Ophthalmologic Abnormalities produced by retinoic in rat F1 offspring.

Retinoic has been known to produce anophthalmia and microphthalmia in the mouse and hamster offspring when administered during organogenesis. However, its potential effect on developing eyes has not been ophthalmologically characterized. In this study, rat offspring prenatally exposed to retinoic were examined for ophthalmic anomalies.

Pregnant rats were treated orally with retinoic at a dose of 2, 4, or 6 mg/kg/day on days 8 to 10 of gestation. In postnatal week 8, eyes of pups were examined with a slit lamp and by indirect ophthalmoscopy.

Ophthalmologic examinations revealed that 6 and 30% of offspring in the 4 and 6 mg/kg/day groups, respectively, had ocular abnormalities, which consisted of red discharge, anophthalmia, microphthalmia, dry eye, corneal vascularization, iris hypoplasia, persistent hyperplastic tunica vasculosa lentis, lack of retinal vessels, and coloboma of the iris, optic disc and choroid. Affected litters of each lesion over dose levels were statistically analyzed. Among these lesions, there were statistically significant increases in anophthalmia, microphthalmia, red discharge, persistent hyperplastic tunica vasculosa lentis, lack of retinal vessels, iris hypoplasia at dose level of 6 mg/kg/day, except red discharge which was significant at 4 mg/kg/day. Other lesions listed above were considered to be toxicologically significant, because the higher incidences as compared with our historical control data. These colobomas were located in the infero-nasal region, and were considered as typical coloboma most likely related to the failure of optic fissure to close.

The no effect dose level for induction of ocular anomalies by retinoic is considered to be 2 mg/kg/day in the rat offspring when administered during days 8 to 10 of gestation.


A procedure for recording the electroretinogram (ERG) in mice with a coiled stainless steel-type electrode was developed in order to examine retinal toxicity. Mice received a single intravenous injection of sodium iodate (SI), a retinotoxic compound, via the tail vein at a dose of 12.5, 25 or 50 mg/kg, and the ERG was recorded periodically for 28 days after dosing. In addition, the retina was examined histopathologically at 30 days after dosing.

1. The mice were anesthetized with mixed anesthetics of urethane, xylazine and ketamine after 30 to 60 min of dark-adaptation. Sixteen responses to repetitive 1.2 joule light stimuli at a frequency of 0.2 or 0.1 Hz were averaged by a microcomputer. Body temperature of the mice was kept constant at 37 to 38°C using a thermostatically controlled heating mat. Under these conditions, stable ERG a-wave, b-wave, oscillatory potentials and c-wave could be recorded for 28 days.

2. SI at doses of 25 mg/kg or more caused depression of the amplitudes of the oscillatory potentials, and enhancement of the a- and b-waves amplitudes, while the c-wave was already extinguished 1 day after dosing. Following these changes, the amplitudes of the a- and b-waves decreased 3 or 7 days after dosing. These changes did not recover until 28 days after dosing.

3. Upon histopathologic examination of the retina, folding of the outer nuclear layer, disarrangement of the rods and cones, decrease of the visual cells and desquamation of the pigment epithelial cells were observed with SI at 25 mg/kg or more.

4. Using this recording technique, it was confirmed that a stable ERG was recorded repeatedly for 28 days in mice, and the effects of SI on the ERG could be detected. Furthermore, histopathologic findings in the retina were confirmed to be correlated well with the portions corresponding to the changes observed in the ERG. These results indicate that the ERG recording procedure developed in this study is useful for evaluating retinal toxicity in mice.