Br. J. clin. Pharmac. (1989), **27**, 43S–45S

Neuropathology of vigabatrin

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1 Neuropathological changes in experimental animals have been observed with vigabatrin treatment in mice, rats and dogs.
2 These changes have comprised intramyelinic oedema which is reversible on cessation of treatment.
3 In human studies so far, no intramyelinic oedema has been noted. It is not clear whether humans will show the neurotoxicity observed in animals; close monitoring of patients is indicated.

Keywords vigabatrin neuropathology intra-myelinic oedema

Introduction

While clinical studies continue to show that the GABA transaminase inhibitor, vigabatrin (γ-vinyl GABA; 4-amino-hex-5-enoic acid) is an effective drug for patients with complex partial epilepsy, approval for use in the therapy of the larger population of epilepsy patients has awaited resolution of prominent neuropathological changes in experimental animals. This paper reviews the neuropathology of vigabatrin as it has been observed in mice, rats, dogs and monkeys, as well as the limited autopsy and biopsy material which has been obtained from patients.

Rodent studies

Mice (CD-1) given vigabatrin at doses from 100 to 500 mg kg^{-1} day^{-1} for 1 month remained clinically normal except for decreased weight gain in the highest dose group. However, vacuolation of myelin was observed in cerebellar white matter, particularly adjacent to cerebellar roof nuclei, in 10% of mice given 100 mg kg^{-1} day^{-1} and in 60–65% of those given 200, 300 or 500 mg kg^{-1} day^{-1}. Occasional vacuoles were present in the reticular formation and in the superior and inferior colliculi.

Rats have been subjected to more intensive study. Unlike mice, who tolerated high doses of vigabatrin, Sprague Dawley rats developed transient alopecia, marked depression of body weight gain at high doses, and convulsions which were dose- and time-related. On cessation of dosing after 6 months of treatment, body weight gain improved markedly after 3 to 6 months of recovery, and convulsions were no longer seen after 4 months of recovery. Convulsions continued to be seen during recovery in some rats treated for 12 months.

The distribution of myelin vacuolation was limited to certain CNS sites in the rat: visual pathways, hypothalamus, fornix columns and cerebellar white matter. At no time were vacuoles seen in the centrum semiovale or subcortical white matter. In addition to routine assessment of paraffin-embedded sections, selected rats have been perfused for study by electron microscopy. These studies (Yarrington *et al.*, 1985; Butler *et al.*, 1987) show that the myelin vacuolation has resulted from separation of myelin lamellae at the intraperiod line, i.e., the membrane formed from fusion of the surface membranes of encircling oligodentrocyte cytoplasm. While identical intramyelinic oedema follows exposure to hexachlorophene (Towfighi

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et al., 1973), triethyltin (Aleu *et al.*, 1963), and isoniazid (Carlton & Kreutzberg, 1966), several features distinguish vigabatrin from these myelin-directed toxicants. In contrast to the effects of these agents, vigabatrin does not result in generalized CNS and PNS intramyelinic oedema; rather, the oedema is limited to a few CNS sites. Second, the vigabatrin effect in the rat appears at some threshold level of exposure (e.g., 30 mg kg^{-1} day^{-1} for 1 year but not for 6 months) but thereafter does not demonstrate a dose-response relationship (greater in rats given 100 mg kg^{-1} day^{-1} for 1 year than in those given 200 or 300 mg kg^{-1} day^{-1} for this period). Third, not only does the oedema not progress in high dose groups (200 and 300 mg kg^{-1} day^{-1}) between 6 months and 12 months of exposure, the quantity actually diminished despite daily dosing. Fourth, intramyelinic oedema after vigabatrin has not been observed to progress to segmental demyelination, as occurs with the other agents. Finally, while the intramyelinic oedema in the early stages of intoxication with hexachlorophene, triethyltin, and isoniazid is reversible, even the most severe oedema seen in rats disappears during a 3 month recovery period.

The cerebellar roof nuclei in the rat have been the loci of neuropathological changes not seen in other species. Eosinophilic spheroids, shown to be swollen axons through staining with monoclonal antibodies against neurofilament antigens, develop in high dose groups, along with foci of extracellular mineral deposits. Neither lesion disappeared during a 3-month recovery period.

The albino Sprague-Dawley rat has an additional vulnerability not shared by the pigmented Lister-Hooded rat, a time- and dose-dependent degeneration of the retina. This effect appears to be an enhancement of the retinal degeneration induced by light in albino species and has occurred with other drugs, such as clonidine (Butler *et al.*, 1987).

Dog studies

While beagle dogs treated with vigabatrin at doses up to 200 mg kg^{-1} day^{-1} for 1 year remained clinically normal, severe intramyelinic oedema developed, which, in common with that in the rat, was reversible and did not progress to segmental demyelination. However, cerebellar white matter was spared, and the oedema was limited to fornix columns, optic tract and chiasm, and hypothalamus. Again, the bulk of the CNS myelin and all of the PNS myelin did not show this change. It is noteworthy that neither swollen axons nor mineralization have been seen in dog tissues. However, rare mild astrogliosis was seen after prolonged intoxication.

Monkey studies

Cynomolgus monkeys (*Macaque fasicularis*) have been given vigabatrin in doses from 50 to 300 mg kg^{-1} day^{-1} and sacrificed for neuropathological examination after 3, 6, and 16 months. While observers have been unable to distinguish treated monkeys from controls after 3 or 6 months of exposure to 300 mg kg^{-1} day^{-1}, blinded examination of coded slides by five neuropathologists yielded an equivocal opinion regarding the presence of vacuolation in excess of that in controls in monkeys treated with 300 mg kg^{-1} day^{-1} for 16 months. Two observers concluded that a treatment-related effect was present. Three others, including this author, held that the groups could not be distinguished from one another.

Human studies

This observer has reviewed slides from one biopsy and two autopsy studies on patients treated with vigabatrin. Doses from 2 to 6 g day^{-1} were given from 7 months to 4 years. In this limited sample no intramyelinic oedema was evident.

Conclusions

It is clear that the proper posture for regulatory agencies, whose *raison d'être* is to protect the public, is to be cautious, even to assume that new drugs are going to be harmful and useless until proven otherwise. Thus, it has been appropriate to view the neuropathological studies on rodents and dogs with concern. However, it is apparent that vigabatrin is different from other agents which result in intramyelinic oedema. Further, humans may not show the toxicity observed in rodents, dogs, and, perhaps, in monkeys. Until we have more data, clinical investigators should proceed with caution and continue to monitor patients with visual evoked potential studies, given the uniformity of visual pathway involvement in the lower species.

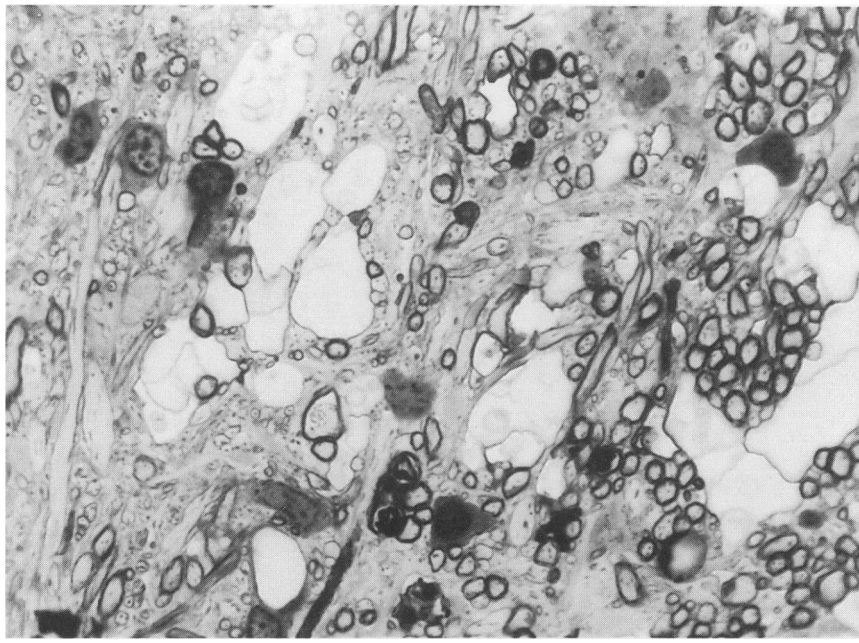

Figure 1 White matter adjacent to roof nuclei in the cerebellum of the rat demonstrates intramyelinic oedema, forming vacuoles several times the diameter of the axons. Neuronal cell bodies remained normal. Magnification × 1000.

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