Comparative Activity of Reserpine and Total Alkaloids of *Rauwolfia serpentina* Benth.

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*Rauwolfia serpentina* has come to stay with the modern medical profession as a useful therapeutic agent. It would be easily the best remedy so far discovered from amongst Indian folk lore and it will be a matter of time involving wide field trials before the drug finds its exact role in the management of two challenging medical problems namely ‘hypertension’ and ‘neuropsychiatric’ conditions. However the judicious use of the drug in therapeutics demands an answer to two questions: (a) What are the therapeutically useful constituents of the plant? Does reserpine represent all that is useful in the plant or is there any other constituent or constituents that also possess therapeutically utilisable properties? (b) What happens to the drug inside the body, i.e. knowledge of metabolism of the drug, which might provide a clue to the mode of action of the drug.

Wilkins\(^1\) appears to be the only worker who has compared the crude drug with reserpine in hypertension. He mentioned: “it appears that 1:1000 proportionality exists between the dosage of reserpine and Rauwolfia which is the same as the known proportionality of reserpine in the crude drug”, thus indicating that the entire activity of the plant is due to reserpine. However, he also remarked: “Perhaps the other active principles which are known to be present in Rauwolfia may be clinically beneficial – we have not yet closed our minds to this possibility.”

After this report of Willkins, isolation of another alkaloid from the plant was reported by Klohs and his collaborators\(^2\). As is now well known, rescinnamine has been claimed to be the second most active alkaloid of *R. serpentina*. However, the yield of the alkaloid has not been mentioned and it is difficult to say how far this alkaloid is responsible for the activity in the plant. Anyhow this report indicated quite clearly that reserpine could not be responsible for the total activity of the plant. An attempt has therefore been made in the present paper to undertake a comparative study of reserpine and the total Rauwolfia alkaloids with a view particularly to answering the first question posed above.

**EXPERIMENTAL**

Reserpine pure or Serpasil injectable solution (Serpasil ampoules were kindly supplied by M/s. Ciba Pharma Ltd.) was employed for the single alkaloid and Serpina tablets (Serpina tablets were kindly supplied by M/s. The Himalaya Drug Co., Bombay) were used where total alkaloids were required throughout this work. Two batches of 4 monkeys each were selected. The animals belonged to both sexes and were of approximately equal weights (1550-1750 g). These animals were kept under uniform husbandry conditions and were observed for 3-4 weeks before using in the experiment and their normal reactions were noted. A dose of Serpentina tablets was worked out from random-preliminary trials earlier and it was found that 6 tablets suspended in water and fed by a stomach tube on empty stomach produced the following effects. Three hours after feeding the animals began to show a state of tranquillity and quiescence. They appeared to be losing interest in their surroundings. In about 6 hours, they lost interest in food and could be approached safely. Even if
they tried to eat, they appeared to be drowsy and the movements were very heavy and slow. There was profuse diarrhoea in some animals and miosis could be noticed from the very beginning. In 24 hours, recovery had started but the residual effects lasted for 48-60 hours. There is however marked individual variation in the behaviour of the animals and some animals reacted violently on approach even with this dose.

While working out the dosage for Serpina, a system of observation and grading the depression in the animals was worked out. The monkeys were observed and entries made against the following items:

1. General attitude (without noticing the observer).
2. Interest in surroundings and activity (after noticing the observer).
3. Reaction on approach by the observer.
4. Interest in food.
5. Diarrhoea.
6. Size of the pupil.

By analysing these observations, each animal could be graded as regards the degree of depression e.g. animals which were found lying on their sides and handling provoked no reaction whatsoever except shrieking were graded as first degree, animals which showed no interest in surroundings but ran away on approach could be graded as second degree; animals which appeared to be drowsy and disinterested in surroundings but became alert with slight disturbance in surroundings were put in third degree and last of all the animals which were activity interested in surroundings and showed normal activity on approach were put as ‘no depression’.

Monkeys: Having worked out the dosage level of Serpina, and corresponding degree of depression caused by it, gradually increasing doses of reserpine were given to obtain as similar a degree of depression as possible compared to depression obtained by Serpina tablets. It was noticed that reserpine tablets or powder when suspended in water and given by the mouth was less active than when equivalent amounts were given from injectable solution. This is probably due to irregular absorption. Further repeated and cross over tests showed that 5 mg of reserpine produced a nearly equivalent degree of depression as 6 tablets of Serpina. It was further shown that 4 mg of reserpine produced a lesser degree of depression as compared with 6 Serpina tablets.

This work was repeated in a fresh set of eight monkeys weighing between 1500-1600 g and the comparison carried out once again confirmed that 6 tablets of Serpina produced nearly the same degree of depression as 5 mg of reserpine and it was also shown that 7 tablets of Serpina caused a greater degree of depression than 5 mg of reserpine.

Dogs: A similar comparison was also carried out in dogs. Eight mongrel dogs of both sexes weighing 5.5 to 14 kg were employed. Following the same procedure as followed in monkeys, dosage of 100 micrograms per kilogram of reserpine was found to produce the following effects:

The animals became quiet and appeared to be sleepy in 4 to 8 hours but they wake up on food being shown or brought near to them. However some animals found it difficult to eat especially meat and other solid food. The animals appeared to be drowsy and showed tendency to fall down. There was marked miosis and profuse to mild diarrhoea. Shivering was noticed in some animals and, in some,
definite inco-ordination. The degree of depression was carefully graded by noticing all the points mentioned above. Repeated and cross-over tests showed that 100 µg/kg of reserpine produced a closely comparable degree of depression that was produced by 0.18 tablet of Serpina/kg.

Serpina tablets were analysed for total pure reserpine by a method described by Dhar et al. 3 25 tablets were found to contain 9.5 mg of reserpine so that each tablet contains 0.38 mg reserpine. Simple arithmetical calculations show that in monkeys 2.28 mg of reserpine in the presence of total alkaloids (Serpina tablets) produces a nearly equivalent effect as 5 mg of pure reserpine in the form of Serpasil solution. In dogs 100 µg/kg of pure reserpine is equipotent with only 68 µg/kg reserpine when total alkaloids were administered.

DISCUSSION AND CONCLUSION
These experiments, though not strictly quantitative, bring out clearly that when total alkaloids of *R. serpentina* are administered orally, the central nervous system depressant effect in monkeys and dogs is greater than can be explained by the amount of reserpine present in the total alkaloids. It may be pointed out here that the total alkaloids were also analysed for rescinnamine which was found to be present in traces only and, therefore, could not be considered responsible for the extra activity in total alkaloids. At this stage, we cannot offer any explanation of this phenomenon. It may, however, be suggested that either there is some other unidentified sedative principle or principles in the total alkaloids or there may be some kind of synergism between the total alkaloids and reserpine, rescinnamine, etc.

It may also be pointed out that it is felt that the methods employed for grading degree of depression are not strictly comparable and liable to subjective error by the observer but the dosage difference is so clear cut and well-marked that the conclusion “reserpine by itself does not explain all the C.N.S. depressant activity of *R. serpentina* alkaloids” appears to be justified.

REFERENCES