Clinical Evaluation of Combined Hydrogenated Ergot Alkaloids (Hydergine) in Arterial Hypertension

With Special Reference to Their Action in Central Manifestations

By RALPH M. TANDOWSKY, M.D.

One hundred patients suffering from sustained arterial hypertension were studied over a period of two years during which time the action of parenterally administered hydrogenated ergot alkaloids (Hydergine) constituted the main drug therapy. An immediate transient reduction of both the arterial blood pressure and the pulse rate was demonstrated in over 80 per cent of the entire group within a period of two hours. The average reduction in systolic and diastolic pressure was 36 mm. and 12 mm., respectively, and the pulse rate was reduced 6 beats per minute. Of interest was a group of 22 patients presenting evidence of early central vascular derangement in whom these alkaloids seemed to accomplish their best therapeutic action and possibly aborted what may have been a sustained cerebral accident. Untoward effects were minimal because of rapid dissipation of the drug, and its use in all types of hypertensive disease was deemed safe in the recommended dosage.

In the evaluation of depressor drugs for the palliation of arterial hypertension the selective action of each must be given prime consideration. The syndrome of arterial hypertension is due to the action of a pressor substance, the origin and composition of which may vary as may its strength and choice of effector. Stoll and Hofman first demonstrated three alkaloids contained in ergotoxin, namely; ergocornine, ergokriptine and ergocristine. They found that one of the double bonds of the lysergic acid component contained in each could easily be hydrogenated. Later, Rothlin and others found that these hydrogenated alkaloids were stable and had selective properties so far as the circulatory system was concerned. These consisted of central vasodilator effect, in the main, and a sympatholytic or adrenolytic effect peripherally.

Recent studies by Barcroft, Konzett and Swan have shown that these alkaloids have little effect on the arterial blood pressure of normal subjects but cause a significant fall in the pressure in hypertensives, particularly in those whose increased pressure is of central origin. They concluded that the vasodilatation brought about was mainly due to inhibition of the vasomotor center with minimal action due to peripheral block at the nerve endings. They found that these alkaloids left the human circulation very rapidly. Gibbs demonstrated a reduction in the arterial blood pressure of 50 hypertensive patients by Hydergine; in 11 the retinal arterioles presented an appreciable dilatation within 10 minutes after injection. He also found a diminished response to the cold-pressor test. Gibbs also pointed out that the subjective symptoms in almost one half of his series were relieved. Inasmuch as these alkaloids act mainly on the vasomotor centers, the probability of their influence on the cerebral circulation must be considered. Using the nitrous oxide method of Kety and Schmidt, J. H. Hafkenschiel and coworkers demonstrated a significant decrease in the vascular resistance of hypertensive patients, using one of these alkaloids, and although the blood flow

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Hydergine supplied by Sandoz Pharmaceuticals; it consists of equal parts of dihydroergocornine, dihydroergocristine and dihydroergokriptine.

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remained constant, the blood pressure decreased.

First mention of their action in the presence of cerebral vascular disturbances was made by Strauss. In a subsequent publication he reported 23 cases of hypertension with cerebral manifestations of which 21 were benefited by this therapy. Lasch published the case history of a hypertensive patient whose cerebral symptoms quickly disappeared after the use of hydrogenated ergot alkaloids. Gross, Leuterer and Matthiessen treated early cases of apoplexy with Hydergine and infiltration of the stellate ganglia with procaine once or twice weekly with satisfactory results. The hydrogenated ergot alkaloids lower the blood pressure by depressing the vasoconstrictor centers and by stimulating the vasodilator centers. In addition, they also stimulate the vagus center, slowing the heart rate. Although they are adrenolytic their action on the peripheral ganglia is felt to be minimal. Clinical observation has shown that they act most effectively when the sodium content of the blood stream is not excessive. For this reason their use in the presence of congestive heart failure and in the nephrotic syndrome may not be impressive.

Because these ergot derivatives reduce blood pressure by action on the vascular centers it was felt that they are best suited for the treatment of hypertension of central origin.

The appearance during the course of hypertension of many subjective and objective manifestations of cerebral origin, which at times assume the magnitude of a cerebral crisis, offers a potential field of study best suited to the hydrogenated ergot alkaloids. As yet a close correlation of these symptoms with the height of arterial pressure has not been made. Inasmuch as these drugs have relieved many of these symptoms from time to time, it was felt that a study laying particular emphasis on this phase of Hydergine action was warranted.

Procedure of a Study

Among a group of 100 patients suffering from sustained arterial hypertension it was found that 22 presented themselves with manifestations of early central vascular derangement complicating their hypertension. This group complained of intractable headache experienced most frequently at night or upon arising, sudden aphasia, hemiplegia of short duration, convulsive seizures, tinnitus, syncope, sudden loss of memory, dizziness, irritability, extreme restlessness and insomnia. Some patients of this group were treated for relief of these disturbing symptoms primarily rather than for the routine palliation of their hypertension. Examination disclosed that the severity of these symptoms did not always go hand in hand with the height of the arterial blood pressure. In the remaining 78, few objective manifestations were noted other than elevated arterial blood pressure.

To the group of 22 presenting outstanding evidence of cerebral vascular derangement, Hydergine was given as an emergency measure since the discomfort that these patients experienced necessitated immediate relief and also because previous methods of therapy had failed. The remaining 78 patients received a period of rest of not less than one hour before Hydergine was given. Each first received normal saline intravenously as a control prior to the actual study, after which the blood pressure and pulse were determined at 15-minute intervals for a period of two hours. In the 22 with cerebral manifestations, normal saline controls were likewise instituted as soon as opportunity presented itself. The saline controls were given under the same prevailing circumstances as the Hydergine. Each then received 0.3 mg. of Hydergine diluted with saline intravenously. Comparison was made of the subjective and objective manifestations prior to and after the drug was given at 15-minute intervals for a period of two hours after which time maintenance therapy was instituted within six hours. At the completion of the study four tablets, each containing 1 mg. of Hydergine, were given either orally or sublingually but were found to be ineffectual in appreciably lowering the blood pressure or pulse rate or in relieving the subjective manifestations present. Ambulatory and maintenance care was then instituted by the use of Hydergine subcutaneously or intramuscularly in dosage of 0.3 mg. once or twice daily for a period of from two weeks to one year. These patients were seen at one- to two-week intervals at which time the blood pressure, pulse rate and subjective manifestations were checked. Of the group presenting cerebral manifestations, maintenance therapy was conducted in a similar manner after emergency therapy until it was felt that the drug had been given a fair chance. Previously instituted medication for the relief of cerebral manifestations was investigated and charted. During the course of ambulatory therapy, normal saline was given from time to time in lieu of Hydergine for additional control study.

Results of Study

This group consisted of 44 female and 56 male patients with an average age of 51 and 56 years, respectively. In a number of those in
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<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis and Complications</th>
<th>Cerebral and Neurologic Manifest. and Duration</th>
<th>Previous Medication and Result</th>
<th>Control Studies and Effect</th>
<th>Effect 0.3 mg. Hydergine I.V.</th>
<th>Comment and Clinical Follow-Up</th>
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</thead>
<tbody>
<tr>
<td>N. S.</td>
<td>56</td>
<td>M.</td>
<td>Essent. hypertens., syphilis</td>
<td>Head., oc., hemipleg., it., deep reflex., it., absent flacc. paral., it.</td>
<td>Nitrates, sedation. Result none</td>
<td>Deleted</td>
<td>240/140 96</td>
<td>160/100 80</td>
</tr>
<tr>
<td>N. C.</td>
<td>60</td>
<td>F.</td>
<td>Malig. nephro., b.br. block, it., cor. scl.</td>
<td>Head., fr. and oc., disturb. vision, reflex. exag., restless</td>
<td>Sedation, physiotherapy, aspirin, I.V. glucose, Sl. and temp. relief</td>
<td>Saline I.V. None</td>
<td>220/130 82</td>
<td>180/110 80</td>
</tr>
<tr>
<td>A. R.</td>
<td>64</td>
<td>M.</td>
<td>Essent., hypertens., congest. ht. fail., mild</td>
<td>Anesthes., tingling it. arm and leg, weak. it. arm, mental confus., deep reflex., exag., it., speech imped. 4 hrs. dur.</td>
<td>Methem, nitrates, sedation. No relief</td>
<td>Saline I.V. No effect</td>
<td>220/126 78</td>
<td>176/105 76</td>
</tr>
<tr>
<td>R. B.</td>
<td>46</td>
<td>M.</td>
<td>Essent. hypertens., V.P.C.</td>
<td>Head., fr. and oc., rigid neck, nausea and vom., restless 1 hr. dur.</td>
<td>Codeine, aspirin, Dramamine. No relief</td>
<td>None</td>
<td>180/100 80</td>
<td>160/90 82</td>
</tr>
<tr>
<td>W. B.</td>
<td>60</td>
<td>F.</td>
<td>Essent. hypertens., diabet., obese</td>
<td>Head., oc., syncope, tingling and pain, rt. arm and leg, reflex. exag., retinitis</td>
<td>Insulin, sedation, veratrum, nitrates. No relief</td>
<td>Saline I.V. No effect</td>
<td>180/110 90</td>
<td>140/90 80</td>
</tr>
<tr>
<td>I. B.</td>
<td>65</td>
<td>M.</td>
<td>Essent. hypertens.</td>
<td>Head., oc., aphasia, mot. and sens. 2 hrs. dur.</td>
<td>No previous medication</td>
<td>None</td>
<td>230/130 88</td>
<td>200/110 78</td>
</tr>
<tr>
<td>A. D. 69 F.</td>
<td>Essent. hyper-tens., rh. ht. dis., aur. fib.</td>
<td>Head., oc., convuls. 60 min. dur., hemipl., rt., aphasia, mot. 1 mo. dur.</td>
<td>No previous medication</td>
<td>None</td>
<td>168/110 88</td>
<td>110/90 78</td>
<td>Relief of convolutions in 2 min.</td>
<td>4 subsequent convulsive seizures each relieved within 5 min. Expired 6 mos. later of cereb. thrombosis</td>
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<tr>
<td>J. B. 81 M.</td>
<td>Artsc. ht. dis.</td>
<td>Aphasia, mot. and sens., convuls. 30 min. dur., stertorous breath.</td>
<td>MgSO₄, and glucose, I.V. No effect</td>
<td>Saline I.V. No effect</td>
<td>188/90 66</td>
<td>110/80 66</td>
<td>Complete relief in 35 min.</td>
<td>Free from cerebral manifestations for 14 mos. without medication</td>
</tr>
<tr>
<td>J. M. 74 M.</td>
<td>Artsc. ht. dis., cholecystitis</td>
<td>Head., fr., mental confus., weak rt. arm and leg, reflex., exag., rt. 4 hrs. dur.</td>
<td>None</td>
<td>Saline I.V. No effect</td>
<td>190/120 92</td>
<td>162/110 84</td>
<td>Relief of headache and right side weakness within 1 hr.</td>
<td>Patient discharged in 2 days</td>
</tr>
<tr>
<td>B. S. 65 F.</td>
<td>Essent. hyper-tens., myo. infarct, old ant.</td>
<td>Head., oc., insomnia 2 hrs. dur.</td>
<td>Aspirin, sedation</td>
<td>Saline I.V. No effect</td>
<td>205/100 72</td>
<td>160/100 72</td>
<td>Relief of headache in 15 min.</td>
<td>Received 0.3 mg. I.M. daily for 2 wks. with continued relief</td>
</tr>
<tr>
<td>I. B. 49 F.</td>
<td>Essent. hyper-tens., early menopause</td>
<td>Head., oc., vom. and syncope before menses 4 hrs. dur.</td>
<td>Sedation, aspirin, codeine, Dramamine. Sl. relief</td>
<td>Saline I.V. No effect</td>
<td>190/110 92</td>
<td>162/100 72</td>
<td>Complete relief within 15 min.</td>
<td>Treatment repeated each month with excellent results</td>
</tr>
<tr>
<td>W. H. 58 M.</td>
<td>Malign. nephro.</td>
<td>Head., oc. and bipar., tinnitus, reflex., exag. 10 days dur.</td>
<td>Sedation. No relief</td>
<td>Saline I.V. No effect</td>
<td>210/120 96</td>
<td>180/100 80</td>
<td>Relief in 20 min.</td>
<td>Received 0.3 mg. q 12 hrs. for maintenance. Expired in 4 wks. with azotemia</td>
</tr>
</tbody>
</table>

Abbreviations:
- bipar.—biparietal
- dur.—duration
- exag.—exaggerated
- flac.—flaccid
- fr.—frontal
- head.—headache
- hemipl.—hemiplegia
- imped.—impediment
- it.—left
- M.H.E.—maximal hydergine effect
- mot.—motor
- oc.—occipital
- rt.—right
- V.P.C.—ventricular premature contractions
- vom.—vomiting
<table>
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<td></td>
<td></td>
<td>Rest. 220/160 90</td>
<td>M.H.E. 200/110 80</td>
</tr>
<tr>
<td>J. G.</td>
<td>40 F.</td>
<td></td>
<td>Angiospast. hypertens., early</td>
<td>Head., oc., giddiness, reflex., deep and superficial., exag. 2 hrs. dur.</td>
<td>Sedation, Methium, nitrites. No result</td>
<td>Saline I.V. No effect</td>
<td>226/120 92</td>
<td>170/100 82</td>
</tr>
<tr>
<td>L. T.</td>
<td>41 F.</td>
<td></td>
<td>Essent. hypertens.</td>
<td>Syncope, disturb. vision, stagger gait, 2 wks. dur.</td>
<td>Sedation. No relief</td>
<td>Saline I.V. No effect</td>
<td>210/120 96</td>
<td>178/110 84</td>
</tr>
<tr>
<td>J. L.</td>
<td>50 F.</td>
<td></td>
<td>Essent. hypertens., diabet., menopause</td>
<td>Head., oc. and fr., tingling, weak, lt. arm and lt. leg, reflex., deep, exag., unsteady gait 2 mos. dur.</td>
<td>Nitrites, Estrogen. No result</td>
<td>Saline I.V. No effect</td>
<td>210/110 86</td>
<td>180/106 80</td>
</tr>
<tr>
<td>Patient</td>
<td>Diagnosis</td>
<td>Headache Description</td>
<td>Previous Treatment Effect</td>
<td>Saline I.V. Effect</td>
<td>Blood Pressure</td>
<td>Relief Duration</td>
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<tr>
<td>A. D.</td>
<td>Malig., nephro., anemia, hypochro.</td>
<td>Head., fr. and oc., nausea, syncope, deep reflex., exag., tremor 3 mos. dur.</td>
<td>No previous treatment. No result</td>
<td>Saline I.V. No effect</td>
<td>240/140 96 160/90 80</td>
<td>Complete relief in 20 min.</td>
<td>B.P. did not drop until 30 min. after I.V. Hyder-gine 0.3 mg. I.M. daily for 1 wk. gave complete relief</td>
<td></td>
</tr>
<tr>
<td>M. R.</td>
<td>Essent. hypertens., cor. insuff.</td>
<td>Head., fr., mental confusion, loss of memory, deep reflex. exag. 4 hrs. dur.</td>
<td>Nitrites, sedatives, aspirin. Relief of angina</td>
<td>Saline I.V. No effect</td>
<td>190/110 110 168/80 82</td>
<td>Relief of headache and mental symptoms in 30 min.</td>
<td>0.3 mg. I.M. for 2 mos. and Peritract T.I.D. gave complete relief</td>
<td></td>
</tr>
<tr>
<td>T. J. H.</td>
<td>Essent. hypertens., cor. insuff., cerebral accident, congest. ht. fall., early</td>
<td>Head., oc. and bipar. tingling and weak. lt. leg, insomnia, disturb. vision, Babinski 3 mos. dur.</td>
<td>Digitalis, rice diet. No relief</td>
<td>Saline I.V. No effect</td>
<td>190/90 90 164/84 82</td>
<td>Relief of headache in 10 min. Lt. leg improved in 1 hr.</td>
<td>0.3 mg. I.M. daily for 2 wks. Headaches relieved. Remaining symptoms obtain</td>
<td></td>
</tr>
<tr>
<td>T. W.</td>
<td>Essent. hypertens., myo. infarct., old</td>
<td>Head., oc., sudden speech imped., weak. rt. arm and leg, deep reflex., exag. 2 hrs. dur.</td>
<td>Nitrites, sedatives, I.V. glucose. No effect</td>
<td>Saline I.V. No effect</td>
<td>178/110 88 166/90 80</td>
<td>Normal function within 12 hrs.</td>
<td>0.3 mg. I.M. every 12 hrs. for 4 days. Then anticoagulants</td>
<td></td>
</tr>
<tr>
<td>H. R.</td>
<td>Essent. hypertens., obese</td>
<td>Head., oc., weak., lt. arm and leg, deep reflex. exag. 4 hrs. dur.</td>
<td>Sedatives, nitrites, Methium. Sl. relief</td>
<td>Saline I.V. No effect</td>
<td>188/120 90 168/100 80</td>
<td>Complete relief in 20 min.</td>
<td>0.3 mg. I.M. every 24 hrs. for 6 wks.</td>
<td></td>
</tr>
</tbody>
</table>
the younger age groups with uncomplicated arterial hypertension, the systolic and diastolic blood pressure presented a most drastic reduction, but the average reduction for the entire group was 36 mm. Hg systolic and 12 mm. diastolic. The average reduction of pulse rate was 6 beats per minute. These figures represent the maximal change in the two-hour period of observation following the introduction of the drug into the blood stream. Only two patients of the entire group developed untoward symptoms which were worth noting. One of these developed extreme hypotension and was probably sensitive to the drug; the other became apprehensive and complained of weakness and air hunger. Twenty-four of the entire group complained of nasal stuffiness while six complained of a tingling sensation over the surface of the body following medication. The two patients with notable reactions recovered spontaneously within one half hour without special therapy.

Although one half of the entire group complained of headache from time to time, the special group with cerebral manifestations had severe or intractable headaches and other evidence of cerebral derangement. Their headaches were of a throbbing character, usually occurring in the small hours of the morning and often being severe enough to awaken the patient. There appeared to be no direct relationship between the height of the blood pressure and the occurrence of this discomfort as on some occasions severe headache was present when the blood pressure was no higher than at other times when no headache was noted.

The group of 22 with cerebral manifestations was equally divided between males and females and the average age was 55.8 years. The average reduction of systolic blood pressure was 40.5 mm. Hg and the diastolic reduction was 20.7 mm. within the two-hour period. The average reduction in pulse rate was 9 beats per minute. Many of the group presented more than one symptom suggestive of cerebral vascular impairment.

Of these 22 patients, 14 complained of severe occipital headache, 5 of frontal headache and 3 of severe biparietal headache. Of these, 14 were relieved by intravenous Hydergine within two hours, 1 received partial relief, while the remainder were unaffected. Although a fall in blood pressure was noted it was not necessarily proportional to the relief obtained. Four patients had signs of early left hemiplegia while three presented evidence of early right hemiplegia. In only one of these could a Babinski reflex be demonstrated although a definite alteration of the superficial and deep reflexes was evident in the remaining six. The patient with the positive Babinski reflex had well established hemiplegia of six hours duration when first examined. Six of this group completely recovered within the two hours, and an appreciable reduction in blood pressure was noted in all. In two with left hemiplegia the recovery was dramatic, occurring within a period of 15 minutes after medication was given. Both presented a rapid drop in blood pressure. The one patient with the established Babinski sign was unaffected. Four patients complained of visual disturbances and in all four relief was obtained. Three had evidence of early motor and sensory aphasia. Two recovered within two hours after treatment, while one had partial recovery. The one with tinnitus was relieved within one half hour. The reduction of blood pressure in the foregoing patients was not always proportional to the relief of the symptoms. Of the four patients who complained of nausea and vomiting when first seen, three were relieved within two hours while one lapsed into coma and died, autopsy subsequently demonstrating a ruptured intracranial aneurysm as the cause of death. Of the three patients complaining of giddiness and unsteadiness of gait, two were improved while one was partially improved. Anesthesia and tingling of the extremities was noted in five of this group and four were relieved within two hours. The remaining patient was relieved during the course of two weeks by daily medication. All of the three who appeared to be mentally confused when first examined had clarification of their mental state within two hours. Of the two with convulsive seizures, one was relieved while the other subsequently died. Both patients with intractable insomnia failed to benefit by the ergot alkaloids and required sedation while under observation. In the five
patients with syncopal attacks, four were relieved of this symptom while under treatment, while one was unaffected. In the foregoing patients the drop in blood pressure was moderate but appeared to have no direct relationship to the relief obtained.

Follow-up therapy of daily injections of Hydergine was given to this group with encouraging relief of the subjective manifestations. It was observed that subcutaneous or intramuscular injections had a more prolonged but less dramatic effect on the patient.

**DISCUSSION**

The action of parenterally administered hydrogenated ergot alkaloids produce an appreciable, transitory drop in the systolic and diastolic blood pressures and pulse rate, the duration of which seldom exceeded two hours. For this reason it was felt that their use would be impractical for the routine palliation of hypertensive disease, particularly in ambulatory patients. Their use orally has not proved to be effective in the treatment of hypertension. In the presence of early and impending cerebral complications, however, their action has been shown to be beneficial and in some instances, the author feels, possibly averted what might have been a serious cerebral accident. These drugs, parenterally administered, seem harmless in the dosage recommended due to their rapid elimination.

The first patient observed in this group was given this drug with the hope of quickly lowering the blood pressure, and little consideration was given at the time to the beneficial effect that would occur to the cerebral circulation. The left hemiplegia completely disappeared within 15 minutes after the injection of 0.3 mg. of Hydergine intravenously. It was felt that this hemiplegia was possibly of a reversible nature and was not due to actual cerebral hemorrhage but to a sudden disturbance of the cerebral circulation which in turn produced cerebral anoxia with subsequent paralysis.

The headaches which were such prominent symptoms apparently began after the onset of hypertension but without definite relationship to the level of the arterial blood pressure. Some headaches were migrainous in character, not unlike those reported by Schottstaedt and Sokolow, and appeared to be directly related to a state of emotional tension. It is probable that in some instances, however, a decreased contractile power of the cerebral arterioles, which did not produce discomfort when the blood pressure was normal, resulted in painful distention of the vessel wall when the pressure was elevated. In these, Hydergine possibly gave relief by its regulatory action on the cerebral vessels.

The dizziness, vertigo and giddiness which was encountered was not of the violent type associated with vomiting, complete loss of equilibrium and nystagmus. There seemed to be no correlation between the severity of the vertigo, the age of the patient or the degree and duration of hypertension. It was felt that this symptom could be accounted for, at least in part, by emotional instability. The mode of action of the hydrogenated alkaloids in this and other manifestations of cerebral derangement seen in this series of patients is not known and no possible explanation will be ventured at this time.

**SUMMARY**

Although Hydergine administered parenterally produces a transient reduction in arterial blood pressure and pulse rate chiefly through a central action, the drug was not shown to be of practical value for the control of ambulatory hypertensives. This study has demonstrated a valuable therapeutic place for these alkaloids in the abolition and relief of certain cerebral manifestations complicating the hypertensive state. The quick abolition of these manifestations may possibly avert organic complications of the central nervous system in at least some hypertensives. Toxic manifestations of these alkaloids are so rare and of so minor a degree as to offer no contra-indication to their use parenterally.

**Conclusions**

1. Combined hydrogenated ergot alkaloids (Hydergine) administered parenterally in a dosage of 0.3 mg. produced a transient reduction in both systolic and diastolic blood pressure and pulse rate.
2. These alkaloids have proven to be of value in the alleviation of early cerebral manifestations complicating arterial hypertension and in some instance apparently averted what may have been a serious organic complication.

3. Their mechanism of action in the presence of cerebral manifestations has been briefly discussed and evaluated.

4. Because of their rapid dissipation when given by the parenteral route, it is felt that untoward symptoms from these alkaloids are minimal and that they may be given without hesitation to hypertensive patients.

SUMARIO ESPAÑOL

Un estudio clínico de cien pacientes sufriendo con hipertensión arterial sostenida fué hecho por un término de dos años durante los cuales la acción de la administración parenteral de los alcaloides hidrogenados del cornezuelo de centeno (Hydergine) constituyó la terapia principal. Una reducción transitoria inmediata en presión arterial y el pulso se demostró en 80 por ciento de todo el grupo en un período de dos horas. El promedio de reducción en presión sistólica y diastólica fué de 36 mm. y 12 mm., respectivamente, y el pulso se redujo en 6 pulsaciones por minuto. De interés fué un grupo de 22 pacientes que presentaban evidencia de desarrollo vascular central en que los alcaloides parecieron efectuar su acción terapéutica mayor y posiblemente abortaron lo que hubiera sido un accidente cerebro-vascular. Los efectos indeseables fueron mínimos debido a la disipación rápida de la droga, y el uso de la droga en la dosis recomendada en todos los tipos de enfermedad hipertensiva se consideró inocuo.

REFERENCES


11 Personal experiences of the author over the past three years.

12 Personal experiences of the author over the past three years.


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