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Preferential distribution of diphenylhydantoin in primary human brain tumors

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ALTHOUGH the distribution of diphenylhydantoin has been studied extensively,[1-3] little is known of its distribution in human primary brain tumors. In this study of a series of eight patients, seven had astrocytomas of grades III and IV and one a meningioma. Samples of primary brain tumors and adjacent areas of normal brain tissue were obtained from these patients during surgery and kept at −4° until analyzed. Histological identification of the tumor type and normal tissue was made by one

TABLE 1. DISTRIBUTION OF DIPHENYLHYDANTOIN IN HUMAN PRIMARY BRAIN TUMORS AND ADJACENT NORMAL BRAIN TISSUES

Patient	Diagnosis	Dose (mg/day) Days pre-op 1	2	3	4	Concentration (μg/g)* Tumor	Normal	Tumor/ normal
1	Grade IV	100	100			1·156	0·659	1·754
2	Grade IV	200	200	400	200	1·080	0·610	1·770
3	Grade IV	100	400			0·592	0·318	1·862
4	Grade IV	100	100	100		2·724	1·377	1·978
5	Grade III	100	200	200		0·652	0·414	1·575
6	Grade III	100	500	200		1·760	1·620	1·086
7	Grade III	400	400	400		2·173	0·714	3·043
8	Meningioma	800				2·848	0·718	3·967
Mean ±						1·623	0·804	2·129
S.E.						0·31	0·16	0·33

0·005 ml/g as estimated by the method of King and Gilchrist.[4] Analysis of diphenylhydantoin was made by the method of Dill *et al.*[1] Average recovery of drug added to normal brain tissue in a concentration of 2·5 μg/g was 86·2 per cent, with a standard error of 3·1 per cent. The tissue blank value for normal brain tissue was approximately 0·069 μg/g.

of us (A.A.S.). The average blood content of brain tissue after washing with saline was approximately

The distribution of diphenylhydantoin was also measured in experimental mouse tumors grown subcutaneously. Two types of experimental tumors were used; one was the Perese ependymoma and the other a spontaneous adenocarcinoma of the breast. An anticonvulsant dose[5] of 14·4 mg/kg was administered intraperitoneally for two consecutive days; the mice then were sacrificed approximately 24 hr after the last dose of the drug had been given.

The concentrations of diphenylhydantoin in human primary brain tumors and in adjacent areas of normal brain tissue are shown in Table 1. The concentrations of the drug were higher in tumor tissues than in normal brain tissues of all patients, thus seeming to indicate a preferential distribution of the drug in human brain tumor tissue (with a statistical probability[6] of P 0·01).

Nine mice bearing adenocarcinomas of the breast were employed in order to determine whether diphenylhydantoin was distributed preferentially in tumors of non-neural origin. The mean concentration of the drug in the tumors was 0·80 $\pm$ 0·35 μg/g tissue, wet weight. The mean drug concentration in the brains was 1·45 $\pm$ 0·13 μg/g, and the mean tumor/brain ratio was 0·58 $\pm$ 0·08. The results indicate that, in this type of experimental tumor the drug showed a greater predilection for brain tissue.

In five mice bearing subcutaneous Perese ependymomas, the mean concentration of drug in the tumors was 0·81 $\pm$ 0·23 μg/g. The mean drug concentration in brains of these mice was 0·94 $\pm$ 0·19 μg/g, and the mean tumor/brain ratio was 0·86 $\pm$ 0·18. These results indicate that, whereas diphenylhydantoin can reach a higher tumor/brain ratio in experimental subcutaneous tumors of neural origin than in tumors of non-neural origin, a preferential distribution in ependymomas was not achieved.

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Departments of Pharmacology and Pathology,
Albany Medical College, and
The Institute of Experimental Pathology and Toxicology,
Albany, N.Y., U.S.A.

IRA ROSENBLUM
ARTHUR A. STEIN

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