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Rauwolfia serpentina, alkaloids, and other drug adjuncts in hypertension and central nervous system disorders

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RAUWOLFIA SERPENTINA, ALKALOIDS, AND OTHER DRUG ADJUNCTS IN HYPERTENSION AND CENTRAL NERVOUS SYSTEM DISORDERS.

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INTRODUCTION

My selection of Rauwolfia Serpentina for the present study has not been entirely fortuitous. In the short span of fifteen years that the dried root of Rauwolfia, in tablet form, has been on the market in India, there has been a growing demand in this country for these tablets. Preparations of the serpentina root have gained such unprecedented popularity for hypertension cases and secondarily psychiatry in this country, that there is hardly a patient with high blood pressure who has not been subjected to its effects in one form or another. One manufacturing firm alone claims to have sold over fifty million tablets of the dried root. One of the aims of the present investigations of the literature therefore has been to determine whether this enthusiastic reception of the drug is warranted.

In this presentation I hope to point out that the nihilistic attitude of the clinician who feels that all he can do about the hypertension of his patient is to " keep the information to himself " is no longer acceptable. Although certain aspects of the treatment of hypertension remain empirical (Vakil 1), the availability of potent hypotensive agents afford the

clinician tools for the treatment of the patient with persistent elevation of blood pressure. Moreover, certain clinical events which follow an effective reduction in blood pressure, such as the improvement in congestive heart failure, the decrease in the incidence of angina, the frequent occurrence of cerebral vascular accidents after cessation of hypotensive therapy, and the marked improvement in retinal hemorrhages and cerebral symptoms, all indicate continuing progress in the treatment of this disease.

The seriousness of hypertension is at once realized because it happens to be the most common and progressive type of cardio-vascular infirmity(Medical Times 2). Ordinarily, it results in an inevitable end of congestive failure and death. The magnitude of the mischief becomes evident at a glance even to the casual observer. In the United States alone, with a population of one hundred and thirty millions, annually one hundred thousand people die from hypertension and another seventy five thousand from its consequence (Mazumdar 3). The treatment of hypertension continues to be a herculean task. Even at the present day of rational medicine, all our lethal weapons hurled at this formidable adversary have failed to crush it.

In the interpretation of results, the factor of natural lability of the blood pressure, so common in hypertensives, is often lost sight of; as a result, perfectly normal or natural fluctuations are mistaken or misconstrued for evidences of the therapeutic value of the drug under trial. Accordingly, any remedy before it can be accepted as having established a claim as a hypotensive agent must satisfy certain standards of efficiency, vis. (1) it should be capable both of reducing a blood pressure that is high and of maintaining it at the lowered value (Travis 4): (2) it should be able to exhibit its hypotensive action consistently and in a high proportion of patients; and (3) it should be free of all toxic ill-effects (Ford 5, Wilkins 6). Therapy with the usual agents has left much to be desired for a long-term regime. Frequently the addition of a second or even a third agent to a regime, has resulted in a greater reduction of blood pressure, often with fewer side effects, than that achieved with a single agent (Wilkins 7).

The drug is undoubtedly very useful in controlling unmanageable mental cases and, for affording symptomatic relief is a noteworthy addition to the armamentarium against mental and nervous diseases. Its

sedative and hypnotic effects are in many respects superior to such agents as the bromides and barbiturates. Repeated administration of Rauwolfia for three to four days at a stretch hastens the beneficial results by its cumulative action. Some persons, however, have an idiosyncrasy for this drug, in whom untoward symptoms appear before the desired therapeutic action and, or prolonged use, some patients acquire a tolerance for it. Rauwolfia serpentina does not " cure " every case of insanity, as is sometimes maintained; but its use for many years by the Indian Kabirajes and Hakims in the treatment of mental disorders is well-founded (Deb 8).

The drugs to be described, however, are effective in a sufficient number of patients to make them valuable additions to the physician's armamentarium (Arnold 9).

HISTORICAL

The leaves and roots of Rauwolfia Serpentina benth, a small shrub, Ophioxylon serpentinum Linn, family Apocynaceae, are mentioned in Sanskrit works describing Ayurvedic Medicines under the name Sarpagandha, and in Hindu under the name Chota Chand. This plant is indigenous to India, Burma, Malaya, Siam, Ceylon, Java, the Phillipines, and some other Asiatic countries.

It is a climbing shrub and grows on rich soil in low altitudes. The parts used are the root, leaves and their juices.

In the indigenous system of medicine this drug has been put to various uses for a very long time. Its root was used as an antidote to the bites of poisonous reptiles and insects. The juice of the fresh leaves has been mentioned for the treatment of corneal opacities. The root decoction has been prescribed as a uterine stimulant to help child-birth. The root is also used as a febrifuge, as a bitter tonic for insanity, epilepsy, insomnia, hysteria,eclampsia, hypertension, painful affections of the bowels, cholagogue, emmenagogue, and as an anthelmintic.

Rauwolfia's reputed success has attracted the attention of numerous writers on the Indian Materia Medica and of numerous clinical research groups up to the present time. Huge amounts have been imported from various districts of India and Malaya by manufacturing pharmaceutical firms and at least three products of this drug have lately appeared on the American market.

Recently the drug has been used for treatment of insomnia, insanity, hysteria, hypochondria, and for reducing high blood pressure. Possibly, the sedative

effects of the drug, by soothing the irritated system of the nervous patient, might be helpful in bringing the blood pressure down; furthermore this may be the only way it acts in lowering the elevated blood pressure of individuals of highly nervous temperament without much affecting the cardio-vascular system (Bhatia 10, Youngken 11, Kapur 12, Wilkins 13, Sen 14, Chowhan 15, Wallis 16, Siddiqui 17).

PHARMACOLOGY

In 1931 in Calcutta, Sen and Bose (14) isolated from the root two alkaloids having different melting-points. Siddiqui and Siddiqui (17) in the same year, working in Delhi, found five alkaloids, which they arranged in two groups and which they named the ajmaline and the serpentine groups, respectively. Other constituents in the roots are oleo-resins, sterols, unsaturated alcohols, oleic acid, fumaric acid, glucose, sucrose, an oxymethylanthraquinone derivative, a fluorescent substance, and mineral salts (Wallis 16).

Although the final analysis of the active principles of Rauwolfia serpentian has not yet been accomplished (Arnold 9), the root has been found to contain alkaloidal groups belonging to the indole alkaloids and showing a relationship to the ergot alkaloids and

yohimbin. The ajmaline group consists of ajmaline, ajmalinine, and ajmalicine; whereas the serpentine groups consists of serpentine, and serpentinine. These two groups of the above with rauwolfinine, rauwolfine, rauwolscine and the sedative alkaloid reserpin, have already been isolated (17-9-Chopra 18). The first group action consists of depression of cardiac musculature, splenic contraction, stimulation of respiratory movements and peristalsis of the intestine. The second group action has an opposite effect on all the organs enumerated above. The pharmacological action of the total alkaloids is sympathicolytic, adrenolytic, spasmolytic (only in high doses), sedative, and effective in decreasing tension on the medullary circulatory centers without interfering with respiration (Chopra 18-17-20).

Rauwolfia therapy reflexly stimulates the flow of saliva and gastric juice; thus it increases the appetite and promotes digestion (8). Nasal congestion is the most common accompaniment of therapy and suggests adrenergic blocking action, but absence of postural hypotension speaks against this mechanism as does the inability to abolish sympathetic vasopressor reactions. Bradycardia is significantly frequent to suggest a

central vagal stimulant effect; however this is not abolished by atropine. There is a sedative effect, resembling more that of muscular relaxation than that of central nervous system depression. An antipyretic action was demonstrated, one which is through the heat regulating center and resembles that of the coal-tar group of drugs (15). The rare presence of dreams is not understood and may be allied to a central effect. Dysuria has been manifest and was described as frequency and urgency. Cystoscopic examinations in the latter revealed hypertonic bladders; after withdrawal of the drug for three to five days, this condition disappeared without recurrence on resumption of the drug (5-6-Vida 21). Vakil (1) enumerated the effects of the root as: action on the vaso-motor center, leading to generalized vasodilation with a lowering of the blood pressure; depression of the cerebral centers and a soothing effect on the nervous system; sedation of the gastric mucosa and stimulation of the plain musculature of the intestinal tract; and stimulation of the bronchial musculature (Gupta 22, Bhatia 23).

A fluorometric method for the estimation of Rauwolfia alkaloids in the urine has been devised, and the urinary excretion of the said alkaloids has been studied. The method involves a standard in which

urine first is mixed with various amounts of the alkaloids, then is fluorometrically measured, and finally is compared with urine excreted by patients treated with the alkaloids. Maximum percentage of the alkaloids excreted in urine in the free state usually occurs in the sample collected between one and two hours after the intake of the same. No alkaloid is eliminated within one-half an hour; the appearance of the drug comes out one hour after the ingestion and usually disappears in sixteen hours. So long as the pressure is being reduced, the excretion of the alkaloids is low; but as soon as the pressure becomes more or less steady, the excretion usually increases to a high level and a total of about fifty to sixty percent of the dose goes out in the urine within three to four hours of the intake of the test dose (Gupta 24).

EXPERIMENTAL

Bhatia (10) found that Rauwolfia alkaloid has a toxic action on lower forms of life like Paramoecia Caudatum in dilution of one in twenty thousand. Its toxicity, however, on higher animals is variable. Frogs were quite tolerant, whereas white mice were susceptible. The toxicity also varied with the route of adminis-

tration, the drug being much more toxic, when given intravenously or intraperitoneally, than when given subcutaneously.

The alkaloids (Sen 14) of Rauwolfia serpentina produced a fall of blood pressure in animals, which was mainly due to vasodilatation. They appeared to decrease the tonus of the peripheral blood vessels and to have a depressant action on the heart muscle, both factors in producing a fall of blood pressure. The alkaloids showed a stimulating effect on the respiration, which seemed to be a direct stimulation of the bronchial musculature, and produced immediate and definite relaxation of the intestines. Relaxation of the virgin cat's uterus occurred, but the effect on the multiparous or pregnant uterus was a contraction. That the hypotensive activity of Rauwolfia is due to the alkaloidal content was borne out by the fact that the resins alone did not produce similar pharmacological effects. Neither the alkaloids nor the resins, however, showed any definite hypnotic effect in the lower species of animals.

Procedures used (Ray 25) to test the reflex excitability of the vasomotor center by temporary occlusion of the common carotid arteries, in cats under chloralose

anesthesia, the carotid sinus reflexes were elicited. At the height of the pressor reflex the intracarotid pressure was raised artifically so that a depressor response was produced. In other experiments, with rhesus monkeys as well as cats, the carotid sinus nerves were stimulated electrically. Large single intravenous doses of Rauwolfia were used in these studies. Observations from these studies showed that the crude extract of Rauwolfia, as well as the total alkaloid fraction, produces a marked reduction of the pressor as well as the depressor responses which can be elicited by means of pressure changes within the carotid sinus. This vasomotor reflex blocking activity of Rauwolfia not only concerns the extent of the pressor and depressor response but also affects the latency of the reflexes: the baro-receptor stimuli have to be applied for longer periods in order to give rise to any systemic pressure changes. Respiratory and circulatory reflexes due to stimulation of the KCN-sensitive chemoreceptors, however, are not affected in a specific way.

Kapur (26) in studying the action of the total alkaloidal extract from Bihar and Dehra roots of Rauwolfia concluded that: 1) both extracts produce a fall in carotid pressure, Bihar being more powerful; 2) the

heart is depressed by both to nearly the same extent; 3) both produce depression on the central nervous system, but no hypnosis; 4) uterine and intestinal musculature are depressed by the two extracts in the same way; 5) and the Bihar extract is more toxic than the Dehra variety determined by lethality tests.

Sublethal doses of alkaloids given albino rats (Gupta 22) caused depression of motor activity; sensory reception was diminished; and respiration was deep and slow, or shallow and frequent. Respiratory failure is first as the heart continues to beat for some time after respiration has stopped. The fall of blood pressure in intact and decrebrated cats (20, 10, 22), not found in animals in which the spinal cord has been sectioned at the level of the second cervical vertebra, suggests that this fall of blood pressure may be partly due to depression of the vasomotor center. Depression of the isolated heart and dilatation of the blood vessels in pithed toads (12, 22) appeared to indicate that the alkaloids lower blood pressure by peripheral action too. The sedative and hypnotic effects of the crude extracts are far more intense than that of the total alkaloid, a fact which indicates the presence of some active non-alkaloidal principle in the crude extract.

Plummer (27) using Reserpin (crystalline) compound isolated from Rauwolfia applied by oral administration to the conscious dog, displayed both sedative and hypnotic action. The central nervous depression was regularly associated with persistent miosis, moderate slowing of the heart, increased intestinal activity resulting in diarrhea in some cases, lacrimation, and relaxation of the nictitating membrane. A study on human volunteers is in progress. Trapold (28) confirmed the above, adding respiratory depression and a gradual persistent fall in blood pressure.

Plummer (27), Bein (29), and Earl (30), using Serpasil (Alkaloid of Rauwolfia) in cats, rabbits and dogs, produced central sedative effects. Other effects noted were gradual lowering of the blood pressure, slight increased depth of respiration with respiratory arrest on a central basis from lethal doses, slight lowering of rectal temperature, increased intestinal motility with diarrhea, and no pathology on sacrificed animals.

Wilkins (31) and others using Rauwiloid (alkaloidal extract of Rauwolfia) produced effects similar to Serpasil, listed above.

DOSAGE

PRODUCTS

Rauwolfia serpentina, as used in the indigenous system of medicine, is either a crude extract of the roots of Rauwolfia (1% alkaloids in alcoholic solution) or is purified total alkaloids isolated from this extract (Ray 25).

Raudixin products "Squibb", are prepared from the whole root, containing 50 mgm. total extracts of the root. Some clinicians use this product with the feeling that the combined products are superior to any fractions or single alkaloids (Nelson 32).

Serpasil is the "Ciba" brand name for reserpin, a pure crystalline alkaloid derived from the roots of Rauwolfia serpentina. Reserpine was first isolated by Ciba (Muller 33). Serpasil tablets are supplied as 0.1 mgm. and 0.25 mgm. of the single alkaloid.

Rauwiloid, an alkaloidal extract obtained from the tropical plant, was developed by a process in "Riker" laboratories, Rauwiloid is generically designated the "Alseroxylon" fraction of the plant, and supposedly all the advantageous features of the crude drug are provided in the reproducible alkaloidal mixture. Rauwiloid is supplied in tablets containing 2 mgm. of

the alkaloid (Ford 5).

TOXICITY

Toxicity studies by Boer (34) reveal the following facts: 1) after poisoning with rauwolfine, the heart rate of frogs, cats and rabbits decreases; 2) refractory period of the frog's heart increases; 3) varied heart rhythm comparable with digitalis poisoning in frogs; 4) artifical changes of heart rhythm in frogs; 5) intraventricular conductivity is delayed; 6) the drug does not prevent auricular nor ventricular fibrillation in either cats or rabbits.

Toxicity tests, in albino rats, showed that sub-lethal doses of the total alkaloids of all three varieties cause a depression of the motor activity. The sensory reception seems to be diminished and respiration is either deep and slow or shallow and frequent. Death, which usually supervenes three to four hours after the minimum lethal dose, is due to respiratory failure; the heart continues to beat for some time after respiration has stopped. The M.L.D. for the Dehra Dun variety was found to be 12.5 mg./100G.; for the Bihar and Bengal varieties, 10 mg./100G., intraperitoneally. The lethal dose of serpentine group of alkaloid was found to be the same as that of the ajmaline group in case of frogs

vis., 0.5 g. per kg. weight of the body, but it was about four times higher for rats, being 0.05 g. per kg. body weight (12 g. for an adult human being) in case of ajmaline. The oral LD_5 of Raudixin in mice is 10 Gm. per kilo of body weight. Rats have survived doses of 120 mg. per kilo daily for five weeks without evidence of toxicity. Dogs fed 320 mg. per kilo daily for ten weeks showed signs of severe malnutrition. Two animals given 80 mg. per kilo per day died of malnutrition, but there were no signs of toxicity in dogs fed 20 mg. per kilo or less (22, 17, 18). The intravenous LD_{50} of Serpasil for the rabbit and rat approximates 10 mg/kg. Studies on rabbits, monkeys and dogs showed that prolonged administration of the drug, daily dose 0.1 mg./kg intravenously for twelve days, or the dose alternately for twenty-four days was well tolerated and no pathology on sacrificed animals. (Drug briefs still to be published).

Vakil (1) vouches for the non-toxicity of the drug with confidence, as in the several thousand cases of treatment he has followed, there has not been a single fatality. Toxic effects in patients treated with Rauwolfia over prolonged periods are uniformly mild. They include drowsiness, nasal congestion, and occasionally diarrhea, nausea or vomiting. Although anorexia has been

reported, improved appetite is more frequent. While the action of the extracts is very similar to the alkaloids, they are safer to administer for therapeutic purposes, since there is a good margin between the therapeutic dose and the lethal dose in extracts. In a few cases of over-dose, watery secretion in the bronchial tubes has been reported. Nasal congestion can be relieved by Neo-Synephrine, lethargy with coffee or dextroamphetamine, and diarrhea by short withdrawal of the drug. Therapy, in sixty patients, receiving 0.25 to 105 mg. daily for an extended period, of reserpine alkaloid produced no ill effects (Ford 36, 4, 10, 26, 6, 1).

Chatterjee (36) reports one case he observed of combined digitalis and Rauwolfia poisoning in a human subject (attempted suicide). The exact amount of drugs consumed was unknown, but from all appearances, Rauwolfia effects lagged the digitalis. The patient did not expire.

ACTION

A classification of hypotensive drugs by Wilkins(6) places these agents in two main groups: the adrenergic-blocking or sympatholytic (subdivided into the ganglionic blocks, drugs which act centrally, and those which act peripherally), and the vasodilator or non-sympatholytic.

The mode of action of Rauwolfia is known in part. Reserpine and alseroxylon alkaloids both act centrally,

and thus would be effective in neurogenic hypertension. Certain manifestations of a central action are observed in man and animals (19). A sedative effect is common and, in the rabbit, there is central disturbance of the body temperature regulating mechanism with large doses of the drug (33). It is not known at this time whether Rauwolfia inhibits the cerebral vasopressor substance of Tayler, Page, and Corcoran or whether its action is on central synaptic junctions or elsewhere in the brain. These alkaloids from Rauwolfia suppress hypertension produced by electrical stimulation of the afferent vagus or of the afferent sciatic nerve, and also that resulting from lowering of pressure in the carotid sinus (33, 19). It was discovered that these agents do not have a direct vasodilating effect on peripheral arteries such as occurs with benzyl-imidazoline (33) (Priscoline), do not inhibit or remove the hypertensive effects of epinephrine or nor-epinephrine such as occurs with methylimidazoline (Regitine) (33, 19) do not block autonomic ganglia as does hexamethonium (33, 19) do not stimulate the para-sympathetic nervous system to produce vasodilation as with acetylbetamethyl choline (19), and do not stimulate the carotid sinus and other peripheral receptor organs, such as occurs with protoveratrine in other experimental studies (Moyer 43) to inhibit the vasomotor center.

Consequently, the action of Rauwolfia, in certain respects resembles the action of hydrazinophthalazine and the hydrogenated alkaloids of ergot (43). Theoretically, it would seem that Rauwolfia would be effective in neurogenic and neurohumoral types of hypertension but not in the pure humoral types of cases. Better effects should be expected from a combination of reserpine or alseroxylon with other adjuncts, such as hydrazinophthalazine (13), acting at least in part through humor mechanisms, than from the alkaloids alone.

Summarizing, Rauwolfia does not cause hypotension (hence is not a "Blocking" drug) (13): By action on vasomotor center, it leads to generalized vasodilatation, with lowered blood pressure; by depressant action on cerebral centers, soothes general nervous system; sedative action on gastric mucosa and stimulating action on plain musculature of intestinal tract; and stimulates bronchial musculature. It does not lower the basal metabolic rate (39).

ADJUNCTS TO OTHER AGENTS

When the response is not adequate with Rauwolfia, alone, it has been found that blood pressure could be well controlled by combining it with another or even a third hypotensive drug. Hexamethonium, a synthetic

compound, acts to lower blood pressure by a specific blocking of transmission at the ganglionic synapse. Postural hypotension must be guarded against; inhibition of autonomic activity also occurs. Undesirable side effects, such as nausea, blurred vision, urinary retention, constipation, and even paralytic ileus, may result. Dosage, moreover, must be determined individually for each patient; and tolerance may develop. Some investigators report alleviation of above symptoms to some extent and lower dosage combined with Rauwolfia (7, 38). Veratrum alkaloids exert their hypotensive action by stimulating the afferent side of the reflex pathway. They also block the carotid-sinus pressor reflex. They can cause significant lowering of blood pressure in some hypertensive patients, regardless of the etiology of the disorder, with rare toxic reactions. Orally, therapeutic doses may also cause nausea and vomiting. Recent evidence suggests that the veratrum alkaloids are more effective when used in conjunction with other hypotensive agents, such as Rauwolfia (Meilman 37, 6). Hydralazine, a central adrenergic blocking agent, may cause severe headaches, tachycardia, and dependent edema which tend to lessen upon chronic administration of the drug. On long-term usage it causes come lowering in pressure, particularly diastolic, in about half the hypertensive patients upon whom it is used.

However, hydralazine may rarely produce an anginal state resembling status anginosus, and aching substernal pain appearing or worsening as this drug is administered is an indication for its discontinuation. Such occurrences seem partly due to tachycardia, which may be controlled by Rauwolfia. Experience has shown that hydralazine in combination with Rauwolfia and with or without veratrum is well tolerated, especially if instituted gradually (2, 7).

Rauwolfia has the advantage of offsetting some of the toxic effects of the other drugs, especially the palpitation and headache sometimes caused by hydralazine. Furthermore, combined medication makes it possible to use smaller doses of these drugs, thus minimizing toxicity. In some cases, after the desired effect has been achieved by combined medications, it can be maintained with the use of Rauwolfia alone.

INDICATIONS AND CONTRAINDICATIONS(ANTIDOTES)

There are no absolute contraindications in the use of Rauwolfia (36). No cardiac depression wasobserved with the usual doses of Rauwolfia, but a few patients with cardiac hypertrophy just giving way to dilatation required a mild cardiac stimulant during therapy. Caffeine, strychnine, or a similar agent was used

(10). Rauwolfia therapy had to be discontinued in two patients because of marked orthostatic phenomena and state of excitement; one a diabetic with glomerular sclerosis and the other with hypertensive encephalopathy respectively. It is recommended, therefore, that in patients with severe circulatory disorders and vascular damage, especially cerebro-or nephrosclerosis, Rauwolfia therapy should be begun cautiously. A small dose, two tablets, daily should be used initially. In the cases studied, mild kidney insufficiency, as determined by tests of albuminuria, hematuria, and so forth, presented no difficulty and was not adversely affected in any case (9). In some patients, it may have been improved by Rauwolfia therapy. In large doses, it can produce gastro-intestinal irritation resulting in Nausea, vomiting, diarrhea and loss of appetite. Some patients feel thirsty. Long continued use of the drug may lead to anemia, and many patients complain of lassitude and general weakness. It may slow the (depress) respiratory system, tending to produce dyspnea with a rolling of the eye-balls upwards, spasmodic contraction of the tongue leading to speech disturbance, tremors of hands and fingers, muscular spasm, and headache and giddiness may seldom occur (8). Decreasing or stopping

temporarily, usually alleviates the above. Neosynephrine helps nasal stuffiness.

Rauwolfia's present indications are not well clarified. It is advocated for the treatment of essential hypertension, mild or moderately labile hypertension, psychiatry, particularly when there is a large element of neurogenic hyperactivity. It is not effective when used alone against the severe forms of hypertension, although it has been recommended for use in combination with hydralazine or veratrum alkaloids (Francke 39,36) and other hypotensives. The drug acts slowly, and the maximum effects are not seen for one to two weeks, and after withdrawal a similar interval elapses before the drug effect has subsided.

ADMINISTRATION

Initially, in a patient with moderately severe hypertension, especially with tachycardia and anxiety, one Raudixin (100 to 125 mgm. crude root) is given once or twice daily. Frequently this will suffice to control the pressure at normal, or near normal, levels and to abolish symptoms of headache, dizziness and palpitation. The patient is checked in a week or a month, as the circumstances permit. The dosage is halved only if the patient becomes too sleepy, and should not be raised above four (100 to 125 mgm. crude root) tablets daily. The dose

should be adjusted to each patient's tolerance, since too much of the drug will lead to excessive sedation and a sense of fatigue. However, Raudixin does not require continual and often difficult adjustment of dosage common to other hypotensive agents (39, 7, 4, 40). Daily dose liquid extract Rauwolfia 5 to 10 minim. (10).

When therapy with Rauwiloid alone was begun, the drug is given in an incremental fashion until an optimal response is obtained. The patients are usually started on doses of 2 mgm. (of alkaloids which represent the therapeutic activity found in approximately 125 mgm. of crude root) four times daily. Dosage was maintained at 32 mgm. daily in most cases, although data indicate that 8 to 12 mgm(4 to 6 tablets) per day are adequate and that there was very little additional hypotensive effect produced by the larger dose (35, 5, 41). Raupina tablets contain 2 mgm. of the total alkaloids and are considered likewise (9).

With Serpasil it is advisable to individualize the dosage for optimal clinical results, and minimal side effects. The daily dosage range is 0.1 to 1.0 mgm. (Hensler 42).

HYPERTENSION

The clinical effects of Rauwolfia will deal only with the use of the drug in human patients. It might be proper and fitting at this point to mention, that much of

the experimental work with this drug, in this country, is of fairly recent origin, and presently at press or to be published. Dosages will not be mentioned in particular in as much as it was priorly mentioned that it was usually necessary to titer it to the individual, and toxic effects are minimal. Charts appended will refer only to use of Rauwolfia; however, with reference to the articles, charted results with adjuncts and so forth will be found. It might be mentioned here that to Vakil (1) who had sent out a questionnaire to fifty physicians throughout India, forty-six replied voting Rauwolfia the best "hypotensive" in their experience.

The patients included in this study presented varying degrees of hypertension and its complications and were selected from various socio-economic groups, such as; charity, veterans, private and so forth. Pretreatment studies, repeated at monthly intervals or more frequently if necessary, consisted of complete blood count, urinalysis, serology, orthodiagram, electrocardiogram, fundoscopic classification, clinical renal function studies (BUN, PSP, Fishberg) and, in many cases intravenous pyelograms. Most patients were followed on an out-patient basis and at each visit a record of blood pressure (recumbent and upright), pulse, and weight was made (conditions standardized).

Vakil (1) selected fifty patients with the diagnosis of essential hypertension, on the basis of clinical ex-

amination and laboratory procedures. Only patients with systolic pressure over 160 and diastolic over 95 mm. were accepted; hypertension other etiology was ruled out. Males and females ages thirty-nine to seventy-six years were involved. After a preparatory period of sedation, Rauwolfia was started and continued for four weeks. Only laxatives, insulin, and occasionally aspirin were allowed. Within a week, seventy-seven per cent of the cases showed a drop of systolic ranging from two to thirty-eight mm. average was thirteen mm; diastolic drop in seventy-three per cent ranging from two to eighteen mm. average six mm. In seventy-three per cent both diastolic and systolic dropped one week after therapy. After five weeks, eighty-five per cent of cases displayed a drop of systolic from two to fifty-four mm. average twenty mm.; and eighty-one per cent diastolic pressure drop of four to thirty-four mm. average of eleven mm. Hypotensive action was apparent in seventy-four per cent even after four weeks of no treatment. A second, two-week course was tried in all cases after an interval of four weeks; the blood pressure response to a second course of tablets was almost as good as during the first.

Ford (36) treated a number of patients with essential hypertension: group one consisted of forty-two patients who were treated with oral Rauwolfia extract; group two

consisted of twenty-five patients who were treated with Rauwolfia extract plus hexamethonium. Six of the latter first received Rauwolfia, later supplemented by oral hexamethonium. The other nineteen received first oral hexamethonium, later supplemented by Rauwolfia extract. Patients responding to Rauwolfia were apparently early or mild hypertensive states with minimal complications. Of twenty-five patients who were unresponsive, twenty-three had abnormal electrocardiograms and the frequency of renal, cardiac, or cerebral complications was two to three times as great as in those who responded. See Table 1. appendix for data.

A summary of Ford's (5) work with patients with varying degrees of hypertension, after pretreatment as mentioned, showed that of the fourteen patients whose control diastolic pressure was less than 120, fifty-seven per cent showed a 20 mm. hg., or greater, decline in mean blood pressure and forty-three per cent became normotensive. This compares with thirty-eight and nineteen per cent, respectively, for sixteen patients whose control diastolic pressure was 120-139, and twenty-five and zero per cent, respectively for the twelve patients whose diastolic pressure was 140 or greater. Of the total group of forty-two patients, therefore, forty per cent showed a 20 mm. hg., or greater, decline in the mean blood pressure and twenty-one per cent became normotensive. Rauwiloid was the drug

used in all the above patients, starting at 2 mg. four times a day, and increased in incremental fashion to maintainance dosage of approximately 32 mg. daily in most cases. The fifty-nine cases of hypertension studied by Wilkins (13), fifteen were treated with Rauwolfia alone (Table 2, appendix), others with Rauwolfia and Veriloid, Rauwolfia and Apresoline, and Rauwolfia, Veriloid, and Apresoline (see article for detail), only the fifteen will be considered here. They were unselected cases and the blood pressure could be controlled within normal range; 150 systolic, and 90 diastolic, or lower. The average level during the control period was only 173 systolic and 107 diastolic. Average blood pressure in the entire group before treatment was 192 systolic, 112 diastolic, and the pulse rate 82, whereas after the treatment with Serpina alone the levels were 165 systolic, 95 diastolic, and 70 respectively. Placebo treatment in 27 patients, whose blood pressures during the control period averaged 196 systolic, 115 diastolic, after the treatment averaged 186 systolic, 111 diastolic, and pulse rates the same. Usually after cessation of placebo substitution the blood pressure rose promptly, not so with Serpina.

Travis (4) studied the effects of Reserpine (alkaloid) on the blood pressure and pulse rate of sixteen patients

with essential hypertension (table 3). Dose varied from 0.1 to 1.0 mg. daily. Before therapy, the average blood pressure was 181.6/111.6 mm. Hg. and the average pulse rate 76.2 beats per minute. After eight weeks of continuous medication, the average fall in systolic pressure was 24 mm. (13.2 %) and the diastolic pressure 18.1 mm. (16.2 %) with an average fall in pulse rate of eight beats (10.5 %). He also studied the effects of the alseroxylon fraction on the blood pressure and pulse rates of forty patients (table 4). Dose varied from 2.0 to 8.0 mg. daily, with average duration of medication at two months. The average control blood pressure was 197.9/117.5 mm. Hg. and the average pulse rate 81.6 beats per minute. Average fall in systolic pressure after medication was 27.6 mm. (13.9 %) and the diastolic fall 14.1 mm. (12.0 %). Average decrease in pulse rate was 11.3 beats per minute (13.8 %). He also studied Rauwolfia in combination with other hypotensive drugs and reference to his work will show the results.

In Kapur's (12) work he reports five patients with whom he used Rauwolfia with good results. Sen (10) in his works feels that after a three-year period in which several hundred patients were treated, that the slow reduction of blood pressure with the sole use of Rauwolfia

in small doses was the best therapy for hypertension. Wilkins (6) reports use of this drug in patients from the labile type hypertensive to the severe with renal impairment, with some success in most cases. Bhatia (10) reports eighteen patients with varied essential hypertension in which beneficial results were observed in all eighteen patients, using Rauwolfia. The latter had two patients in the second group, who represented cases of severe renal damage, with cardiovascular changes, and Serpina lowered the blood pressure in both, at the same time with relief of symptoms. Ford (38) treated twenty-five patients, the severity of the hypertension was variable from patient to patient, but the group as a whole presented a fair cross section of the disease. Nineteen of the patients had been given oral hexamethonium alone for at least six months prior to Rauwolfia therapy; in six patients Rauwiloid alone was the initial drug three months prior to hexamethonium. He found in his study one-hundred per cent of all patients treated demonstrated a significant reduction of blood pressure (MBP reduced more than 20 mm. Hg.) and eighty per cent became normotensive. Vida (21) studied twenty-five patients treating them with Rauwolfia, cases of essential and renal hypertension included. There was a definite fall in the diastolic as well as in the systolic pressure, and symptoms

attributable to the high blood pressure were improved. Arnold's (9) series of forty-four cases were treated with Rauwolfia and evaluated. Twenty-three patients had primary benign hypertension, twelve had primary malignant hypertension, and nine had secondary hypertension. Rauwolfia therapy produced a definite hypotensive effect in fifty per cent of the forty-four hypertensives, and a lowering of blood pressure was observed in both primary and secondary hypertensives, with partial alleviation of the subjective symptoms. Two patients were discontinued (one with glomerular sclerosis-diabetic, and the other with hypertensive encephalopathy) due to orthostatic phenomena and state of excitement. However, he feels that Rauwolfia therapy can be begun in most all hypertensives if used cautiously.

PSYCHIATRY

Roy (44) recently employed Rauwolfia in two manic patients with some beneficial effect. Motor symptoms were controlled, that is; excitement, restlessness, shouting, as were hallucinations. With large doses of the drug, delusions of grandeur and of influence were variably affected.

Fifteen patients, all inmates of a mental institution who were suffering from various types of mental disorders, received Rauwolfia therapy and were studied by Gupta (40).

Five patients had an affective reaction type of mental disorder (some form of chronic or acute mania); seven were schizophrenics; two showed an organic type reaction (confusional insanity); and one was afflicted with chronic epilepsy. In every case reported here, Rauwolfia therapy induced sedation and subsequent clinical improvement. Sleep ensued two to three hours after each dose of the drug and lasted six or more hours (46). The patients became quiet and behaved more normally. Particularly those suffering from affective disorders showed considerable improvement. The drug also stimulated peristalsis of the alimentary tract. This was considered a desirable side effect, as in most psychopathic patients there is a retardation of alimentary function. The improved appetite noted in these patients was attributed to the action of Rauwolfia. In the epileptic, the major fits were stopped completely, and minor attacks occurred at longer (2 to 3 day) intervals. With the control of major fits the patient showed great clinical improvement; he was able to be treated at home.

Bhatia (10) treated one patient, a boy who was highly emotional and nervous and subject to fainting fits, Rauwolfia proved useful although in all probability the fainting attacks were of functional origin. In his several hundred patients of hypertension, Sen

(10) employed the drug for treatment of all types of insanity but found it effective in only that type characterized by maniacal symptoms. Such patients exhibited a full, hard, plethoric pulse, violent movements and insomnia. Hypnotic effect, reduction in blood pressure, decrease of violent symptoms, and improvement in mental condition were usually evident within a week, though the patient might still show some mental abberations (47). In the demented and morose type of insanity, Rauwolfia was not effective. Instead, it would appear to be contraindicated, for such cases are usually characterized by low blood pressure and asthenia and require a different type of therapy.

Chowhan (15) reported on a group of forty-four mental patients treated with Rauwolfia; improvement was thirty per cent (1 in 3 cases) in melancholia, one-hundred per cent (1 case) in acute confusional insanity, and one-hundred per cent (1 case) in mania. In maniac depressive insanity, twenty-five per cent (4 cases) recovered, sixteen per cent (3 cases) improved, but fifty-nine per cent (13 cases) showed no improvement. From the figures it appears that improvement was noticed only in cases which had marked nervous excitement, restlessness, and loss of mental balance. The patients became dull, quiet, clearer in cerebration, and could sleep for a long

time without any disturbance; later they became clearer in mind and memory. This authority felt the drug markedly reduces the nervous irritability generally noticed in epileptics and in many ways is superior to the barbiturates and bromides. Withdrawal of opium from the addict has been found to be relieved by Rauwolfia as it quieted the patients and induced a sound and refreshing sleep.

Deb (8, 41) in mental hospital work found that certain symptoms remarkably well controlled by judicious and repeated administration of the drug, namely; insomnia, excitement (both physical and mental), violence (destructive habits and homicidal tendencies), depression and suicidal tendencies, stupor and mutism. He considered it is superior to bromides and barbiturates. Maniac-depressive psychotics tolerate comparatively large doses (60 grains or more); whereas schizophrenic cases, who are usually under weight and malnourished, feel very weak even with small doses (15 grains). Patients suffering from depression, mutism, and stupor may become active and alert on receiving the drug for several days. The sedative effect is well marked in cases of alcoholism, drug addiction, and toxic infective psychoses, and is worth a trial in cases of epileptic insanity. Senile and demented patients sleep well after the drug; however in cases of psychoneuroses the results usually are not as satisfactory as in disorders

of psychotic origin.

De (45) treated two cases of Paranoia in which he felt that favorable results were encountered by use of the drug. He described clinical history and effects on the patients in his article.

SUMMARY

First we might state that Rauwolfia is a mild hypotensive agent, and there are no known contraindications to its use. It appears to mitigate the distressing side effects of oral hexamethonium, the most potent oral hypotensive agent available today. There is a close correspondence in rise and fall of the systolic with the diastolic pressure. The fall is not always maintained, it may rise and fall again and be fluctuating or paroxysmal in nature. Symptoms have been greatly relieved by the use of Rauwolfia and resultant fall in blood pressure is not such as to cause anoxemia, or diminished circulation to the vital parts. Positive relief of symptoms and mental rest and quiet are attained. Sleep is much promoted, craving for the drug is not produced nor does it cause blood pressure to fall to a pathological level. It attains often what bed rest, controlled diet and purgatives do not. Rauwolfia in the usual oral clinical dosage is well tolerated for weeks and months; its action rarely appears before three to six days, and is slow to

disappear after withdrawal of the therapy. The chronic effect of the drug may not be fully apparent in less than six weeks. No serious side effects are produced, although occasionally it may produce nightmares, and sedation value is high. Usually there is bradycardia from its use, occasionally nasal congestion, tendency to promote a gain in weight, and bowel habits may change to one of slightly increased frequency. Apparently Rauwolfia does not cause tolerance and administration may be easily stopped for several days to relieve any unpleasant side effects. It is most useful as an adjunct to more powerful hypotensive drugs.

In severe but not rapidly progressive hypertensive disease, the patient can be treated with Rauwolfia products alone. If the response is not adequate at the end of six to eight weeks, hexamethonium may be added to a better stabilized individual who will have fewer and less severe side actions than when hexamethonium is used alone. The dose of hexamethonium must be arrived at by a titration procedure in which the amount of drug is progressively increased until the desired results are obtained. In the severe and rapidly progressing type (but not acute emergency) of hypertensive disease, without renal failure, therapy should be initiated with more potent hypotensive drugs, such as hexamethonium and

Rauwolfia added later or used concurrently. In severe malignant hypertension and in cases of hypertensive emergencies, initial oral therapy under hospital conditions is indicated. For this purpose, parenteral Veriloid (intravenous and intramuscular) or intramuscular hexamethonium are the agents of choice. When the hypertension is well regulated, long term therapy can then be substituted for the emergency therapeutic approaches.

The use of the drug after labor may be worthy of trial in view of the pharmacological effects of this agent on the uteri of experimental animals, and even as a febrifuge. With regard to psychiatry reports, indications merit further clinical and pharmacological investigation of Rauwolfia. The depression on the respiratory system, usually mild, in a few asthma cases may contraindicate its use. I do not hesitate to indicate, however, that Rauwolfia is a drug which may be far superior in many ways to other drugs now in use. It is impossible to quote dosages specifically and they should be titrated to the patient.

The extracts, total alkaloids, and serpentine show marked hypotensive properties, serpentine producing the maximum effect amongst them. It is suggested that the Rauwolfian alkaloids probably act on the vasomotor system and also directly on plain muscles of the blood

vessels and intestines.

Fall in blood pressure, that is classified response to therapy, may be of five types; 1) a gradual fall continuous throughout therapy, 2) the plateau type, where the systolic level showed little or no alteration throughout treatment, 3) a precipitate initial drop with a gradual subsequent decline, 4) an initial plateau with a subsequent gradual decline, 5) a precipitate initial drop with subsequently a plateau.

From the results of this investigation, it can be said that Rauwolfia serpentina satisfies all the criteria of a successful hypotensive agent and has a definite place in the treatment of nervous diseases and high blood pressure.

CONCLUSION

The past decade has shown greater advancement in the treatment of hypertension than all the centuries preceding it. An armantarium has accumulated which, by simple criteria, permits a more intelligent approach. On the basis of the severity of the situation confronting him, the physician now is enabled to choose the drug or combination of drugs which hold the greatest promise for each individual patient. A progressive yet relatively simple screening process assures that optimal treatment may be obtained for each hypertensive.

Fall of blood pressure without any relief of the general symptoms is not to the best interest of the patient; sluggish circulation to vital parts and insufficiency of vital organs end in disastrous consequences. Rauwolfia is highly successful as a sedative and soporific although control of blood pressure is not often spectacular nor even remarkable. Yet fall of blood pressure always takes place, often to a considerable extent even though the drop is not always maintained, particularly when such a fall would result in poverty of circulation which is a natural sequence to degeneration of arteries and arterioles which have been subjected to sustained hypertensive strain.

From this study I hope it is apparent that Rauwolfia alone is a hypotensive agent of moderate intensity and

usually will not bring the blood pressure down to within normal range except when it is only moderately elevated. Rauwolfia is more effective in young, labile hypertensive patients with tachycardia than upon those with long established, fixed hypertension with organic vascular disease. The latter usually require combination treatment.

When Rauwolfia was stopped, or when placebos were substituted, in the clinical work, the blood pressure slowly rose. It is to be noted that combination of Rauwolfia with other drugs is well tolerated and definitely adds to their hypotensive effects. The side effects are minimal and easily controlled.

This study presents clinical proof of the hypotensive activity of the alkaloids as well as Rauwolfia and indicates their use in medical therapy of benign and malignant arterial hypertension. The entire group of drugs are effective in cases of primary and secondary hypertension, and is particularly suited to treating the ambulatory patient, since they are well absorbed from the gastrointestinal tract. I feel, moreover, that it was demonstrated in this study that chronic nephritic hypertension can respond exactly as the so-called essential hypertension, as hypertension with malignant sclerosis and hypertension occurring after pregnancy, suggesting that in the origin

of all forms of hypertension, the autonomic system itself is a basic influence. Rauwolfia is of value always in the preparation or stabilization of a more severe hypertensive prior to therapy, and in combination with more potent hypotensive agents. Hypertension resulting from polycystic kidneys, Goldblatt mechanism, and so forth are in most instances incurable regardless of therapy. Rauwolfia as a trial is well justified.

Rauwolfia is a drug undoubtedly very useful in controlling unmanageable mental cases and, for affording symptomatic relief, is a noteworthy addition to the armamentarium against mental and nervous diseases. Its sedative and hypnotic effects are in many respects superior to such agents as the bromides and the barbiturates. Repeated administration of the drug for three to four days at a stretch hastens the beneficial results by its cumulative action. Some persons, however, have an idiosyncrasy for this drug, in whom untoward symptoms appear before the desired therapeutic action and, on prolonged use, some patients acquire a tolerance for it. Rauwolfia does not "cure" every case of insanity, as sometimes is claimed, but its use for many years by the Indian Kabirajes and Hakims in the treatment of mental disorders is well founded.

Until more is known about the site and mode of action of the sedative principle of Rauwolfia, it is not possible to state exactly how the drug acts in the treatment of psychopathics. The drug, however, does induce sedation and sleep in certain mental patients, with undoubted clinical improvement. I feel that in so far as continuous bodily and mental agitation prevent recuperation of body and mind, thereby preventing cure, sedation which depressed the mechanism that started the disorder may, at least in some forms of mental disorder, act almost as a specific.

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TABLE 1

BLOOD PRESSURE AND PULSE RESPONSES TO THERAPY (AVERAGE VALUES).

Drug	Blood pressure* Before treatment	After optimum treatment	Pulse Before	Pulse After	No. Pts. treated	Response** No.	Response** %
Severe hypertension (diastolic over 140 mm.)							
Rauwiloid alone	228/145	215/132	80	74	12	3	25
Hexamethonium alone	241/151	154/103	80	76	3	3	100
Rauwiloid plus C6	241/151	130/93	80	71	3	3	100
Moderate hypertension (diastolic 120-140 mm.)							
Rauwiloid alone	202/124	181/112	82	73	16	6	37
Hexamethonium alone	202/129	142/88	82	79	7	7	100
Rauwiloid plus C6	202/129	131/81	82	73	7	7	100
Mild hypertension (diastolic under 120 mm.)							
Rauwiloid alone	196/110	177/96	79	73	14	8	57
Hexamethonium alone	182/114	125/83	81	78	9	9	100
Rauwiloid plus C6	182/114	122/81	81	71	9	9	100

*Average upright.

**Decrease in mean blood pressure of 20mm. Hg. or greater.

Ford (36)

TABLE 11

EFFECTS OF SERPINA ALONE IN 15 PATIENTS

			Control Observation			Treatment Observation		
Patient	Age yr.	Sex	Duration Observ.	Blood Press.	Pulse min.	Duration Therapy	Blood Press.	Pulse
C.C.	51	F	wk. 4	220/125	70	wk. 20	180/105	60
F.D.	43	F	12	175/115	88	12	140/90	65
K.Z.	52	F	6	230/130	88	24	205/120	78
L.F.	56	F	4	230/120	88	16	215/95	65
T.N.	53	F	3	260/130	67	24	225/115	64
E.D.	62	F	8	190/100	97	20	190/95	76
W.W.	28	M	100	140/100	84	16	115/80	70
L.F.	52	M	2	180/110	85	24	160/90	70
O.B.	44	M	1	160/110	88	13	125/80	72
H.F.	43	F	4	160/90	100	60	120/70	84
R.P.	40	F	8	160/100	84	16	125/75	76
S.B.	39	M	1	210/130	84	24	120/75	64
W.F.	58	M	100	175/95	76	18	150/90	64
E.R.	54	M	2	160/90	80	30	120/80	76
E.C.	57	F	3	190/120	91	3	160/100	80

Wilkins (13)

TABLE 111

			CONTROL			RESERPINE		DIFFERENCE		
Pt.	Age	Sex	Blood press.	Pulse	Dose mg/24h.	Blood press.	Pulse	Blood press. S	Blood press. D	Pulse
39	58	M	182/100	82	0.10	158/90	60	-24	-10	-22
19	38	M	160/110	75	0.10	132/100	68	-28	-10	- 7
1	28	M	150/110	100	0.25	138/102	100	-12	- 8	0
25	65	F	184/110	64	0.50	180/100	68	- 4	-10	↗ 4
49	60	F	210/110	84	0.50	150/80	84	-60	-30	0
33	47	M	152/90	88	0.50	138/80	78	-14	-10	-10
50	67	F	170/90	75	0.50	150/80	84	-20	-10	↗ 9
7	54	F	184/120	84	0.50	142/92	60	-42	-28	-24
5	64	M	218/136	84	0.50	200/110	60	-18	-26	-24
14	68	M	164/112	72	0.50	130/90	54	-34	-32	-18
10	57	F	192/126	62	0.50	170/104	66	-72	-22	↗ 4
16	42	M	190/120	80	0.50	165/90	68	-25	-30	-12
51	24	M	174/100	68	1.00	138/80	66	-36	-20	- 2
3	60	M	195/102	54	1.00	180/100	52	-15	- 2	- 2
4	60	M	200/130	64	1.00	200/110	60	0	-20	- 4
41	52	M	180/120	84	1.00	150/98	64	-30	-22	-20
MEAN	52.7		181.6/111.6	76	0.54	158/94	68	-24	-18	-8
MIN.	24		150/90	54	0.10	130/80	52	0	- 2	0
MAX.	68		218/136	100	1.00	200/110	100	-60	-32	-24
% decrease from mean B/P and P/R.								-13.2	-16.2	-10.5

S--systolic
D--diastolic

RESERPINE PRODUCED A SIGNIFICANT FALL IN B/P AND P/R WITH THE DOSES EMPLOYED

Travis (4)

TABLE IV

			CONTROL			ALSEROXYLON ALK		DIFFERENCE		
Pt.	Age	Sex	Blood press.	Pulse	Dose mg/24h.	Blood press.	Pulse	Blood press. S	D	Pulse
22	65	F	250/108	88	2.00	180/100	80	-70	- 8	- 8
26	63	M	190/100	72	2.00	160/100	68	-30	0	- 4
31	42	M	140/110	95	2.00	134/90	72	- 6	-20	-23
33	47	M	170/100	78	2.00	142/92	80	-28	- 8	↗ 2
40	50	M	220/130	100	2.00	220/120	70	0	-10	-30
9	59	M	180/120	80	2.00	172/112	72	- 8	- 8	- 8
18	55	F	155/100	90	2.00	160/110	88	↗ 5	↗10	- 2
8	48	F	205/130	60	4.00	162/110	52	-43	-20	- 8
10	57	F	192/ 126	62	4.00	160/102	60	-32	-24	- 2
14	60	M	240/140	86	4.00	160/100	76	-80	-40	-10
15	53	M	180/120	60	4.00	150/110	63	-30	-10	↗ 3
16	43	M	160/98	100	4.00	138/80	64	-22	-18	- 8
17	63	M	210/105	72	4.00	190/120	80	-20	↗15	-20
1	30	M	150/100	100	4.00	120/90	82	-30	-10	-18
19	36	F	170/110	80	4.00	130/100	72	-40	-10	- 8
23	48	M	200/108	92	4.00	150/90	88	-50	-18	- 4
27	68	M	160/90	72	4.00	140/90	68	-20	0	- 4
28	24	F	145/98	84	4.00	142/90	80	- 3	- 8	- 4
30	70	F	200/120	88	4.00	176/84	64	-24	-36	-24
32	68	F	214/112	100	4.00	170/100	76	-44	-12	-24
35	57	M	210/130	78	4.00	150/100	72	-60	-30	- 6
37	58	M	220/120	75	4.00	210/105	68	-10	-15	- 7
41	58	F	192/120	86	4.00	190/110	70	- 2	-10	-16
42	50	F	192/120	76	4.00	134/82	64	-58	-32	-12
25	65	F	248/138	80	4.00	176/100	68	-22	-12	-12
45	40	F	160/100	90	4.00	138/88	84	-10	-10	- 6
2	38	F	168/120	90	4.00	168/120	86	0	0	- 4
3	64	M	190/100	54	4.00	180/110	34	-10	↗10	-18
11	53	F	220/90	80	4.00	200/100	78	-20	↗10	- 2
47	65	M	208/110	70	4.00	150/90	64	-58	-20	- 6
12	55	F	248/150	74	8.00	240/140	66	- 8	-10	- 8
13	60	F	184/106	96	8.00	175/98	76	- 9	- 8	-20
21	26	F	270/190	100	8.00	130/105	74	-140	-85	-26
29	67	M	230/112	90	8.00	200/102	85	-30	-10	- 5
38	47	M	220/100	65	8.00	190/98	65	-30	- 2	0
39	58	M	190/110	80	8.00	180/90	60	-10	-20	-20
7	54	F	184/120	84	8.00	170/90	64	-14	-30	-20
36	42	F	250/160	100	8.00	230/140	96	-20	-20	- 4
6	63	M	230/120	74	8.00	190/100	60	-40	-20	-14
4	57	M	180/120	64	8.00	184/130	60	↗ 4	↗ 10	- 4

Alseroxylon Alkaloid produced a significant fall in B/P and P/R with the doses employed.

Travis (4)