PHENYTOIN (Group 2B)

A. Evidence for carcinogenicity to humans (*limited*)

Cases of cancer, mainly neuroblastoma, were reported in ten children under the age of four years who had been diagnosed as having an unusual constellation of congenital abnormalities (fetal hydantoin syndrome) thought to be induced by prenatal exposure to phenytoin or who had just received prenatal exposure to phenytoin[1-9]. Although the number of patients is small, the concordance of rare events suggests that phenytoin may be a transplacental carcinogen in humans. There is also one report of malignant mesenchymoma in an 18-year-old patient with phenytoin-associated malformations[10]. In a large case-control study[11] of 11 169 pairs of childhood cancer cases (about 8% of which would have been neuroblastomas[12]) and matched controls, epilepsy was reported among the mothers of 39 cancer cases compared with 22 controls (relative risk [RR], 1.77 [95% confidence interval, 1.02-3.10]). Review of available antenatal records indicated that 37% of case mothers had used phenytoin during pregnancy (RR, 1.57 [0.56-4.48]) and 67% had used phenobarbital (RR, 1.67 [0.78-3.62]).

There have been a number of case reports of lymphomas among individuals receiving phenytoin[1,13-21] with or without other antiepileptic drugs. No significant excess of lymphoma, however, was reported in two follow-up studies of epilepsy patients: the observed and expected numbers of lymphoma-leukaemia were 23 and 23.7 in the larger survey[22], and 6 and 4.7 in the smaller survey[23]. An excess of brain and other neurological tumours during 1969-1976 (8 observed, 0.5 expected) was reported among 954 people prescribed phenytoin during 1969-1973[24]. The excess is similar to that reported among epileptics [see summary of data on phenobarbital, p. 313] and may reflect the underlying disease rather than use of the drug *per se*. There was also no appreciable excess of phenytoin use in cases of Hodgkin's disease in a small case-control study[25].

B. Evidence for carcinogenicity to animals (*limited*)

Phenytoin and its sodium salt have been tested for carcinogenicity in mice by oral and intraperitoneal administration, producing lymphomas and leukaemias[1,26,27]. The effects of oral administration varied with the strain of mouse: no effect was observed in the resistant C3Hf strain; in the C57BL strain, thymic lymphomas were produced in 12% of treated mice, starting at about eight months of age, as compared with 4% in control mice starting at about

18 months of age; 25% of SJL/J mice had thymic lymphomas early in the study, but late in the study the majority of both treated and control SJL/J mice had extrathymic tumours[26]. The experiments were complicated by the use of a liquid diet. Studies by oral administration in rats were considered to be inadequate[1].

C. Other relevant data

Conflicting results have been obtained concerning the induction of sister chromatid exchanges in patients treated with phenytoin; no increase in the incidence of chromosomal aberrations was found[28].

Phenytoin induced sperm abnormalities and micronuclei but not dominant lethal mutations in mice treated *in vivo*; it did not induce chromosomal aberrations in bone-marrow cells of rats. It did not induce chromosomal aberrations in cultured human lymphocytes. It enhanced virus-induced transformation of Syrian hamster embryo cells and was a weak inhibitor of intercellular communication in Chinese hamster V79 cells. Phenytoin induced prophage but was not mutagenic to bacteria[28].

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