Review

Hemodynamic and vascular responses to antihypertensive treatment with adrenergic blocking agents: A review

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Patients with established, uncomplicated arterial hypertension are characterized by a normal resting cardiac output and an increased systemic vascular resistance affecting the renal vascular bed most prominently.[1-3] The elevated blood pressure can, generally speaking, be lowered by reducing the cardiac output, lowering the systemic vascular resistance, or through a combination of both. An ideal antihypertensive agent should lower the blood pressure by reducing both the systemic and particularly the renal vascular resistance both at rest and during stress situations of various kinds.

As this field is reviewed it becomes apparent that the available information on antihypertensive drugs is based mainly on acute animal experiments and parenteral administration to human subjects. Our knowledge on possible changes induced by long-term treatment is poor. This discussion, therefore, considers three widely used hypotensive agents with adrenergic blocking properties—Rauwolfia preparations, guanethidine, and methyldopa—and separately deals with: (1) acute effects, (2) effects of short-term treatment (less than 4 weeks), and (3) effects of long-term treatment.

Rauwolfia preparations

Acute effects. Only two studies of the acute effects on cardiac hemodynamics are available.[4,5] In one of them, the effect of 2.5 mg. of reserpine given intramuscularly was observed 4 hours after administration.[4] The blood pressure dropped in all cases. In patients with borderline hypertension and elevated cardiac output, the cardiac output decreased, while in those with normal cardiac output but elevated systemic vascular resistance, the latter decreased. The heart rate did not change. During head-up tilting, five of eleven reserpine-treated patients fainted, indicating an orthostatic action which is not generally seen with this agent. In the other study on only four subjects, both cardiac output and systemic resistance fell after intravenous administration of 1.0 to 5.0 mg.[5]

After intravenous administration of reserpine, a slight reduction in glomerular filtration rate was noted, and the excretion of water and electrolytes decreased.[6]

Parenteral reserpine increased digital blood flow significantly in both normotensive and hypertensive subjects.[7] The mean blood pressure and systemic resistance fell without consistent changes in heart rate.

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The overshoot of blood pressure following the Valsalva maneuver is not apparently inhibited by reserpine given parenterally in moderate doses,[8] but the pressor response to infused norepinephrine may be slightly increased.[4]

Effects of short-term treatment. Syrosingopine, in a dosage of 1.5 to 6.0 mg. given intramuscularly daily for seven days to normal volunteers, resulted in a lower blood pressure, but there were no definite changes in heart rate or cardiac output.[9] It did not interfere with the response to recumbent exercise.

In hypertensive patients studied for one week before and after oral syrosingopine, it was noted that although the resting arterial pressure was almost brought to normal, there was still a considerable pressure rise during sitting exercise.[10] Similarly, the pressor responses to noxious stimuli, such as the cold pressor test, were unaltered.[11]

In hypertensive patients, oral reserpine in large doses resulted in a marked reduction in systemic resistance and even an increased cardiac output after one week of treatment, while renal blood flow decreased and renal resistance increased.[12]

Effects of long-term treatment. In the study mentioned above, the systemic resistance continued to be reduced after 6 weeks of treatment, but the renal blood flow had returned to about control levels.[12] Likewise, the renal hemodynamics in hypertensive patients treated for three months with oral reserpine, 3.0 to 6.0 mg. daily, did not show consistent changes.[6]

After three months of treatment with oral reserpine, a dosage of 0.75 mg. daily, a fall in both resting and exercising blood pressure levels was reported to occur in hypertensive patients.[13] The decrease was felt to be due to a lowered resistance, as there were no changes in the resting cardiac output or the output response to exercise.

Reserpine was shown to block both arterial and venous reflex vasoconstriction in normal subjects after oral treatment for up to four months.[14]

The weight gain seen during treatment with Rauwolfia drugs is probably not due to fluid retention in most of the cases, as the extracellular fluid volume was shown to maintain a constant ratio to total body weight after reserpine given orally from four weeks to four months.[15] This is supported by studies on the body fluid compartments before and after parenteral administration of reserpine for six days.[16]

Conclusion. Most authors report a favorable pattern of response to oral reserpine with lowered systemic vascular resistance as the main feature, without reduction in the renal blood flow. There is conflicting evidence concerning the effect of reserpine on the hemodynamic responses to stressful procedures.

The weight gain seen during treatment with Rauwolfia preparations is probably not due to fluid retention. It should also be noted that most of the data for reserpine were obtained for dosage levels which are not recommended for continued therapy.

Guanethidine

Acute effects. The acute effects of parenterally administered guanethidine, usually in doses of 10 to 25 mg. intravenously, have been studied by several authors.[17-23] Within 10 minutes after an intravenous injection, there is usually a short-lived pressor phase with increased systolic and diastolic pressures in both normotensive and hypertensive subjects.[20] The depressor phase which follows is characterized by a substantial reduction in cardiac output. The systemic resistance is not altered.[23] The effect on the heart rate is variable.[20] In patients with pulmonary hypertension, there is a reduction in pulmonary pressure without change in pulmonary resistance.[18] In normal subjects and in patients with arterial hypertension, a small reduction in pulmonary vascular resistance has been described.[19]

After taking guanethidine intravenously, the response to supine exercise has been reported to be largely unchanged in both normotensive and hypertensive subjects,[19] but the increase in heart rate was smaller. The blood pressure increased in the same manner as in the control study.

The reduction in cardiac output at rest in recumbency is accompanied by a decrease in renal blood flow and glomerular filtration rate. In both normotensive and hypertensive subjects, the water and sodium excretion diminish.[22,24] The cerebral and hepatoportal blood flows have been reported to fall.[17,20] If the patient is tilted, a further decrease of both the blood pressure

and cardiac output is obtained, and systemic resistance falls.[22]

The blood pressure overshoot following the Valsalva maneuver is completely blocked by guanethidine, and other vasoconstrictor reflexes are markedly inhibited.[19,20,25] The response to tyramine and ephedrine infusions is not significantly altered, but the pressor effect of single doses of norepinephrine is enhanced.[20,25]

Effects of short-term treatment. After 4 to 10 days of oral guanethidine, the cardiac output in hypertensive patients was lower in the recumbent position, and the decrease became more marked after tilting, while the systemic resistance was only moderately lowered.[26] The heart rate decreased and an impaired pressor response to noxious stimuli, such as the cold pressor test, was reported.[27]

Both the renal plasma flow and glomerular filtration rate were found to decrease in hypertensive subjects, but the vascular resistance was unchanged.[26] These changes became more marked after tilting. In normal subjects, on the other hand, an increased renal blood flow and a decreased resistance after taking oral guanethidine in a dosage of 10 mg. daily for 5 to 7 days have been described.[24]

The digital vascular reactivity to norepinephrine increased after oral guanethidine given to hypertensive patients, but the drug did not produce vasodilatation in the digit with the subjects in the resting recumbent position.[28] In normal subjects the drug was shown to block both arterial and venous vasoconstriction.[14]

Effects of long-term treatment. After stabilization of the blood pressure on treatment of 12 patients with oral guanethidine, neither supine nor standing cardiac output was significantly changed, and the systemic vascular resistance was lower.[22,29] The heart rate had decreased. On walking, the systemic pressures of the hypertensive subjects were lower than before treatment with no significant change in cardiac output.[29] Others observed a fall in blood pressure, instead of the usual increase, during exercise with guanethidine.[30]

Guanethidine in large oral doses to normal subjects for four weeks resulted in a lower resting heart rate, but there were no significant changes in mean arterial pressure or cardiac index.[31] During supine exercise, the cardiac index and mean pressure were lower than in the control study.

After 8 to 30 days of oral guanethidine, in patients with severe hypertension the renal plasma flow and glomerular filtration rate were found to be decreased in both the lying and standing positions, as were the excretion of sodium, potassium, and water.[32]

The blood volume has been reported to be significantly increased in hypertensive patients after oral guanethidine for 7 to 21 days.[33] Similar results were found after one year of treatment.[34] Total exchangeable sodium increased, and creatinine clearance fell. In normal subjects, on the other hand, oral guanethidine for 7 to 21 days was found to increase the plasma volume without any sodium retention.[35]

Conclusion. There are a fairly large number of reports on the acute and subacute effects in man of guanethidine, but long-term studies are few.

The hemodynamic responses to guanethidine are similar to those with ganglionic blocking agents. The main immediate effect is probably on the cardiac output, leaving the systemic vascular resistance little changed; but the long-term studies indicate that cardiac output may return to normal. Hypotension during exercise can occur.

Impairment of the renal blood flow is to be anticipated during treatment with guanethidine. The weight gain seen is due to increased plasma volume, probably secondary to sodium retention.

Methyldopa

Acute effects. The decrease in recumbent blood pressure, seen after parenteral administration of methyldopa to hypertensive patients, is ascribed by some authors to a lower systemic vascular resistance with only minor changes in the cardiac output.[23,26] Renal vascular resistance is reduced substantially, and therefore the renal blood flow and glomerular filtration rate are left uncompromised despite the blood pressure reduction.

It has been reported that the same pattern of systemic and renal hemodynamic changes is maintained while in the erect position, and the increase in systemic and renal resistance seen after tilting in the

control state is abolished after methyldopa.[36]

Different results have, however, been reported by others, who have found the blood pressure reduction to be due to a decreased output with an unchanged systemic vascular resistance.[37,38] The heart rate fell significantly in one study,[37] but not in another where it even increased when methyldopa was given to a series of labile hypertensives.[38] Also in that series, the recumbent blood pressure reduction was due to a decreased cardiac output. However, the greater reduction in mean blood pressure with 60 degree head-up tilting occurred without a further reduction in cardiac output, and the systemic resistance was lowered in this position. This was thought to be due to orthostatic loss of reflex arteriolar constriction.

Methyldopa given intravenously has not been shown to produce consistent effects on the hypertensive overshoot seen after the Valsalva maneuver.[37]

Effects of short-term treatment. After taking oral methyldopa for 7 to 16 days, the blood pressure in hypertensive patients fell without change in cardiac output, indicating a lowered systemic resistance.[39] The heart rate was unchanged. Tilting feet downward did not produce an exaggerated fall in blood pressure or cardiac output when compared with the control study.[40]

During upright exercise, the blood pressure level was reported to be markedly lower than before treatment, but without tendency to exercise hypotension.[39,41,42] The pressor response to noxious stimuli, such as the cold pressor test, was described to be impaired in hypertensive patients on oral methyldopa,[27] and the response to the Valsalva maneuver was completely abolished in eight of ten patients after oral treatment with methyldopa.[39]

Oral methyldopa taken for 6 to 19 days on the whole did not produce consistent changes in glomerular filtration rate.[39] Patients responding to methyldopa with a blood pressure decrease showed an increased renal blood flow with lower calculated renal vascular resistance. These results have been confirmed for hypertensive patients with reduced renal function.[43]

The pressor response to norepinephrine was only slightly increased, but strikingly prolonged, after treatment with methyldopa.[40] After tyramine, on the other hand, the pressor effect was markedly enhanced. An increased digital vascular reactivity to norepinephrine has also been demonstrated.[28] The drug produces significant digital vasodilatation in the recumbent hypertensive patient,[28] and blocks both arterial and venous reflex vasoconstriction in normal subjects.[14]

When administered as therapy for hypertensive patients, methyldopa has been shown to have a smaller orthostatic effect than guanethidine for a given change in recumbent blood pressure.[23,44]

Effects of long-term treatment. After stabilization of therapy on oral methyldopa, the systemic resistance was lower in both the supine and standing positions in eight of ten hypertensive patients studied.[29] The heart rate was also reduced. On walking, the blood pressure level was lower than before treatment. The exercise cardiac output was, nevertheless, more than 20 per cent higher than in the control study, resulting in markedly lower resistance levels during exercise.

Conclusion. Though opinions differ, it seems that methyldopa acts primarily to reduce systemic resistance with no appreciable effect on cardiac output.

Hypotension during exercise does not occur. The renal blood flow appears to be maintained. However, little information is available on the long-term effect.

Summary

While the pharmacological effects of the three agents discussed (reserpine derivatives, guanethidine, and methyldopa) appear to depend upon interference with sympathetic nervous activity, they differ in their effects in man.

After acute administration, there is a fall in blood pressure with each agent, but with reserpine and methyldopa, cardiac output is little affected. With methyldopa, the renal resistance appears to fall. Guanethidine produces a sharp fall in the cardiac output and renal blood flow.

After treatment for a few days with these agents, the differences in their actions are less apparent, and from the very limited information available on long-term

therapy, each of these agents achieves its hypotensive effect without reduction in cardiac output. The renal blood flow remains at control levels with reserpine and methyldopa but is still somewhat reduced with guanethidine.

From the practical point of view, therefore, the decision to use one or another of these agents should rest upon differences in their clinical effectiveness and side effects. There is an urgent need for information on the changes in the action of these drugs during long-term therapy. These changes could be caused by the drugs' pharmacological effects or by physiological adaptations within the patient.

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