Acta Paediatrica Hungarica 31(1), pp 53-65 (1991)

NEONATAL EFFECTS OF METHYLDOPA THERAPY IN PREGNANCY HYPERTENSION[x]

E. SULYOK[1], J. BÓDIS[2], G. HARTMAN[3], T. ERTL[2]

County Children's Hospital, Pécs[1], Department of Obstetrics Gynecology, University Medical School, Pécs[2], Department of Physiology, University Medical School, Pécs

Received 23 Oct 1989

This study has been performed to assess the effect of methyldopa (MD) therapy in pregnancy hypertension on the neonatal adaptation. Infants born to mothers on MD for several weeks prior to delivery and presenting with excessive tremor and irritability were evaluated according to the dose of maternal MD. Pregnancy hypertension and high dose MD was associated with impaired placental perfusion, compromised function of fetoplacental unit and more frequent surgical delivery. Infants of mothers on high (1.25-2.0 g/day) or low (less than 1 g/day) MD had gestational age, head circumference, acid-base balance, Apgar score and blood pressure similar to those born to healthy control mothers. The birth weight of infants of the high MD group, however, were significantly lower than in the low-dose or control groups. MD therapy resulted in a dose-dependent increase in plasma levels of prolactin, thyrotropin and triiodthyronine indicating decreased dopaminergic inhibition of pituitary hormone release. Plasma thyroxine concentration, however, decreased significantly. Cerebrospinal fluid noradrenaline was found to be markedly depressed after maternal MD showing disturbed central nervous system monoamine metabolism. It is suggested that MD administration to mothers presenting with pregnancy hypertension interferes with cerebral monoamine metabolism of the neonate and induces alterations in some endocrine functions under dopaminergic control. The possible role of chronic fetal distress frequently associated with pregnancy hypertension should also be considered.

INTRODUCTION

Methyldopa (MD) has been widely used for the control of hypertension in pregnancy and it has been shown to improve

[x]Presented in part at the 1st Congress of the European Society for Developmental Pharmacology, Les Diablerets, Switzerland, 1988

Akadémiai Kiadó, Budapest

perinatal outcome without short-term or long-term major adverse effects on the infant and child /7,18,19,22,23/.

However, systolic blood pressure of full-term newborn infants of the treated mothers was lower during the first two days after delivery and boys born to mothers taking MD from 16-20 weeks of gestation had smaller head circumference at birth and when aged between 4 and 7 1/2 years /7,17,22/.

Boutroy et al recently observed episodes of arterial hypotension, bradycardia, disturbances of respiratory adaptation, decreased urine flow rate and functional ileus in newborn infants exposed to maternal MD /5/.

In a preliminary study we reported on 3 infants presenting with excessive tremor and irritability whose mothers were given MD for pregnancy hypertension in a dose of 1.5-2.0 g/day for 8-10 weeks before delivery. These neurological symptoms were associated with markedly depressed noradrenaline levels in the cerebrospinal fluid without clinical and laboratory evidences of perinatal asphyxia, infection, electrolyte and metabolic disturbances. They were assumed, therefore, to represent the neonatal equivalent of iatrogenic parkinsonism probably due to the reduction of dopaminergic tone in the central nervous system /3/.

On the basis of these observations we extended our clinical investigations to explore in more details the influences of MD prescribed during pregnancy on neonatal adaptation, in particular on cerebrospinal fluid noradrenaline levels and on pituitary release of hormones under dopaminergic control (prolactin, thyrotropin).

PATIENTS AND METHODS

Three groups of newborn infants were enrolled in the study. Infants of group I and II were born to mothers on MD for pregnancy hypertension and presented with excessive tremor and irritability lasting for several days, therefore, as a part of routine clinical evaluation lumbar puncture was performed.

Pregnancy hypertension was defined as systolic and diastolic pressure repeatedly higher than 140 and 90 mmHg, respectively,

under strictly controlled conditions. Patients whose blood pressure could not be controlled with MD alone other drugs such as beta-adrenergic blockers, diuretics and hydralazine were given, but these patients were excluded from the study. Infants of the trial were allocated to group I or II according to the daily dose of maternal MD needed to achieve good blood pressure, i.e. maintain systolic and diastolic pressure below 140 and 90 mmHg, respectively.

Group I consisted of 10 newborn infants of mothers treated with methyldopa (Dopegyt, EGYT, Budapest) in a dose of up to 1 g/day (mean daily dose: 0.7 g, range: 0.5-1.0 g) for a period of 8.7 weeks (range: 6-12 weeks) prior to delivery.

Group II included 15 newborn infants whose mothers were given MD in a higher dose (mean: 1.83 g/day, range: 1.25-2.0 g/day) for a period of 8.9 weeks (range. 5-14 weeks).

Group III comprised 20 neonates born to healthy normotensive mothers without any drug therapy during their pregnancy. The indication for lumbar puncture in this group was suspected perinatal infection which was excluded later on.

All infants were carefully monitored and checked for perinatal asphyxia, infection, hypocalcemia, hypomagnesemia, hypoglycemia, and hypo/hypernatremia but no pathological alterations could be detected and the therapeutical trial with glucose, calcium, magnesium and pyridoxine proved to be unsuccessful.

Lumbar punctures were performed and blood samples were taken at 8-10 a.m. for hormone measurements (prolactin PRL, thyrotropin TSH, thyroxine T_4, triiodthyronine T_3) at the 12-76 hours of postnatal age (mean: 38.2 hours).

Patients with pregnancy hypertension were admitted to the department where placental functions and fetal well-being were regularly assessed as follows:

Serum beta$_1$-glycoprotein (SP_1), human placental lactogen (HPL) and urinary excretion of estriol were measured twice a week, fetal ultrasonography and non-stress test were performed weekly, fetal movements were counted twice a day and after the 38th week of gestation regular amnioscopy was carried out. Placental perfusion parameters were also measured before and about one week after MD therapy when adequate blood pressure control could be achieved using the method described by Lunnell et al /15/ and modified by Bódis et al /4/.

Pregnant women of the three groups did not differ significantly in age, parity and weight gain during their pregnancy. 1 mother in group I and 4 in group II had proteinuria of greater than 1 g/day.

In addition to routine laboratory procedures, neonatal cerebrospinal fluid noradrenaline was determined by spectrofluorimetry according to Hahn /12/, and radioimmunoassays were applied for TSH /16/, PRL /1/, and also for T_4 and T_3 determination using commercial kits. The inter - and intraassay coefficient of variation was less than 10 % for each hormone.

Results are expressed as means $\pm$ SDM, statistical evaluations were done by using Student's t-test and X^2-test.

Approval of the institutional ethical comittee and informed parental consent were obtained for the study.

RESULTS

Placental perfusion parameters, the results of biochemical tests assessing the condition of foetoplacental unit and the mode of delivery in the three groups are shown in Table I and II.

It can be seen that pregnancy hypertension resulted in impaired placental perfusion as indicated by the significantly longer vascular and intervillous phase, the significantly greater intervillous perfusion index and uteroplacental vascular resistance and by the significant fall of blood flow index. In response to MD therapy the control of blood pressure was associated with a significant improvement of time parameters of placental perfusion and a significant decrease of uteroplacental vascular resistance. However, intervillous perfusion index remained unaltered and there was only a moderate, insignificant increase in blood flow index. (Table I).

As shown in Table II biochemical tests of the function of foetoplacental unit yielded pathological results more freqently in the high-dose MD group than in those mothers treated with low-dose MD.

Clinical and laboratory data of newborn infants of mothers with or without MD treatment are summarized in Table III. There were no significant differences in gestational age, head circumference, Apgar score and acid-base parameters of the neonates born to treated or untreated mothers. High-dose MD, however, was found to be associated with a significantly lower birth weight which may be accounted for the more severe maternal hypertension and the subsequent impaired placental perfusion independent of MD administration. Similarly, fetal systolic blood pressure appeared to be uninfluenced by MD therapy.

Table IV demonstrates neonatal hormone parameters on the first day of life after maternal MD. In response to MD therapy a dose-dependent increase occurred in the plasma levels of PRL, TSH, and T_3 indicating decreased dopaminergic inhibition of pituitary hormone release. Interestingly, plasma T_4

TABLE I

Placental perfusion parameters in patients with pregnancy hypertension before and after Methyldopa administration (mean ± SDM)

		T_{max} sec	T_V sec	T_i sec	IPI %	BFI	UVR	Blood pressure mmHg systolic	diastolic
Control (n=20)		65.5 ±12.5	44.1 ±8.8	21.4 ±8.6	31.6 ±10.7	22.0 ±16.0	5.36 ±2.8	118.0 ±3.2	82.1 ±2.2
	before Methyldopa	207.0^{xx} ±44.0	76.8^{x} ±18.0	130.0^{xx} ±33.0	60.0^{x} ±15.2	6.0^{xx} ±4.8	26.3^{x} ±8.4	158.5^{xx} ±7.5	96.0^{xx} ±4.4
	after Methyldopa	132.6^{x} ±76.0	±40.5 18.0	92.2^{x} ±86.0	64.2^{x} ±12.8	9.2^{xx} ±5.4	14.3^{x} ±6.1	132.0^{x} ±5.6	88.0^{x} ±3.6

$^{x}p < 0.01$
$^{xx}p < 0.001$

Asterisks indicate significant differences from the control value

T_{max} = time of maximum activity
T_V = time of vascular phase
T_i = time of intervillous phase
IPI = intervillous perfusion index
BFI = blood flow index
UVR = uteroplacental vascular resistance

TABLE II

Results of intensive monitoring of the function of fetoplacental unit and the mode of delivery in healthy and hypertensive pregnant women on Methyldopa therapy

		Methyldopa g/day 1.25-2.0	Methyldopa g/day <1.0	Control
Number of patients		15	10	20
Serum SP_1	pathological	7	4	3
	normal	8	6	17
Serum HPL	pathological	8^{xx}	2	2
	normal	7	8	18
Urinary estriol	pathological	8^{xx}	2	3
	normal	7	8	17
Non stress test	pathological	5^{xx}	1	1
	normal	10	9	19
Aminioscopy	pathological	5^{xx}	1	0
	normal	10	9	20
Delivery	vaginal	9	7	19
	forceps	1	1	0
	caesarean sect	5	2	1

$^{x}p < 0.05$
$^{xx}p < 0.025$

Asterisks indicate significant differences from the control group

TABLE III

Clinical and laboratory data of the newborn infants born after maternal Methyldopa (mean ± SDM)

Methyldopa g/day	Gest. age weeks	Birth weight g	Head circ. cm	Acid-base balance			Apgar score		Blood pressure mmHg	
				pH	BE mEq/l	pCO_2 mmHg	1 min	5 min		
1.25 - 2.0 n = 15	38.1 ±1.6	2528^{xx} ±438	33.6 ±1.6	7.32 ±0.08	-4.8 ±3.0	38.8 ±7.9	9.0 ±0.2	9.5 ±0.3	78	±8.5
1.0 n = 10	38.6 ±1.7	2910 ±294	34.2 ±1.4	7.34 ±0.10	-5.2 ±2.8	36.4 ±6.8	9.2 ±0.5	9.9 ±0.2	81	±9.2
control n = 20	38.7 ±1.4	3055 ±254	34.1 ±1.0	7.29 ±0.09	-6.9 ±3.1	40.6 ±9.2	8.7 ±0.6	9.8 ±0.3	83	±10.1

$^{x}p < 0.05$ Asterisks indicate significant differences from the control values

$^{xx}p < 0.01$

TABLE IV

Neonatal hormone parameters on the 1st day of life after maternal Methyldopa (mean ± SDM)

Methyldopa g/day	PRL	TSH	T_4 nM/l	T_3 nM/l	CSF-NA ng/ml
1.25 - 2.0 n = 15	2410^{x} ±507	-16.0^{xx} ±5.2	84.1^{xx} ±35.1	2.76^{x} ±0.81	0.91^{xx} ±0.18
1.0 n = 10	2011 ±384	11.1 ±4.8	121.4 ±46.4	1.68 ±1.0	1.81 ±0.68
control n = 10	1884 ±404	9.6 ±3.1	149.8 ±38.1	1.29 ±0.12	2.35 ±0.94

$^{x}p < 0.05$ Asterisks indicate significant
$^{xx}p < 0.01$ differences from the control values

concentration decreased significantly. The reason for this decrease is not apparent, one can speculate, however, that the enhanced peripheral conversion of T_4 to T_3 induced by MD may play a role.

As in our preliminary study cerebrospinal fluid noradrenaline was found to be markedly depressed after maternal MD providing strong evidence that in this group of selected patients the central nervous system monoamine metabolism is disturbed.

DISCUSSION

The antihypertensive effect of MD has been claimed to be accounted for by its ability to deplete endogenous catecholamines and to induce synthesis of false neurotransmitters in the central nervous system. In support of this notion MD administration has been found to reduce hypothalamic noradrenaline, adrenaline and dopamine and to increase its metabolic product - methyl-noradrenaline which can be stored and released as false neurotransmitter in place of noradrenaline /26/.

Clinical and pharmacological studies of the placental transfer of MD to human fetus and neonates have revealed similar free and conjugated MD concentrations in maternal and umbilical cord plasma /13/. Moreover, its elimination from the newborn plasma was found to be markedly prolonged with a halflife of about 14 hours as opposed to the value of less than 2 hours in healthy adults /5/. Interestingly, the conjugated and total MD concentration appeared to be higher in the amniotic fluid than in the corresponding plasma providing evidence that:
1.) the drug is mainly eliminated by the fetal kidney and
2.) the fetus is exposed to an environment containing MD in a relatively high concentration /13/.

In agreement with these observations the results of the present study indicate that MD therapy for pregnancy-induced hypertension may have serious influences on neonatal adaptation by interfering with fetal-neonatal central monoamine metabolism and inducing alterations in some endocrine functions under dopaminergic control.

The most striking clinical findings in this study were that infants born after maternal MD exhibit excessive tremor and irritability unrelated to the well-known clinical and biochemical disturbances of neonatal adaptation and unresponsive to therapeutic measures commonly applied. We assume a causal relationship of MD administration to the observed neurological symptoms and depletion of central

catecholamines. In support of this assumption we found significantly depressed cerebrospinal fluid noradrenaline in infants of treated mothers and rapid improvement in clinical symptoms of hyperactivity and irritability after atropine therapy /3/.

This latter finding can be interpreted to indicate that the reduction in adrenergic tone in favour of cholinergic tone may contribute substantially to the development of these neurological symptoms.

In addition to this interpretation, an alternate mechanism for the observed changes in monoamine metabolism and clinical symptoms should also be considered. Chisholm et al reported strong correlation between newborn irritability and second trimester mean arterial pressure without specific antihypertensive drug therapy /6/.

It seems therefore, that newborn irritability is more likely the result of impaired placental perfusion and chronic fetal distress frequently associated with hypertension than that of antihypertensive drug therapy.

In an attempt to explore whether the observed clinical symptoms and biochemical alterations are the result of the maternal MD therapy or they are due to pregnancy hypertension independent of drug administration pregnant rats were given MD in a dose of 14 mg/kg/day from the 10th day of their pregnancy until delivery.

MD administration during pregnancy resulted in a significant decrease of noradrenaline and dopamine but not of serotonin in brain tissue homogenate on day 5, but such alterations could not be seen on day 21 (Bódis, J. unpublished observation).

In this regard it is of interest that exposure to moderate hypoxia induced significant reduction in central nervous system monoamine biosynthesis as reflected by the decreases in brain monoamine levels /14,20/ and by the delayed and long-lasting decrease in brain dopamine when hypocarbic hypoxia was applied /21/. Furthermore, we have recently demonstrated decreased cerebrospinal fluid noradrenaline in premature infants recovering from perinatal asphyxia /2/.

Data presented in this study on plasma levels of PRL and TSH provide indirect evidence that the pituitary release of these hormones is under dopaminergic control and MD administration to the mothers during late pregnancy relieves dopaminergic inhibition and results in elevated plasma PRL and TSH in the neonate. It is of concern, however, that when metoclopramide, a dopamine receptor antagonist, was given to mothers in term labor no significant influence on cord PRL and TSH could be observed /24,25/.

The clinical significance of elevated hormone levels in the immediate neonatal period is not completely understood, PRL, however, has been shown to play a role in respiratory adaptation /11/, in the control of neonatal tissue hydration /8/ and in the regulation of renal handling of water and electrolytes /9,10/.

The increase in plasma TSH levels appears to have less clinical significance. When neonatal TSH screening program is performed, however, the possible effects of maternal MD therapy should be carefully evaluated.

In conclusion, MD administration to mothers presenting with pregnancy hypertension seems to interfere with central monoamine metabolism and to induce alterations in neuroendocrine functions of the neonates. Further studies are to be conducted to explore whether the observed clinical symptoms and biochemical changes are the result of maternal MD therapy or they are at least in part due to the associated chronic fetal distress.

REFERENCES

1. Aubert ML: Radioimmunoassay for human prolactin. In Abraham, Handbook of radioimmunoassay, pp. 179, Dekker, New York 1977

2. Bódis J, Sulyok E, Hartmann G, Ertl T, Csaba IF: Noradrenaline content of cerebrospinal fluid in preterm and term infants recovering from perinatal asphyxia. Acta Paediatr Hung 25: 343, 1984

3. Bódis J, Sulyok E, Ertl T, Varga L, Hartmann G, Csaba IF: Methyldopa in pregnancy hypertension and the newborn. Lancet II. 498, 1982 (letter)

4. Bódis J, Zámbó K, Nemessányi Z, Máthé E, Csaba IF: Application of the parametric scan in the investigation of uteroplacental blood flow. Eur J Nucl Med 10: 286, 1985

5. Boutroy, MJ, Pepin Minot L, Tenot JP, Bianchetti G, Vert P, Morselli P: Clinical and pharmacological study in infants from hypertensive treated mothers: Methyldopa versus Acebutolol. Dev. Pharmacol Ther (in press)

6. Chisholm JS, Woodson RH, da Costa Woodson EM: Maternal blood pressure in pregnancy and newborn irritability. Earl Hum Devl 2: 171, 1978

7. Cockburn J, Moar VA, Ounsted MR, Reman OWG: Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet I: 647, 1982

8. Coulter DM: Prolactin: a hormonal regulator of neonatal tissue water reservoir. Pediatr Res 17: 665, 1983

9. Ertl T, Sulyok E, Varga L, Csaba IF: Postnatal development of plasma prolactin level in premature infants with and without NaCl supplementation. Biol Neonate 44: 219,1983

10. Ertl T, Sulyok E, Bódis J, Csaba IF: Plasma prolactin levels in full-term newborn infants with idiopathic edema: response to furosemide. Biol Neonate 50: 10, 1986

11. Gluckmen RD, Ballard PL, Kaplan SL, Liggins CG, Grumbach M: Prolactin in umbilical cord blood and the respiratory distress syndrome. J Pediatr 93: 1011, 1978

12. Hahn E: Centrifugal microfiltration: A simple way to enhance the sensitivity of the aluminium oxide adsorption method of fluorimetric catecholamine determination. J Biochem Biophys Methods 2: 163, 1980

13. Jones H, Cummings AJ: A study of the trasfer of alfa-methyldopa to the human foetus and newborn infants. Br. J Clin Pharm 6: 432, 1978

14. Koob GF, Annau Z: Behavioral and neurochemical alterations induced by hypoxia in rats. Amer J Physiol 227: 73, 1974

15. Lunell NO, Sarby Bl, Lewander R, Nyland L: Comparison of uteroplacental blood flow in normal and in intrauterine growth-retarded pregnancy. Measurements with Indium-113m and computer-linked gammacamera. Gynecol Obstet Invest 10: 106, 1979

16. Martin MJ, Landon J: The use of ammonium sulphate and dextran together with second antibody at the separation stage in radioimmunoassay. In Pasternak, Radioimmunoassay in clinical biochemistry. p. 269, Heyden, London 1975

17. Moar VA, Jefferies MA, Mutch LMM, Ounsted MR, Redman CWG: Neonatal head circumference and the treatment of maternal hypertension. Br J Obstet Gynecol 85: 933, 1978

18. Mutch LMM, Moar VA, Ounsted MR, Redman CWG: Hypertension during pregnancy with and without specific hypertensive treatment. I. Perinatal factors and neonatal morbidity. Early Hum Devl 1: 47, 1977

19. Mutch LMM, Moar VA, Ounsted MR, Redman CWG: Hypertension during pregnancy with or without specific hypertensive treatment. II. The growth and development of the infant in the first year of life. Early Hum Devl 1: 59, 1977

20. Olson EB, Vidruk EH, McCrimmon DR, Dempsey JA: Monoamine neurotransmitter metabolism during acclimatization to hypoxia in rats. Resp Physiol 54: 79, 1983

21. Olson EB: Separate effects of low carbon dioxide and low oxygen content on rat brain monoamine metabolism during hypoxemia. Life Sci 42: 1469, 1988

22. Ounsted MR, Moar VA, Good FJ, Redman CWG: Hypertension during pregnancy with and without specific treatment: the development of the children at the age of four years. Br J Obstet Gynaecol 87: 19, 1980

23. Redmen OWG, Beilin LJ, Bonnar J Ounsted MR: Fetal outcome in trial of antihypertension treatment in pregnancy. Lancet II. 753, 1976

24. Robuschi G, Emanuele R, D'amto L, Salvi M, Dallaglio E, Gardini E, Fatone M, Foscolo S, Gnupi A, Roti E: Effect of metoclopramide on maternal and fetal hyperprolactinaemia. J Endocrinol Invest 6: 107, 1983

25. Roti E, Robuschi G, Emanuele R, D'amato L, Gnudi A, Fatone M, Benassi L, Foscolo MS, Gualerzi D, Braverman LE: Failure of metoclopramide to effect thyrotropin concentration in the term human fetus. J Clin Endocrin Metal 56: 1071, 1983

26. Tung C-S, Goldberg MR, Hollister AS, Sweetman BJ, Robertson D: Depletion of brainstem epinephrine stores by alfa-methyldopa: possible relation to attenuated sympathetic outflow. Life Sci 42: 2365, 1988

E. SULYOK, MD
H-7601 Pécs
Box. 76., Hungary