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Drug interactions involving vasodilators and alpha-adrenoceptor blocking drugs

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1. INTRODUCTION

Vasodilators (Fig. 9.1) and alpha-adrenoceptor blocking drugs (Fig. 9.2) are used in four main areas of cardiovascular therapeutics – hypertension, angina pectoris, peripheral vascular disease and congestive heart failure – and we have classified them on this basis (Table 9.1). The antihypertensive group includes those used in the management of congestive heart failure. It is not possible to classify these drugs more rationally as they are a disparate group, particularly the drugs used in peripheral vascular disease. Furthermore, the classification is not comprehensive as there is mention of other vasodilators and alpha-adrenoceptor blocking drugs in the literature, but as these are not currently in clinical use they have been excluded. Trimazosin and binazin are still being evaluated, as is bupicomide, which was initially introduced as a dopamine beta-hydroxylase inhibitor but possibly exerts its main hypotensive effect by direct vasodilation (Velasco et al., 1975). Tolmesoxide is another new vasodilator (Collier et al., 1978) which may prove to be of value in hypertension and congestive heart failure but as yet there is little information on this drug.

2. PHARMACODYNAMICS

2.1. Antihypertensives

The pattern of effect observed with this group depends in part on the cardiovascular status prior to use. For example, prazosin reduces preload and afterload in congestive heart failure, whereas in hypertension its main action is arteriolar dilation. Diazoxide,

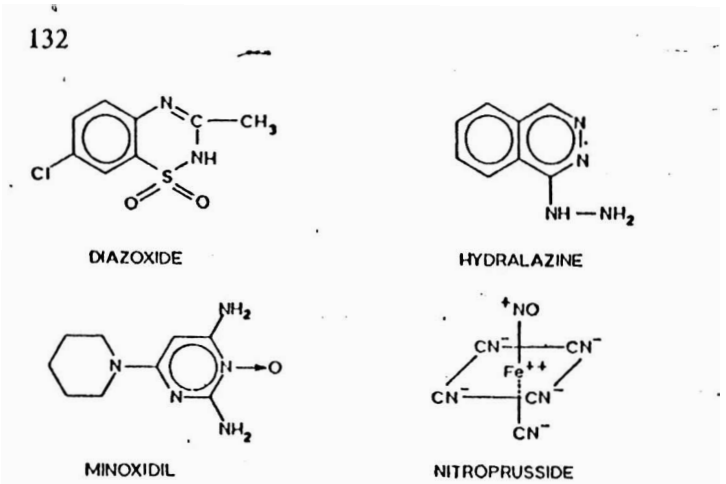
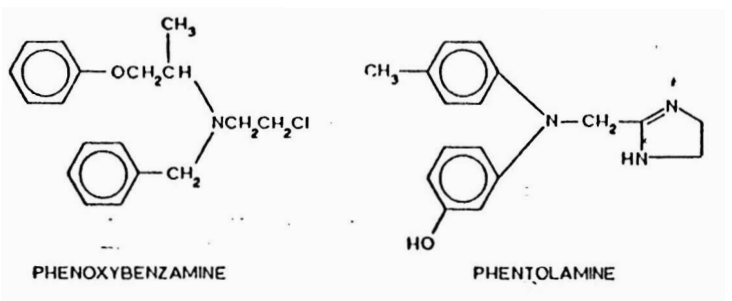


Fig. 9.1. Structural formulae of representative direct vasodilators.



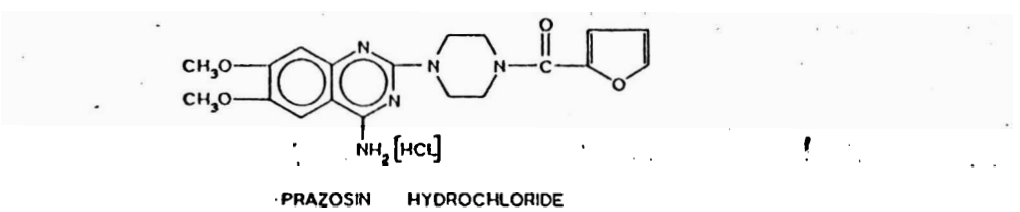


Fig. 9.2. Structural formulae of representative alpha-adrenoceptor blocking drugs.

hydralazine and minoxidil reduce resistance vessel tone and this is presumably their main haemodynamic effect in hypertension.

At a cellular level the exact mechanism of action is not known. Hydralazine may act by chelating trace elements necessary for smooth muscle contraction (Kochs-Weser, 1976a). Diazoxide and minoxidil relax vascular smooth muscle probably by competing with calcium (Wohl et al., 1967; Rhodes and Sutter, 1971). Nitroprusside inhibits either calcium release or the effect of calcium on contractile proteins (Chidsey and Gottlieb, 1974). As with vasodilators, alpha-adrenoceptor blocking drugs also act by interfering with calcium movement, probably by preventing the entry of calcium into the cell (Levitzki, 1976).

Prazosin was initially considered to be a direct vasodilator without receptor blocking activity (Constantine et al., 1973), but is now known to be a selective post-

TABLE 9.1

Therapeutic classification of vasodilators and alpha-adrenoceptor blocking drugs

Group	Vasodilators	Alpha-adrenoceptor blocking drugs
1 Antihypertensives	Diazoxide Hydralazine[a] Minoxidil Nitroprusside[a]	Phenoxybenzamine Phentolamine Prazosin[a]
2 Antianginal drugs (nitrites, nitrates)	Glyceryl trinitrate Erythrityl tetranitrate Pentaerythrityl tetranitrate Isosorbide dinitrate Amyl nitrite	–
3 Peripheral vascular disease	Cinnarizine Cyclandelate Inositol nicotinate Isoxsuprine Nicotinic acid Nicotinyl tartrate Tolazoline[b]	Thymoxamine

[a] Also used or under investigation in the management of congestive heart failure.
[b] Also has weak alpha-adrenoceptor blocking effect.

synaptic alpha-adrenoceptor blocking drug (Cambridge et al., 1977a). It does not block the presynaptic alpha-adrenoceptor and thus does not interfere with the feedback inhibition of noradrenaline release from the nerve ending (Cambridge et al., 1977b). Consequently, prazosin does not cause high levels of circulating noradrenaline, a possible explanation for its haemodynamic advantages over conventional non-selective alpha-adrenoceptor blocking agents. Indeed the latter are of little value as antihypertensive agents other than in the management of phaeochromocytoma and even for this purpose they may be superceded by prazosin (Wallace and Gill, 1978) and labetalol (Rosei et al., 1976).

Diazoxide (Sellers and Koch-Weser, 1969), hydralazine (O'Malley et al., 1975), minoxidil (Mehta et al., 1975), and prazosin (Brogden et al., 1977) have a long duration of action in contrast with nitroprusside which has a transient action. In the case of hydralazine, minoxidil and prazosin the hypotensive effect is longer than would be expected on the basis of their plasma half-lives which are typically short (Gottlieb et al., 1972; Lesser et al., 1974; Hobbs et al., 1978). Hydralazine (Moore-Jones and Perry, 1966) and minoxidil (Pluss et al., 1972) are concentrated in the muscular walls of the arteries and this would explain the relatively long hypotensive effect. On the other hand, the half-life of diazoxide is about three times as long as its hypotensive effect and this may be related to its high affinity for protein binding sites (Sellers and Koch-Weser, 1969). The transient hypotensive effect of nitroprusside is due to its rapid conversion in the body to thiocyanate.

2.2. Antianginal drugs

The relative contribution of coronary dilatation and peripheral dilatation to the antianginal effects of these drugs is still a contentious matter. Recently, Collier et al. (1978) demonstrated that the peripheral dilatation is predominantly venodilatory. Dilatation of capacitance vessels reduces preload and systolic wall tension, a major determinant of myocardial oxygen demand, which would explain the benefit of these drugs in angina pectoris (Nickerson, 1975).

The time course of activity varies widely within this group. Amyl nitrite, which of course is taken by inhalation, is almost immediate in onset of action and has a brief duration of action. Isosorbide dinitrate is an example of a longer acting nitrate which, after oral administration, has an onset of action in 20 min and a duration of action of 6 h (Dahany et al., 1977). It has been postulated that the nitrite is the active form of this group of drugs (Nickerson, 1975). Isosorbide dinitrate is probably unique among organic nitrates in that conversion to nitrite does not occur.

2.3. Drugs used in peripheral vascular disease

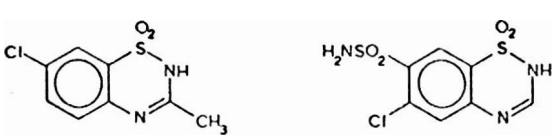
The value of these drugs in the management of chronic atherosclerotic vascular disease is highly questionable, whereas in vasospastic disease there is a more reasonable basis for their use. This is a heterogeneous group of compounds with varying modes of action.

Cyclandelate is a weak phosphodiesterase inhibitor (Nickerson, 1975). Nicotinic acid and nicotinyl alcohol, which is converted to nicotinic acid, have a dilatory effect on the cutaneous vessels in the blush area, but are probably of placebo value in peripheral vascular disease (Nickerson, 1975). Tolazoline is a mild direct vasodilator but also has alpha-adrenoceptor blocking effects, which may not be significant in the doses used clinically. Thymoxamine is an alpha-adrenoceptor blocking drug.

3. ADVERSE DRUG INTERACTIONS

3.1. Diazoxide

Diazoxide is a thiazide (Fig. 9.3); however, it has no diuretic action and in fact causes fluid retention frequently necessitating concurrent administration of a diuretic (Hutcheon and Barthalmus, 1962; Johnson, 1971). Diazoxide may interact with the following groups of drugs.



DIAZOXIDE CHLOROTHIAZIDE

Fig. 9.3. Structural formulae of diazoxide and chlorothiazide.

3.1.1. Diuretics

Both thiazide diuretics (Shapiro et al., 1961) and diazoxide (Okun et al., 1964) may each cause hyperglycaemia. Hyperosmolar non-ketotic coma (Charles and Danforth, 1971) and acute diabetic ketoacidosis (Updike and Harrington, 1969) have been reported with the use of intravenous diazoxide alone. However, both of these patients were uraemic and the decreased plasma protein binding in uraemia (O'Malley et al., 1974) may explain the severity of these reactions.

Dollery et al. (1962) described two cases of hyperglycaemia in patients taking diazoxide and thiazides. Subsequently, Okun et al. (1963) reported five patients who developed hyperglycaemia and acidosis while on both drugs. They also noted a higher incidence of hyperglycaemia when both drugs were used than had previously been attributed to diazoxide alone (Hutcheon and Barthalmus, 1962). A further study suggests that the severity of hyperglycaemia with diazoxide and thiazide is greater than with diazoxide alone (Okun et al., 1964). Seltzer and Allen (1969) showed that a combination of diazoxide and a thiazide consistently induces a reversible hyperglycaemia. Concurrent use of frusemide or ethacrynic acid may also potentiate the hyperglycaemic effects of diazoxide (Koch-Weser, 1976b). Okun et al. (1962) noted that the hyperglycaemic interaction of oral diazoxide and thiazides occurred especially but not exclusively in patients with diabetic glucose tolerance tests. The increased hyperglycaemic effect seen when thiazides and diazoxide are combined may be due to competition for protein binding sites (Sellers and Koch-Weser, 1969).

The concurrent use of thiazides, frusemide or ethacrynic acid may also potentiate the hyperuricaemic effects of diazoxide (Koch-Weser, 1976b). These drugs cause hyperuricaemia by inhibition of tubular excretion of uric acid (Johnson, 1971).

Thiazide diuretics, by reducing plasma volume, may cause postural hypotension when combined with diazoxide (Koch-Weser, 1976b). This reaction is rare with diazoxide alone.

Diazoxide decreases the binding of frusemide to human albumin in vitro (Prandota and Pruitt, 1975) but clinically significant effects have not been documented.

3.1.2. Anticoagulants

Warfarin is displaced from plasma protein binding sites in vitro by diazoxide (Sellers and Koch-Weser, 1970). While the relevant studies have not been carried out in the clinical setting, the possibility of a potentiated anticoagulant response should be kept in mind (see also Chapter 10).

3.1.3. Anticonvulsants

Diazoxide has been reported to reduce serum phenytoin levels in children (Roe et al., 1975). In the two cases reported diazoxide and phenytoin were used to treat hypoglycaemia and convulsions respectively. Therapeutic serum phenytoin levels were not achieved while on diazoxide despite adequate doses of phenytoin. After diazoxide was discontinued serum phenytoin levels returned to therapeutic levels but fell to undetectable levels within 4 days of reintroduction of diazoxide in one case. Decreased plasma protein binding of phenytoin was observed and may lead to increased

clearance of the drug. However, an increase in volume of distribution would also account for this decrease in plasma levels.

Pruitt et al. (1973) have shown conversely that phenytoin does not significantly affect the binding of diazoxide to human albumin. On the other hand, anticonvulsants have been shown to shorten the half-life of diazoxide. This may reflect induction of microsomal metabolism of diazoxide (Pruitt et al., 1973). The precise interaction with anticonvulsants is not clear but doses of these compounds may have to be modified to achieve therapeutic effect in some patients.

3.1.4. Antihypertensives

Vasodilators when given alone rarely cause excessive lowering of blood pressure. This is probably due, at least in part, to intact homeostatic mechanisms. However, the prior administration of sympatholytic drugs, e.g. adrenergic neurone blockers or beta-adrenoceptor blockers, may in susceptible individuals augment the hypotensive effect of a bolus of diazoxide such that dangerous hypotension results.

The hypotensive effects of combining diazoxide and hydralazine are discussed under hydralazine (see below).

3.1.5. Chlormethiazole

Diazoxide crosses the placenta (Boulus et al., 1971) and may arrest labour when used in hypertensive crises of eclampsia (Koch-Weser, 1976b). It has been suggested that a combination of chlormethiazole and diazoxide acts synergistically to produce severe respiratory depression in the newborn, when used in mothers with eclampsia (Johnson, 1976). However, the evidence presented is weak.

3.2. Hydralazine

3.2.1. Hypnotics

In rats barbiturates have been shown to antagonise the hypotensive effects of hydralazine. However, the interaction appeared to depend on the functional state of the circulation, the schedule of administration and the kind of barbiturate used (Czyzewska-Sjafran and Wutkiewicz, 1977). They have also suggested from further experiments in rats that the haemodynamic sequelae of hydralazine may alter the kinetics and pharmacological effects of hypnotics. There have been no similar clinically significant interactions documented in vivo.

3.2.2. Diazoxide

Profound hypotension, complicated by myocardial infarcts, cerebrovascular accidents and renal failure, has been documented following a combination of hydralazine and diazoxide. These drugs are often used together in hypertensive emergencies and severe supine hypotension has occurred if one is given shortly after the other, irrespective of which is given first (Tansey et al., 1973; Henrick et al., 1977; Romberg et al., 1977). In two cases severe hypotension occurred following a combination of diazoxide and a single oral dose of hydralazine (Kumar et al., 1976; Henrick et al., 1977), the dose of hydralazine in one case being only 25 mg.

3.3. Prazosin

3.3.1. Hypotension

The "first dose" phenomenon is well documented (Rosendorf, 1976; Wood et al., 1976; Stokes et al., 1977a) and may be severe enough to cause loss of consciousness (Gabriel et al., 1975). This response would seem to be dose-related rather than idiosyncratic in view of the more marked effects of high doses (Wood et al., 1976). It has been shown that this response may be exaggerated in patients on a low sodium diet who are in addition receiving beta-adrenoceptor blocking drugs and a diuretic (Graham et al., 1976). In these patients marked falls in blood pressure may accompany initial doses as low as 0.25 mg (Simpson et al., 1977). Stokes et al. (1977b) have shown that orthostatic symptoms are less likely during a sodium intake of 250 mEq daily than during an intake of 100 mEq daily. Bolli and Simpson (1975) noted postural hypotension in nine patients taking a beta-adrenoceptor blocking agent, who were given a mean dose of 12.4 mg of prazosin.

Brogden et al. (1977) have suggested that the dose of prazosin should be reduced when a thiazide or other antihypertensive agent is added. Subsequently, the prazosin dosage may be readjusted as necessary. It would also seem wise to exercise caution when using prazosin concurrently with diuretics or beta-adrenoceptor blocking agents or in a patient who may be salt-depleted.

3.3.2. Clonidine

Studies in rats on the interaction with the central alpha-adrenoceptor agonist clonidine suggest that the hypotensive effect of clonidine is antagonised by prazosin in a dose-related fashion and the authors suggest that the combination should be avoided in clinical practice (Van Zwieten et al., 1978). This antagonism has not been confirmed in clinical studies (Stokes et al., 1977a).

Studies in pithed rats have demonstrated that the pressor effect of clonidine is antagonised by low doses of prazosin (Van Zwieten et al., 1978). It has been suggested that prazosin may be usefully employed in the hypertensive crises of clonidine withdrawal (Oates et al., 1978). These aspects of prazosin have not been adequately studied in vivo to make further comment (see Chapter 8).

4. CONCLUSION

Serious adverse interactions with vasodilators and alpha-adrenoceptor blocking agents are rare. Many of the putative adverse interactions may be anticipated from a knowledge of the pharmacokinetic and pharmacodynamic properties of these agents, particularly with regard to protein binding and antihypertensive and hyperglycaemic effect. However, several of the interactions predicted from animal and in vitro studies have not been confirmed in vivo and appear to be of no practical importance.

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