IMPAIRMENT OF VISUAL SYSTEM OF BEAGLES ORALLY INGESTING CLIOQUINOL

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Abstract...Visual system was examined in 3 beagles given clioquinol for a long period and in 2 control beagles. Ophthalmoscopic examination revealed the decreased diameter of the optic disks of the treated dogs except for one dog. There were degenerative changes of the optic nerves in all of the treated dogs. The changes included disruption of the axons and the myelin sheaths. It was difficult to observe the morphological change of the retinae of the treated dogs. The findings demonstrate that the changes in the visual system after clioquinol administration are severe in the optic nerves rather than in the retinae.

Key words: Clioquinol, retina, optic nerve, beagle

INTRODUCTION

Clioquinol (CQ), 5-chloro-7-ido-8-hydroxyquinoline, is now regarded as a possible etiological factor to induce the neurological disorder called subacute myelo-optico-neuropathy in man (Sohue et al., 1971, 1972; Tamura et al., 1973). In the experimental study, CQ administration to dogs developed ataxia and motor paralysis of both hindlimbs (Tateishi et al., 1971, 1973; Heywood et al., 1976; Worden et al., 1978; Schaumburg and Spencer, 1980; Goto et al., 1982). In our previous study, we reported disappearance of the spinal reflex response with long latency in beagles given CQ for a long period (Goto et al., 1982). During the oral administration of CQ in the study, it was noticed that a dog showed the impairment of visual acuity. When the dog walked around in a room, the animal had difficulty in avoiding colliding with the wall. Moreover, when the dog ate food, the animal could not find a dish easily.

The purpose of this work is to extend our basic knowledge about the influence of CQ on the visual system such as the retinae and the optic nerves. It is described that the optic disks of the treated dogs with the impairment of the visual acuity are apparently narrow compared with those of the control and the treated dogs reveal the degenerative

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changes of the optic nerves.

**MATERIALS AND METHODS**

Beagles used in this work were the same as described previously (Goto et al., 1982). Briefly, three dogs were given CQ once a day. The 10% carboxymethylcellulose suspension of CQ was suspended in the powdered milk used for babies. The other two dogs (control) were given only carboxymethylcellulose suspended in the powdered milk. All of the treated dogs (dogs 1, 2 and 3) developed ataxia of both hindlimbs without impairment of the forelimbs and control dogs (dogs 4 and 5) did not develop any symptoms. Net periods of administration of CQ were 87, 80 and 85 days for dogs 1, 2 and 3, respectively. Those for dogs 4 and 5 (control) were 93 and 91 days, respectively. Ophthalmosclropic examinations of the retinæ were made 1 to 8 days before killing dogs using an ophthalmoscope (Kowa, RC-2).

Dogs were killed under pentobarbital anesthesia. An eye of each dog was proptosed by placing forceps around the optic nerve close to its exit from the eye. The optic nerves about 1.5 cm distant from the exit from the eye were prepared for the histological examination. The globes were transected along their equators and the corneas and lenses were removed. Paraffin sections of the retinæ and the optic nerves were prepared after fixation with 10% buffered formalin. The sections of the retinæ were stained with Hematoxylin-eosin, and those of the optic nerves were stained with luxol-fast blue and cresyl violet.

**RESULTS**

As to the clinical observation, dog 3 developed behaviorally apparent impairment of the visual acuity after the onset of ataxia as mentioned in introduction, but in other two treated dogs it was difficult to confirm the impairment of the visual acuity at the time when the ophthalmoscopic examinations were made.

Fig. 1 represents the ophthalmoscopic views of the left and right sides of the retinæ of the treated and control dogs. There were no abnormalities in the blood vessels of the retinæ of the treated dogs. The diameter of the optic disk of treated dog 1 was almost the same as that of control dogs, but other treated dogs (dogs 2 and 3) revealed the narrow diameters of the optic disks in both left and right sides of the eyes compared with control dogs.

Histological examinations of the retinæ were made for dogs 1, 3, 4 and 5. Although there appeared to be some degree of decrease in the density of the ganglion cells in the treated dogs compared with control (Fig. 2), it was difficult to observe the morphological changes in the retinæ of the treated dogs.

Histological examinations of the optic nerves were made in all 5 dogs. Degenerative changes of the optic nerves were evident in all of the treated dogs, whereas the optic nerves of control dogs demonstrated no morphological changes (Fig. 3). The changes included swelling of the axons, disruption of the myelin sheath and formation of vacuoles in the optic bundles.
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Fig. 1. Ophthalmoscopic views of the retinae of beagles given clioquinol. Photographs of left and right sides represent the left and right retinae, respectively. Numbers in the photographs mean dog number. Dogs 1, 2 and 3 are treated with clioquinol, and dogs 4 and 5 are controls.
Fig. 2. Morphology of the retinae of beagles given clioquinol. A, B, C and D are from treated dogs 1 and 3, and control dogs 4 and 5, respectively. 840×.
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Fig. 3. Morphology of the optic nerves of beagles given clioquinol. Optic nerves about 1.5 cm distant from the exit from eyeballs were examined. Magnification is 270×. 1) Longitudinal section of treated dog 1. Demyelination of the optic nerves and proliferation of glial cells are evident. 2) Transversal section of treated dog 2. Histological characteristics are the same as in dog 1. 3) Longitudinal section of treated dog 3 developing behavioral impairment of visual acuity. Histological characteristics are the same as in dog 1. 4) Transversal section of control dog 4. 5) Longitudinal section of control dog 5.
DISCUSSION

In the previous work, the motor paralysis in the hindlimbs and the degenerative changes at the dorsal column of the cervical level were evident in the dogs given CQ orally for a long period (Goto et al., 1982). In the present work, it was confirmed that when the preparations of the optic organs already made in the previous study were examined histologically, the optic nerves of the treated dogs were degenerative. Thus, morphological changes observed in dogs were the same as in man intoxicated by CQ.

Ophthalmoscopic examinations revealed the decrease of diameter of the optic disk in 2 treated dogs. However, the degenerative changes of the optic nerves were evident in all of the treated dogs. The changes in the treated dogs are severe in the distal part of the optic nerves as observed in the spinal cord where the degenerative changes are intense at the cervical level (Tateishi et al., 1973; Worden et al., 1978; Goto et al., 1982).

In the case of dog 1, there was no change of the diameter of the optic disk in the ophthalmoscopic examination, but histological examination revealed the intense degenerative changes in the optic nerve. Apparent discrepancy between ophthalmoscopic and histological examinations may be due to the fact that axonal degeneration starts from the peripheral part of the nerve. Therefore, it is reasonably considered that the decrease of the diameter of the optic disk comes from the degenerative change of the optic nerve by CQ.

The results in the present study demonstrate that changes in the visual system after CQ treatment are severe in the optic nerves rather than in the retinæ.

REFERENCES

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induced by clioquinol in animals. Lancet II, 1263-1264.