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Amlodipineのラット・ウサギを用いた生殖・発生毒性試験

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Reproductive and Developmental Toxicity Studies with Amlodipine in Rats and Rabbits

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Amlodipine, a calcium channel blocker, was examined for reproductive and developmental toxicity in Sprague-Dawley rats and Japanese White rabbits.

1. Fertility study in rats

Amlodipine was administered orally to female rats at daily doses of 25, 10, 2 and 0 (control) mg/kg from 14 days before mating to day 7 of gestation. The females were mated with males given the same doses for 71 days prior to mating. Growth inhibition was seen in both sexes at the top dose level. Food consumption was slightly inhibited in males receiving the top dose and in females receiving the top or middle dose. No significant difference in the copulation or pregnancy index was found between the control and treated groups. No embryolethal or teratogenic effect was observed at any of the dose levels used.

2. Teratogenicity study in rats

Amlodipine was administered orally to pregnant rats at daily doses of 25, 10, 4 and 0 mg/kg from day 7 to day 17 of gestation. Body weight gain and food consumption were slightly reduced in dams at the top dose level. No teratogenic effect nor any other adverse effect on fetal development was noted. There was no evidence of adverse effects on the viability, postnatal development, behavior, or reproductive performance of the first (F_1) generation offspring, nor were there external abnormalities of the second (F_2) generation fetuses.

3. Teratogenicity study in rabbits

Amlodipine was administered orally to pregnant rabbits at daily doses of 25, 10, 4 and 0 mg/kg from day 6 to day 18 of gestation. Gain in body weight was slightly reduced in dams at the top dose level. Food consumption was slightly decreased in dams at the top and middle dose levels. No teratogenic effect nor any other adverse effect on fetal development was noted.

4. Peri- and post-natal study in rats

Amlodipine was administered orally to pregnant rats at daily doses of 10, 4, 2 and 0 mg/kg from day 17 of gestation to day 21 after parturition. Parturition disorders (prolongation and/or dystocia) were observed in 13 of 24 dams at the top dose level; 6 out of the 13 dams died. With this dose there occurred a prolongation of the gestation period, an increase in stillborn pups, a decrease in litter size and a reduction in the viability index of pups on day 4. However, there was neither adverse effect on the postnatal development, behavior or reproductive performance of the F_1 offspring nor abnormalities of the F_2 fetuses at any dose levels.

Key words: Amlodipine／Fertility／Teratogenicity／Peri- and post-natal toxicity (rat, rabbit).

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