angiotensin receptor blocker substrates	Losartan	Losartan	Losartan
	Irbesartan	Irbesartan	Irbesartan
		Valsartan[a]	
		Candesartan cilexetil[a]	
Other substrates	Amitriptyline	Fluvastatin	Amitriptyline
	Clomipramine	NSAIDs	Benzodiazepines
	Clozapine	Phenytoin	Calcium channel antagonists
	Imipramine	Tolbutamide	Cisapride
	Propranolol	*S*-Warfarin	Cyclosporin
	Theophylline		Erythromycin
	R-Warfarin		Ethinylestradiol
			Ketoconazole
			Lovastatin
			Sertraline
			Terfenadine
			Theophylline
			Verapamil
Inhibitors	Fluoroquinolone antibacterials	Azole antifungals	All antidepressants
	Fluvoxamine	Fluoxetine	Azole antifungals
	Grapefruit juice	Grapefruit juice	Cimetidine
		Sertraline	Clarithromycin
			Diltiazem
			Erythromycin
Inducers	Omeprazole	Fluvastatin	Carbamazepine
	Phenobarbital (phenobarbitone)	Rifampicin	Phenobarbital
	Phenytoin		Phenytoin
	Rifampicin (rifampin)		Rifampicin

a Weak affinity only.

left ventricular dysfunction or previous cerebrovascular accident), an excessive reduction of blood pressure during the night may predispose to myocardial ischaemic, optic nerve damage and stroke.[25-27] Changes in nocturnal blood pressure are not detectable unless occasional ambulatory blood pressure monitoring is employed. By contrast, blood pressure may be less well controlled if the second drug has a hypertensive effect. The inadequate control of blood pressure, even if relatively short lasting, increases the risk of cardiovascular events. The regular monitoring of blood pressure is an important element in the management of any hypertensive patient, but more frequent measurement of blood pressure should be conducted in patients who are also taking non-antihypertensive drugs that can affect blood pressure. Ambulatory blood pressure monitoring may be a viable proposition; however, it incurs additional expense and inconveniences the patient.

4. Angiotensin Receptor Blocker Interactions

4.1 Losartan

One of the most frequent reasons for interactions is the induction or inhibition of drug-metabolising enzymes, the most common being the family of cytochrome P450 (CYP) isoenzymes (table II).[28] *In vitro* screening has found that the angiotensin receptor blocker losartan has affinity for CYP2C9.[29] CYP2C9 brings about the conversion of relatively inactive losartan to the carboxylic acid derivative E-3174 (EXP-3174), which possesses 10–14 times

more antihypertensive activity than the parent compound.[30] Losartan also has modest affinity for the CYP1A2 and CYP3A4 isoenzymes,[29] with CYP3A4 being involved in the formation of E-3174. There is, thus, the potential for the modification of active drug levels and, as a consequence, the clinical efficacy when losartan is co-administered with any of the other drugs that are substrates, inhibitors or inducers of the same isoenzymes (table II). There is pharmacokinetic evidence that some interactions do occur.

Fluconazole is a CYP2C9 inhibitor that is now available as an OTC product in some countries for the treatment of vaginal thrush. Fluconazole interacts with losartan and results in the suppression of its conversion to the active metabolite E-3174. Studies in healthy volunteers have shown that the mean peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of losartan were elevated, with corresponding reductions in the amounts of E-3174 in plasma, when losartan was co-administered with fluconazole.[31,32] The clinical significance of the observed fluconazole-losartan interaction is unclear, but the possibility of a decreased antihypertensive efficacy resulting from reduced E-3174 levels should be considered, with a possible increase in the dose of losartan. Itraconazole, another azole antifungal agent, was shown not to have any significant pharmacokinetic effects on the conversion of losartan to E-3174.[31]

Phenobarbital is an inducer of CYP3A4 (table II). When phenobarbital was co-administered with losartan to healthy volunteers, statistically significant reductions in plasma concentrations of losartan and E-3174 were observed.[33] Although these observations were considered not to be of major clinical relevance, the possibility of an adverse interaction with loss of antihypertensive activity cannot be excluded.

Fluvastatin, the first fully synthetic HMG-CoA reductase inhibitor, has been shown to reduce cholesterol in patients with hyperlipidaemia. In addition to being a CYP2C9 substrate (table II), fluvastatin demonstrates inhibitory effects on CYP2C9 both *in vitro* and *in vivo*. The oral clearance of losartan is reduced by about 20% when the potassium salt is co-administered with fluvastatin, although this effect has not been shown to be of clinical significance.[34]

Hypothetically, there is a possibility of interactions between losartan and several different classes of antibacterial agents. Rifampicin (rifampin), which is used in the treatment of brucellosis, tuberculosis, leprosy, staphylococcal infections and legionnaires' disease, is a potent inducer of CYP3A4 (table II). When losartan and rifampicin were taken concurrently by healthy volunteers, the AUC of losartan was reduced by 35% and that of E-3174 by 40%, and the half-lives of losartan and E-3174 were reduced to 50% of the values observed in the absence of rifampicin.[35] Because of the magnitude of the pharmacokinetic effect, the interaction is likely to be clinically significant and may necessitate an increase in dose. By contrast, erythromycin, a drug used for the treatment of community-acquired respiratory bacterial infections including legionnaires' disease and an inhibitor of CYP3A4 (table II), did not have any significant effect on the AUC or half-life of either losartan or E-3174.[35]

The NSAIDs can increase blood pressure by a number of specific and nonspecific mechanisms, including increasing vascular resistance in the renal and non-renal beds and retention of sodium.[36] Concurrent administration of indomethacin significantly attenuated the 24-hour ambulatory diastolic blood pressure response to losartan in hypertensive patients.[37] However, aspirin (acetylsalicylic acid) exerted no marked effect on blood pressure control in patients with essential hypertension receiving losartan.[38]

On the basis of studies conducted in healthy volunteers, there appears to be no pharmacokinetic evidence of clinically significant interactions between losartan and cimetidine (a CYP3A4 inducer; table II), digoxin or warfarin.[39,40] In the case of concurrent administration of losartan and cimetidine, an 18% increase in the bioavailability of cimetidine was observed.[41] It would be prudent for any patient receiving a combination of drugs to be closely observed for evidence of potential interac-

tions, such as poor blood pressure control, and to adjust the dose accordingly.

In addition, there is evidence of a pharmacokinetic drug interaction between losartan and cyclosporin, a substrate of CYP3A4 (table II), based on the data collected from 100 transplant patients.[42] The age of the patient did not influence the likelihood of this drug interaction; transplant patients in the age range 60–75 years experienced similar interactions to those occurring in younger patients. The clinical significance of any pharmacokinetic interactions is unclear.

Grapefruit juice is a well-recognised inducer of CYP1A2 (table II). Losartan and grapefruit juice when taken simultaneously in healthy volunteers resulted in a delay in the absorption of losartan. Furthermore, the AUC for E-3174 was reduced and the ratio of the $AUC_{losartan}$ to $AUC_{E\text{-}3174}$ was increased.[43] The presence of lower proportions of active metabolite may result in poorer blood pressure control in hypertensive patients.

Compared with other angiotensin receptor blockers, such as candesartan cilexetil and telmisartan, urinary excretion of losartan is relatively high, with 35% being excreted via the kidneys.[44] If the renal route contributes to more than 30% of drug elimination, there is a potential for interactions with other renally excreted agents.[45] For this reason, losartan could increase urinary excretion of uric acid, xanthines and oxipurinol by acting on their common renal transport pathways. The effect of losartan on oxipurinol appears to be clinically important and could increase the possibility of calculi in the urinary tract.[46]

Observations in hypertensive patients suggest that there is no clinically significant effect of hydrochlorothiazide on the pharmacokinetics of losartan or E-3174. Based on urinary recovery of hydrochlorothiazide over a 24-hour period, losartan did not affect the pharmacokinetics of hydrochlorothiazide in hypertensive patients.[47] The synergistic pharmacodynamic effect of losartan and hydrochlorothiazide on blood pressure when co-administered provides superior blood pressure control in patients who respond inadequately to monotherapy.[48] Similar synergy has been observed between hydrochlorothiazide and other angiotensin receptor blockers, as will be discussed.

4.2 Valsartan

The enzyme or enzymes responsible for valsartan metabolism have not been identified, but there is minimal oxidative metabolism.[49] *In vitro* screening using human hepatic microsomes found that valsartan had relatively low affinity for CYP2C9 (table II).[29] The findings of *in vitro* studies also show that valsartan is highly bound to plasma proteins, mainly albumin, and is not displaced by hydrochlorothiazide, diclofenac, furosemide (frusemide), or warfarin.[50]

Despite the relative unimportance of CYP metabolism, transplant patients receiving cyclosporin were found to be at risk of pharmacokinetic drug interactions if they were also treated with valsartan.[42] However, there are no reports of clinically significant interactions necessitating dose adjustment of either agent.

There is also a recent report of a potentially serious drug interaction between valsartan and lithium.[51] A patient with a history of bipolar disorder who had been treated with lithium for 5 years experienced ataxia and delirium when valsartan was given to treat hypertension. The adverse response suggestive of lithium toxicity was resolved when an alternative antihypertensive was given.

The simultaneous administration of valsartan and the diuretic furosemide did not have any effect on the pharmacokinetics of valsartan. However, the C_{max}, AUC and urinary excretion of furosemide were significantly reduced when co-administered with valsartan.[52] Despite the reduced bioavailability of furosemide, valsartan did not bring about any reduction in diuresis resulting from furosemide. Also, valsartan and furosemide given in combination resulted in a greater reduction in blood pressure.[52]

No clinically significant pharmacokinetic interactions between valsartan and concurrently administered amlodipine, digoxin, glibenclamide (glyburide), hydrochlorothiazide or indomethacin have been detected in healthy volunteers.[53] Co-adminis-

tration of a single dose of cimetidine resulted in a 51% increase in the valsartan C_{max}, but there was no variation in cimetidine pharmacokinetics.[54] Cimetidine-related changes in the rate of elimination of valsartan are not anticipated, since the clearance from plasma occurs mainly by biliary excretion of unchanged valsartan; metabolism and renal excretion are only minor contributors. Although the effect of multiple-dose co-administration has not been studied, the increase in the C_{max} of valsartan was not considered likely to be clinically relevant.[54]

Unlike the other angiotensin receptor blockers, there is a clinically significant reduction in valsartan bioavailability when taken with food. Thus, it is recommended that valsartan should be taken 1 hour before or 2 hours after a meal.[55] Compliance is enhanced if the patient develops the habit of taking their medication at a specific time of day. In the case of antihypertensive therapy, many patients prefer to take their medication in the morning and usually with their breakfast.[56] This is clearly not appropriate for valsartan.

4.3 Candesartan Cilexetil

The prodrug candesartan cilexetil is completely converted to candesartan during absorption from the gastrointestinal tract.[57] Candesartan is mainly eliminated unmetabolised in both urine and faeces, but an inactive metabolite is formed in the presence of a cytochrome of the CYP2C family (table II).[57] The affinity of candesartan for this enzyme is very low.

Changes in the pharmacokinetics of candesartan and other drugs have been detected when given simultaneously, but at present there is considered to be no clinically relevant pharmacokinetic interaction between candesartan and hydrochlorothiazide, nifedipine, digoxin, glibenclamide or oral contraceptives based on studies conducted in healthy volunteers.[58] Candesartan brought about a 7% reduction in trough plasma warfarin concentrations, but the prothrombin time was unaffected.[58] In the case of hydrochlorothiazide, when candesartan cilexetil was administered concurrently, the AUC of candesartan was significantly reduced. This reduction in plasma candesartan concentration was compensated by a substantial potentiation of the antihypertensive effect because of the addition of hydrochlorothiazide.[59] Enhanced antihypertensive activity has also been noted with the simultaneous administration of candesartan cilexetil and amlodipine.[60]

4.4 Irbesartan

CYP plays a major role in metabolism of irbesartan (table II).[61] In common with losartan, irbesartan has marked affinity for CYP2C9 and CYP3A4 isoenzymes, and for CYP1A2.[29] The possibility of drug interactions is reinforced by the observation that tolbutamide and warfarin competitively inhibit the oxidation of irbesartan.[61] Also, nifedipine is capable of inhibiting irbesartan metabolism *in vitro*.[61]

A study in healthy volunteers showed that irbesartan did not affect the steady-state pharmacodynamics and pharmacokinetics of warfarin.[62] There also appears to be no pharmacokinetic evidence of any interaction between irbesartan and hydrochlorothiazide, nifedipine, tolbutamide, magnesium and aluminium hydroxides, or digoxin.[63] The *in vitro* and *in vivo* data are contradictory. Fluconazole co-administration brought about a 19% increase in the steady-state peak plasma irbesartan concentration and a 63% increase in the AUC.[63] Neither of these increases was regarded as likely to be clinically significant. Another study showed that irbesartan had no significant effect on the single-dose pharmacokinetics of total simvastatin acid.[64]

4.5 Eprosartan

Eprosartan is eliminated primarily as unchanged drug via the biliary and renal routes.[65] The CYP isoenzymes appear to have little role in eprosartan metabolism. About 37% of the eprosartan dose is excreted in urine, thus suggesting that there is a potential for some drug interactions with other renally excreted drugs.[45]

A series of studies conducted in healthy volunteers has assessed the effect of eprosartan on the pharmacokinetics of digoxin and hydrochlorothiazide, and the pharmacodynamics of warfarin and

glibenclamide, as well as the effects of ranitidine and hydrochlorothiazide on eprosartan pharmacokinetics.[66] Eprosartan appears to have no significant effects on the pharmacokinetics of digoxin and hydrochlorothiazide, nor on the pharmacodynamics of warfarin and glibenclamide.[66] A further study found that there was no apparent effect of eprosartan on the anticoagulant effect of warfarin, as measured by the international normalised ratio.[67] Also, ranitidine, hydrochlorothiazide, ketoconazole or fluconazole co-administration did not significantly modify eprosartan pharmacokinetics.[66]

4.6 Telmisartan

An *in vitro* study has shown the absence of any CYP-dependent metabolites of telmisartan.[68] Telmisartan is a highly lipophilic compound – the most lipophilic of the currently available angiotensin receptor blockers – and is predominantly excreted via the bile.[68] Thus, in two respects there is a very low potential for drug interactions.

Studies in healthy volunteers have shown that there was no significant modification of pharmacokinetic parameters of telmisartan when it was co-administered with amlodipine,[69] hydrochlorothiazide,[70] ibuprofen,[71] paracetamol (acetaminophen),[71] simvastatin,[72] warfarin[73] or glibenclamide.[74] Also, the pharmacokinetics of amlodipine[69] and hydrochlorothiazide[70] were unaltered by the presence of telmisartan. Similarly, telmisartan had no effect on the pharmacodynamics of warfarin.[73] An additional antihypertensive effect is achieved when a combination of telmisartan and hydrochlorothiazide is administered.[75] This enhanced antihypertensive activity was apparent in normally difficult-to-treat Afro-Caribbean patients.[76]

The C_{max} of digoxin was increased by 50% when telmisartan was administered concurrently.[77] However, trough concentrations in the presence and absence of telmisartan at steady-state were bioequivalent. No adverse events suggestive of digoxin toxicity have been observed in healthy volunteers or in patients studied during preregistration clinical trials. In one study comparing the efficacy of telmisartan with that of enalapril in patients with congestive heart failure, 39% of those enrolled were receiving concomitant digoxin.[78] In this study, telmisartan and enalapril were equally well tolerated. Similarly, in a post-marketing surveillance of 19 870 patients in Germany receiving telmisartan for 6 months, 7.3% were treated concurrently with digoxin. There was no evidence of adverse events related to digoxin.[79] The transient elevation of digoxin serum concentration observed in healthy volunteers is unlikely to be clinically significant, and no dose adjustment is required.[77] It is recommended that digoxin-treated patients should be monitored when first receiving telmisartan and also if the telmisartan dose is changed. There are no specific requirements to reduce the digoxin dose.

5. Angiotensin Receptor Blocker Interactions Compared with Those of Other Frequently Used Antihypertensives

5.1 Diuretics

Potentially significant interactive effects of the thiazide diuretics with other drugs involve the changes in balance of cations and water. The mode of action of thiazides means that they may cause hypokalaemia.[80] Consequently, they should be used with caution if prescribed concurrently with other drugs that decrease potassium levels, such as corticosteroids, amphotericin or itraconazole.[81] The hypokalaemic effect of hydrochlorothiazide can be overcome by the concomitant use of drugs that increase serum potassium. Angiotensin receptor blockers, when used together with a thiazide such as hydrochlorothiazide, not only provide enhanced blood pressure control, enabling relatively low doses of hydrochlorothiazide (usually 12.5mg) to be used, but also, as has been demonstrated in the case of telmisartan, prevent potassium loss.[82] As with all patients receiving diuretic therapy, periodic determination of serum electrolytes should be performed.

Lithium clearance can also be affected by thiazide diuretics to such an extent that toxic levels, which necessitate haemodialysis, occur.[83] The concurrent use of hydrochlorothiazide and lithium

should be avoided because of this potentially serious interaction. Valsartan is the only angiotensin receptor blocker for which there is evidence of lithium intoxication.[51] NSAIDs increase water and sodium retention, thus counteracting the beneficial effects of hydrochlorothiazide.[84] The use of NSAIDs should be avoided in patients treated with hydrochlorothiazide. Alternatively, different antihypertensive therapy may be more appropriate.

5.2 β-Adrenoceptor Antagonists (β-Blockers)

A number of β-blockers inhibit CYP.[85] The lipophilicity of β-blockers is an important predictor of the affinity for cytochrome CYP2D6 and of their potential to cause specific competitive drug interactions, but more complex structural factors appear to be important as well.[86] In general, the interactions that induce or inhibit the metabolism of β-blockers and affect the plasma concentrations are not severe and may be of little clinical significance. Nevertheless, when drugs like cimetidine, quinidine, rifampicin, phenobarbital and certain fluoroquinolone antibiotics are given concurrently with β-blockers that are metabolised by the liver (e.g. propranolol, metoprolol, bisoprolol), patients should be monitored for any excessive antihypertensive effect, with possible adjustment of the dose.[87] By comparison, the CYP-mediated interactions are in general unlikely when angiotensin receptor blockers are given, although there is greater potential in the case of losartan and irbesartan, which are extensively metabolised by CYP isoenzymes.[30,61]

Particularly important examples of interactions that result in the decline in antihypertensive activity of β-blockers include that of propranolol or pindolol with the antipsychotics thioridazine and chlorpromazine. Because of the potential seriousness, it is recommended that co-administration of these agents should be avoided if possible.[88] If it is considered that these agents are the most appropriate for a specific patient, scrupulous monitoring is essential to detect any attenuation of the action of either drug. To date, there is no evidence of any serious interaction between any antipsychotic and any angiotensin receptor blocker.

Some β-blockers (e.g. talinolol, arvedilol) may significantly increase the bioavailability of digoxin, necessitating a reduction in the dose to avoid digoxin toxicity.[89,90] Although a pharmacokinetic study suggests the possibility of an interaction between digoxin and telmisartan,[77] this has not been substantiated clinically.

Concomitant use of β-blockers and hypoglycaemic agents is not contraindicated, but patients receiving such treatment should be warned of the possibility of prolonged hypoglycaemia and should be educated about how to recognise the signs of hypoglycaemia and how to respond.[91] In the case of valsartan,[53] candesartan cilexetil,[58] eprosartan[66] and telmisartan,[74] no pharmacokinetic evidence for interaction was observed when glibenclamide was administered simultaneously. Thus concomitant use of an angiotensin receptor blocker and a hypoglycaemic agent is unlikely to present any problems.

5.3 Calcium Channel Antagonists

Many calcium channel antagonists, including verapamil, diltiazem, nifedipine, darodipine and isradipine, inhibit CYP3A4. Pharmacokinetic interactions occur with other drugs that inhibit CYP3A4, such as azole antifungals (e.g. fluconazole, itraconazole), macrolide (but not azalide) antibiotics (e.g. erythromycin, clarithromycin), cimetidine and grapefruit juice.[92] The pharmacodynamic impact is an increased blood pressure lowering. As a consequence, the dose of the calcium antagonist may need to be reduced. Grapefruit juice, however, poses a more difficult problem as it may only be drunk occasionally. Patients should therefore be advised not to drink grapefruit juice. To most patients, this should not create major problems, but some may regard this as contributing to a reduction in their quality of life. The relatively insignificant role of CYP3A4 in the metabolism of most angiotensin receptor blockers suggests that interactions of a similar nature are unlikely. The only exception is losartan, for which there is pharmacokinetic evidence of an interaction with grapefruit juice, with a significant reduction in the AUC of E-3174, the pharmacologically active metabolite.[43]

Unlike angiotensin receptor blockers, there is also the possibility of serious interactions between calcium channel antagonists,[93-95] and anticonvulsants, bronchodilators and histamine H_2 receptor blockers.[95] It is important when patients receive combinations of such drugs that they are closely monitored, with the immediate adjustment of the dose of either drug if any untoward events are experienced.

A particularly important interaction is that of verapamil, nisoldipine, nifedipine, diltiazem, felodipine or nicardipine with digoxin.[96,97] Concurrently administered verapamil, for example, may increase digoxin levels by 50% and result in digoxin toxicity, such as ventricular arrhythmias.[94] Reduction of the digoxin dose is essential if such a combination of treatments is considered the most appropriate. By contrast, there is no evidence of digoxin toxicity in association with any of the angiotensin receptor blockers.

5.4 ACE Inhibitors

ACE inhibitors, which in common with angiotensin receptor blockers target the renin-angiotensin-aldosterone system, have a greater propensity for drug interactions than angiotensin receptor blockers. Some may have serious clinical consequences.

One of the potentially serious features is the ability of ACE inhibitors to enhance insulin sensitivity;[98] hence, ACE inhibitors may increase the hypoglycaemic effect of antidiabetic agents. There have been reports of hypoglycaemia when an ACE inhibitor and a hypoglycaemic agent are co-administered.[99,100] Interactions of ACE inhibitors with antacids have also been detected, with a reduction in the efficacy of the antihypertensive.[101] Patients should be informed of the possibility and told how to react should a problem occur.

Hypotension and postural syncope may occur with the co-administration of antipsychotics and ACE inhibitors.[88] Scrupulous patient monitoring for attenuated or enhanced activity of either agent is essential whenever antipsychotics and any antihypertensive that is metabolised by CYP are given concurrently.[88] The dose of agents should be adjusted accordingly. This may prove a time-consuming and expensive process, and it may be more appropriate to prescribe an alternative antihypertensive in a patient already being treated with antipsychotics.

NSAIDs may attenuate the haemodynamic effect of ACE inhibitors because of the inhibition of cyclooxygenase, so overcoming the vasodilatory effect of ACE inhibitors mediated via prostaglandins, and thus resulting in less effective blood pressure control.[102] In general, there is no evidence for an interaction between angiotensin receptor blockers and NSAIDs, with the exception of the attenuation of the diastolic blood pressure response with the concomitant administration of losartan and indomethacin.[51] Because of the possibility of an interaction, it may be prudent to monitor patients treated with ACE inhibitors for any loss of antihypertensive efficacy if long-term NSAID therapy is required.

There is currently little information on the interaction of ACE inhibitors with cyclosporin. However, it is recommended that caution should be exercised when co-administering an ACE inhibitor and cyclosporin.[102] Other than with losartan,[42] there is no evidence of an interaction of angiotensin receptor blockers with cyclosporin.

Some interactions are restricted to specific ACE inhibitors. For example, captopril interacts with digoxin,[103] with a 20% increase in serum digoxin levels when captopril is co-administered.[104] In common with angiotensin receptor blockers, there is no evidence of digoxin toxicity and dose adjustment is not generally necessary.

One other potentially very serious interaction is between lithium and an ACE inhibitor. There have been reports of lithium toxicity in patients with bipolar disorder given ACE inhibitors.[102] Consequently, co-administration of lithium and an ACE inhibitor should be undertaken with extreme caution and serum lithium concentrations should be monitored regularly to avoid lithium toxicity. Because elderly patients may be uniquely predisposed to this interaction, avoidance of this medication combination in older subjects should be considered.[105] A

report of a potential interaction with valsartan and lithium has also been published.[51]

6. Selection of Antihypertensive Therapy

In the management of hypertension, prescribing an antihypertensive agent is clearly not simply a matter of selecting any agent with proven clinical efficacy and that can maintain antihypertensive activity throughout the period between doses as demonstrated by ambulatory blood pressure monitoring. The patient profile must also be taken into account and a number of questions should be asked (table III).

To maximise blood pressure control, the drug or drugs prescribed should be well tolerated and have a low potential for detrimental interaction with other drugs that may be taken concurrently, whether occasionally or on a day-to-day basis. The available data, based almost exclusively on pharmacokinetic/pharmacokinetic studies in healthy volunteers, suggest a low potential for clinically significant drug interactions when angiotensin receptor blockers are coadministered with other agents. A review of the literature also suggests that drug interactions are less likely with angiotensin receptor blockers than in the case of other antihypertensive agents.

In general, evidence for interactions is provided by small-scale studies performed under highly standardised conditions, and thus may not be representative of the real-life situation where the diet is very varied and patients may smoke and drink alcohol, which can lead to the induction of certain CYP isoenzymes and the modification of drug metabolism.[106,107] Furthermore, genetic differences can result in 10- to 20-fold variations in the activity of CYP isoenzymes in different individuals.[108] As a result, some patients may be more susceptible to compounds whose activity is modulated by the CYP isoenzymes.[109] In the future, it will be possible to reconcile the likelihood of drug interactions produced by specific combinations of drugs and predict those individuals who are at risk from such interactions, as a consequence of their genetic makeup.[110] At present, however, physicians should err on the side of caution and recognise that there is greater possibility of interactions with some drugs than with others.

Table III. Factors to consider when prescribing antihypertensive therapy

Is the patient likely to be compliant?
Has the patient failed to respond to previous antihypertensive therapy?
Has the patient reported adverse effects?
What other medication is the patient taking on a regular basis?
What is the patient's attitude to self-medication and the use of natural remedies?

7. Conclusions

Some antihypertensive drugs are more likely to cause interactions than others. Potential detrimental combinations should be avoided whenever possible. If a specific combination of drugs is deemed unavoidable, close patient monitoring is important. Between examinations, patients should be educated to identify not only potentially serious interactions, but any changes in wellbeing that may suggest an interaction of some kind. As well as the possibility of prescribed drugs interacting, patients should also be aware that OTC products might interact with their antihypertensive therapy. It is also important to remind patients that what is natural is not necessarily best and that the use of complementary medicine could do them more harm than good. The onus is not exclusively on the patient. The prescribing physician should also contribute to minimising drug interactions by using agents with little or no potential for drug interactions.

The recently developed angiotensin receptor blockers, as a class, provide effective blood pressure control whether given alone or in combination with hydrochlorothiazide. They have the advantage of being well tolerated; clinical studies have consistently shown that the incidence of adverse effects was similar to that of placebo and that their potential for interactions with other drugs is low in comparison with other classes of antihypertensive agents. These favourable features will all contribute to greater compliance and more assured control of blood pressure.

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