# HYPOTHERMIA AND ALPHAMETHYLDOPA TREATMENT

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**Summary:** The hypotensive drug alphamethyldopa, an inhibitor of serotonin synthesis, caused significant hypothermia ranging from 33.4 to 34.8°C ($t=3.09$ at $P<0.05$) in four out of nine hypertensive patients, with evidence of cerebral atherosclerosis. The anti-serotonin effect of alphamethyldopa correlated with statistically significant ($t=6.8$ at $P<0.001$) fall in the 24 hour urinary 5-hydroxyindoleacetic acid on the third day of the therapy. The possible mode of hypothermic side effect is discussed.

**Key words:** human thermoregulation antiserotonin and body temperature drug toxicity cerebral - atherosclerosis and thermoregulation urinary - 5-hydroxyindoleacetic acid hypothermia methyldopa

## INTRODUCTION

Profound hypothermia was observed as a side effect of alphamethyldopa (Aldomet, AMD) therapy in three of our hypertensive patients. This observation, the first report in world literature, has since been published (4). It was postulated that inhibition of serotonin synthesis by AMD is responsible for the hypothermic side effect. As a follow up on this postulate we have undertaken the estimation of 24 hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) (11) in nine hypertensive patients, before and on the third day of therapy with AMD, as an index of serotonin turnover in these patients (10,5,15).

## MATERIALS AND METHODS

Nine hypertensive male patients receiving AMD formed the subjects for the study. Their ages ranged from 16 to 67 years. They were hospitalised under standard uniform conditions of diet, physical activity and sleep wakefulness schedule. Care was taken to exclude banana in the diet which would give false high values of 5-HIAA. Three healthy adult men formed the controls. Twenty four hours urine collections were made on each of the patients, on hospitalisation, prior to commencement of therapy and on the third day after commencement of therapy

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with AMD. Three consecutive twenty four hours urine samples were obtained from the control subjects. The urinary 5-HIAA was estimated by spectrophotometry (11).

Rectal temperature was recorded twice a day at 7 A.M. and 7 P.M. with clinical thermometer (Rectal). Temperatures below 35°C were re-recorded with ELLAB electrical thermometer to eliminate the possible error of any inaccuracy from the use of clinical thermometer. The hypothermia was based on the criterion of a rectal temperature below 35.0°C (6).

## RESULTS

The average excretion of twenty four hours urinary 5-HIAA in three healthy adult males was 10.33 *mg* (ranged 9.5 to 11.5 *mg*), the daily fluctuations being 0.5 to 2 *mg*/24 hrs in three days. In all the patients there was a fall in urinary 5-HIAA excretion following treatment with AMD (Table I). The mean reduction was $4.44 \pm 1.9$ *mg* and was statistically significant ($t=6.8$ at $P<0.001$). But in four patients hypothermia ranging between 33.4°C and 34.8°C (Table I) was observed on the third day of therapy which was statistically significant ($t=3.09$ at $P<0.05$). These patients had evidence of general cerebral atherosclerosis as indicated by hypertensive retinopathy grade III to IV (12). On prompt recognition of hypothermia, stoppage of AMD with slow rewarming, led the body temperature to return to normal level.

TABLE: I Age, ocular fundal changes, dose of alphamethyl dopa, change in blood pressure, urinary 5-HIAA before and on 3rd day of therapy with fall in the levels and average value of body temperature on the Ist and 3rd day of therapy.

| *Patient number and name* | *Age* | *Ocular Fundii grades of hypertensive retinopathy* | *Dose of alpha-methyl dopa per day* | *Fall in blood pressure* | *Urinary 5-HIAA in 24 hours in mg* | | | *Average value of rectal temperature (°C)* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Before therapy* | *3rd day of therapy* | *Fall* | *1st day of therapy* | *3rd day of therapy* |
| 1. S.D. | 45 | IV | 1.50 G | Yes | 12.96 | 8.10 | 4.86 | 37.2 | 34.8* |
| 2. V.B. | 55 | III | 0.75 G | No | 3.00 | Too low to detect | — | 37.4 | 34.0* |
| 3. A.K. | 42 | III | 2.25 G | No | 15.80 | 9.50 | 6.30 | 37.0 | 33.4* |
| 4. V.R. | 67 | III | 1.50 G | No | 14.12 | 8.80 | 5.32 | 37.2 | 34.8* |
| 6. S.A. | 40 | III | 1.50 G | No | 10.10 | 8.56 | 1.54 | 37.4 | 37.2 |
| 6. M.I. | 48 | I | 1.50 G | Yes | 12.62 | 7.40 | 5.22 | 37.6 | 37.4 |
| 7. M.S. | 33 | I | 1.50 G | No | 14.74 | 7.19 | 7.55 | 37.2 | 37.0 |
| 8. R.G. | 26 | I | 1.50 G | Yes | 10.00 | 7.80 | 2.20 | 37.8 | 37.4 |
| 9. G.M. | 16 | Nil | 0.50 G | Yes | 8.50 | 6.00 | 2.50 | 37.4 | 37.2 |

Urinary 5-HIAA - Mean difference $\pm$S.D. $=4.44 \pm 1.9$., $t=6.8$ at $P<0.001$.

The fall in urinary 5-HIAA was found to be statistically significant, employing student's "t" test.

The fall in rectal temperature was found to be statistically significant employing student's "t" test. $t=3.09$ at $P<0.05$.

*Hypothermia (temperature below 35°C) (6).

## DISCUSSION

Feldberg and Myers have shown in their studies on animals with techniques of intraventricular injections (7) and microinjection in the anterior hypothalamus (8) that anterior hypothalamus regulates body temperature, involving mechanisms that provide a balance between the monoamines : serotonin on the one hand and noradrenaline and adrenaline on the other, the former being hyperthermic and the latter hypothermic in action. Therefore a reduction of serotonin and/or an excess of catecholamines or their analogues, the false neurotransmitters alphamethyl noradrenaline (AMN) and alphamethyl adrenaline (AMA) (1), would impair thermostability and result in hypothermia. The situation is almost the same in our patients who showed hypothermic side effect with AMD.

Alphamethyldopa as a hypotensive agent acts by inhibiting the aromatic L-aminoacid decarboxylase, and blocks the synthesis of dopamine and noradrenaline; and lends itself as the substrate for the synthesis of false neurotransmitters, alphamethyldopamine, AMN and AMA. In addition it interferes with the formation of serotonin, blocking the same decarboxylase, which converts 5-hydroxy tryptophan to serotonin (10,14). Our results indicate that all the nine patients showed a significant fall in the urinary 5-HIAA on the third day of AMD therapy. Similar results have been reported by Kedarnath *et al.* (13). Urinary 5-HIAA is a reliable index of turnover of serotonin synthesis in the body (10, 5, 15) including the central nervous system (CNS). Hence the reduction in urinary 5-HIAA would show that AMD has inhibited serotonin synthesis in the body and CNS.

Five of the nine patients have shown signs of hypertensive retinopathy grade III to grade IV, which indicate general cerebral atherosclerosis (12). This cerebral atherosclerosis results in a general ischaemia to CNS consequent on permanent changes in the microvasculature, microcirculation, precapillary arteriovenous anastomoses with "thoroughfare channels" and the phenomenon of luxury perfusion, in the cerebrovascular system (18, 19). This ischaemia is accompanied by a reduction in supply of all or many of the nutrients and oxygen to the CNS (12) including tryptophan (monoamines do not cross the blood brain barrier and depend on their precursors for synthesis). The impact of the deficiency in tryptophan supply is felt maximally in the hypothalamus where the serotonin turnover is at peak in the human brain (2,3,16). The additive effect of cerebral ischaemia and the action of AMD, is therefore to bring about a marked reduction in synthesis of serotonin in the CNS, particularly the hypothalamus.

Our results also indicate that four out of the five patients (No. 1 to 4 in Table I) with cerebral ischaemia exhibited significant hypothermia ranging from 33.4°C to 34.8°C ($t = 3.09$ at $P < 0.05$). Hypothermia and fall in urinary 5-HIAA has been observed in a 58 year old patient, suffering from carcinoid syndrome, while being treated with Parachlorophenylalanine, an inhibitor of serotonin synthesis (17). The three patients in our previous case report of profound hypothermia (29°C to 32°C) during AMD therapy had evidence of cerebral atherosclerosis (4).

Fox *et al.* (9) in their large scale survey of body temperature on 1020 persons of 65 years of age and above (with cerebral atherosclerosis) have observed that 10% of them were in hypothermic state, below 35.5°C. This survey with our present study and the two case reports point to the common denominator, cerebral atherosclerosis as an important factor for the unstable thermoregulation.

Patient No. 5 (Mr. S.A.) did not suffer from hypothermic side effect even though he had grade III hypertensive retinopathy. This can be explained by a possible escape of the vessels supplying the hypothalamus from atherosclerotic changes and hence the tryptophan supply might have been kept up at the physiological level to maintain the thermostability. In spite of the induction of hypothermia in patients 2,3, and 4, no fall in systemic blood pressure was noted with AMD therapy (Table I). This could be due to formation of sizable amount of AMA in brain a most potent hypothermic agent by virtue of hypothalamus possessing an unusual quantity of phenylethanol-amine N-methyl transferase, which is a catalytic enzyme for methylation of AMN to AMA (14). So AMA might have induced hypothermia before the hypotensive action of AMD can be achieved in these patients. Allen and Marley (1) have shown that alphamethyldopa derivatives AMN and AMA, given intravenously in one to twenty three days old chicks, consistently lowered body temperature. They also observed that alphamethyl derivatives are more potent hypothermic agents than noradrenaline and adrenaline and AMA is the most potent among the four agents. Hence it is likely that the fall of body temperature induced by AMD in the patients studied might also be, due to the effect of AMN and AMA (formed *in vivo*) potentiating the hypothermic effect of a low serotonin content in the anterior hypothalamus.

These observations point to the possibility that hypothermia observed in our patients is the result of reduced serotonin synthesis in the CNS, consequent on inhibition of serotonin formation by AMD and reduction of tryptophan supply to CNS due to cerebral atherosclerosis and the hypothermic effect of AMN and AMA. This postulation points that in human beings also serotonin is a hyperthermic agent and probably noradrenaline, adrenaline, AMN and AMA are hypothermic agents and correlates with the findings of Feldberg *et al.* who have shown the same effects in the animals like dog, cat and monkey (7, 8).

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