The term alpha blockers covers a range of drugs, but for the purposes of this section it is primarily used to describe the selective alpha blockers that are mainly used for managing hypertension and benign prostatic hyperplasia. Other drugs that have alpha-blocking actions are covered elsewhere in this publication. The selective and non-selective alpha blockers are categorised and listed in Table 4.1, below.

The principal interactions of the alpha blockers are those relating to enhanced hypotensive effects. Early after the introduction of the selective alpha blockers it was discovered that, in some individuals, they can cause a rapid reduction in blood pressure on starting treatment (also called the ‘first-dose effect’ or ‘first-dose hypotension’). The risk of this might be higher in patients already taking other antihypertensive drugs. A similar hypotensive effect can occur when the dose of the alpha blocker is increased, or if treatment is interrupted for a few days and then re-introduced.

The first-dose effect has been minimised by starting with a very low dose of the alpha blocker, and then escalating the dose slowly over a couple of weeks. Some manufacturers recommend giving the first dose on retiring to bed, or if not, avoiding tasks that are potentially hazardous if syncope occurs (such as driving) for the first 12 hours. If symptoms such as dizziness, fatigue, or sweating develop, patients should be warned to lie down, and to remain lying flat until they abate completely.

It is unclear whether there are any real differences between the alpha blockers in their propensity to cause this first-dose effect. However, tamsulosin is reported to have some selectivity for the alpha receptor 1A subtype, which are found mostly in the prostate and so have less effect on blood pressure: an initial titration of the dose is therefore not considered to be necessary. Nevertheless, it would be prudent to exercise caution with all the drugs in this class.

Other alpha blockers are also used to increase urinary flow-rate and improve obstructive symptoms in benign prostatic hyperplasia. In this setting, their effects on blood pressure are more of an adverse effect, and their additive hypotensive effect with other antihypertensives might not be beneficial.

Some alpha blockers (e.g. alfuzosin, doxazosin, silodosin, tamsulosin) are in part metabolised by the cytochrome P450 isoenzyme system, particularly by CYP3A4, and therefore potent CYP3A4 inhibitors might increase their exposure, see ‘Alpha blockers + Ketoconazole and other CYP3A4 inhibitors’, p.93. Some alpha blockers form conjugates and the potential for interactions with drugs that inhibit glucuronidation has been noted for silodosin, see ‘Alpha blockers + Miscellaneous’, p.94.

Drowsiness or increased somnolence has been reported as an adverse effect of many alpha blockers. However, with the exception of indoramin (see ‘Alcohol + Alpha blockers’, p.53), there appear to be no reports of alpha blocker interactions associated with additive CNS depressant effects. This is probably because sedation occurs more frequently with indoramin than with other alpha blockers and is one of its commonest adverse effects.

### Table 4.1 Alpha blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Principal indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective alpha1 blockers (Alpha blockers)</strong></td>
<td></td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>BPH</td>
</tr>
<tr>
<td>Bosantan</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>BPH; Hypertension</td>
</tr>
<tr>
<td>Indoramin</td>
<td>BPH; Hypertension; Migraine</td>
</tr>
<tr>
<td>Prazosin</td>
<td>BPH; Heart failure; Hypertension; Raynaud’s syndrome</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>BPH</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>BPH</td>
</tr>
<tr>
<td>Terazosin</td>
<td>BPH</td>
</tr>
<tr>
<td><strong>Other drugs with alpha-blocking actions</strong></td>
<td></td>
</tr>
<tr>
<td>Moxisylyte</td>
<td>Peripheral vascular disease; Erectile dysfunction</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Hypertensive episodes in phaeochromocytoma</td>
</tr>
<tr>
<td>Tolazoline</td>
<td>Peripheral vascular disease; Pulmonary hypertension</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Erectile dysfunction; Hypertensive episodes in phaeochromocytoma</td>
</tr>
<tr>
<td>Urapidil</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>
The first-dose effect seen with alpha blockers (particularly alfuzosin, prazosin, and terazosin) is likely to be potentiated by ACE inhibitors and probably angiotensin II receptor antagonists. There is no pharmacokinetic interaction between doxazosin and enalapril, and the hypotensive effects appear to be additive. In one small study tamsulosin did not have any clinically relevant effects on blood pressure that was already well controlled by enalapril.

Clinical evidence

(a) Bunopirin

A patient taking bunopirin developed severe first-dose hypotension after being given bumetanide, resulting in this interaction being further studied in 6 healthy subjects. When doxazosin 400 microgram daily, the mean blood pressure over 6 hours was reduced by 9.3/6.7 mmHg. When bunopirin was given one hour after enalapril the blood pressure fell by 27/16 mmHg. Blood pressure (all fall by 19/22 mmHg) even when the dose of enalapril was reduced to 2.5 mg.1

(b) Doxazosin

In a study in 12 healthy normotensive subjects given either enalapril 10 mg daily or doxazosin 1 mg daily, the pharmacokinetics of both drugs were not affected during steady-state administration of the second drug. The hypotensive effects of the drugs in normotensive subjects were additive.2 For comment that doxazosin appeared to have less effect on blood pressure in patients with BPH receiving ACE inhibitors than in those taking beta blockers or diuretics, see ‘Alpha blockers + Beta blockers’, below.

(c) Tamsulosin

In a placebo-controlled study in 6 hypertensive men with blood pressure well controlled with enalapril, the addition of tamsulosin 400 microgram daily for 7 days, then 800 microgram daily for a further 7 days, had no clinically relevant effects on blood pressure (assessed after 6 and 14 days of tamsulosin). In addition, no first-dose hypotensive effect was seen on the day tamsulosin was started, or on the day the tamsulosin dose was increased.3

(d) Terazosin

Retrospective analysis of a large multinational study in patients with BPH given terazosin 1 mg daily for 10 weeks only found that terazosin reduced the blood pressure of patients taking ACE inhibitors (enalapril, lisinopril, or perindopril) if the blood pressure was uncontrolled. No change in blood pressure was seen in those with normal blood pressure (i.e. those without hypertension and those with hypertension controlled by ACE inhibitor). The most common adverse effect in the 10-week terazosin phase was dizziness, and the incidence of this appeared to be lower in those taking tamsulosin (13 to 16%) than in those not taking terazosin (21 to 23%). Similarly, another, subsequent retrospective analysis found that terazosin did not affect the blood pressure of hypertensive men whose blood pressure was controlled with an ACE inhibitor. However, the UK manufacturer of terazosin notes that the incidence of dizziness in patients taking terazosin was higher than those receiving an ACE inhibitor.4

Mechanism

The first-dose effect of alpha blockers (see ‘Alpha blockers’, p.87) might be potentiated by ACE inhibitors. Tamsulosin possibly has less effect on blood pressure since it has some selectivity for alpha receptors in the prostate.

Importance and management

Direct information about the interaction between alpha blockers and ACE inhibitors is limited, but what is known is in line with the way the alpha blockers interact with other antihypertensive drugs. Acute hypotension (dizziness, fainting) sometimes occurs unpredictably with the first dose of some alpha blockers, particularly alfuzosin, prazosin, and terazosin; but there is insufficient evidence to suggest that the alpha blockers differ in their propensity to cause this effect. Note that the acute hypotensive reaction appears to be short-lived.

When starting an alpha blocker it is often recommended that those already taking an antihypertensive should have their dose reduced to a maintenance level, while initiating the alpha blocker at a low dose, with the first dose taken just before going to bed. Patients should also be warned about the possibility of postural hypotension and how to manage it (i.e. lay down, raise the legs, and, when recovered, get up slowly). Similarly, when adding an antihypertensive to an alpha blocker, it might be prudent to decrease the dose of the alpha blocker and re-titrate as necessary.

Angiotensin II receptor antagonists would be expected to interact in the same way as ACE inhibitors. Some manufacturers of angiotensin II receptor antagonists state that enhanced hypotensive effects can occur with other antihypertensive drugs, but alpha blockers do not appear to be specifically mentioned.


Indomethacin reduces the blood pressure lowering effects of prazosin in some individuals. However, indomethacin does not appear to interact adversely with other alpha blockers.

Clinical evidence

(a) Diclofenac

The UK manufacturer of diclofenac states that it has been given without any evidence of adverse interaction to patients taking NSAIDs.5

(b) Prasidone

A study in 9 healthy subjects found that indomethacin 50 mg twice daily for 3 days had no statistically significant effect on the hypotensive effect of a single 5-mg dose of prasidone. However, in 4 subjects it was noted that the maximum fall in the mean standing blood pressure due to prasidone was 20 mmHg less when they were taking indomethacin. Those of the 4 that fell whilst given prasidone alone, but not while they were also taking indomethacin. The manufacturer states that prasidone has, in clinical experience, been given with indomethacin (and also aspirin and phenylbutazone) without any adverse interaction.6

(c) Tenoxicam

The UK manufacturer of tenoxicam states that no adverse interactions have been reported between tenoxicam and angiotensin/anti-inflammatories.7

Mechanism

Not established. It seems probable that indomethacin inhibits the production of hypotensive prostaglandins by the kidney, resulting in an increase in blood pressure in some cases and reducing the hypotensive effect of prasidone.8

Importance and management

Information about the interactions between alpha blockers and NSAIDs or aspirin appears to be limited, but the general picture suggests that no interaction of clinical importance occurs. A possible exception is the use of indomethacin with prasidone, which is consistent with the way indomethacin reduces the effects of other different antihypertensives (e.g. see ‘ACE inhibitors + NSAIDs’, p.18, and ‘Beta blockers + Aspirin or NSAIDs’, p.100). This interaction apparently does not affect every patient. If indomethacin is added to established treatment with prasidone, be alert for a reduced antihypotensive response. It is not known exactly what happens in patients taking both drugs long-term, but note that with other interactions between antihypertensives and NSAIDs the effects seem to be modest.9

A marked hypertensive reaction (dizziness, pallor, sweating) occurred in 3 out of 6 hypertensive patients taking alprazolam 400 mg twice daily when they were given the first dose. In those patients, the reduction in blood pressure was greater after the first prazosin dose than after 2 weeks of treatment with prazosin 5 mg daily, and 12 mg daily with the alpha blocker (mean reduction 22/11 mmHg compared with 4/4 mmHg). A further 3 patients already taking prazosin 500 micrograms three times daily had no unusual decrease in blood pressure when they were given a 200 mg dose of alprazolam. The severity and the duration of the first-dose hypotension were also found to be reduced in healthy subjects given a single dose of prazosin.10

In a crossover study, 24 healthy subjects were given either a single 8-hour dose of silodosin, or placebo, with a single 5-hmg dose of metoprolol. There was no clinically relevant effect on orthostatic blood pressure or heart rate on concurrent use.3

Terazosin

In a placebo-controlled study in 8 men with hypertension well controlled by atenolol, the addition of terazosin 400 micrograms daily for 7 days, then 800 micrograms daily for a further 7 days, had no clinically relevant effect on blood pressure (assessed after 6 and 14 days of terazosin). No hypertension was seen with the first dose or when the dose of terazosin was increased.13

In a study involving 236 patients, with hypertension controlled with a single antihypertensive drug, investigated the effects of adding doxazosin for BPH. The dose of doxazosin was increased gradually to 4 mg daily and then the patients were monitored for 14 weeks. The addition of doxazosin was found to be well tolerated, and adverse effects mainly occurred early after the onset of treatment or in patients with lower systolic and diastolic blood pressures. The antihypertensive effect of doxazosin was maintained in those patients taking beta blockers or diuretics, but diastolic blood pressure was uncontrolled. No change in blood pressure was seen in those patients who had been taking an alpha blocker alone (i.e. those without hypertension and those with hypertension controlled by beta blockers). The most common adverse effect in the 10-week treatment phase was orthostatic hypotension, and the incidence of this appeared to be less in those taking antihypertensives (13%) than in those not taking antihypertensives (21% to 25%).

In a study in healthy subjects given doxazosin 2 mg daily, alone or with extended-release nifedipine 20 mg twice daily, the AUC and maximum plasma concentrations of nifedipine were increased by 13% and 23%, respectively, and the maximum and average plasma concentration of doxazosin were decreased by 17% and 14%, respectively. As would be expected, blood pressures were lower when both drugs were given. For comment that doxazosin appeared to have less effect on blood pressure in patients with BPH receiving calcium-channel blockers than in those taking betablockers or diuretics, see ‘Alpha blockers + Beta blockers’, p.90.

Alpha blockers + Calcium-channel blockers

A study in 6 normotensive subjects were given nifedipine 20 mg twice daily for 20 days with doxazosin 2 mg daily for the last 10 days. Although there was a tendency for first-dose hypotension, no serious adverse events or postural symptoms were seen. The same results were noted in 6 other normotensive subjects given the drugs in the opposite order, and no pharmacokinetic interaction was found.8

In a study with healthy subjects given doxazosin 2 mg daily, alone or with extended-release nifedipine 20 mg twice daily, the AUC and maximum plasma concentrations of nifedipine were increased by 13% and 23%, respectively, and the maximum and average plasma concentration of doxazosin were decreased by 17% and 14%, respectively. As would be expected, blood pressures were lower when both drugs were given. For comment that doxazosin appeared to have less effect on blood pressure in patients with BPH receiving calcium-channel blockers than in those taking beta blockers or diuretics, see ‘Alpha blockers + Beta blockers’, p.90.

Alpha blockers

1. Nifedipine

In a placebo-controlled, crossover study, 12 subjects with hypertension were given nifedipine 20 mg and prazosin 2 mg, separated by one hour. The combination of the two drugs reduced blood pressure more than either drug alone, although the effect of prazosin was delayed until 4 hours after it was given alone. The studies of 17 hypertensive patients given prazosin 2 mg, or 4 mg taken sublingually, or 5 mg taken orally, found that the peak serum prazosin concentrations were increased by 85% (from 1.2 to 2.2 ng/ml) and 70% (from 1.2 to 2.1 ng/ml), respectively. Blood pressure 4 hours after dosing was unchanged after verapamil alone, but fell from 114/82 mmHg to 99/73 mmHg with prazosin alone, and was further reduced to 86/68 mmHg when both drugs were given together. A similar pharmacokinetic interaction was noted in another study in hypertensive patients.2 In this study, the first 1- to 2-hour dose of prazosin alone caused a 23% fall in standing systolic blood pressure.2

2. Cardura XL (Doxazosin mesilate). Pfizer Ltd. UK Summary of product characteristics, August 2012.
pressure, and half of the patients (3 of 6) experienced symptomatic postural hypotension. A similar reduction in blood pressure occurred when the first 1 mg dose of prazosin was given to 6 patients who had been taking tamsulosin for 5 days. Two patients experienced symptomatic postural hypotension.

(d) Terazosin

1. Nitrdipine. In a placebo-controlled study in 8 men with hypertension well controlled by nitrdipine, the addition of tamsulosin 400 micrograms daily for 7 days, then 800 micrograms daily for a further 7 days, had no clinically relevant effect on blood pressure (assessed after 6 and 14 days of tamsulosin). In addition, no first-dose hypotension was seen on the first day of tamsulosin, when the tamsulosin dose was increased.

2. Verapamil. A study into the safety of tamsulosin, with particular regard to the use of other medications, found that the concurrent use of verapamil increased the risk of adverse events related to tamsulosin 3-fold. The use of other calcium-channel blockers (not specified) did not appear to increase adverse effects, although there was a trend towards an increased risk.

(e) Tamsulosin

1. Dihydropyridine calcium-channel blockers. Retrospective analysis of a large multinational, in patients with BPH given tamsulosin 5 or 10 mg daily, found that tamsulosin only affected the blood pressure of patients taking calcium-channel blockers (amlodipine, felodipine, flunarizine, isradipine, and nifedipine). If the blood pressure was uncontrolled, no change in blood pressure was seen in those with normal blood pressure (i.e. those without hypertension and those with hypertension controlled by calcium-channel blockers). The most common adverse effect in the 10-week treatment phase was dizziness, and the incidence of this appeared to be lower in those taking calcium-channel blockers.

2. Verapamil. When verapamil 120 mg twice daily was given to 12 patients with hypertension taking tamsulosin 5 mg daily, the maximum plasma concentrations and the AUC of tamsulosin were increased by about 25%. In contrast, in another 12 patients taking verapamil 120 mg twice daily, the addition of tamsulosin 11 mg increased to 5 mg daily did not affect verapamil pharmacokinetics.

Other H2-receptor antagonists would not be expected to interact (see Mechanism).

Mechanism

Not fully understood. It would seem that the vaso dilatory effects of the alpha blockers and the calcium-channel blockers can be additive or synergistic, particularly after the first dose.4,5 Tamsulosin possibly has less effect on blood pressure because it has some selectivity for alpha receptors in the prostate. It has been suggested that the interaction between tamsulosin and verapamil occurs because verapamil has alpha adrenergic antagonist properties, and verapamil inhibits the bioavailability of alfuzosin which has a longer half-life.

The reduction in blood pressure seen with prazosin or terazosin and verapamil might, in part, result from a pharmacodynamic interaction, involving reduced hepatic metabolism, although the exact mechanism is not certain.6,7 The pharmacokinetic interaction between alfuzosin and diluzezum appears to occur because diluzezum is a moderate inhibitor of CYP3A4, which is the principal enzyme involved in the hepatic metabolism of alfuzosin.

Importance and management

The interaction between calcium-channel blockers and alpha blockers would appear to be established and of clinical importance, although the documentation is limited. Further studies of the interactions are required when concurrent use is first intended, and the effects might be increased if a pharmacokinetic interaction also occurs (e.g. with verapamil and diluzezum, diluzezum or prazosin with verapamil). When starting an alpha blocker it is recommended that patients already taking a calcium-channel blocker should have their dose of calcium-channel blocker reduced and begin with a low dose of alpha blocker, with the first dose taken just before going to bed. Caution should also be taken when calcium-channel blockers are added to established treatment with an alpha blocker. Patients should be warned about the possibility of a prolonged initial effect, and what to do if they feel faint and dizzy (i.e. lay down, raise the legs, and, when recovered, get up slowly). There is limited evidence that tamsulosin and possibly terazosin might not cause an additional hypotensive effect when taken longer term in patients with BPH who have hypertension already well controlled with calcium-channel blockers. Nevertheless, caution should be exercised in this situation, and a dose reduction of the calcium-channel blocker might be required. It seems likely that any pharmacokinetic interaction will be accounted for by this dose reduction. However, in some situations the pharmacokinetic and pharmacodynamic interactions of tamsulosin with moderate CYP3A4 inhibitors such as alfuzosin and verapamil might be of more clinical relevance. For further information, see ‘Alpha blockers + ketoconazole and other CYP3A4 inhibitors’, p.93.

Ketosildenafil, a potent CYP3A4 inhibitor, moderately increases the exposure to alfuzosin, silodosin, and tamsulosin: other potent CYP3A4 inhibitors also interact similarly. In vitro studies suggest that the metabolism of doxazosin might also be inhibited by potent CYP3A4 inhibitors.

Clinical evidence, mechanism, importance, and management
(a) Alfuzosin

The US and UK manufacturers of an extended-release preparation of alfuzosin briefly mention a study in which ketosildenafil 400 mg daily for 8 days increased the AUC and maximum concentration of a 10-mg dose of alfuzosin 3.6-fold and 2.3-fold, respectively. A further increase in dose of ketosildenafil of 200 mg daily increased the AUC of alfuzosin 2.5-fold.14 The US manufacturer therefore cautions the concurrent use of ketosildenafil and alfuzosin. For a list of potent CYP3A4 inhibitors, see Table 1.9, p.11. Based on the information available, this combination with alfuzosin seems somewhat cautious; however, note that the US manufacturers of the BE/BE studies generally contraindicate their concurrent use with alfuzosin because the increased alfuzosin concentrations could result in hypotension. If any potent CYP3A4 inhibitor is given with alfuzosin, it would seem prudent to use the minimum dose of the alpha blocker and titrate the dose as necessary, monitoring for adverse effects, particularly hypotension, when the dose is increased. Be aware that the risks are likely to be greater in patients also taking other anti-hypertensives.

(b) Doxazosin

Doxazosin is extensively metabolised in the liver, and in vitro studies suggest that CYP3A4 is the primary isozyme involved, although CYP2D6 and CYP2C19 also contribute to its metabolism.15 The US manufacturer advises caution when a potent CYP3A4 inhibitor is given with doxazosin. For a list of potent CYP3A4 inhibitors, see Table 1.9, p.11. The clinical relevance of these predictions is unclear, but until more is known some caution seems prudent. If concurrent use is undertaken, be aware that the adverse effects of doxazosin (such as dizziness, headache, postural hypotension) might be increased.

(c) Silodosin

The US manufacturer of silodosin reports that in a study, ketosildenafil 400 mg daily for 4 days increased the maximum plasma concentration and AUC of a single 3-mg dose of silodosin 3.6-fold and 3.2-fold, respectively. In another study, a lower dose of ketosildenafil of 250 mg daily for 4 days caused a similar increase in the AUC of a single 4-mg dose of silodosin (2.9-fold). Other potent inhibitors of CYP3A4 (see Table 1.10, p.11) for a list) are expected to interact similarly, and the manufacturer cautions concurrent use. The manufacturer also states that the concurrent use of silodosin with moderate CYP3A4 inhibitors (see Table 1.9, p.11) for a list) has not been evaluated. However, as they might increase silodosin exposure, the manufacturer advises caution and monitoring for adverse effects (e.g. dizziness, drowsiness, orthostatic hypotension) on concurrent use.5

(d) Tamsulosin

In a pharmacokinetic study in 24 healthy subjects, ketosildenafil 400 mg daily for 5 days increased the AUC of a single 400-microgram dose of tamsulosin (taken on day 1) 2.6-fold. However, this increase in exposure did not alter systolic or diastolic blood pressure during 8 hours of dosing. All of the subjects in this study had normal CYP2D6 isozyme activity (extensive metabolisers).16 A moderate increase in tamsulosin exposure with ketosildenafil did not result in any clinically relevant adverse effects in this study. However, the authors considered the increase was equivalent to doubling the tamsulosin dose, which would be expected to be clinically important in some patients. Note that as 400 micrograms is the smallest fixed dose available, it is not easy to reduce the dose of tamsulosin if adverse effects did occur. In addition, although there are no data, the tamsulosin exposure in CYP2D6 poor metabolisers (those lacking or deficient in this isozyme) given ketosildenafil would be expected to be greater than that seen in this study. For this reason, the UK manufacturer states that tamsulosin should not be given with potent CYP3A4 inhibitors, such as ketosildenafil, in patients who are CYP2D6 poor metabolisers. In other patients, they advise caution.16 Because CYP2D6 metaboliser status is generally unknown, the US manufacturer states that tamsulosin 400 micrograms daily should not be given with potent CYP3A4 inhibitors. The manufacturers also suggest that tamsulosin should be used with caution with moderate inhibitors of CYP3A4,17 particularly at doses higher than 400 micrograms daily. If concurrent use is undertaken, be aware that the adverse effects of tamsulosin (e.g. dizziness, headache, postural hypotension) might be increased. For a list of moderate and potent CYP3A4 inhibitors, see Table 1.9, p.11.

References
incidence of this appeared to be lower in those taking antihypertensives (13 to 16%) than in those not taking antihypertensives (22.2 to 25%). However, the British Medical Journal noted that food had little or no effect on its absorption and extent of bioavailability, but the UK manufacturer advises against giving Flomaxtra XL immediately after a meal.

(c) Finasteride

A study in 24 subjects given finasteride 500 micrograms daily for 14 days found that food increased the rate and extent of absorption of finasteride. Although the concurrent use of tamsulosin and finasteride is beneficial and generally well tolerated, it might modestly increase adverse effects (24% for terazosin and 13%).

(d) Silodosin

No clinical important interaction has been found to occur between finasteride and doxazosin. In one study terazosin did not interact with finasteride, but the possibility of modestly increased finasteride concentrations, No relevant interaction appears to occur between dutasteride and tamsulosin or terazosin.

Clinical evidence, mechanism, importance and management

A study in 24 subjects given dutasteride 500 micrograms daily for 14 days found that food increased the rate and extent of absorption of dutasteride. Although the concurrent use of tamsulosin and dutasteride is beneficial and generally well tolerated, it might modestly increase adverse effects (24% for terazosin and 13%).

A further sub-analysis of 325 Asian patients, and 2,925 European patients (983 taking both drugs) found a similar modest increase in adverse effects on concurrent use.

In a parallel study, 48 healthy subjects were divided into three groups. One group took terazosin 10 mg daily for 14 days, another took finasteride 5 mg daily for 18 days, and the third group took both drugs. The pharmacokinetics of both drugs remained unchanged, and the serum concentrations of testosterone and dihydrotestosterone were also unchanged by concurrent use.25 However, another study, comparing groups of healthy subjects taking finasteride and tamsulosin, found that the rate and extent of the more important drug interactions were not significantly affected by concurrent use. The clinical significance of the possible modestly increased finasteride concentrations with terazosin is not clear, but it is likely to be small.

The UK manufacturer of **alpha blockers** states that it might interact with **nitrates**. Although this interaction is not specifically mentioned for other alpha blockers, most manufacturers warn of enhanced hypotensive effects with other drugs that can lower blood pressure. Consider also **Antihypertensives + Other drugs that affect blood pressure**, p.1054.

The UK manufacturer of **prazosin** states that when prazosin is initially given to patients with congestive heart failure who have undergone vigorous diuretic or other vasodilator treatment, the resultant decrease in left ventricular filling pressure might be associated with a clinically relevant decrease in cardiac output and systemic blood pressure. Observation of the recommended starting dose of prazosin followed by gradual dose increase is particularly important in such patients.1

It has been predicted that the concurrent use of indoramin and MAOIs might lead to hypertension.

Clinical evidence, mechanism, importance and management

The concurrent use of MAOIs is contraindicated by the UK manufacturers of indoramin. This contraindication was included in the datasheet at the time indoramin was first licensed, and was based on a theoretical suggestion that the effects of noradrenaline (norepinephrine) might be potentiated by indoramin, leading to vasoconstriction, and resulting in a possible increase in blood pressure. However, the pharmacology of these drugs suggests just the opposite; namely that hypotension is the more likely outcome. In addition, the hypertensive effects of noradrenaline (norepinephrine) can be treated with a non-selective alpha blocker such as phentolamine, and the MAOIs are not contraindicated with any of the other alpha blockers. A clinically relevant interaction resulting in hypertension therefore seems unlikely.


Paroxetine, a potent CYP2D6 inhibitor, slightly increases tamsulosin exposure. Other potent inhibitors of CYP2D6 are expected to interact similarly.

Clinical evidence

In a pharmacokinetic study in healthy subjects, paroxetine (10 mg daily for 3 days then 20 mg once daily for 9 days) increased the AUC of tamsulosin by 65% when a single 400 microgram dose of tamsulosin was taken on day 11. All subjects in this study were CYP2D6 extensive metabolisers (that is, they had normal activity of this isoenzyme). This slight increase in tamsulosin exposure did not alter systolic or diastolic blood pressure during orthostatic stress testing.

Mechanism

Tamsulosin is partially metabolised by CYP2D6, of which paroxetine is a potent inhibitor. Concurrent use therefore leads to an increase in tamsulosin exposure.

Importance and management

The slight increase in tamsulosin exposure in the presence of paroxetine is unlikely to be clinically important. However, the US manufacturer suggests that tamsulosin should be used with caution with moderate and potent CYP2D6 inhibitors (see Table 1.7, p.9, for a list), particularly at doses higher than 400 micrograms daily. A greater increase in exposure would be expected if CYP3A4 inhibitors were also given, see ‘Alpha blockers + Ketoconazole and other CYP3A4 inhibitors’, p.93.