Experimental Myelo-optic Neuropathy Induced by Clioquinol

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Summary. To elucidate the neurotoxicity of clioquinol, 20 mongrels, 8 beagles, 27 cats and a Japanese monkey were given clioquinol orally for a long period. 12 mongrels, 7 beagles and 6 cats manifested neurologic signs clinically which began with side-swaying of the hips and ataxic gait followed by muscle weakness and increased tendon jerks in the hindlegs. The longer the period of administration, the more severe the signs became. Visual acuity was also impaired in long surviving animals. Autopsy of these severely affected animals revealed marked degenerative changes in the distal portions of nerve fibres in the posterior spinal column and optic tract predominantly. The changes involved axons first, then demyelination and later these foci were replaced by fat granules and glial cells. Spinal root ganglia and peripheral nerves were also affected. Postmortem examination of the animals with none or minimal clinical manifestations showed, nevertheless, mild pathological changes in the same portions as above mentioned.

The myelo-optic neuropathy seen in these animals is well in accord with the changes observed in "subacute myelo-optic neuropathy" (SMON) in humans. There are, however, differences in strains as well as species of animals for the neurotoxicity of clioquinol.

Key words: Subacute Myelo-Optic Neuropathy — Clioquinol — Iodochlorhydroxyquinoline — Animal Experiment.

Introduction

A form of subacute myelo-optic neuropathy of unknown etiology has been observed in Japan since the end of 1950's. The number of patients reported reached 7856 by the end of October 1970 (Kono, 1971). This syndrome is preceded by abdominal pain or diarrhoea. Neurological disorders are characterized clinically by sensory disturbances and motor paralyses starting at a distal portion of the lower limbs, often by disturbances of autonomic functions and by loss of visual acuity (Sobue et al., 1970).

Pathologically, this syndrome is characterized by systemic degeneration of the long tracts of the spinal cord, starting at a distal portion of Goll's and the corticospinal tracts, accompanied by degeneration of the spinal root ganglia and peripheral and optic nerves (Matsuyama et al., 1969; Shiraki and Oda, 1969; Miyakawa et al., 1970, 1971; Okuda and Ueno, 1970; Shiraki, 1971).

Concerning the etiologies of this syndrome, several conceivable hypotheses, such as toxic or infectious, have been discussed. In 1970, a green-coloured tongue and greenish urine were noticed in some patients with this syndrome (Igata et al., 1970; Takasu et al., 1970). This green pigment was analysed to be the chelate of clioquinol (5-Chloro-7-Iodo-8-Hydroxyquinoline) with ferric iron (Yoshioka and Tamura, 1970). Since then, many clinico-epidemiological surveys have been performed and a close relationship between long term administration of a large
dosage of clioquinol and the onset of the neurological syndrome have been discovered (Igata, 1971; Nakae et al., 1971; Tsubaki et al., 1971).

In order to reproduce this syndrome in animals, we have conducted a series of animal experiments. The results were briefly communicated previously (Tateishi et al., 1971, 1972a). In another paper (Tateishi et al., 1972b), we reported a myelo-neuropathy in 5 mongrels induced by long-term oral administrations of clioquinol. However, the pathological features seen in the dogs who had been ill for only a short time were less severe than those in typical cases in humans. After the above report, the same but more advanced symptoms involving the optic system were found among other long surviving animals. These results are summarized here.

Materials and Methods

Animals. 24 mongrels (Table 1), 20 were given, twice a day, Japanese-made clioquinol suspended in milk and 4 were controls. 12 pure bred beagles (Table 2), 14-month-old bitches, were divided into 3 groups of 4 beagles each. The first group (nos.1—4) and the second group (nos.5—8) were given twice a day Japanese-made and Swiss-made clioquinol, respectively. The third group was used as controls. 27 cats (Table 3) were given the substance in their food and 5 were controls. Water suspension of Japanese-made clioquinol was given once a day through a nasal tube to a Japanese monkey. Another monkey was a control.

Clioquinol and Combination Procedures. Japanese-made clioquinol: Emaform® (90% clioquinol plus 10% carboxy methyl cellulose as an emulsifying agent) and Swiss-made clioquinol: Enterovioform® (93% clioquinol plus 7% sapamine) were supplied through SMON Research Commission. Generally the dose of clioquinol given to the animals was increased gradually to avoid death from acute poisoning. Detail of the administration is shown in Table 1 to 3.

Preparations to cause constipation were given to some mongrels as previously reported (Tateishi et al., 1972b). To prevent detoxication and excretion of clioquinol, CCl₄ (0.5 cc per kg orally for 6 days) and Viomyein (300 mg per kg injected for 2 days) were administered to some animals.

Histological Examinations. Some animals with chronic poisoning and some of the controls are still alive. Autopsy was undertaken in all animals who died or were killed under anaesthesia with Nembutal. Materials were taken from visceral organs and nervous tissues. After fixation in 10% neutral formalin, frozen and paraffin sections were made. As for peripheral nerves, teased fibre method and also Epon-embedding were applied. Hematoxylin-eosin staining for all sections and Woelke and Bodian stains for nervous tissues were done. Nissl, Holzer, Masson and Sudan III stains were added when needed.

Results

Clinical Observations

Of 20 mongrels (Table 1) administered with the substance, 3 did not develop clinical manifestations, 5 died of acute poisoning with epileptic convulsions or general weakness and 12 showed symptoms indicating chronic poisoning. The daily and total doses of clioquinol required to elicit symptoms of chronic poisoning ranged from 60—144 and 1688—16578 mg per kg, respectively, in all 12 dogs. The mean of the total dosage given to 9 mongrels was 4161 mg per kg, the dosage given to 3 mongrels (nos.6, 7 and 12) was different and could be excluded statistically as below the 1% confidence limit. A study on 5 of the above chronically poisoned 12 mongrels has been reported already (Tateishi et al., 1972b). Clinical manifestations observed in the remaining mongrels were identical with our earlier series, although they were more advanced. Side-swaying of the hips and muscle weakness of the hindlegs became so advanced that some mongrels could not keep standing even to eat. Many scratch wounds and skin excoriations, due to dragging themselves, were found in the hindlegs, especially in the dog no.8. This dog was having urinary incontinence. Insipie of muscle atrophy of the hindlegs,