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Captopril: Association with Fetal Death and Pulmonary Vascular Changes in the Rabbit (41446)

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Abstract. Captopril (D-3-mercapto-2-methylpropanoyl-L-proline) has recently been approved for the treatment of refractory systemic hypertension. Administration of this agent has been shown experimentally to decrease circulating levels of angiotensin II and to increase levels of bradykinin and prostaglandins. In order to examine the effect on the pulmonary vasculature of the neonate, captopril was administered to rabbits from the middle of pregnancy to term, at doses comparable to those used in man. Fetal death in 20 treated rabbits was 86%, in contrast to 1% in 12 control rabbits. Some of the rabbits were made hypoxic in a hypobaric chamber (522 mm Hg pressure) during the period of captopril administration. Under these conditions, captopril administered to the maternal rabbits had a demonstrable cardiopulmonary effect in the neonates, as demonstrated by a significant reduction in pulmonary arteriolar medial thickness and both left and right ventricular weights compared to the hypoxic untreated controls. In view of these observations it would be prudent to avoid using captopril for the treatment of hypertension during pregnancy, until the mechanism of fetal death and the reasons for species variation are known.

Captopril (SQ 142325, D-3-mercapto-2-methylpropanoyl-L-proline) is a relatively new, orally effective inhibitor of angiotensin converting enzyme (1, 2). It has recently been approved for the treatment of refractory systemic hypertension (3, 4), and has also been used as an investigational drug in some patients with heart failure (5, 6). Angiotensin-converting enzyme (ACE), also referred to as peptidyl dipeptidase, is known to inactivate kinins and hydrolyze both Met^5- and Leu^5-enkephalins, as well as to convert angiotensin I to angiotensin II (7). One effect of the chronic administration of captopril and the inhibition of ACE is therefore an increase in circulating kinins (8). We consider that kinins may play an important role in the control of pulmonary vascular tone (9). Consequently we wished to determine if chronic oral administration of captopril to pregnant rabbits would alter the histologic appearance of the fetal pulmonary vasculature. In the initial experiment there was an unexpectedly high incidence of abortion and fetal deaths in the rabbits treated with captopril. This finding was confirmed in a subsequent experiment as described in this report, together with the changes in the pulmonary vasculature.

Materials and Methods. The effect of oral captopril on fetal survival was assessed in pregnant adult New Zealand White rabbits (approximately 4 kg each) (20 treated with captopril and 12 controls). To determine whether hypoxia would increase the medial thickness of the pulmonary arterioles in the fetus, or if it might alter the response of the arterioles to captopril treatment, 17 of the does were housed in individual cages in a hypobaric chamber at a pressure of 522 mm Hg (equivalent to the altitude of Leadville, Colo.; 10,000 feet) from the 15th day of pregnancy to term. The pressure was normalized for 30 min each day for feeding and cleaning. Animals were checked daily for evidence of abortion. The captopril (either 2.5 or 5 mg/kg/day) was administered from the 15th day of pregnancy to term (Day 30) by adhering the crystals to commercial food pellets soaked in corn oil. Control does ate the same quantity of food pellets soaked in corn oil without captopril. The rabbits had a preference for the corn oil-treated pellets and the

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cages and pans were checked daily to assure that all treated pellets were consumed. The number of does in each treatment group is shown in Table I. Caesarian section was performed if the does had not delivered or aborted by the second day after term (30 days). Implantation sites in the uterus were counted when abortion had occurred, in order to determine the total number of fetuses. Two hundred and fifty fetuses were studied in which 130 were hypoxic and 120 were normoxic. The effect of captopril on fetal survival was assessed by χ^2 analysis.

Cardiopulmonary changes were assessed 6 hr after birth in those neonates which had delivered spontaneously. In order to determine the ratio of left to right ventricular weights, the atria were removed from the ventricles and the right ventricle (RV) was dissected from the left ventricle and interventricular septum (LV + S). The two ventricles were weighed separately and the [LV + S]/RV ratios were calculated. To assess changes in the medial thickness of pulmonary arterioles sagittal sections of lung were stained with elastic Van Gieson. Ten cross-sectional pulmonary arterioles with outer diameter (OD) of 50–100 μm were measured per neonate. Each vessel was measured twice at right angles because they were not usually perfectly circular. The medial thickness (MT) is expressed relative to vessel size (MT/OD). Comparison between the groups was made by analysis of variance and Duncan's multiple range test using the mean value for each rabbit.

Results. Mean litter size was 7.7 fetuses in hypoxic does and 8.0 in normoxic does. Eighty of the eighty-one fetuses (99%) of untreated does survived to term. In contrast only 24 of 169 fetuses (14%) of does treated with captopril (2.5 or 5 mg/kg/day) survived to term (Table I). Fetal mortality tended to be higher in those does given 5 mg/kg/day (74/80) rather than 2.5 mg/kg/day (71/89), but this difference was not statistically significant, so the mortality data for the two treated groups was pooled for comparison with the untreated group. Exposure of the does to hypoxia did not significantly increase fetal mortality in the control or treated rabbits.

The dead fetuses were mummified and appeared to have died at different developmental stages. External examination of the fetuses did not show any structural abnormalities. Fetuses implanted nearest the uterine cervix were small and their size indicated that they had died within one or 2 days of the start of captopril. Larger and more developed fetuses were found closer to the terminal or most distal portion of the uterine horn. Treated does either aborted in the last week of pregnancy, started to resorb the fetuses, or went past term (30 days) without delivery. The treated does

TABLE I. CAPTOPRIL ADMINISTRATION AND FETAL DEATH RATES

Dose (mg/kg/day)	Number of does		Total fetuses			
			Hypoxic from 15th day of pregnancy		Normoxic throughout pregnancy	
	Hypoxic	Normoxic	Live	Dead[a]	Live	Dead[a]
5.0	5	5	1	35	5	39
2.5	6	4	9	46	9	25
0	6	6	38	1	42	0
Level of significance between pooled treated and untreated			$P < 0.001$		$P < 0.001$	

Note. Captopril administration at two dose levels to rabbit does from midterm to parturition resulted in significantly different fetal death rates between controls and treated does. No significant difference could be attributed to dose, therefore data from groups were pooled. An hypoxic environment (522 mm Hg barometric pressure, equivalent to an altitude of 10,000 feet) had no effect on fetal survival.

[a] Observed fetuses or implantation sites.

TABLE II. CARDIOPULMONARY MORPHOMETRIC DATA IN SPONTANEOUSLY DELIVERED LIVE NEONATAL RABBITS FROM CAPTOPRIL-TREATED DOES (2.5 mg/kg/day) AND CONTROLS ON THE DAY OF BIRTH[a]

Treatment of does	No. of neonates	Body weight (g)	Medial thickness/ outer diameter	Left ventricle plus septum/right ventricle
Normoxia only	20	43.5 ± 1.7*	0.102 ± 0.004	1.93 ± 0.10*
Hypoxia	20	52.5 ± 1.8	0.103 ± 0.005	1.72 ± 0.05
Normoxia plus captopril	9	53.4 ± 2.6	0.102 ± 0.007	1.59 ± 0.07
Hypoxia plus captopril	9	50.7 ± 2.6	0.082 ± 0.006*	1.68 ± 0.06

[a] The data are given as the mean ± standard error of the mean.
* Different from the other groups ($P < 0.05$).

showed no difference in food intake or body weight compared to the controls. On postmortem microscopic examination of eight treated does there was no indication that captopril induced any change which would explain the fetal mortality. In particular, there was no gastrointestinal ulceration, or gross pathology of lung, adrenals, liver, or kidneys.

Surviving neonates of normoxic untreated control does were significantly lighter than all other groups, probably because they tended to be delivered 1 or 2 days earlier. (Table II). The medial thickness of the small pulmonary arterioles was significantly less in neonates of hypoxic captopril-treated does than in the other groups (Table II). Furthermore, both LV + S and RV weights were significantly lower in neonates of hypoxic-treated does (0.137 ± 0.008 and 0.084 ± 0.005 g) compared to neonates of hypoxic untreated does (0.174 ± 0.009 and 0.102 ± 0.005 g) ($P < 0.01$). This reduction was unrelated to body weight.

Discussion. These observations indicate that the administration of captopril to pregnant rabbits causes a marked increase in fetal mortality. The doses of captopril administered to the does (2.5 or 5 mg/kg/day) were comparable on a weight to weight basis with those which have been used clinically in man: up to 400 (5), up to 600 (10), or up to 1000 mg/day (3, 11). It is now recommended that the maximum dose should not exceed 450 mg/day. Fetal death appears to occur with lower doses of captopril in rabbits than in some other species, as fetal death does not occur in rats or hamsters when doses greater than 50 times those used clinically are given (12). There was no maternal or fetal death in rats given captopril (3000 mg/kg/day) from Days 7 to 16 of pregnancy or in hamsters given 1000 mg/kg/day from Days 7 to 13 of pregnancy. It may be relevant to note that the uterine and renal renin concentrations are higher in rabbits than in other species (13, 14). Fetal death has been observed in four of five pregnant ewes given a single intravenous injection of captopril (160 mg) (15). The same preliminary report also described an increased number of stillbirths in rabbits given a relatively high dose of captopril orally from Days 24 to 28 of gestation (3.3 mg/day compared to an average of 1.25 mg/day in the present study). It is important to note that the captopril was administered as a single daily dose and may therefore have attained particularly high peak plasma levels.

If captopril caused severe systemic hypotension in the maternal rabbit, then the fetal mortality might be explained. However, captopril (1 mg/kg, iv) produces only a small decrease in arterial pressure in nonpregnant rabbits (16). The arterial pressure measured one day before term in one of our treated does (captopril, 5 mg/kg/day) was not different from that recorded in two of the control does. Although higher oral doses (124 mg/kg mean dose) than those we used have been found to reduce the systemic blood pressure in pregnant rabbits

significantly (17), it seems unlikely that maternal hypotension explains the observed fetal mortality at the doses used.

Captopril could theoretically alter uterine vascular resistance, or the ratio of placental to myometrial blood flow, in a manner deleterious to the fetus. Angiotensin II probably causes a net increase in the resistance of the uteroplacental bed (18, 19), though the experimental data are somewhat contradictory (13, 20). Bradykinin increases uterine and placental blood flow (21, 22). Thus the reduction in angiotensin II and the increase in bradykinin, together with the increase in prostaglandin E_2 (23) and prostacyclin (24) produced by captopril, would tend to decrease the overall uteroplacental vascular resistance. It is not known whether this alone would have an adverse effect on the fetus.

In addition to these theoretical changes that captopril might cause in the maternal uteroplacental circulation, the cardiopulmonary data from surviving neonates in the present study suggest that captopril exhibits a transplacental effect. The medial thickness of the pulmonary arterioles and both left and right ventricular weights were reduced in the neonates of hypoxic does treated with captopril, in comparison to those untreated. A reduction of systemic diastolic blood pressure, noted in fetuses of captopril-treated normoxic ewes (15), provides further evidence of a transplacental effect of the drug.

In the fetal circulation several hemodynamic factors help to determine the ratio of the left and right ventricular weights. One of these factors may be the degree of patency of the ductus arteriosus. The presence or absence of a pressure gradient across the ductus arteriosus of the fetal rabbit is unknown. If the pressures do not equalize across the ductus arteriosus, then an increase in pulmonary vascular resistance, for instance occurring during hypoxemia, could result in right ventricular hypertrophy and a decrease in the ratio LV + S/RV. Bradykinin can cause constriction of the ductus arteriosus *in vitro* (25) and might contribute to constriction of the ductus arteriosus at birth (26). Captopril is known to increase circulating levels of bradykinin in the dog (8). In theory at least, captopril could cause constriction of the ductus arteriosus in the fetus. This mechanism might explain the relatively low LV + S/RV ratios observed in both normoxic and hypoxic groups treated with captopril. It also provides a possible explanation for the fetal deaths, as the *in utero* constriction of the ductus arteriosus by indomethacin given to pregnant rabbits is associated with intrauterine death (27).

The neonates born to maternal rats maintained for the last 10 days of gestation in an atmosphere containing 13% O_2, show increased medial thickness of the pulmonary arterioles (28). In the present study the untreated hypoxic rabbit neonates did not demonstrate an increase in medial thickness. This may represent a species difference or the fact that the experiment involving rats used more severe maternal hypoxia. In adult rats the earliest pulmonary vascular response to hypoxia is distal extension of muscle into small peripheral arteries, which is closely correlated with the level of pulmonary artery pressure (29). This possible mechanism for an increase in pulmonary vascular resistance was not examined in this study. The administration of captopril reduced pulmonary arteriolar medial thickness in the hypoxic neonates. This finding is similar to the observation that another angiotensin converting enzyme inhibitor, teprotide (SQ 20881), reduces the medial thickening and right ventricular hypertrophy caused by hypoxia in adult rats (30). It has been suggested that inhibition of the converting enzyme reduces pulmonary vascular pressure and resistance in man, especially when renin levels are high (31). Chronic hypoxia is known to increase renal renin formation (32). The reason that captopril reduces the pulmonary arteriolar medial thickness in the hypoxic group but not in the normoxic group is not yet certain. However, hypoxia itself will inhibit converting enzyme activity (33), and therefore it may be that the actions of hypoxia and captopril are additive.

Under hypoxic conditions captopril seemed to have an effect on both pulmo-

nary and systemic circulations, as, in addition to the reduction in pulmonary arteriolar medial thickness, both right and left ventricles were lighter in the treated group. This could be the result of systemic as well as pulmonary vasodilatation. Regardless of the interpretation of the cardiopulmonary changes, the increased fetal mortality in the rabbits treated with captopril is clear. Until the mechanism by which captopril causes fetal death is known and the reason for the species variation is understood, captopril should not be used to treat hypertension during pregnancy. A possible exception to this precept might occur in a patient whose hypertension was unresponsive to other hypotensive agents.

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