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CORRELATION OF PHARMACOLOGICAL EFFECTS WITH PLASMA LEVELS OF ANTIHYPERTENSIVE DRUGS IN MAN

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This review is restricted to blood pressure lowering and related pharmacological effects of selected antihypertensive drugs in man. Data from animal studies, which may have important clinical significance, are included. Detailed mechanisms of action, clinical pharmacology, and pharmacokinetics of antihypertensive drugs are not included (see 1–15).

The number of clinically effective antihypertensive agents available is ever increasing. However, these may be classified into five main categories according to their major mechanism of action: (*a*) drugs with CNS mode of action, (*b*) adrenoceptor blocking drugs, (*c*) vasodilators, (*d*) diuretics, and (*e*) angiotensin analogues and angiotensin converting enzyme inhibitors.

It is quite difficult to show the existence of simple relationships between the plasma concentration of most antihypertensive drugs and their circulatory effects, especially the antihypertensive effect. This is because of at least 14 reasons, further detailed in the following paragraphs.

COMPLEXITY OF DISEASE The genesis of hypertensive disease is an extremely complex phenomenon where many different factors and systems,

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such as peripheral resistance, cardiac output, vascular reactivity, blood viscosity, the autonomic nervous system, and CNS, are all involved in a very complex and interdependent manner involving closed feedback loops (2, 11, 16–19).

In addition, a complex and delicate balance in the level and/or activity of a number of endogenous chemicals (including catecholamines, catecholamine-related enzymes, antidiuretic hormone, renin-angiotensin-aldosterone, kallikrein-kinins, prostaglandins, antirenin phospholipids, renomedullary antihypertensive neutral lipids) maintains the normotensive state, and abnormalities in any of these (unless corrected by reflex mechanisms) result in physiological changes which become manifested as hypertension.

MULTIPLE SITES OF ACTION Many antihypertensive agents act at several sites (and to different degrees; 1, 18). The lowering of blood pressure is the overall result of the various effects. Sometimes, the same drug may have opposing effects. For example, the centrally mediated antihypertensive effect of clonidine is attenuated by the peripheral α-adrenergic stimulatory effect (vasoconstriction) of the drug, at plasma concentrations which are normally achieved with therapeutic doses (20, 21). During long-term therapy with guanethidine (22), α-methyldopa (23), diazoxide (13), hydralazine (3, 24), prazosin (25), minoxidil (13), and guanethidine (13), sodium and fluid retention may interfere with the antihypertensive action of the drugs. The increase in cardiac output during hydralazine therapy partly offsets the hypotensive effect of the arteriolar dilation (3).

TOLERANCE Development of tolerance or pseudo tolerance to antihypertensive drugs (26), such as guanethidine (22, 26, 27), reserpine (26), α-methyldopa (26, 28), thiazides (29), and prazosin (25), has been observed.

ALTERATION OF THE DISEASE PROCESS WITH CHRONIC THERAPY Long-term antihypertensive therapy may alter the hypertensive disease process such that normal pressures may persist in patients for variable lengths of time after discontinuation of therapy (30, 31). For example, the antihypertensive effect of α-methyldopa lasts much longer than the rate of decline of plasma levels of the drug, after cessation of therapy, would indicate (32–34). An explanation may be that in response to blood pressure reduction, peripheral resistance decreases due to structural vascular adaptation, e.g. regression of medial thickening (35). Chronic administration of antihypertensive agents to spontaneously hypertensive rats has been shown to reverse cellular hypertrophy of vascular smooth muscle (by clonidine; 36) and of heart (by α-methyldopa and reserpine; 37).

DEEP COMPARTMENT The presence of a deep compartment for certain antihypertensive drugs may explain the prolonged antihypertensive effect observed after cessation of therapy with drugs such as reserpine (6) and hydralazine (38). A small fraction of the administered dose of reserpine binds in a specific and irreversible manner to monoaminergic granular membranes. This probably results in a persistent, nonstoichiometric inhibition of monoamine uptake (until newly synthesized uninhibited granules arrive in the nerve terminals), resulting in continuous hypotensive effect (6). In the case of hydralazine, the drug concentrates in the blood vessels of rats (39, 40) and is released very slowly.

ACUTE VERSUS CHRONIC DOSING The change in hemodynamic variables, in response to acute administration, may be different from the change resulting from chronic administration of a drug. For example, the cardiac output, renal blood flow, and glomerular filtration rate decrease when therapy is initiated with reserpine, but these variables return to pretreatment values with long-term therapy (41, 42). Peripheral resistance increases after administration of a single dose of propranolol, but a gradual decrease in peripheral resistance may occur after long-term therapy (43, 44).

POLYPHARMACY In many cases, two or more antihypertensive agents are prescribed for effective control of the disease. It is generally accepted that all hypotensive agents, given to man in submaximal doses, are likely to have additive effects with all other hypotensive agents which have a different mode of action (45). However, potentiation of action of one drug by another is known; for example, propranolol potentiates the antihypertensive action of hydralazine and prazosin (9, 46). Diuretics enhance the antihypertensive activity of clonidine, guanethidine, α-methyldopa, and reserpine (13). A synergism between hydralazine and clonidine has been demonstrated (47).

One drug may inhibit or enhance the transport of another to the receptor site (e.g. in the brain), and thus the pharmacologic effect of the second drug may not correlate with its plasma level.

BINDING OF DRUGS The concentration of the free drug in plasma is not always proportional to the total drug present. The percentage of binding of most drugs decreases with increased concentration of the drug and, in many cases, nonlinearly. The level of drug at the receptor responsible for pharmacological effect is proportional to the concentration of the free drug in plasma, rather than total drug (free and bound)—the level usually measured and reported in literature. Other drugs and endogenous substances can affect binding.

MULTIPLE FORMS OF HYPERTENSION The response to a drug may be different in various forms of hypertension. For example, in low renin hypertension, the response to diuretics is often greater than in normal renin hypertension (48, 49). On the other hand, the antihypertensive effect of propranolol and other β-blockers is more pronounced in patients with high renin hypertension (50–53). In some patients, propranolol may even increase blood pressure (54). In some hypertensives, the effect of propranolol on the lowering of blood pressure is observed within minutes; in others, it may take 48–72 hr (50, 55, 56).

Rapid intravenous infusion of clonidine (150–450 μg in 30 sec) produces a good antihypertensive response in patients with stable essential hypertension, but not in patients having accelerated hypertension (57).

DRUGS ACTING VIA METABOLITES Drugs acting centrally via metabolites may not follow the apparent response–plasma level relationship. In some cases, the antihypertensive effect is mostly due to metabolites produced in the CNS (e.g. α-methyldopa). The central metabolism may be modified by alteration in cerebral blood flow and presence of other drugs in the CNS, quite independently of levels of drug(s) in the plasma.

The major metabolite of propranolol, 4-hydroxypropranolol, contributes significantly to the β-blocking effect after a single oral dose of propranolol (58, 59). Therefore, plasma levels of propranolol alone may not be proportional to the overall pharmacologic effects observed after single oral doses of the drug.

RATE OF METABOLISM (FAST AND SLOW METABOLIZERS) If a drug elicits its pharmacologic effect in a body "compartment" which is kinetically distinct from the plasma, one would, on a mathematical basis, anticipate a shift in the effect-versus-log plasma drug concentration relationship for population groups that eliminate (i.e. metabolize or excrete) drugs rapidly or slowly.

Rapid metabolizers of propranolol are apparently more "sensitive" to the drug than slow metabolizers (60). This apparent increase in sensitivity to propranolol is attributed to a difference in distribution which may accompany the observed difference in propranolol elimination between rapid and slow metabolizers (61).

SENSITIVITY AND SPECIFICITY OF ASSAY PROCEDURES Methods of measurement of many drugs (and active metabolites) are not specific and/or sensitive enough to obtain levels in plasma at a late phase of elimination. For example, a relationship was observed between pharmacological effects and plasma clonidine levels below 2 ng/ml and, until a sufficiently sensitive

method became available for measurement of the drug, such a relationship was not apparent. On the other hand, the antihypertensive response was correlated with the plasma levels of hydralazine (60, 62) when measured by nonspecific methods, but not when measured by a specific method (14, 63). This disparity may be due to the presence of active conjugates of hydralazine which are indistinguishable from hydralazine in the assay procedure.

CIRCADIAN VARIATION The effectiveness and toxicity of drugs have been shown to vary predictably with the time of day (64, 65). Blood pressure in normotensives and labile hypertensives is lowest in the morning and highest in the late afternoon and evening (11). This diurnal fluctuation in blood pressure is often exaggerated in patients on large doses of guanethidine (66).

VARIATION IN THE INTRINSIC RESPONSE TO A DRUG There are responders and nonresponders to antihypertensive drugs (e.g. α-methyldopa; 67, 68) who do not differ in terms of absorption, metabolism, or plasma levels of the drug. If the hypotensive effects of antihypertensive agents are mediated by adaptive changes, some drugs may not initiate or express homeostatic processes in nonresponders. In responders, the decrease in diastolic blood pressure was related to the blood levels of atenolol, but not so in nonresponders (69).

In spite of the above-described limitations, correlations have been observed between plasma levels of some antihypertensive drugs with their hemodynamic effects in certain groups of patients. Interrelationships observed or deduced from the available data for some antihypertensive drugs are presented. A discussion of diuretics is not included. Correlations between plasma levels and pharmacological effects of angiotensin analogue and angiotensin-converting enzyme inhibitors have not yet been reported.

DRUGS WITH CENTRAL MODE OF ACTION

Clonidine

The mechanism of action of clonidine is considered to be mainly via the central stimulation of the postsynaptic adrenergic α-receptors in the vasomotor centers in the medulla (18, 70–72) and/or presynaptic α-adrenoceptors in the nucleus tractus solitarii (73). This results in inhibition of sympathetic outflow from the CNS. Clonidine also enhances vagal stimulation resulting from facilitation of the pressure-sensitive baroreceptor reflex (70). The fall in arterial blood pressure with clonidine is associated with a decrease in heart rate and cardiac output (by inhibition of the bulbar sympathetic cardioaccelerator center), and absence of effect on renal blood flow

or glomerular filtration rate (74). Clonidine suppresses renin secretion (75, 76).

After intravenous administration, clonidine exhibits a biphasic effect: initial transient rise in arterial blood pressure, by peripheral α-adrenergic stimulation (18, 71), followed by a pronounced and longer lasting hypotensive effect (central; 70, 71). The central effect of clonidine predominates as a result of (*a*) accumulation of the drug in the CNS and (*b*) the resultant very low plasma levels, as shown in animal studies with clonidine-^{14}C (18, 77). This initial stimulation of α-adrenergic receptors could be prevented by using the "intravenous cumulative technique" for administration of clonidine (78).

The sedation produced by clonidine is centrally mediated. The effect on salivary flow may also be a central action expressed via the parasympathetic innervation to the salivary glands (79). Clonidine depresses cardiac rate and output by a stimulating effect on α-adrenergic receptors inhibitory to the cardiovascular control center in the brain stem. Clonidine has also been noted to increase urine flow (80), which may result from stimulation of prostaglandin synthesis (and, thus, interference with the antidiuretic hormone effect in the kidney; 81).

BLOOD PRESSURE In 10 untreated hypertensive patients and 10 normotensive subjects, the effect of clonidine on systolic and diastolic pressure, in each individual, was related to the plasma clonidine concentration of 0.2 to 2 ng/ml. At higher levels, there was a diminished hypotensive effect, probably due to the peripheral α-adrenoceptor stimulation. Interindividual variations in sensitivity to the hypertensive effect of clonidine was noted (20, 21, 82).

A hypotensive effect was not induced in six tetraplegic subjects by a dose of clonidine (300 μg) which caused effective hypotension in five normotensive healthy individuals; this further confirmed the direct action hypothesis of the drug in the brain (72). The plasma levels (0.2–1.6 ng/ml) and half-life of clondidine (9.4 $\pm$ 1.4 hr) were similar in the two groups of subjects.

The average time for blood pressure to return halfway between pretreatment and end-treatment values, in eight patients, after cessation of intravenous clonidine, was 10 hr (78), which is in the range of its reported plasma half-life of 10–12 hr (20, 21).

SEDATION The change in sedation score in 18 normotensive subjects, after a single dose of clonidine (300 μg, i.v. or oral), was directly proportional to the plasma clonidine concentration from 0.2 to 2 ng/ml (20, 82). At 2 ng/ml, the maximum effect (i.e. sleep) was observed. At higher plasma

levels, the maximum effect was maintained (20). In another study, a similar relationship in five hypertensives was not apparent (21). Dollery and associates (83) obtained variable response in five normotensives after an oral dose of clonidine (300 μg). Tolerance to the sedative effect of clonidine has been observed during chronic dosing (21, 84).

SALIVARY FLOW In 28 normotensive and hypertensive subjects, a good relationship was observed between the plasma concentration of clonidine (0.2–1.0 ng/ml) and the reduction in salivary flow. The maximum effect was evident at about 1 ng/ml. During chronic dosing with clonidine, the effect on saliva production was less marked (20, 21, 82, 83).

α-Methyldopa

The decarboxylation of α-methyldopa is a prerequisite for the hypotensive effect of the drug (18, 84). The drug is converted in the CNS to the active metabolites: α-methylnorepinephrine and α-methyldopamine. Previously, it was reported that α-methylnorepinephrine played the major role in the hypotensive effect of α-methyldopa (18, 71, 85). Recently, however, it was shown that the hypothalamic levels of α-methyldopamine, and not of α-methylnorepinephrine (in rats), were closely related to the hypotensive effects of α-methyldopa (86).

The reduction in supine blood pressure after acute or chronic administration of α-methyldopa is associated with a fall in systemic vascular resistance. The cardiac output is variably affected, while renal blood flow and glomerular filtration rate are maintained (87).

Saavedra et al (88) found no close correlation between the magnitude of the fall in blood pressure and plasma levels of either free α-methyldopa (1–8 μg/ml) or its conjugate (0.2–4 μg/ml) after oral (1 g) or i.v. (250 mg) administration of the drug in seven hypertensive patients. Other workers have also been unable to correlate hypotensive action with plasma concentration following oral administration of α-methyldopa (67, 89), although a correlation between the blood pressure–lowering action and the amount of 3-O-methylated metabolities has been suggested (67).

Dollery & Harrington (90) showed that after single oral doses of α-methyldopa, in four patients, an antihypertensive effect began within 4 to 5 hr, and some effect was still noticeable 24 hr later. In other studies, excellent blood pressure control was achieved in 20 hypertensives with single daily doses (0.4–1.5 g, p.o.) of α-methyldopa (33, 34). These data suggest that the antihypertensive effect of this drug persists for a longer period than the plasma half-life of $<$ 2 hr (32) would indicate.

However, Walson and co-workers (91) observed a highly significant correlation between the decrease in the mean systolic blood pressure and the

steady state blood levels of α-methyldopa in three normotensive, unanesthetized, restrained rhesus monkeys that were administered the drug as slow infusion for 48 hr. A similar correlation between blood pressure response and plasma levels of α-methyldopa was not observed when the drug was given as a single intravenous bolus. These authors concluded that blood levels of α-methyldopa at steady state bear a quantitative relationship to the agonist activity of the active species at the site of action.

Centrally acting drugs, such as α-methyldopa, exhibit multicompartment pharmacokinetic characteristics and inconsistent dose-response relationships (91). Therefore, studies aimed at establishing correlations between plasma levels of these drugs and their pharmacological effects should be carried out under steady state conditions.

ADRENOCEPTOR BLOCKING AGENTS

Reserpine

The mechanism of antihypertensive action of reserpine is complex and insufficiently understood. Part of the hypotensive action of reserpine is of peripheral origin, resulting from the depletion of endogenous catecholamine stores in the postganglionic adrenergic neurons (18). The degree of adrenergic blockade appears to be closely related to the level of noradrenaline depletion (92). The central effect may be due to mobilization of endogenous norepinephrine which then stimulates central α-adrenergic receptors (18, 71).

The reduction in arterial pressure, which accompanies the acute administration of reserpine, is associated with decreases in cardiac output, total peripheral resistance, renal blood flow, and glomerular filtration rate. With long-term therapy, the cardiac output and the kidney functions return to pretreatment levels, while peripheral vascular resistance remains reduced (41, 42).

Studies with reserpine-^{3}H in animals have shown that the drug accumulates in the microsomal (i.e. granular) fraction of the brain and in components of amine storage organelles of the heart, adrenals, spleen, platelets, and mast cells (6). Thus, reserpine distributes into several organs from which it may be released very slowly. A small fraction of the dose, which becomes associated with monoaminergic granular membranes, probably results in a persistent nonstoichiometric inhibition of monoamine uptake.

Reserpine is extensively metabolized in man and, therefore, measurement of radioactivity in plasma, after a dose of labeled reserpine (93, 94), does not provide the true levels of reserpine in plasma. Tripp et al (95) have developed a sensitive and specific fluorometric assay for reserpine. Using this rather lengthy procedure, these authors were able to show that peak

plasma levels of reserpine, achieved 2–3 hr after 1 mg of oral and intramuscular dose to human volunteers, were quite low (0.4–0.6 and 1.6–3.5 ng/ml, respectively).

Because of the very low levels of reserpine achieved in plasma after administration of therapeutic doses of the drug, and the limitations on specific determination of reserpine at low concentration, studies to evaluate the relationship between plasma levels of reserpine and its antihypertensive effect have not been carried out. A study to determine the relationship between the antihypertensive effect and very low steady state plasma levels of reserpine can be performed by taking advantage of the radioimmunoassay procedure developed by Levy (96).

Guanethidine

Guanethidine acts selectively on the sympathetic nervous system by serving as a substrate for the norepinephrine pump. Guanethidine is actively transported into the adrenergic neuron where the drug binds to norepinephrine storage vesicles, depletes norepinephrine, and blocks the ability of nerve stimulation to release norepinephrine (97, 98). The neuronal blocking action of guanethidine persists longer than its inhibitory action on the neuronal uptake of norepinephrine (99).

The long plasma elimination half-life of the drug (5–10 days; the half-life of the late-phase pool) corresponds with the time course of antihypertensive effect after stopping the drug, which may persist for 7–10 days (13). This evidence supports the concept that the late-phase pool represents primarily guanethidine stored in the adrenergic neuron and is, therefore, the pool that determines the kinetics of the drug's pharmacologic effect in man (100).

After administration of a single intravenous dose of guanethidine, plasma levels of the drug fell rapidly and it was difficult to correlate plasma guanethidine levels with effect on blood pressure (101). Following chronic oral administration of guanethidine in 17 hypertensive patients, Walter et al (102), using a sensitive and specific assay for guanethidine, found that steady state plasma levels of the drug did relate to adrenergic blockade (as measured by decreased venous reflex). Plasma levels of guanethidine above 8 ng/ml were associated with a high degree of sympathetic blockade; above 17 ng/ml, complete blockade was observed. Plasma levels between 5–8 ng/ml appeared to represent a border zone where some patients had effect and others did not.

Bethanidine

Bethanidine, like guanethidine, possesses postganglionic sympathetic neuronal blocking activity. It has to be transported to its site of action in the adrenergic neuron by the norepinephrine pump (103, 104).

Corder & McDonald (105) found a highly significant correlation between the dose and plasma levels of bethanidine in 11 hypertensive patients (given 30–150 mg of the drug daily), but there was no correlation between dose and effect. They concluded that the plasma levels of bethanidine would not necessarily reflect the antihypertensive effect. However, the duration of clinical effect of bethanidine (8–12 hr), after a single oral dose (106, 107), parallels the late-phase elimination half-life of the drug (7–15 hr; 108, 109), a situation similar to that for guanethidine (see above).

Since bethanidine (unlike guanethidine) is not metabolized in man (108), it is an ideal drug to seek correlations between the antihypertensive effect and the plasma levels of the drug.

Prazosin

Prazosin appears to exert its antihypertensive effect by relaxation of peripheral arterioles as a consequence of functional blockade of postsynaptic α-adrenoceptors, rather than by direct relaxation of arteriolar vascular muscle (110, 111). It also relaxes the smooth vascular muscle of the systemic venous bed (112).

Prazosin does not affect renal blood flow, glomerular filtration rate, or other kidney functions. It does not change cardiac output, does not stimulate the renin-aldosterone axis, and causes less tachycardia than hydralazine (9, 25, 110).

The relatively short plasma half-life of prazosin (2.5–4 hr; 113) contrasts with the duration of antihypertensive response, which lasts much longer (about 10 hr; 9), probably due to the persistence of drug in effective concentrations at target sites. Interestingly, the drug concentrates in the smooth muscle walls of the vascular tissue (114). Recently, Lowenthal et al (115) did not find a correlation between the plasma levels of prazosin and decrease in blood pressure in 16 hypertensive patients with chronic renal failure.

β-Blockers

Despite considerable work, the mode of action of β-adrenoceptor blockers in lowering blood pressure remains uncertain. Several theories have been advanced to explain the antihypertensive effects of this class of drugs: (*a*) reduction of plasma renin activity, (*b*) centrally mediated decrease of sympathetic outflow, (*c*) reduction in cardiac index, (*d*) resetting (change in sensitivity) of baroreceptors, (*e*) action via metabolite(s), and (*f*) peripherally mediated input damping (50, 56, 116–120). None of these explanations are totally satisfactory. The essential action of β-blockers may be to diminish sympathetic nerve output by damping sensory input to the CNS from a heart whose capacity to respond to exercise and stress is blunted by β-adrenoceptor blockade (120).

A theory of dual antihypertensive action of β-adrenoceptor antagonists has been proposed (119, 121). According to this theory, the first and principal antihypertensive effect occurs with low serum concentration of the drug, and is associated with the drug's renin-lowering properties. The second effect, which requires higher serum concentration and is independent of plasma renin, may represent an action of the drug (*a*) with a lower affinity receptor or (*b*) at a poorly accessible site (such as the CNS).

More than 11 β-blockers have been used clinically. Of these, only propranolol is available in the United States.

All β-adrenergic blocking drugs will lower the arterial pressure in at least 60% of all hypertensive patients. There is little evidence that the efficacy is different between the members of this class of drugs (13, 122).

The β-adrenolytic activity is almost entirely due to the levorotatory isomers of β-blockers. It has been shown in animals that the dextrorotatory propranolol has less than 2% of the β-receptor blocking effect of the levorotatory isomer (123). In 12 hypertensive patients whose blood pressure was decreased by racemic propranolol, the dextrorotatory isomer had no antihypertensive effect (124). These data indicate that the hypotensive effect of propranolol is due to β-receptor blockade. In another study of five volunteers, it was shown that the action of racemic propranolol on inhibition of plasma renin activity was dependent on the β-adrenergic antagonist action of levoisomer (125).

β-BLOCKING EFFECT Most of the studies carried out to demonstrate relationships between plasma levels and β-blocking effect of this group of drugs in man have used the following two tests: (*a*) endogenous sympathetic stimulation by strenuous exercise and (*b*) intravenous infusion of the specific β-receptor agonist, isoproterenol. The degree of β-blockade is assessed by inhibition of the tachycardia, induced by adrenergic stimulation. In some studies, reduction of resting heart rate has been used as an index of β-blockade.

Excellent correlations have been obtained between β-blocking effect and the log of the plasma levels of a number of β-blockers (Table 1), both after acute and chronic administration of the drugs.

On the other hand, some investigators were unable to obtain good correlations between plasma levels and the degree of β-adrenergic blockade. Hansson (159) did not find a correlation between plasma levels of propranolol and reduction in heart rate in a group of hypertensive patients. Leaman et al (160), using noninvasive procedures, found a disparity between the rate of decline in serum levels of propranolol and the return of hemodynamic functions (heart rate, cardiac output, and triple product) toward their baseline values after discontinuation of the drug (p.o., q.i.d.,

Table 1 Studies in which the β-blocking effect has been correlated with the plasma levels of drug

Drug	Test method[a]	Subjects and number[b]	Concentration (ng/ml)[c]	Reference
Acebutol	I	V	200–2000	(126)
Alprenolol	E	5 V	2–150	(127)
	E	4 V	3–30	(128)
	E, I	18 PH	11–141	(129)
	I	16 PH	10–140	(130, 131)
	E	7 PH	2–35	(132)
Atenolol	E, I	V	200–500	(133)
	E	13 PH	100–5000	(69)
	E	4 V	20–1200	(134)
Labetalol	E	5 V	10–200	(135)
Metoprolol	E, I	16 PH	20–341	(136)
	E	5 V	3–100	(137)
	E	6 V	30–110	(138)
	R	14 P	30–100	(139)
	E, I	16 PH	20–340	(140)
Oxprenolol	E	7 V	20–650	(141)
	E, I	6 V	100–250	(142)
Pindolol	E, I	4 V	2–9	(143)
	E	8 V	8–200	(144)
	R	15 P		(145)
Practolol	E, I	7 V	200–2000	(146)
	E	12 V	200–2000	(147)
	E	11 V	200–4000	(148)
	I	V		(126)
Propranolol	E, I	6 V	6–150	(149)
	I	2 P, 4 V	20–100	(150)
	I	5 V	15–80	(58)
	I	28 P	10–100	(151)
	E, I	4 V	2–100	(143)
	M	9 PH	9–200	(152)
	E	7 V, 10 PA	4–100	(153)
	R	20 PH	6–440	(55)
	R	9 V	60–120	(154)
	I	8 V, 8 PH	20–50	(121)
	R	23 PH	2–30	(51)
	I	6 PE	5–90	(155)
Sotalol	E	35 V	300–5000	(156)
	R	12 PH	2000–5100	(157)
Tolamolol	E, I	V		(158)

[a] E = Exercise-induced tachycardia; I = isoproterenol-induced tachycardia; R = resting heart rate.

[b] V = Healthy volunteers; PH = hypertensive patients; PA = angina patients; PE = patients with essential tremor.

[c] Range of concentration in which correlation was observed.

7 days) in nine healthy male subjects. These authors concluded that serum level of propranolol was not an accurate indicator of hemodynamic depression at any given period of time. Brunner, Imhof & Jack (141) observed that marked β-receptor blockade still persisted in seven healthy volunteers, 8 hr after oral administration of 40 or 80 mg of oxprenolol ($T_{1/2} = 1.3$ hr), at which time the drug could not be detected in plasma.

Sundquist, Anttila & Arstila (157) did not observe a significant correlation between the decrease in resting heart rate and plasma concentration of practolol (700–6400 ng/ml) in 22 hypertensive patients. However, their data indicate a good relationship between the reduction in heart rate and plasma practolol in the lower range of concentration (700–2900 ng/ml).

BLOOD PRESSURE Plasma levels of β-adrenoceptor blocking drugs do not always relate to the antihypertensive effect. There is a great variation in the plasma levels that produce the same therapeutic effect in different patients. For example, plasma levels of propranolol ranged from 125 to 2000 ng/ml in patients whose blood pressure was adequately controlled with propranolol at daily doses of 400–2000 mg. The same oral dose of propranolol, in different individuals, may produce plasma levels differing by as much as a factor of 20 (59).

PROPRANOLOL Several investigators have reported significant correlations between plasma concentration of propranolol and its effect on blood pressure. Hansson et al (44) found a correlation between the effects of propranolol on the systolic blood pressure (but not on the diastolic blood pressure) and plasma levels. Nies & Shand (59) observed that the effect of propranolol declined exponentially as a function of the plasma concentration. Leonetti et al (55) found highly significant correlations between the log of plasma propranolol concentration (160–440 ng/ml) and the percentage of change in supine and standing systolic and diastolic pressure in 20 hypertensive patients receiving at least three different doses of the drug. Lehtonen, Kanto & Kleimola (161) reported that the plasma levels of propranolol and its hypertensive action (in 16 patients with essential hypertension) were not correlated. But, their data do show a correlation between the blood pressure reduction and plasma propranolol levels below 100 ng/ml, a situation similar to that observed with clonidine (20, 21). Esler et al (51) found a biphasic relationship between fall in blood pressure and log of plasma concentration of propranolol in 23 patients with medium to moderately severe essential hypertension. There was an early antihypertensive response almost complete at plasma propranolol levels of 10 ng/ml, and a later component at concentration above 30 ng/ml; the response seemed to plateau at plasma propranolol concentration of above 100 ng/ml. This observation is consistent with the dual theory of action of β-blockers (119).

In patients with high plasma renin or norepinephrine, the relationship was direct at propranolol levels of 3–30 ng/ml and the effect was more pronounced. On the other hand, no relationship was found between serum levels of propranolol (21–134 ng/ml) and reduction in blood pressure in nine angina patients given 40 mg of the drug t.i.d. (162).

In view of the short half-life of propranolol in systemic blood after a single dose (2–3 hr; 150) or chronic dosing (5 hr; 8), it is still not clear why propranolol, given twice daily, is as effective in controlling arterial pressure as it is when given four times daily (155, 163). This may be related to the increased bioavailability with larger doses, or an active metabolite which persists much longer in the body.

ALPRENOLOL Orme et al (129) obtained a significant correlation between fall in blood pressure and steady state plasma levels of alprenolol (11–14 ng/ml) in 18 hypertensive patients. On the other hand, there was no correlation between steady state plasma concentration of alprenolol and changes in mean arterial blood pressure or in the systolic or diastolic pressure in a group of 16 hypertensives, which included three nonresponders (131). However, when the data from the nonresponders were excluded, a significant relationship was observed between the fall in supine mean blood pressure and the log of mean steady state plasma concentration of alprenolol (131).

An interrelationship between steady state plasma levels of alprenolol (5–40 ng/ml) and the change in blood pressure was not observed in seven hypertensive patients maintained on 200 mg b.i.d. of alprenolol (132).

ATENOLOL Amery et al (69) did not find a correlation between plasma levels of atenolol (100–5770 ng/ml) and the hypotensive effect in 35 hypertensive patients. However, in 12 patients who were good responders, the decrease in diastolic and systolic pressure was somewhat related to the log of the plasma concentration of the drug (69). In view of the short plasma half-life (5 hr), the time taken for blood pressure to return to pretreatment levels, after discontinuation of atenolol (600 mg daily for 3 weeks), was quite long (3 weeks). Myers et al (164) also did not obtain a correlation between plasma levels of atenolol and the fall in systolic or diastolic arterial pressure in 18 patients with benign essential hypertension.

METOPROLOL There was no correlation between the fall in supine blood pressure and steady state plasma levels of metoprolol (20–340 ng/ml) in 16 hypertensive patients (136). In another 14 hypertensives, there was a weak, but statistically insignificant, correlation between plasma concentration of the drug (30–200 ng/ml) and decrease in systolic blood pressure (139).

Similarly, plasma concentration of metoprolol (given in combination with hydrochlorothiazide) in 14 patients with primary hypertension was poorly correlated with blood pressure response (165).

In another study involving 16 patients with essential hypertension (given 25–100 mg of metoprolol, t.i.d., for 5 weeks), the decrease in the mean supine arterial blood pressure was not correlated with the steady state plasma levels of metoprolol (20–200 ng/ml; 10, 140).

In spite of its short plasma half-life (3–4 hr; 138), single daily doses of metoprolol can satisfactorily control blood pressure in patients with moderate hypertension (10). This is another indication of the lack of correlation between plasma levels and antihypertensive effect of metoprolol.

PINDOLOL In 15 previously untreated hypertensive patients given a single oral dose of 20 mg of pindolol, the systolic and diastolic blood pressure fell significantly in 1 hr. The effect reached a maximum at 4 hr, and persisted for at least 8 hr. There was a significant correlation between peak plasma levels (reached at 2–3 hr) and maximal hypotensive response (145). In another 99 hypertensive patients on daily oral doses of 15–80 mg of pindolol, there was a good correlation between the blood pressure response and levels of pindolol in plasma obtained at 2–3 hr after the daily dose (145).

Traub & Rosenfeld (166) observed that the reduction of blood pressure in 18 patients maintained on daily doses of 20–40 mg of pindolol lasted much longer than would be expected from the relatively short plasma half-life (3.5 hr). In these patients with mild to moderate hypertension, once-a-day dose was sufficient to control blood pressure.

PRACTOLOL The reduction in both systolic and diastolic blood pressure in 22 hypertensive patients was not related to the plasma levels of practolol (700–6400 ng/ml); maximum response was obtained at 2700 ng/ml (157). In another study involving seven volunteers, practolol suppressed the increase in systolic blood pressure induced by exercise or isoproterenol infusion. The decrease in blood pressure was proportional to plasma practolol concentration (700–2000 ng/ml; 146).

SOTALOL A correlation between the decrease in supine systolic and diastolic blood pressure and steady state concentration of sotalol in plasma (2000–5100 ng/ml) was obtained in 12 patients with mild to moderate hypertension (157) maintained on daily doses of 200–600 mg of sotalol.

Although most β-blockers have a relatively short plasma half-life, the duration of the antihypertensive effect is relatively long lasting, persisting for up to 24 hr for some agents. Often, single daily doses can satisfactorily control blood pressure in patients with moderate hypertension (10, 69, 155,

163, 166). Furthermore, for most β-blockers there is a lag time between maximum blood levels and the maximum antihypertensive effect (8, 50, 56). This is probably a reflection of the time required to reach tissue receptors (e.g. CNS).

These observations may be rationalized on the basis of the central component of the antihypertensive action of β-blockers via active metabolites. In the case of propranolol, an active metabolite has been implicated in its centrally mediated hypotensive action (167).

PLASMA RENIN ACTIVITY A relationship between plasma levels of propranolol and plasma renin activity was reported by Bühler et al (56). A similar relationship was found by Esler and co-workers (51) between plasma renin activity and log of plasma propranolol levels. The effect was maximum at 10 ng/ml with no additional change up to 300 ng/ml. Velasco et al (152) obtained a good correlation between plasma levels of propranolol (20–60 ng/ml) and reduction of plasma renin activity in nine hypertensive patients treated with minoxidil. At propranolol levels of $>$ 60 ng/ml, the effect on plasma renin activity was not consistent. In another study of 16 hypertensive patients, Leonetti et al (55) found a complex relationship between plasma propranolol levels and reduction in plasma renin activity. Although a significant correlation was observed between plasma propranolol levels (6–440 ng/ml) and both the supine and standing plasma renin activity, a very marked suppression of plasma renin activity occurred even at the lowest propranolol concentration (6 ng/ml).

von Bahr et al (140) found no correlation between steady state plasma levels of metoprolol (20–340 ng/ml) and reduction in plasma renin activity in 16 hypertensive patients.

There was no correlation between the steady state plasma levels of alprenolol and fall in plasma renin activity in 16 hypertensives (131).

VASODILATORS

Hydralazine

Hydralazine exerts its hypotensive action by reducing vascular resistance through direct relaxation of arteriolar smooth muscle by an unknown cellular mechanism. The peripheral vasodilation is not uniform (3); postcapillary capacitance vessels are much less affected than the precapillary resistance vessels (18, 168). Hydralazine produces sympathetically mediated reflex tachycardia and increase in cardiac index (3).

Zacest & Koch-Weser (60) reported a relationship between the plasma concentration of hydralazine (0.1–1.6 μg/ml) and its hypotensive action. The study was carried out in 20 hypertensive patients on chronic drug

therapy (hydralazine, propranolol, and diuretics). The levels of "hydralazine" were measured in plasma at 2 hr after the last oral dose of the drug (70–350 mg/day), by a procedure which we now know is not specific (169).

In 23 patients with mild to moderate essential hypertension, treated chronically with a combination of hydralazine (37.5–150 mg/day, p.o.) and oxprenolol, the antihypertensive response to hydralazine correlated well with plasma hydralazine levels (0.1–0.8 μg/ml; at 2–4 hr after the last oral dose). Hydralazine was measured by a nonspecific spectrophotometric method (62). A significant correlation was found between daily doses of hydralazine and the plasma hydralazine levels, both in slow and rapid acetylators.

On the other hand, Talseth et al (14, 63) were unable to find any correlation between the serum concentration of hydralazine (measured by a gas chromatographic method) and the magnitude of its hypotensive effect in a group of hypertensive patients, although there was a significant correlation between the daily dose of hydralazine and the minimum steady state serum concentration of the drug in individual subjects.

It may be noted that in the first two studies, patients were receiving drugs other than hydralazine, whereas in the last study, only hydralazine was given.

The plasma half-life of hydralazine, given orally or intravenously, in the rapid and slow acetylators (as measured by "nonspecific" and "specific" methods) has been reported to be in the range of 0.6–8 hr (normally 2–3 hr; 12, 14). However, the duration of the hypotensive effect of hydralazine far exceeds that predicted from the rate of elimination of the drug from plasma. Furthermore, successful treatment of hypertension with a twice daily dose schedule has been reported (38, 170). If the concentration of the unchanged drug in the blood is the main determinant, one would expect a twice daily dose regimen to cause pronounced fluctuations in blood pressure and pulse rate during the course of the day. However, remarkably stable blood pressures were achieved with such a regimen (38). The half-life of the return of blood pressure toward pretreatment levels, after cessation of 2-week treatment in four patients, was 30–140 hr (av 97.5 hr; 38).

One explanation for this very slow dissipation of the hypotensive effect of hydralazine may be that the drug accumulates and then is slowly released from the blood vessels. Accumulation of ^{14}C in the blood vessels has been observed after administration of hydralazine-^{14}C to rats and mice (39, 40, 171, 172). Using a specific procedure for measurement of hydralazine involving extraction, derivatization, and isotope dilution, we found that blood vessels of rats given hydralazine-^{14}C (2 mg/kg, i.v., tail vein) sequestered the drug. About 75% of the ^{14}C in the blood vessels was associated with hydralazine, 25% as the free drug and 50% as base-labile conjugate (Z. H.

Israili et al, unpublished results). The tissue levels of ^{14}C were maintained for at least 72 hr, while plasma concentration decreased by a multi-exponential pattern (half life = 6 hr and 56 hr for 4–24 hr and 48–72 hr periods, respectively).

The role of any active metabolite(s), possessing long elimination half-life, in the persistence of hypotensive effect is not known. Among the known metabolites, only the pyruvate hydrazone of hydralazine was active in the dog (39, 169). The hydrazone with acetone, a possible metabolite, was also active in the rat (173). Both of these compounds may exhibit activity due to enzymatic or nonenzymatic conversion to hydralazine.

It appears that the antihypertensive effect of hydralazine is proportional to the plasma levels of "apparent hydralazine" (i.e. hydralazine, certain conjugates, etc; 169, 174) under steady state conditions. The assumptions are made that certain unidentified metabolites of hydralazine (which are included in the estimation for "apparent hydralazine") contribute significantly to the overall hypotensive action of hydralazine and that the "apparent hydralazine" in plasma is in equilibrium with hydralazine (and its active metabolites) at the site of action. Studies in rats (normotensive and hypertensive) may confirm this hypothesis.

Minoxidil

Minoxidil exerts a direct relaxant effect on arteriolar smooth muscle without any effect on the venous capacitance vessels. The decrease in arterial pressure is associated with a fall in peripheral resistance and a reflex increase in cardiac output (15, 175). Minoxidil produces hyperreninemia and is associated with marked sodium and fluid retention (15, 176).

A correlation between plasma level and pharmacological effect of minoxidil has not been observed. The removal of minoxidil (labeled with ^{14}C) from plasma, after a single oral dose, was found to be rapid (half-life = 4.2 hr; 177). The short plasma half-life contrasts with the duration of hypotensive activity, which may be as long as 5 days in hypertensive patients (177–179).

The disparity between plasma levels and pharmacologic effect can be rationalized by assuming that, in man, the site of action of minoxidil resides in a kinetically "deep compartment," which may very well be the muscular wall of the arterioles (179). In fact, accumulation of minoxidil has been shown in the arterial vascular tissues of rats (180). Studies to establish relationships between plasma levels of minoxidil (at steady state) with its hypertensive effect will be facilitated by the recently developed radioimmunoassay of Royer et al (181).

Diazoxide

Diazoxide is a potent vasodilating agent devoid of natriuretic activity. The antihypertensive effect of diazoxide is mediated by a reduction of peripheral

vascular resistance, presumably by direct action on arteriolar smooth muscle (182, 183). The hypotensive effect of diazoxide is associated with a sympathetically mediated increase in heart rate and cardiac output (4), and transient fall in renal blood flow and glomerular filtration rate (184). Diazoxide does not have an effect on venous capacitance vessels and myocardium (185).

In the treatment of accelerated hypertension, diazoxide (5 mg/kg) has to be injected intravenously, within seconds, to produce rapid hypotensive effect (within 5 min) and a sustained lowering of blood pressure; the response is strongly dependent on the rate of injection (186). In view of the high plasma protein binding of diazoxide (90–93%; 187), it appears that high initial free concentration of diazoxide (calculated value, 300–400 μg/ml; 186) is required to dilate maximally arteriolar muscle. However, the resulting hypotensive action (16–18 hr; 186) greatly outlasts this transient period (10–15 sec; 186) of high free drug level, possibly because of slow reversibility of the relaxation of the arterial smooth muscle.

Slow infusion of diazoxide (3–5 mg/kg in 10–30 min), in benign essential hypertension or nonaccelerated hypertension, produced a tolerable and predictable moderate fall in blood pressure, lasting only for 70 min (188).

The duration of action of diazoxide, after slow or rapid infusion, is relatively short compared to its plasma half-life of 20–53 hr (187). Furthermore, Sellers & Koch-Weser (186) made the observation that accumulation of this drug in plasma (by repetitive administration) was not associated with an increase in hypotensive response. Therefore, it appears that the plasma levels of diazoxide do not correlate with its hypotensive effect.

Sodium Nitroprusside

The cellular mode of action of sodium nitroprusside is not known. The drug relaxes both arteriolar and venous smooth muscles by direct effect of the nitroso group (189). The venodilation results in a decreased cardiac preload as the capacitance vessels dilate (100, 190). The reduction in arterial pressure accompanies the decrease in total peripheral resistance, and a variable response in cardiac output and heart rate (7, 15). The onset of action of nitroprusside infusion is extremely rapid (~ 30 sec), and the effects dissipate within minutes of cessation of therapy.

Although there are no data available regarding the plasma levels and half-life of nitroprusside after therapeutic doses, it has been assumed that the plasma half-life of the drug, in man, is very short. Therefore, it appears that the hypotensive action of the drug parallels its plasma concentration. Recently, a sensitive assay has been developed for the measurement of nitroprusside, involving conversion of nitroprusside to cyanide and then measurement of the latter by a spectroscopic method (191). These authors infused nitroprusside in a baboon at a dose of 200 nmol/kg/min (therapeu-

tic dose in man = 1–27 nmol/kg/min) for 1 hr; plasma level of nitroprusside reached a peak value of 1500 nmol/l, and the elimination half-life, after cessation of infusion, was 15 min. This assay procedure may be used in the future to establish correlations between plasma levels and hypotensive effect of nitroprusside.

CONCLUSIONS

Hypertension is a very complex disease with variable pathophysiologic and biochemical bases. Antihypertensive drugs act on a number of sites with a multitude of mechanisms of action. Correlations between plasma levels and pharmacologic effects have been observed for *some* antihypertensive drugs and *only* in certain groups of patients (probably those with a similar pathophysiology of hypertension).

The chances of obtaining correlations between plasma levels of drugs, and especially the free fraction, with their pharmacological effects may be enhanced by using single drugs under steady state conditions, in patients with a similar pathophysiology of hypertension who are "responders" to the antihypertensive effect of the drug.

In view of the large interindividual differences in plasma levels obtained from the same dose of an antihypertensive drug, it is impossible to predict the therapeutic response on the basis of the dose of the drug. Furthermore, a great variation has been observed in the plasma levels of drugs that produce the same therapeutic effect in different patients. For these reasons, determination of plasma levels of antihypertensive drugs may have limited value in routine therapy. However, when a relationship has been established between the therapeutic effect and the plasma level of the drug, for an individual patient, plasma level monitoring might be valuable to maintain the optimum dose. Plasma level monitoring is quite important in patients with kidney or liver dysfunction.

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