Postural Hypotension

Variations in Different Drugs and Different Patients

By Philip L. Dern, M.D.

Clinical experience suggests that there are differences in the extent to which hypertensive patients respond with falls in blood pressure after administration of effective doses of ganglion-blocking drugs. In this study attempts are made to define the relative magnitudes of the postural and nonpostural falls in blood pressure that are produced by these drugs. Frequent measurements of the blood pressure were made in hypertensive human subjects before and after the administration of ganglion-blocking agents. Drug-induced falls in blood pressure are calculated with reference to the baseline levels of blood pressure established in various ways for the individual patients.

It is well known that ganglion-blocking drugs produce postural hypotension. With some other drugs, for example reserpine, a drug acting mainly centrally, additional falls of blood pressure in the erect posture are usually inconspicuous. Claims have been made that some ganglion-blocking drugs may also have a central nervous system action. A major central effect is claimed for the drug IN 292 by Cavallito et al. and Dontas and Nickerson consider that hexamethonium acts partly at a preganglionic location. It was thought of interest to examine the extent of the postural and nonpostural falls of blood pressure induced by a number of ganglion-blocking agents with the idea that their relative magnitudes might differ if some of the drugs acted also on the central nervous system.

It was held in mind that postural hypotension is not confined to ganglion-blockers and that it occurs after nitrates, acting on smooth muscle, and after adrenolytic drugs. In contrast reserpine, canescine, and rescinamine—rauwolfa alkaloids that appear to have a predominantly central action—cause postural hypotension only after very large doses. Whether this postural effect might be due to the peripheral musculotrophic effect demonstrated by McQueen, Doyle, and Smirk is speculative.

An additional reason for making a more extended study of postural hypotension is that most studies have not taken sufficient account of the time spent in the erect posture.

The formulas of the drugs studied are given in figure 1. It is noteworthy that mecamylamine differs from the others in being a secondary amine.

Method

The study of the relationship between falls of blood pressure that take place in the lying posture and the additional falls of blood pressure that occur on changing to the erect posture, following ganglionic blockade, become more complicated as attempts are made to obtain sufficient accuracy to justify a comparison of different ganglion-blocking drugs.

Correction for Postural Changes in Blood Pressure Present before Drugs are Given

1. If the control blood pressure in the lying posture is C1 and the blood pressure in the lying posture during drug action is D1, the fall of blood pressure in the lying posture (the after-drug nonpostural effect) is C1 — D1.

2. If C2 is the control blood pressure (systolic or diastolic) in the standing posture before drug administration then C2 — C2 = the “before-drug posture.”

3. If D2 is the blood pressure (systolic or diastolic) in the standing posture before drug action then D2 — D2 is the additional fall of blood pressure, after the drug, on assumption of the erect posture. We call this the after-drug postural effect (uncorrected).

4. In determining the effect of drugs on posturally induced falls of blood pressure it is desirable to correct for any postural changes that

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may have been present before the drug is given. When there is a fall of blood pressure on standing before administration of the drug, \( C_1 - C_2 \) is positive; when there is a rise of pressure on standing, \( C_1 - C_2 \) is negative.

The difference between the after-drug postural effect (uncorrected) and the before-drug postural effect refers to the postural effect actually due to drug action = the after-drug postural effect (corrected). This is: \( (D_1 - D_2) - (C_1 - C_2) \).

In representing the data graphs have been drawn relating the nonpostural drug effect \( (C_1 - D_1) \) to the after-drug postural effect, corrected \( (D_1 - D_2) - (C_1 - C_2) \). It is considered that this relationship is the most appropriate one to study. The formula may be written, alternatively, \( (C_1 - D_2) - (C_1 - D_2) \). It could be argued that the subtraction of \( (C_1 - D_2) \) is inappropriate as it appears in both the nonpostural drug effect and the after-drug postural effect corrected. The conclusions drawn are similar whether we relate the nonpostural drug effect \( (C_1 - D_2) \) to the corrected \( (C_1 - D_2) - (C_1 - D_2) \) or alternatively to the uncorrected \( (C_1 - D_2) \) postural drug effect.

Selection of Representative Control Level of Blood Pressure

There is difficulty involved in the selection of a proper control level of the blood pressure from which the pressure may be said to fall as a result of drug action.

1. Before-Treatment Control. The casual blood pressure in the morning following several days of placebo administration may be used, and has the advantage that it is unaffected by the results of previous drug administration, a factor of importance, since some ganglion-blocking drugs, such as mecamylamine, produce effects lasting over 24 hours. An objection to the use of this "placebo control" is that it does not allow for any further downward drift in morning blood pressure readings that may occur during the study period and may be independent of drug action. This type of control is satisfactory for drugs administered on the day after the control period ends but may be too high a control value for drugs administered several days later.

2. Daily Control. To avoid the above difficulty the blood pressure readings obtained on the day of each test, and just prior to the administration of a drug, may be used alternatively as control values from which extent of the fall is estimated. Any error due to persistence of drug effects from previous administration will be slight, but a lowering of the base line due to treatment, yet not to persistent drug action, cannot be eliminated altogether. The control values taken in this way, therefore, may be too low.

For these reasons both the above types of control values of the blood pressure were used in calculating data. It will be seen that the conclusions drawn do not depend on which type of control is used.

Effect of Length of Time Spent in Lying and Standing Postures

The length of time spent in the lying posture or in the standing posture influences the results obtained. On assuming the erect posture, the blood pressure may show an initial drop followed by some recovery. If only one measurement of the blood pressure is made after standing it may not be representative. The technic used here was to make 6 measurements of the blood pressure at intervals of 30 seconds in the lying and standing postures. The averages of these blood pressures represent the "lying" and "standing" pressures at a particular stage of drug action. Several such sets of blood pressure readings were made in each patient during the action of each of the drugs studied, with the object of exploring the relationship of postural to nonpostural falls of blood pressure with varying intensities of drug action.

Administration of Ganglion-Blocking Drugs

Initially drug administration was by mouth—later, in order to have a better control over blood pressure levels, a number of experiments were
Fig. 2. The systolic blood pressure in the lying posture plotted against the systolic blood pressure in the standing posture. In series P the results were obtained from a patient given pentolinium on 2 days. In series R the values were obtained from a different patient given reserpine over several days (5.0 mg. per day).

made in which the drugs were given by injection. The route of injection had no significant effect on the results obtained. The amount of drug given was adjusted so as to reduce the blood pressure in the standing posture to normotensive or slightly hypotensive levels.

RESULTS

A simple graph relating the systolic blood pressures in the lying posture to those taken in the standing posture (fig. 2) shows that after moderately large doses of reserpine, the falls in the blood pressure are about equal in the lying and standing postures; but after pentolinium the falls of blood pressure are much greater in the standing posture.

The differences between the effects of the 3 ganglion-blocking agents to be studied (IN 292, mecamylamine, and pentolinium) were smaller than the difference between the effects of reserpine and of any one of these agents, and the more exact type of investigation mentioned earlier became necessary.

Observations Relating to Differences Between the Nonpostural Falls of Blood Pressure after Administration of Three Ganglion-Blocking Drugs. The relationships between the nonpostural and postural drug effects of IN 292, mecamylamine, and pentolinium are summarized in figure 3A—F. Figure 3A—C represents the relationship (systolic pressures) of the after-drug nonpostural fall of blood pressure to the after-drug postural fall (corrected), and figure 3D—F shows the corresponding relationship for diastolic pressures. In each case the before-treatment control referred to under “method” was used.

It will be seen that there is a difference between the effects of the 3 drugs on systolic and diastolic pressures. In each of the graphs the straight line at 45° from the zero point is drawn so as to pass through all points in which the nonpostural effect of the drug is equal to the postural effect. Where many points tend to lie to the left of this line, as in figure 3A, D (with the drug IN 292), it is evident that the fall of blood pressure in the lying posture often is greater than the additional fall of blood pressure that takes place on assumption of the erect posture. In contrast, when pentolinium is given (fig. 3C, F), most of the points lie to the right of the straight line, indicating that usually the postural fall of blood pressure that takes place under assumption of the erect posture is much less than the nonpostural fall.

Additional graphs were prepared relating the after-drug nonpostural falls of blood pressure to the after-drug postural falls of blood pressure, but without correction for any postural falls or rises of blood pressure occurring under control conditions before drug administration. The graphs of uncorrected data are not reproduced as they are essentially similar to those of figures 3A—F (which are corrected).

It has been pointed out already that use of the before-treatment control tends to cause an overestimation of the falls of blood pressure due to drug action, whereas the “daily controls” (referred to under “method”) may lead to an underestimate. The relationships between the nonpostural and postural drug effects of IN 292, mecamylamine, and pentolinium have therefore been analyzed with the use of “daily controls.” The results are set out in figure 4A—F. The remarks made
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Fig. 3 Left. Data derived from 9 different hypertensive patients given IN 292 (A and D), mecamylamine (B and E), and pentolinium (C and F). For each drug the after-drug, nonpostural effect (C1—D1) plotted against the after-drug postural effect (corrected) (D1—D2) — (C1—C2). Pretreatment controls used for calculating magnitude of blood pressure falls.

Fig. 4 Right. Data derived from 9 different hypertensive patients given IN 292 (4A and D), mecamylamine (4B and E), and pentolinium (4C and F). For each drug the after-drug nonpostural effect (C1—D1) plotted against the after-drug postural effect (corrected) (D1—D2) — (C1—C2). Daily controls are used for calculating the magnitude of the blood pressure falls.

about figure 3A—F, apply equally to the analysis in terms of "daily controls."

It may be concluded that IN 292, relative to pentolinium, has more effect on the nonpostural falls of blood pressure whereas pentolinium, relative to IN 292, has more effect on postural falls of blood pressure. Mecamylamine occupies an intermediate position but resembles IN 292 more closely.

Since patients exhibit striking variations in their individual responses to a hypotensive drug, it is necessary to compare the effect of the 3 drugs studied in the same individual. An example of a striking difference in the responses to different ganglion-blocking drugs is shown in figure 5. The other patients showed the same phenomenon to a greater or lesser degree.

It will be seen (fig. 5) that in this patient the after-drug nonpostural falls of blood pressure are relatively high after IN 292 and the after-drug postural falls of blood pressure are relatively high after pentolinium and mecamylamine.

Observations Relating to the Differences between the Nonpostural and Postural Falls of Blood Pressure in Different Individuals. There are differences between individual patients as well as differences between drugs. In the treatment of patients with ganglion-blocking drugs certain patients respond with large falls in blood pressure in the lying posture while others only exhibit appreciable falls of blood pressure on standing. In seeking an explanation for this variation it was noted that the response of a patient's blood
pressure to standing prior to drug administration was related in an unexpected way to the magnitude of the postural response after a ganglion-blocking drug.

**Relationship between the Magnitude of Postural Changes in the Blood Pressure before Giving a Ganglion-Blocking Agent and the Magnitude of the Postural Changes Afterwards.** In figure 6 the before-drug postural falls of systolic blood pressure (expressed as a percentage of the control blood pressure lying posture) are related to the after-drug postural fall, also expressed as a percentage of the control blood pressure lying posture. The patients who had large before-drug postural falls in systolic blood pressure, paradoxically, tended to have small postural falls (fig. 6) but similar or possibly larger nonpostural falls. Those patients with before-drug rises in systolic or small falls in systolic pressure had relatively large postural falls of blood pressure and similar or possibly smaller nonpostural falls during drug action. The relationship was clearly demonstrable whether the after-drug postural effect was corrected or uncorrected for postural changes in blood pressure present before drug administration. The control pressures used were those taken before any active drug had been administered. Corresponding results were obtained with the diastolic pressure.
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DISCUSSION

Clearly there are differences in the relative magnitudes of the nonpostural and postural falls in blood pressure induced by IN 292, mecamylamine, and pentolinium. It is notable that IN 292 tends to produce relatively marked falls of blood pressure in the lying posture, whereas the falls of blood pressure after pentolinium are more dependent on assumption of the erect posture.

No opinion is expressed about the possibility of relatively large nonpostural falls of blood pressure after IN 292 being related to the existence of a central nervous system action of the type suggested by Cavallito et al. The topic deserves further study.

The observation that postural falls of blood pressure prior to receiving a drug are related to the magnitude of the postural fall of blood pressure after a ganglion-blocking drug is of interest. The patients with postural falls in blood pressure prior to drug action had, paradoxically, a tendency to small falls in blood pressure in the standing posture following drug action. A possible explanation is that a postural rise in blood pressure on standing in the absence of drug action represents an exaggeration of the compensatory reflex normally maintaining the level of the blood pressure on assumption of the erect posture; and that in patients with postural hypertension there is an increase in the neurogenically maintained fraction of the blood pressure (Doyle and Smirk). Under these circumstances the administration of a ganglion-blocking drug should cause a larger fall of blood pressure. In the patients who had postural hypotension before receiving a ganglion-blocking drug it seems likely that the neurogenic response to assumption of the erect posture is insufficient to maintain the blood pressure level, and that the administration of a ganglion-blocking drug then causes a smaller fall of blood pressure because the neurogenically maintained part of the blood pressure is a smaller proportion of the whole.

O‘Donnell has described a variety of conditions that are likely to cause increases or decreases in the neurogenically maintained part of the blood pressure and lead to corresponding increases and decreases in the response to ganglion-blocking drugs.

SUMMARY

1. Attention is directed to the need, when evaluating the magnitude of postural and nonpostural falls of blood pressure, to give consideration to (a) the time spent in the lying and standing postures, (b) the desirability of correcting for postural changes in blood pressure not dependent on drug action, and (c) the need to justify the choice of control blood pressure readings from which the blood pressure is said to fall.

2. There are differences in the relative magnitudes of the postural and nonpostural falls in blood pressure produced by IN 292, mecamylamine, and pentolinium. IN 292 produced large falls in blood pressure not dependent on the assumption of the erect posture, whereas pentolinium produced mainly postural effects.

3. Paradoxically, patients demonstrating postural rises in pressure under control conditions prior to receiving ganglion-blocking drugs tend to have large postural falls in pressure following the action of these agents. A possible explanation is discussed.

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SUMMARIO IN INTERLINGUA

1. Es signalate le necessitate, in evaluatar le magnitude del reduction postural e non-postural del pression de sanguine, de prender in consideration (a) le tempore passate in position jacente e in position erecte, (b) le desirabilitate de effectuar correctiones pro alterationes postural in le pression de sanguiine le quales non depende del action de un droga, e (c) le necessitate de justificar le selection del pression de controlo ab que le reduction es mesurate.
2. Il existe differentias inter le magnitudes relative del reductiones postural e non-postural del presision de sanguine effectuate per IN 292, mecamylamina, e pentolinio. In 292 produceva forte reductiones del presision de sanguine non dependente del prender un postura erecte, durante que pentolinio produceva principalmente effectos postural.

3. Paradoxemente, patientes con augmentos postural del presision sanguinee sub conditions de controlo ante le administration de drogas a blocage ganglionie tende a exhibir forte reductiones postural del presision sanguinee post le action del agentes mentionate. Un explication possibile de iste phenomeno es discutite.

REFERENCES


One hundred sixty-eight patients with blood pressures of over 200/120 mm. Hg were subjected to partial or total adrenalectomy alone or in combination with various forms of sympathectomy. One hundred eighteen of the patients have lived and 50 died over the observation period from 3 months to 8 years. Forty-eight patients have responded with blood pressures in the range of 150/100 mm. Hg and 27 with blood pressures below that. Improvement in funduscopic examination has occurred in these patients. In 55 there was improvement in the electrocardiogram and decrease in heart size during the follow-up period. Blood urea nitrogen determination was a reliable index for renal function. In 70 of the 118 patients headache was a major complaint before operation, and in 62 patients the headache was relieved or disappeared entirely. Thirty-six of the survivors of adrenalectomy developed some pigmentation of the Addisonian distribution. Eight patients developed recognizable peptic ulcer. All patients with total adrenalectomies were treated with replacement cortisone and desoxy corticosterone acetate. In hot weather supplementary salt was given.

The authors believe that fully 50 per cent of individuals with severe hypertensive disease subjected to adrenalectomy and sympathectomy exhibit a total improvement, that this type of operation is quite justified, and that the results obtained by these procedures are rarely equaled by the administration of antihypertensive drug therapy. The authors point out that there is no successful procedure for selecting patients capable of a highly favorable response to the operation. At the present time they limit the operation to those in urgent need of control of hypertensive disease or those who respond poorly to antihypertensive drugs or who are unable to tolerate antihypertensive drugs.

Harvey
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insufficiency, for instance, in parents and children, in siblings, and in twins. In such observations the author sees further evidence that an inherited predisposition must be present for the acquisition of extraneous cardiovascular diseases.

Pick

REVIEWS IN
CARDIOVASCULAR DISEASE


Errata

Various authors have requested that the following changes be made in their published papers:


On page 348, paragraph 3 under Method, should read "If D is the blood pressure (systolic or diastolic) in the standing posture during drug action . . ."


On page 572, table 5, Lead V₆, Group Range, 56.0 under LVII should be 36.0; table 5, Lead V₁, No. pts., — (INC) under RVH & IRBBB should be 1.

On page 576, table 6, Lead V₅-V₆, No. pts., 48 (N) and 17 (PRO) under Total should be 49 (N) and 16 (PRO).

On page 577, table 8, R/S Ratio in Lead V₁, No. pts., 37 (N) under Total should be 27.

On page 578, table 9, R Wave in V₁ + S Wave in V₅-V₆, No. pts., 18 (N) under Total should be 19.


On page 831, line 13, should read "... workers may expend energy at a higher rate off the job than on it."