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PHARMACOLOGICAL BASIS FOR COMBINATION THERAPY OF HYPERTENSION

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COMBINATION THERAPY OF HYPERTENSION

One of the basic concepts of modern therapeutics is that drugs should be used only for specific purposes and that blunderbuss therapy should be discouraged. Many clinical scientists are outraged when they learn that patients with severe hypertension often receive treatment with three, four, or even five drugs at the same time, not one of which is directed at an identified etiological factor or specific deviant physiological mechanism. Their concern is justified, but multidrug therapy of hypertension does have a rationale although few of the many combinations in use have had their efficacy, safety, and side effects defined in comparison with possible alternatives.

Originally antihypertensive drugs were combined out of desperation to try to save the lives of patients with accelerated hypertension whose pressure control was inadequate. The hope was to find drugs with a synergistic effect, but what was demonstrated was usually some degree of additive effect.

As the number of effective drugs has increased it has become rare to be confronted with a patient whose blood pressure cannot be reduced with one of the available drugs. The emphasis has shifted to finding means of minimizing the unwanted effects of therapy or producing a more favorable profile of hemodynamic effects (1, 2).

Investigation of Drug Combinations

Demonstration of synergy between two or more antihypertensive drugs in man is no easy matter. In animals, where the number of experiments is not a limiting factor, the normal method is to construct dose-response curves of one drug at one or more dose levels of the second. From these families of dose-response curves the dose ratio can be calculated as a convenient measure of potentiation.

In man it is rarely possible to examine the whole of a dose-response curve because of the risk of excessive hypotension or side effects. The number of subjects and

measurement points is also likely to be less than ideal for reaching a precise conclusion.

The usual method for studying drug combinations in man is to add a fixed or variable dose of one drug to a constant dose of another. It is important that the experiment should be double-blind and placebo controlled. Both bias and digit preference are important problems in blood pressure recording and they can be avoided by using a sphygmomanometer that prevents bias (3) or automatic equipment such as the arteriosonde. Placebo responses can confuse the interpretation of results unless a control period on the placebo is included. In the British MRC trial through the use of either bendrofluazide or propranolol in mild hypertension the fall in pressure in the actively treated groups averaged about 24/12 mm Hg but the fall on placebo was about half of this so that the response due to the drug was only about 12/6 mm Hg.

Another problem of clinical trial design lies in the recording of drug side effects. As the choice between drugs often rests upon a claimed lesser incidence of side effects, this is a matter of great importance. The most reliable method is to use a printed questionnaire which is completed by the patient at intervals during the trial; reliance upon symptoms recorded in case notes or checklists is much less satisfactory (4, 5).

Prediction of Response to Antihypertensive Drugs

Efforts to define a specific cause for most cases of human hypertension have not succeeded. In the absence of a known cause, efforts to identify pathophysiological factors that influence the response to particular drugs have also failed, the sole exception being the relationship between renin status and response to β-blocking drugs and diuretics.

Hypertensive patients who maintain a low plasma renin on a low sodium diet do not respond to low doses of propranolol with a fall in pressure (6, 7). However, there may be a dual mechanism of response to propranolol, and the blood pressure of low renin patients can be reduced by higher doses of propranolol (8). Furthermore a combination of a diuretic and a β-blocker may have an additive effect in lowering the blood pressure irrespective of the renin status (9).

Although the pretreatment renin may be of some value in predicting the patients who will respond to propranolol or, in the case of low renin patients, to diuretics there is a poor correlation between the magnitude of the fall in renin with β-blockers and the fall in blood pressure (10). It appears that renin release can be blocked by lower doses of propranolol than are needed to produce a maximal fall in the blood pressure (11).

Thus the specificity of response to β-blockers and diuretics in relation to renin status does not invalidate the concept of using these drugs in combination.

REGULATION OF BLOOD PRESSURE

"Arterial pressure is not regulated by a single pressure controlling system but instead by several interrelated systems that perform specific functions" (12). The level of blood pressure is set by the output of the heart and the level of the systemic

vascular resistance, but both output and resistance are under the control of more than one system.

The rapidly acting control systems rely upon the baroreflex and the release of hormones such as norepinephrine, epinephrine, angiotensin, and vasopressin. Of these the baroreflex is the most important for buffering short-term changes of blood pressure but it is probably unimportant in the long term because the baroreceptors reset to a new level of pressure over 24–48 hr. Release of norepinephrine and epinephrine from the adrenal is a useful supplement to the sympathetic innervation of blood vessels in emergency situations, but it is not clear whether these hormones circulate in sufficient concentrations in normal circumstances to play a significant role in maintaining blood pressure. Both the renin-angiotensin system and vasopressin are activated in low pressure states in man and animals, and they play a role in the restoration of blood pressure in an emergency. It is unlikely that angiotensin plays a role in normal pressure regulation because the competitive antagonist saralasin does not lower blood pressure if infused into a normal person on a normal sodium intake (13). Longer-term regulation of blood pressure appears to rely upon other mechanisms. Reduction of blood pressure disturbs the Starling equilibrium of hydrostatic forces in the capillary and brings about a movement of fluid from the tissues into the vascular compartment. However, a much more important mechanism is the kidney's role in changing the output of salt and water in accordance with the level of blood pressure. Guyton has suggested that the relationship between blood pressure and salt and water output by the kidney is fixed and that this system has infinite gain. This would accord a dominant role to this system in all circumstances, but there is some evidence that the relationship is not completely fixed and that adaptive changes take place which alter the renal pressure threshold for sodium excretion. Another important long-term adaptive mechanism is hypertrophy of the vascular smooth muscle in response to pressure elevation (14). Smooth muscle hypertrophy makes the artery better able to withstand a high vascular pressure, moves the high and low autoregulatory breakpoints upwards, and enhances the pressor response to a given degree of fiber shortening in the smooth muscle because of the greater thickness of the wall (15). Guyton assigns an important role to vascular autoregulation in the determination of the long-term level of pressure. If the kidney retains salt and water, the cardiac output will rise because the filling pressure of the heart will increase. Increased perfusion of the tissues will ultimately bring about an increase in vascular resistance as a tissue autoregulatory response to excessive flow. This is the mechanism of the rise in pressure in animals or man without kidneys and explains the excessive sensitivity to fluid overload in the "renoprival" state.

The pharmacological activity of hypotensive agents must be interpreted against this background. Diuretics that increase salt and water output at a given level of blood pressure would be expected to lower blood pressure—perhaps to be more effective than they have proved to be. Reduction of cardiac output by inhibition of the sympathetic innervation of the heart should lower the blood pressure, after the baroreflex has fatigued, by an autoregulatory mechanism. Disabling vascular regulation by sympathetic inhibition or direct dilatation of vascular smooth muscle should also be an effective means of lowering the blood pressure.

However, all these systems are interrelated. A sudden fall in blood pressure activates all of them. The baroreflex fires, sympathetic nerves discharge, the adrenal gland releases catecholamines, the kidney secretes renin, the pituitary, vasopressin. Capillary pressure falls and fluid begins to pass from tissues into the vascular compartment. Renal output of salt and water is restricted or, if the pressure fall is severe, it ceases. All these restorative mechanisms come into play to try to minimize the fall in blood pressure. It is surprising that single antihypertensive drugs are effective in some patients with hypertension. It might be anticipated that these mechanisms would be able to overcome the action of a drug that had disabled only one control system. The rationale of combined drug therapy is that by disabling more than one control system simultaneously these feedback loops are inhibited and there is a greater pressure fall for a given degree of inhibition of a particular control system. As the physiological consequences of disabling any one control system completely may be undesirable, e.g. postural hypotension, such a line of reasoning provides a logical reason for partial inhibition of several systems at the same time.

THE RATIONALE FOR COMBINED USE OF DRUGS IN HYPERTENSION

If two drugs when coadministered have a greater effect than either alone in lowering the blood pressure there may be a case for using them together in a therapeutic regime. However, if this is all they do the advantage would be small and it might be simpler to use a larger dose of one of the drugs by itself. In practice the advantages that are looked for are either a more favorable profile of circulatory effects or a reduction of side effects or toxicity.

The main problem of using sympathetic inhibitory drugs to treat high blood pressure is that these agents interfere with normal circulatory reflexes and lead to a greater fall in blood pressure on standing or after exercise. If addition of a second drug to the first achieved a proportional increase in the fall in blood pressure in recumbency and on standing it would have no therapeutic advantage. For this reason, drugs that have a postural effect upon blood pressure are rarely coadministered (16). However, if the second drug has a different type of action it may be possible to achieve a fall in recumbent pressure without exaggeration of the postural fall. This is why diuretics are combined with many other antihypertensive drugs, particularly sympathetic inhibitors.

An additional reason for administering two or more drugs together is to reduce unwanted effects of some members of the combination while retaining an adequate hypotensive effect. At its simplest this may involve no more than using smaller doses of two drugs together to reduce the side effects of each while retaining the desired effect. Alternatively the properties of one drug may be used to overcome unwanted actions of another. Examples are: (*a*) use of a potassium-retaining diuretic such as amiloride, triamterene, or spironolactone with a potassium-losing one such as a benzothiadiazine (17); (*b*) use of a β-receptor–blocking drug with a vasodilator to minimize the tachycardia and palpitations that would otherwise result from stimula-

tion of the baroreflex (18); (*c*) use of a diuretic with a vasodilator or other hypotensive agent that is liable to cause salt and water retention to prevent this (19).

A convenient way of subdividing the combinations to be discussed is by the number of drug components in the combination, two, three, or four.

Drug Pairs

DIURETIC COMBINATIONS WITH OTHER SINGLE DRUGS Benzothiadiazine diuretics and related structures are among the most widely used antihypertensive drugs, and it has become almost universal practice to start treatment with them and to add other drugs as required. One of the advantages of diuretics is that they have a flat dose-response curve (20) with a nonpostural effect and thus can be prescribed in a fixed dose.

The mechanism of the hypotensive action of diuretics has not been completely explained but there is little doubt that it is due to depletion of salt and water. Early suggestions that the effect was brought about by a fall in plasma volume were disputed on the grounds that the effect was transitory. However, some long-term contraction of plasma volume persists and this may be one mechanism of the hypotensive action (21). Combination of diuretics with other hypotensive agents increases the magnitude of the fall of pressure obtained with either drug alone. This point has been established with almost all antihypertensive drugs in use.

Diuretics with β-adrenoceptor–blocking agents Richardson et al (22) studied the effect of a placebo, propranolol, 120 mg daily; chlorthalidone, 50 mg daily; and of propranolol with chlorthalidone in the same doses. The blood pressures were placebo, 172.0/106.7; propranolol, 162.8/98.7; chlorthalidone, 148.6/97.7; combination, 138.7/92.1 mm Hg. Angervall & Bystedt (23) demonstrated that this type of effect was synergistic. They established that alprenolol in a dose of 700 mg was equihypotensive to chlorthalidone in a dose of 50 mg. If the effect was additive it might be expected that half the dose of each would be needed to achieve the same effect, but it turned out that one quarter of the dose of each drug combined was sufficient to match the effect of either alone.

The potentiation of the hypotensive action by combining β-receptor–blocking drugs and diuretics has been established for a great many individual compounds (24–26).

Diuretics with centrally acting drugs Smith et al (27) showed that a fall of recumbent blood pressure of 17.5/13.7 mm Hg on 1.5 g/day of methyldopa was increased to 23.3/14.9 mm Hg when 500 mg/day of chlorothiazide was added. Other authors have obtained similar results (28, 29). Rosenman (30) observed a blood pressure of 163/99 mm Hg in patients treated with 50 mg/day of chlorthalidone which fell to 142/83 mm Hg when an average of 0.37 mg/day of clonidine was added to the treatment.

Diuretics with reserpine Fixed ratio drug combinations containing reserpine and a diuretic are among the most popular hypotensive drugs. Their use was called into

question in 1974 when several papers were published (31, 32) suggesting an association between the ingestion of reserpine and an increased incidence of breast cancer in middle-aged women. Later work has not confirmed the earlier findings which were critically dependent upon the methods used to choose controls (33, 34). However, the argument still rumbles on and the last word has not yet been written (35). While doubt remains, the tendency to switch to combinations including β-blockers rather than reserpine is likely to continue. The combination of chlorothiazide and reserpine is undoubtedly effective, and in one study it reduced the mean arterial pressure by 20 mm Hg in over two thirds of patients (36).

Diuretics with adrenergic neurone–blocking drugs Many published reports have demonstrated that the hypotensive effect of adrenergic neurone–blocking drugs is increased to a modest extent by addition of a diuretic (37, 38).

Diuretics with hydralazine At one time this was also a popular combination (39), but it is used less often now because the triple combination including a β-receptor–blocking drug is preferred.

DIURETICS AND THE PREVENTION OF FLUID RETENTION BY OTHER DRUGS Most antihypertensive agents apart from the diuretics have been reported to cause salt and water retention in a proportion of patients. Guyton's hypothesis (12) can be invoked to explain this phenomenon. If this pressure threshold is not reset downwards, salt and water retention would be a normal regulatory response whose aim would be to restore the previous level of pressure.

Dustan et al (40) studied changes in plasma volume in 16 patients treated long-term with antihypertensive drugs. Plasma volume was normal or high, and there was a correlation between plasma volume as percentage of normal and the blood pressure. Intensive diuretic therapy lowered the plasma volume below normal and reduced the arterial pressure. Finnerty and his colleagues (19, 41) demonstrated that resistance to diazoxide, hydralazine, or reserpine that developed in the course of treatment was associated with fluid retention. In a group of patients treated with intravenous diazoxide for ten days there was an average increase in weight of 3.1 kg and a rise in extracellular fluid volume of 3.3 liters. Ronnov-Jessen & Hansen (42) showed a rise in exchangeable sodium of 210 meq after 8–14 days treatment with guanethidine with a rise in blood volume of 382 ml. Diuretic treatment returned these values to normal. Fluid retention appears to be especially prominent with powerful vasodilators such as minoxidil. Wilburn et al (43) reported that the average dose of furosemide required to prevent fluid retention was 578 mg/day and some patients require 1200 mg/day.

Thus one justification for using a diuretic as a basic component of the treatment regime is to prevent this fluid retention and thus to avoid the development of resistance in some patients.

THE CASE AGAINST ROUTINE USE OF DIURETICS AS A COMPONENT OF ANTIHYPERTENSIVE COMBINATIONS There has been some controversy concerning the routine use of diuretics as the first component of antihypertensive regimes.

The argument has never been clearly formulated in public but some of the strands in it are as follows:

1. Diuretics elevate the plasma renin and renin may be a factor responsible for vascular damage (44). There are two main weaknesses to this argument, first, that most subsequent work does not support the assertion that renin does damage blood vessels (45, 46), and, second, that the elevation of plasma renin during prolonged diuretic treatment is modest (21, 47).
2. Diuretics have undesirable metabolic effects such as hypokalemia, hyperuricemia, hyperglycemia, and retention of calcium. This statement is true but the evidence that diuretics cause harm is wanting. A mild degree of hypokalemia does not appear to cause either symptoms or adverse effects upon long-term kidney function (48). Hyperuricemia caused by thiazides rarely appears to cause gout. There may be more room for concern about the long-term effect of thiazides upon glucose tolerance but further evidence is needed before any conclusion can be reached about its clinical significance (49). The mild elevation of serum calcium caused by thiazides appears unimportant unless there is also some other reason for hypercalcemia.
3. Use of diuretics confuses the interpretation of the serum potassium concentration and makes it more difficult to detect primary hyperaldosteronism and to investigate renin mechanisms. These arguments may be important to an investigator whose center of work is renin and aldosterone, but they need not be taken too seriously in therapeutics.

Against these arguments is the important consideration that thiazides are cheap, effective, and easy to use. If the thiazides were not available, the treatment of hypertension would be appreciably more difficult.

OTHER DRUG PAIRS

Vasodilators and sympathetic inhibitors Vasodilators are one of the most important groups of antihypertensive drugs although only hydralazine has been widely used over long periods. The combination of hydralazine with a ganglion-blocking drug, hexamethonium, was tried as early as 1955 (50). Combinations of reserpine and hydralazine have been thoroughly studied and extensively used. In one study of 426 patients given reserpine 0.5 mg daily and hydralazine 200 mg daily, the changes in pressure were placebo +3.7/+2.0 mm Hg; reserpine alone -3.0/-5.1 mm Hg; and reserpine plus hydralazine -4.9/-10.5 mm Hg (51).

More recently, hydralazine has often been combined with a β-receptor–blocking drug (52–56). It is of interest that there has been some disagreement concerning the effect of combining a β-blocking–drug and hydralazine in animals (57, 58).

Several new and powerful vasodilators have been introduced, including diazoxide, prazosin, and minoxidil. One of the reasons for the revival of interest in vasodilators has been the availability of β-receptor–blocking drugs and diuretics which can be used to overcome the tachycardia and fluid retention which commonly occur when they are used alone (59). A further advantage of combining a vasodilator and a

β-blocker is that this prevents the rise in plasma renin caused by the vasodilator (60, 61).

Adrenergic neurone blocking drugs, centrally acting drugs, and β-blockers Day & Prichard (62) reported an additional fall of blood pressure of 20 mm Hg when propranolol was added to patients under treatment with bethanidine and 12 mm Hg when it was added to treatment with methyldopa. Pearson et al (63) demonstrated a fall in blood pressure averaging 5.7/10.9 mm Hg in patients treated with a mean dose of 27 mg of guanethidine. When oxprenolol 240 mg daily was added, the fall in pressure increased 21.8/17.4 mm Hg. Oxprenolol alone caused a fall in pressure of 17.2/12.2 mm Hg, so the fall on the combined treatment was almost exactly the sum of the individual effects.

Breckenridge & Dollery (64) demonstrated an additive hypotensive effect when bethanidine was added to treatment with methyldopa.

Triple Combinations

Various triple combinations are possible but those that have been most extensively studied have involved the use of a diuretic, vasodilator, and sympathetic inhibitor. Most often the diuretic has been a thiazide, the vasodilator has been hydralazine, and the sympathetic inhibitor reserpine or a β-receptor–blocking drug.

DIURETIC-HYDRALAZINE-RESERPINE The most significant clinical trials of antihypertensive agents on outcome which have so far been completed were those arranged by the Veterans Administration in the United States (65). These trials used a combination of hydrochlorothiazide (100 mg), hydralazine (75–150 mg), and reserpine (0.2 mg) daily as the therapeutic regime. A particularly instructive study of this combination was conducted by Clark & Troop (66). They treated 114 patients who had previously been on other drugs with a tablet containing reserpine (0.1 mg), hydralazine (25 mg), and hydrochlorothiazide (15 mg) (Ser-Ap-Es) as the sole treatment. The patients had an average pretreatment diastolic pressure of 126 mm Hg, and the average fall in diastolic pressure on the triple combination tablet was 19 mm Hg compared with previous therapy with individual drugs in separate tablets.

DIURETIC–HYDRALAZINE–β-BLOCKING DRUGS This combination is becoming a very popular one in therapeutics. One of the most convincing studies was that of Zacest and his colleagues (55). They used a regime consisting of hydrochlorothiazide (100 mg), hydralazine (average dose 225 mg/day), and propranolol (average dose 143 mg/day). The recumbent blood pressures of the group of patients were 188/118 on the diuretic alone, 162/102 mm Hg on diuretic plus propranolol, and 142/88 mm Hg on the triple combination. This study provides good evidence to support the contention that each component is making a useful contribution to the end result.

Gottlieb and co-workers (56) reported a fall from 191/128 mm Hg to 169/108 mm Hg when hydralazine was added to a regime that already included a thiazide diuretic and propranolol.

It has proved possible to use the triple combination safely in patients with angina pectoris in whom hydralazine alone would have been contraindicated because of the risk of worsening the angina. Plasma renin values on the triple combination were not significantly different from pretreatment values.

DIURETIC–MINOXIDIL–β-BLOCKING DRUGS Minoxidil is the most effective of the currently available vasodilatory agents and several studies attest to its effectiveness in treating patients who have proved relatively unresponsive to large doses of other drugs (43, 56, 67). Gottlieb et al compared the efficacy of adding hydralazine or minoxidil to a treatment regime that already included a diuretic and propranolol. Minoxidil proved more effective and reduced the average recumbent pressure to 142/92 compared with 169/108 with hydralazine. This regime has also been used successfully in patients who had angina without worsening their condition (43). The addition of propranolol to treatment with minoxidil produces a further fall in blood pressure, prevents the rise in heart rate which otherwise occurs, and reduces the rise in plasma renin activity caused by minoxidil, although not to control values (60).

There has been less interest in triple combinations which include a centrally acting drug such as methyldopa or clonidine, or an adrenergic neurone–blocking drug. Probably the future of such combinations lies with the β-receptor–blocking agents because of their effectiveness in blocking low rates of traffic such as may be the case in recumbency. Adrenergic neurone–blocking drugs are more effective in blocking higher rates of traffic and thus more likely to cause postural hypotension.

PRACTICAL PROBLEMS

The real world of therapeutics is very different from the pharmacology laboratory or the ward of a university hospital. Things that succeed in the ivory tower sometimes fail outside it. Problems with compliance and the consequent return to respectability of the fixed ratio drug combination illustrate these problems in respect of combined drug treatment of hypertension.

Compliance

Patients often do not take their medicines as prescribed (68). In the Veterans Administration trial of antihypertensive therapy, half the patients were rejected as unreliable pill takers during a run-in period. Urine tests on patients taking para-amino salicylic acid for tuberculosis showed that, on average, only half the patients were taking the medicine at the time of the random tests (69). Children with bacteriologically proven streptococcal sore throats were even less reliable. On the ninth day of treatment only 8% had penicillin in their urine (70).

Factors such as social status, educational attainment, and seriousness of the disease process have not proved to be accurate predictors of which patients will take their medicines regularly (71). The problems of treatment dropout and poor compliance are so serious that they threaten the basis of long-term treatment of symptomless conditions (72).

Both the complexity of the therapeutic regime and the severity of drug side effects appear to contribute to noncompliance. Patients who receive more attention comply

better than those given routine care (73). It might be expected that a fixed ratio combination drug might have advantages over the same drugs given as individual tablets, but this is yet to be established conclusively (74).

Compliance problems are a powerful argument against multidrug, multitablet regimes unless the patient is in great danger and there is no effective alternative.

Fixed Ratio Drug Combinations

If the treatment of hypertension could be reduced to one tablet once a day it would be much more convenient for the patient and compliance would probably improve. The only candidates for such a combination are various types of three drug combination in a fixed ratio in the same tablet. Some physicians and pharmacologists object that such a product is irrational, confusing, does not permit individualization of treatment, and is illogical in pharmacokinetic terms because of the differing half-lives of the components. Each argument must be taken seriously. Evidence already presented shows that there is a rational justification for simultaneous moderate inhibition of different blood pressure control loops. The product could be confusing if it were marketed under a snappy uninformative name. But it is possible to use a name to convey the nature of the mixture, e.g. Ser-Ap-Es. The fixed ratio does not permit individual adjustment of the components, but if the ratio is near optimal for a large fraction of the patients this is not a matter of great importance. The pharmacokinetic objection is not insuperable because the amount of each constituent and the dosage interval can be adjusted to the requirements of the shortest acting component.

It is probable that in the future most patients with mild to moderate hypertension will be treated with a fixed ratio combination product although it will be necessary to demonstrate by clinical trials that each exerts a biologically significant effect at the chosen dose in the combination.

CONCLUSION

It would be preferable if the theoretical and experimental basis for the use of drug combinations in the treatment of hypertension were better established. At present, the generalization 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 appears to be true. The value of combinations rests upon their efficacy in relation to side effects and toxicity, and the number of studies that permit a firm conclusion on all of these points is few. However, a very large clinical experience attests to the value of drug combinations in the treatment of hypertension and it is probable that their use will continue to increase.

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