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EVALUATION OF "APRESOLINE" AND "SERPASIL" IN THE MANAGEMENT OF PRE-ECLAMPTIC TOXAEMIA

by

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The aetiology of pre-eclamptic toxaemia still remains obscure. As the present conception of the pathology of this condition stresses the importance of pressor activity it has become almost a habit to use some kind of hypotensive drug to reduce the spasm and thus bring about a reduction of blood pressure. Varying claims have been made as each new drug was put forth. What is required in pre-eclamptic toxaemia is a hypotensive drug which will bring down the blood pressure (in minimum time) and continue to maintain this lowered level at normotensive levels throughout pregnancy while at the same time it should have no adverse effects. It should be safe to mother and child and free from intolerable side-effects.

"Apresoline" is a pthalazine derivative. It is a hypotensive drug, centrally acting, lowering the diastolic pressure more than the systolic and is more effective in hypertensive individuals than in normal patients. The hypotensive action has been attributed to a central action either on the hypothalamus or vasomotor centres. It has the further advantage that it increases the cerebral

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and renal blood flow, diminishes the peripheral and cerebral vascular resistance and increases the cardiac output. These properties are specially advantageous in the treatment of pre-eclamptic toxaemia and hence it was thought worth while to treat a series of cases of pre-eclamptic toxaemia with "Apresoline".

"Serpasil" is an alkaloid obtained from Rauwolfia Serpentina plant. It is crystalline in nature and has a complex structure. It has a gradual sustained vasodepressor effeet which seems to be due to direct depression of the blood pressure-regulating centre in the hypothalamus and the cerebral cortex. It has in addition a sedative effect. It has no effect of a ganglion-blocking type nor has it any inhibitory effect on the sympathetic nerves.

Conflicting reports on the efficacy of this drug in the management of toxaemia led us to try it out on a series of cases.

Methods and Material

Only cases of pre-eclamptic toxaemia were chosen for the study. If there was any doubt about the diagnosis, the case was discarded from the final assessment. Cases of hypertension complicating pregnancy, with or without superimposition of pre-eclamptic toxaemia, therefore, do not find a place in this study. These cases of toxaemia were divided into two groups arbitrarily — Grade-A (Mild) and Grade-B (Severe).

The criteria were as follows:

Grade-A — Mild — Pre-eclampsia: These patients had a blood pressure between 140 and 160 mm. systolic and between 90 and 100 mm. diastolic. They had one plus or less albuminuria, and oedema was not greater than 2 plus. Symptoms like headache were usually absent but if present were mild.

Grade-B — Severe — Pre-eclampsia: Patients in this category had two plus or more oedema, blood pressure constantly over 160 mm. systolic and 100 mm. diastolic and two plus or more albuminuria. In addition the majority of them had symptoms like headache, some had vomiting, restlessness and visual disturbances.

All patients in this study were admitted into hospital and treated for 48 hours with complete rest in bed, sedation with phenobarbitone, restricted salt in diet, and Diamox 250 mgm. a day. At the end of 48 hours they were graded into "A" and "B" and treatment with "Apresoline" or "Serpasil" started, in addition to the usual general lines of management. No sedatives were administered while on the drug.

Apresoline Series

Grade-A: The cases were given Apresoline orally. The dosage was 50 mgm. to start with, increased daily by 50 mgm. till a normotensive effect was obtained. Not more than 400 mgm. daily was given to any patient in this series. When a normotensive effect was obtained that dose was maintained for 48 hours and then gradually reduced by 50 mgm. daily.

Grade-B: A few were treated by Apresoline orally as in the grade A cases. The results being thoroughly unsatisfactory, "Apresoline" injec-

tions intravenously were resorted to. It was difficult to adjust the dosage. Each case was therefore individualised and treated. For all patients the initial dose was 20 mgm. in 20 cc. of 5% glucose intravenously, given slowly. The blood pressure was recorded every five minutes after the injection for the first half an hour, thereafter every fifteen minutes for the next hour and then every hour for four hours and thereafter every four hours. The injections were repeated depending upon the response and in no patient was it repeated more than three times in 24 hours. When a marked hypotensive effect or a normotensive state was obtained the injections were discontinued and Apresoline tablets in 100 mgm. doses per day given orally.

"Serpasil" Series

Grade-A cases were given "Serpasil" orally. In the first few cases we were dissatisfied with the results obtained from doses of 0.25 mgm. 3-4 times a day. The dosage was then increased to 1 mgm. 3-6 times a day.

Grade-B cases: A few were treated first by intramuscular injection of Serpasil 2.5 mgm.-5 mgm. every six hours. The majority were treated by intravenous injections of "Serpasil." It was difficult to adjust the dosage and no standardisation could be effected. Each case had to be individualised. On an average the dosage schedule has been 2.5 mgm.—5 mgm. every 4-6 hours, not more than 20 mgm. intravenously being given in 24 hours. In a few cases we have given 10 mgm. intravenously as an initial dose but in the majority of cases the initial dose has been 5 mgm. After the injection the blood pressure was recorded as in the Apresoline series (Grade B).

The pulse, urinary output and any reactions to the drugs were all recorded. Every attempt was made to carry pregnancy to beyond 36 weeks to improve foetal prognosis. If however response to treatment was poor and patient's condition deteriorated, labour was induced prematurely. The method of choice has been intravenous pitocin drip combined with artificial rupture of membranes. The duration of pregnancy in Grade A and Grade B ranged from 28 weeks to 36 weeks. A response was considered "good" when a normotensive state was achieved and maintained throughout the hospital stay. When a hypotensive effect was achieved without a normotensive state being attained or if a normotensive effect was achieved but could not be maintained, it was considered a "fair" response. Results were classified as "poor" when there was either no response or when the hypotensive response was transitory. All assessments were made prior to delivery. These were the principles employed in this study. The large number of cases treated previously without hypotensives formed the controls.

Observations

Grade A cases: Table 1 below shows the results of oral therapy in both series. It also shows the results for comparison obtained in the same type of cases treated without any hypotensives. Only cases with complete records including delivery are included.

TABLE I

Type of management	No. of cases	Good response	Fair response	Poor response	Induction rate	Pre-maturity rate	Peri-natal mortality rate	Eclampsia
Apresoline—Oral	50	15 (30 %)	27 (54 %)	8 (16 %)	2 (4 %)	5 (10 %)	5 (10 %)	nil
Serpasil—Oral	58	35 (60.4%)	18 (31.1%)	5 (8.5%)	2 (3.4%)	6 (10.3%)	5 (8.6%)	1 case
No hypotensive—Control	110	69 (62.8%)	32 (29.1%)	9 (8.2%)	4 (3.6%)	11 (10 %)	10 (9.1%)	4 cases

It is obvious that in the milder group of pre-eclamptics the use of Apresoline orally has not resulted in any improvement in the foetal salvage rate nor has it helped to reduce the rate of induction. We further observed that with oral administration it was difficult to achieve a good response in the majority of cases and it took on an average 8.2 days for a normotensive effect to be obtained while in the control series it took only 6.2 days. It is possible that had we started on higher initial doses the time taken could have been less. The drop in blood pressure obtained by oral therapy was very gradual and slow. No untoward symptoms were noticed and the pulse rate increased by 8 beats.

In Grade A cases of pre-eclamptics the use of Serpasil has not resulted in any marked improvement in the premature birth rate or the perinatal mortality rate. It may however be stated that of the 58 cases one mother developed eclampsia while in the control series four mothers did. The average time taken for the blood pressure to come down to normotensive levels was 5.3 days in the Serpasil series while in the control series it was 6.2 days.

Grade B Pre-eclampsia: 70 cases of Grade B were treated by Apresoline — of these 10 were given the drug orally and the remaining 60 treated by injections and later supplemented by oral therapy. The response to oral therapy in the 10 cases was so unsatisfactory that it was discarded.

Grade B Pre-eclampsia — Severe: 75 cases of severe pre-eclampsia were treated with Serpasil. 12 patients were treated by intramuscular injections and 63 by intravenous injections. The dosage schedule has been an arbitrary one and individualised for each case.

Only those treated by injections are discussed. Table II below gives the results of treatment.

In the Apresoline series we observed that within a few minutes after the intravenous injection (usually within 10 minutes) the blood pressure begins to fall steeply. The maximum drop obtained has been 55 mm. systolic and 30 mm. diastolic with an average of 35 mm. systolic and 25 mm. diastolic. In 75% of cases normotensive levels or near normotensive levels (140/90)

TABLE II

Type of management	No. of cases	Good response	Fair response	Poor response	Induction rate	Pre-maturity rate	Peri-natal mortality rate	Eclampsia
Apresoline injection	60	36 (60 %)	18 (36 %)	6 (10 %)	5 (8.3%)	10 (16.6%)	8 (13.3%)	1 case
Serpasil	75	16 (21.3%)	27 (36 %)	32 (42.7%)	8 (10.5%)	17 (22.6%)	13 (17.3%)	2 cases
Controls	150	30 (20 %)	60 (40 %)	60 (40 %)	19 (12.6%)	32 (21.3%)	29 (19.3%)	3 cases

were reached within 3 hours of the injection. The hypotensive effect lasted from 3 hours to 26 hours, the average being 14.6 hours. The pulse rate in all cases showed a tendency to increase, the average increase being 16 beats per minute. In 96% of cases the urinary output was quite adequate. A comparison of results with controls treated without hypotensives shows that Apresoline when given intravenously is a very useful drug in controlling the blood pressure. It also shows that some reduction is obtained in the prematurity rate and perinatal mortality rate—16.6% and 13.3% as against 21.3% and 19.3% and hence the foetal salvage in the Apresoline series appears better. One mother developed eclampsia in this series and there were two cases of accidental haemorrhage. Unless larger number of cases are tried on this line of treatment it will be presumptuous to draw definite conclusions. But we are convinced of its effectiveness in lowering the blood pressure. This hypotensive effect is almost immediate, marked, dependable and lasts in our opinion for a longer time than any other hypotensive we have used.

The side reactions have been negligible. Tachycardia was present in all, the pulse rate going up by 16 beats and three patients complained of palpitation; 10 complained of flushing and feeling hot and 3 of headache and mild vomiting. No other untoward symptoms were met with.

In the Serpasil series we observed that when 5 mgm. of Serpasil was given intravenously in nearly 20% of cases there was no fall of blood pressure at all even for nearly four hours. In the rest, the earliest appreciable fall was observed on an average in about 45 minutes. In the cases responding favourably the average time taken for a drop to normotensive level or an appreciable hypotensive effect was 4.6 hours. The maximum fall observed was 50/30 mm. Hg. The pulse rate showed a tendency to bradycardia but in none did it go below 50. In 90% of cases the urinary output was quite adequate. A comparison of results with controls treated without hypotensives shows that in the ultimate analysis the premature birth rate or perinatal mortality rate has not been influenced favourably by the use of Serpasil. Premature births include

cases where labour had to be induced prematurely for failure to respond. Two cases out of 75 developed accidental haemorrhage and 2 eclampsia.

Marked drowsiness was observed in 6.8% of cases, nasal congestion was observed in 2.4%, gastrointestinal symptoms in those on oral therapy were observed in 5% and in one case urticarial rash was seen. Otherwise no complications followed the drug therapy.

Serpasil in Labour

In 50 patients with pre-eclamptic toxaemia, who were in labour, Serpasil was used intravenously to control the blood pressure. These patients had no hypotensives administered to them prior to labour. The blood pressure ranged from 160/100 to 190/110 in 40 patients and in 10 patients the blood pressure ranged from 190/110—210/130 mm. of Hg. In the former group the initial dose was 2.5 mgm. intravenously while in the latter it was 5 mgm. intravenously. It was observed that only in 28.6% of cases was any appreciable fall obtained (40/20—30/15). In 42.4% of cases we did not find any response. Normotensive levels in labour were obtained only in 10% of cases. It took on an average 45 minutes for the blood pressure to drop and the drop was sustained for an average of 1.8 hours. The injections were repeated after four hours in 70% of cases. Two cases developed intrapartum eclampsia in spite of the use of "Serpasil". We observed that in labour the control of blood pressure especially in the severe cases by "Serpasil" is rather uncertain and cannot be relied upon.

Fricis and his co-workers using Apresoline noticed an 8-16% fall in diastolic blood pressure after a latent period of 8-10 minutes by intravenous and oral routes in hypertensive patients. Some of their patients showed no response to oral therapy. Assali reported good results with Apresoline injections in pre-eclamptic toxaemia. The diastolic showed a larger drop than systolic and the hypotensive effect was maintained from 4-22 hours. Inconsistent results were obtained with oral therapy. McCall used 40 mgm. intramuscularly and reported good results in 13 patients. Jorden using 20 mgm. of Apresoline intravenously reported good results. Chapman, Roberts and William also reported favourable results.

Our results are generally in line with the workers above quoted. We have realised the ineffectiveness of oral therapy with "Apresoline" in toxaemia. To obtain an immediate control of blood pressure in pregnancy or to control the blood pressure in labour Apresoline can be safely relied upon.

The literature teems with contradictory reports on the values of the Serpentina group of alkaloids in pre-eclamptic toxaemia. Dr. Rakshit from Calcutta reported on 31 cases of pre-eclamptic toxaemia treated with 0.25 mgm. of Serpasil orally twice or thrice daily and reported excellent results. Not even a single baby was lost and no mother developed eclampsia or cerebral haemorrhage. In our series of mild pre-eclamptics treated with much larger doses the perinatal mortality was 9.4%. The

same results were obtainable in the control series without the use of Serpasil.

In severe cases majority favour the intravenous route. While many recommend 2.5—5 mg. as an initial dose, few have given as much as 10 mgm. intravenously at one injection. The results are conflicting. Lamsman et al came to the conclusion that Serpasil displays no apparent influence on the eventual superimposition of toxaemia during the entire course of pregnancy. The foetal mortality in his series was 24%.

Roger, Findley and Moyers reported good results but most of the severe cases were treated in addition with injections of Apresoline to which the good results could be attributed. Their conclusions are more in favour of a combination of Serpasil and Apresoline than Serpasil alone. Finerty reported significant hypotensive effect in 56% of 162 cases of pre-eclamptics treated by Serpasil. Moore at al using doses of 5-10 mg. parenterally came to the conclusion that "the haemodynamic effects of Serpasil indicate that it may serve as an adjunct to the management of toxaemia of pregnancy."

It is rather difficult to assess accurately the values of any hypotensive drug in pre-eclamptic toxaemia. The hypotensives are certainly useful in hypertension complicating pregnancy. But if we accept the theory that the hypertension in pre-eclamptic toxaemia is more humoral in origin than neurogenic, it is conceivable how varying and uncertain responses are obtained by the use of hypotensives. In the ultimate analysis the value of the hypotensive drug should be based upon the foetal salvage rate and the prevention of eclampsia and accidental haemorrhage in these mothers. By controlling the blood pressure the obstetrician should be enabled to carry on the pregnancy to near term, the rate of premature induction of labour and premature birth rate and perinatal mortality should show reduction, as also the incidence of maternal complications like eclampsia. If these are accepted as the guiding principles for assessment, from an analysis of our results we are forced to conclude that the use of "Serpasil" has not helped us in improving our results. Almost the same results have been obtained without the use of hypotensives.

Summary and Conclusions

1. A preliminary report on the use of "Apresoline" in the management of 110 cases of pre-eclamptic toxaemia is presented. Along side is presented the results on the use of "Serpasil" in 183 cases of pre-eclamptic toxaemia (133 ante-partum and 50 intrapartum).

2. These cases are divided into Grade A (Mild) and Grade B (Severe). 50 cases of Grade A were treated with Apresoline tablets orally 50 mgm. as initial dose increasing by 50 mg. daily according to response and not more than 400 mgm. being given in 24 hours. 60 cases of Grade B were treated with 20 mgm. Apresoline intravenously repeated if necessary twice daily and after stabilisation continued with oral Apresoline. 58 cases of Grade A were treated with 1 mgm. of Ser-

pasil 3—6 times a day orally and 75 cases of Grade B were treated with injections 2.5—5 mg. initially repeated every 4—6 hours.

3. The results were assessed as "Good" response "Fair" and "Poor" response.

4. In Grade A cases with oral Apresoline "Good" response was obtained only in 30% of cases and with oral Serpasil in 60.4%. The control of blood pressure and foetal salvage rate was in no way superior to that obtained without any hypotensives.

5. 60 cases of severe pre-eclamptic toxaemia were treated by Apresoline injections. The blood pressure dropped to almost normotensive level in 75% of cases within 3 hours of injections and was maintained at this level or appreciably hypotensive levels on an average for 14.6 hours. The drop in blood pressure begins within a few minutes of the injection. Good response was obtained in 60% of cases, 30% showed fair response and it was poor in 10%. Using Serpasil injections in Grade B cases good response was obtained only in 21.3%, fair in 36% and poor response in 42.7%.

6. Tachycardia was observed in all cases treated with Apresoline. Side reactions giving rise to any concern were not met with in either series.

7. There seems to be some improvement in prematurity rate and perinatal mortality rate when Apresoline is used intravenously in toxaemia. But more cases have to be done to confirm this finding. For immediate significant reduction of blood pressure intravenous Apresoline is useful, especially in labour and in imminent eclampsia. We are not impressed with the value of "Serpasil" in the management of pre-eclamptic toxaemia.

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