The standard error of the difference between the means is

$$\text{SE diff} = \sqrt{\frac{SD^2}{n_1} + \frac{SD^2}{n_2}}$$

When the difference between the means is divided by this standard error the result is t.

$$\text{Thus } t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{SD^2}{n_1} + \frac{SD^2}{n_2}}}.$$

The table of the t distribution (table 11.1) is entered at $(n_1 - 1) + (n_2 - 1)$ degrees of freedom.

Dr Silver's figures work out like this:

		Treatment A	*Treatment B*
n	=	15	12
Σx	=	1026	1001
$\bar{x}$	=	68·4	83·42
Σx^2	=	73978	86921
$(\Sigma x)^2$	=	1052676	1002001
$\frac{(\Sigma x)^2}{n}$	=	70178·4	83500·083
$\Sigma(x - \bar{x})^2$	=	3799·6	3420·917

$$SD^2 = \frac{3799{\cdot}6 + 3420{\cdot}917}{(15 - 1) + (12 - 1)} = 288{\cdot}82$$

$$\text{SE diff} = \sqrt{\frac{288{\cdot}82}{15} + \frac{288{\cdot}82}{12}}$$

$$= \sqrt{288{\cdot}82\left(\frac{1}{15} + \frac{1}{12}\right)}$$

$$= 6{\cdot}582$$

$$t = \frac{83{\cdot}42 - 68{\cdot}4}{6{\cdot}582} = 2{\cdot}282$$

The table of t distribution shows that at 25 degrees of freedom, that is $(15 - 1) + (12 - 1)$, when $t = 2{\cdot}282$, it lies between 2·060 and 2·485. Consequently, $0{\cdot}05 > P > 0{\cdot}02$.

This degree of probability is just smaller than the conventional level of 5%. The null hypothesis that there is no significant difference between the means is therefore somewhat unlikely. There probably is a real difference on average between the alimentary transit times in patients on these two preparations of bran.

Exercise 12. In Dr Pink's 18 patients the mean level of plasma phosphate was 1·7 mmol/l, standard deviation 0·8. If the mean level in the general population is taken as 1·2 mmol/l, what is the significance of the difference between that mean and the mean in Dr Pink's patients? *Answer:* $t = 2{\cdot}652$, $0{\cdot}02 > P > 0{\cdot}01$.

In two wards for elderly women in a geriatric hospital the following levels of haemoglobin were found: Ward A: 12·2, 11·1, 14·0, 11·3, 10·8, 12·5, 12·2, 11·9, 13·6, 12·7, 13·4, 13·7 g/dl; Ward B: 11·9, 10·7, 12·3, 13·9, 11·1, 11·2, 13·3, 11·4, 12·0, 11·1 g/dl. What is the difference between the mean levels in the two wards, and what is its significance? *Answer:* 0·56 g/dl; $t = 1{\cdot}243$, DF = 20, $0{\cdot}5 > P > 0{\cdot}1$.

Today's Treatment

Diseases of the cardiovascular system

Hypertension—II

J C PETRIE

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Methyldopa

The use of low doses of methyldopa (500-750 mg/day) either alone or in combination with other drugs reduces the troublesome adverse effects, such as drowsiness, that occasionally limit its usefulness as a single drug used in high doses (2 g/day or more). The explanation of the mode of action has undergone considerable change. The main hypotensive action of methyldopa is now believed to be mediated through the action of a metabolite, perhaps α-methylnoradrenaline, on the central nervous system to stimulate central alpha-receptors rather than through peripheral effects. Methyldopa also lowers renin activity.

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An appreciable reduction in blood pressure may be obtained within three to six hours in the bedfast patient if a high initial oral dose (750-1000 mg) is used. Such doses are rarely employed because rapid and dramatic reduction of blood pressure is indicated only in the severest grades of hypertension. Furthermore, the starting of methyldopa treatment is often delayed because it interferes with the estimation of catecholamines to show a false-positive reaction in the screening test for phaeochromocytoma. Used in conventional doses (500-3000 mg/day) methyldopa reduces supine, erect, and post-exercise blood pressures. Few carefully controlled comparative studies have been carried out but it appears that the hypotensive efficacy is at least equivalent to that of beta-blockers, adrenergic neurone blockers, and clonidine. When added to other hypotensive agents a lower starting dose (375-500 mg/day) should be used and the dose of the other agent also reduced until the effectiveness of the combination can be assessed. If a further hypotensive effect is required or tolerance develops increases in doses are usually by 250 mg increments at intervals of two to three days, preferably at night because of possible sedation. Methyldopa is largely excreted by the kidney and smaller doses are recommended in renal insufficiency. A rise in blood urea may occur

during treatment as with other antihypertensive agents. There is no clear evidence that methyldopa regularly reduces the renal glomerular filtration rate in hypertensive patients. Indeed, glomerular filtration is usually maintained or even increased.

Methyldopa is contraindicated in hepatitis and active cirrhosis and is not recommended in patients with a history of liver disease. Jaundice, hepatocellular damage, cholestasis, and abnormal liver function values have been reported. In 10 to 20% of patients a positive reaction to the direct Coombs test develops, usually within 12 months of starting treatment. An association has been shown with doses greater than 1 g/day. The Coombs test result becomes negative within months of stopping methyldopa. An acquired haemolytic anaemia associated with methyldopa treatment is another uncommon reason for stopping it. Reversible effects on white blood cells, especially granulocytes, have been reported in a few cases. The most common adverse reactions are drowsiness, sedation, failure of concentration, and weakness, especially during the initial period of treatment. Some patients cannot tolerate even low doses. Gastrointestinal disturbance, drug fever, rashes, weight gain, giddiness, nightmares, depression, dryness of the mouth, nasal congestion, sexual dysfunction, non-puerperal lactation, and Parkinsonism also occur. A paradoxical pressor response has occasionally been reported, particularly after parenteral administration.

Bethanidine, debrisoquine, and guanethidine

Adrenergic neurone blockers may be used in all grades of hypertension, although some doctors reserve them for moderate or severe hypertension. In such patients the adrenergic neurone blocker is added, usually in low doses, to existing antihypertensive treatment. The selection of drug is a matter of personal preference, although bethanidine and debrisoquine appear to have some advantages over guanethidine. The mode of action of adrenergic neurone blockers is complex, and effects have been shown on the storage and release of noradrenaline. The duration of action of bethanidine (2-12 hours) and debrisoquine (4-24 hours) allows more rapid adjustments of dosage to be made than with guanethidine, which is longer-acting. On the other hand, once the optimal maintenance dose is known, more frequent daily dosage may be a disadvantage with the shorter-acting drugs and the compliance of patients with treatment may be better with debrisoquine or guanethidine given once daily.

The recommended initial dose is small (say, bethanidine 5-10 mg thrice daily, debrisoquine 10-20 mg once or twice daily) and small increments in dosage should be made at short intervals (bethanidine 1-2 days, debrisoquine 2-4 days, guanethidine 5-7 days). Assessment of effect should include measurement of the standing and preferably post-exercise blood pressure levels, because postural and post-exercise hypotension may be troublesome. Reduction of supine blood pressure is variable. In patients who prove difficult to control, more satisfactory levels of blood pressure may be achieved by combination with another hypotensive drug rather than by using high doses of adrenergic neurone blocker alone, and the occurrence of unpleasant adverse reactions may be reduced. In renal insufficiency a reduction in dosage is recommended. On the rare occasions that large and rapid reductions in blood pressure are essential and other parenteral preparations such as diazoxide, hydrallazine, clonidine, or guanethidine are not available the cautious use of a higher initial oral dose of a short-acting agent (say, bethanidine 20-30 mg) is effective in the bedfast patient.

The principal adverse reactions of adrenergic neurone blockers include postural and post-exercise hypotension, which may be troublesome in the elderly or in warm climates; diarrhoea; and aggravation of peptic ulcer symptoms, particularly in patients taking guanethidine. Failure of ejaculation, weakness, nasal stuffiness, and fluid retention may also occur. If parenteral guanethidine is indicated it should be given preferably by intramuscular injection or slow intravenous infusion, as an initial hypertensive response may occur.

The awareness of doctors of clinically important adverse drug reactions involving adrenergic neurone blockers is low. Pressor responses or a reduction of the hypotensive action may develop if concurrent treatment is prescribed. Examples include tricyclic antidepressants, sympathomimetic agents present in cold and cough cures and decongestants, monoamine oxidase inhibitors, chlorpromazine, and appetite suppressants.

Clonidine

Clonidine is an effective antihypertensive agent and is a useful alternative. Its mode of action is not fully understood. An alpha-adrenoceptor agonist effect has been shown, and the central hypotensive effects can be antagonised by alpha-adrenoceptor-blocking drugs such as phentolamine. In addition, a reduction in the activity of sympathetic nerves, peripheral effects on smooth muscle, and inhibition of neuronal uptake mechanisms have been shown. Clonidine reduces renin activity.

The starting dose should be low (0·15-0·3 mg/day). The maximum effect occurs two to four hours after a single dose. A thrice-daily dosage scheme is recommended, although recent pharmacokinetic studies suggest that a twice-daily regimen may be feasible. The need to take clonidine tablets regularly must be emphasised. The drug should not be discontinued abruptly —for example, around the time of emergency surgery—because sudden withdrawal of long-term oral clonidine treatment may be associated with severe "rebound" hypertensive response and symptoms of headache, anxiety, and hyperirritability. This hypertensive effect may be increased if the patient is taking beta-blockers. Pretreatment with desipramine may antagonise the hypotensive action of clonidine. After oral treatment bradycardia, sedation, reduced salivary flow, fluid retention, mild aggravation of renal insufficiency, depression, and gastrointestinal symptoms may also occur. In emergencies intravenous clonidine may be given by slow injection to minimise a transient initial rise in blood pressure that occurs in some patients.

Hydrallazine

The combination of oral hydrallazine and other vasodilators such as prazosin or minoxidil with beta-blockers is useful, effective, and increasingly popular. Other agents such as thiazides or methyldopa may be added to the "cocktail" of treatment, particularly in patients with unsatisfactory levels of blood pressure. Hydrallazine has a direct effect on arteriolar smooth muscle. Used alone it reduces blood pressure, diastolic levels often more than systolic, and peripheral vascular resistance. This is associated with an increase in heart rate, stroke volume, and cardiac output and with symptoms such as palpitations, aggravation of angina, and headache, which limit its usefulness. Plasma renin activity rises. The addition of a beta-blocker, however, reduces or abolishes the apparently reflex effects such as tachycardia and increases the efficacy and acceptability to the patient of vasodilators. In addition, the combination allows lower doses of hydrallazine to be used (75-200 mg/day in three or four divided doses). Hydrallazine may also be given parenterally in hypertensive emergencies. Twenty to 40 mg should be given by slow intravenous injection.

Hydrallazine should be used with care in patients with severe ischaemic heart disease, particularly if concurrent beta-blockers are not prescribed. In some patients long-term administration of high doses—for example, 400 mg/day or more —results in an acute rheumatoid state or in a syndrome similar to systemic lupus erythematosus and treatment should be stopped. Adverse reactions may also be troublesome at low doses. These include gastrointestinal upsets, sweating, fluid retention, conjunctivitis, and nasal congestion. The metabolism of hydrallazine is partly through N-acetylation, which is under genetic control. In patients who are "slow" acetylators and in severe renal insufficiency, accumulation may develop with an associated increase in adverse effects.

Diazoxide

Intravenous diazoxide should be reserved for the emergency reduction of blood pressure in hypertensive crises. The patient should be lying flat and 300 mg (or 5 mg/kg) should be given intravenously over 10 seconds. This usually reduces severely raised levels of blood pressure within five to 10 minutes, although further doses may be required (up to 1200 mg in 24 hours). Diazoxide is related chemically to the thiazide group. It has a direct effect on vascular smooth muscle. The amount of fall in blood pressure is unpredictable and may be hazardous in the elderly or in patients with cerebrovascular disease. Diazoxide treatment is also associated with a reflex tachycardia and fluid retention, which may be troublesome in patients with myocardial insufficiency. Concurrent diuretic treatment may be required. Diazoxide is also available as an oral hypotensive agent and has been used in patients with severe renal failure. The efficacy of oral treatment is not clearly established. Hyperglycaemia and hyperuricaemia occur. These adverse reactions and the occurrence of extrapyramidal signs during long-term oral treatment reduce its acceptability to patients.

Several other agents—old and new—are available as alternatives to the above drugs.

Rauwolfia derivatives

Many rauwolfia derivatives are available either alone (seven preparations) or in combination (14 preparations). Their effectiveness in lowering blood pressure is well established. Despite the number of preparations marketed their popularity as first-choice treatment, alone or in combination with other drugs, is waning. Adverse reactions include mild sedation, increased dreaming, and occasionally adverse effects on mood, particularly in patients with a tendency towards depression. In addition, an association between rauwolfia derivatives and an increased incidence of breast cancer has been claimed, and disputed.

Prazosin

This is an effective new hypotensive agent that acts directly on the relaxation of vascular smooth muscle. Side effects are predictable on the basis of a knowledge of the mode of action but some individual variations in response have been reported. In particular some patients have experienced a sudden loss of consciousness within 30 to 90 minutes of receiving the initial dose. It is recommended that the starting dose, 2 mg, should be taken with food, preferably in the later part of the day. Prazosin is usually prescribed thrice daily up to a total daily dosage of 20 mg. Increments in doses should not be made at more than four- to six-week intervals.

Ganglion-blocking agents

Ganglion-blocking agents such as pentolinium are now seldom used.

Conclusion

The decision to start treatment and the choice of drug depends on a knowledge of patient and drug factors. Treatment should not be started on the basis of flimsy evidence of raised blood pressure. The reduction in blood pressure should not be associated with unacceptable adverse effects. In patients with severe hypertension, treatment with a combination of low doses of different agents may increase the compliance of the patient with long-term tablet taking. A dramatic reduction in blood pressure over the space of a few minutes is essential only in hypertensive crises, and the uncritical and overenthusiastic use of potent parenteral antihypertensive agents should be discouraged.

Letter from . . . South Australia

Congress in South Island

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The Seventh New Zealand Congress of Obstetrics and Gynaecology was not a mammoth affair. The big congresses are often impersonal and something of a trial for the participants. So many things are going on at the same time that the plethora of choice induces Alvin Toffler's "Future Shock," perhaps leading to anxiety neurosis. There was nothing of this at Nelson in the South Island, where this small congress was held, and it was the better for that. There were no more than about 200 people, so that nearly all could be accommodated in the same hotel and all could take part in the whole programme. There grew up a camaraderie, which was valuable in allowing for uninhibited discussion. All sessions were plenary ones, and the only fragmentation induced by choice was in the social occasions. There are immense advantages in package deals arranged by someone else. There is no wonder that travel agencies have found them so lucrative.

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Why attend a congress?

Congresses as phenomena are an interesting form of human behaviour. They are now a feature of commerce, industry,