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Exposure to Barbiturates *in Utero* and during Childhood and Risk of Intracranial and Spinal Cord Tumors[1]

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ABSTRACT

Barbiturate exposure during childhood was assessed from medical records of 237 children with intracranial and spinal cord tumors and 474 matched controls in a prepaid health plan. *In utero* exposure was also examined in a subset of 86 "cases" and 172 controls whose mothers were health plan members during pregnancy. No association of *in utero* exposure to barbiturates was found [odds ratio (O.R.) = 0.96, 95% confidence interval (C.I.) = 0.47, 1.94]. An association was noted for barbiturate use during childhood (O.R. = 1.80, 95% C.I. = 1.18, 2.74) but was reduced (O.R. = 1.41, 95% C.I. = 0.89, 2.21) when history of epilepsy was taken into account and was no longer significant. An apparent dose-response effect disappeared after adjustment for a history of epilepsy. Although barbiturate use for epilepsy due to preexisting brain tumors clearly explains some of the observed association, the small, residual risk prevents us from ruling out a possible carcinogenic effect of barbiturates. Further study of cohorts of adult as well as childhood users of barbiturates and other anticonvulsants is recommended.

INTRODUCTION

Brain cancer is second only to leukemia as a cause of cancer death among children in the United States (1). In 1985, the 422 deaths from brain cancer in children <14 years old represented 23% of all childhood cancer deaths in this country. Current treatment of brain tumors appears to offer limited promise. Identification of risk factors for this disease, however, may provide useful clues for preventing this important cause of childhood morbidity and mortality.

The possibility that exposure to barbiturate medications, either *in utero* or during early childhood, could increase risk for childhood brain tumors was raised in a relatively small, case-control study by Gold *et al.* (2). Although findings did not quite reach statistical significance in this study, an approximate doubling of risk was suggested among children exposed to barbiturates at either stage of development and this risk appeared consistent whether the comparison group was "normal" children or children with other cancers.

Barbiturates can cause hepatic tumors in mice and in some strains of rats (3, 4). They are known to promote growth of hepatocellular carcinoma *in vitro* (3, 5). Because they are potent inducers of hepatic mixed function oxidases, enzymes involved in both the activation and detoxification of known carcinogens (6), barbiturates could also increase cancer risk by modifying the metabolism of other carcinogens.

Three large follow-up studies in cohorts of adults treated with phenobarbital for epilepsy (7–9) have reported a higher than expected occurrence of brain cancer. However, in each study risk was noted to decline as duration of barbiturate use increased. The authors suggested that the association was more likely due to inclusion in their cohort of patients with undiagnosed brain tumors that led to seizures and phenobarbital use than to a carcinogenic effect of the medication. Such slowly growing, intracerebral tumors have been reported to give rise to seizures that may predate tumor diagnosis by 20 years or more (10).

Confounding by the presence of epilepsy could explain the association of brain cancer with childhood exposure to barbiturates noted by Gold *et al.* (2). In fact, the authors reported that in 3 of the 5 brain cancers associated with barbiturate exposure, the barbiturate was taken for treatment of epilepsy. This confounding factor clearly does not explain the association of *in utero* barbiturate exposure with childhood brain tumors reported in the same study.

In the present study, childhood barbiturate exposure was investigated as a possible risk factor in children with central nervous system cancers and other intracranial tumors identified during a 23-year period within the KPMCP[3] of Northern California. Risk associated with *in utero* exposure was also assessed in a subgroup of these children for whom maternal prenatal medical records were available. Evidence of a dose-response relationship with exposure was sought, and the possible role of epilepsy due to preexisting brain tumors as an explanation for the association with childhood exposure was examined.

MATERIALS AND METHODS

The KPMCP of Northern California is a large, prepaid group practice that grew from fewer than 100,000 members in the early 1950s to approximately 2 million members by the mid-1980s. Comprehensive in- and outpatient services are provided as well as prescription drugs. Members tend to use the plan exclusively (>90% of members in the mid-1970s had no other form of health insurance).

Records of all members hospitalized in KPMCP hospitals with diagnoses of cancer from 1960 to the present have been compiled on computer. These files, supplemented by state and federally supported cancer registry data for five San Francisco Bay Area counties (covering more than 50% of the KPMCP membership), were used to identify children with diagnoses of malignant intracranial or spinal cord tumors. Computerized hospital discharge data beginning in 1971 were used to identify additional cases of nonmalignant tumors of interest to this study.

A total of 304 children, ages 0–19 years, were identified between 1960 and middle 1983. Confirmation of their tumor diagnoses was sought by medical record review. For 275 children, tumor diagnoses were confirmed histologically. For 11 children, confirmation was by clinical diagnosis only. The remaining 18 could not be confirmed because of missing medical records and were excluded from further analyses.

For our study of barbiturate use during childhood, we included 237 of the children who were health plan members at least 6 months prior to their first tumor diagnosis. For our study of *in utero* barbiturate exposure, we included 86 of the children who were born in KPMCP hospitals to mothers who were members of the program during their pregnancies.

For each study child ("case"), two control children ("controls") were selected from the KPMCP membership at the time of the case's tumor diagnosis. Controls were matched to the case on year of birth, sex, date of entry into the KPMCP (nearest medical record number), and birth

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[3] The abbreviations used are: KPMCP, Kaiser Permanente Medical Care Program; C.I., confidence interval.

Table 1 *Distribution of brain and central nervous system tumors by location, histological type, age, sex, and race*

Tumor type	N	% of Total	% of tumor type: <10 yr at diagnosis	% of tumor type: Female	% of tumor type: White
Gliomas	170	72	56	46	88
Astrocytoma	72	30	53	49	94
Ependymoma	20	8	45	30	85
Glioblastoma	6	3	33	50	100
Medulloblastoma	37	16	68	51	78
Other/Unspecified	35	15	63	43	86
Meningiomas	5	2	20	40	100
Pinealomas	8	3	0	38	88
Pituitary	22	9	27	82	95
Craniopharyngiomas	9	4	67	78	100
Adenomas	13	5	0	85	92
Other tumors	15	6	47	67	87
Unknown tumors	17	7	24	53	100
Total	237	100	48	51	90

at a KPMCP hospital (yes or no). Race is not routinely recorded and could not be matched. Controls for 57 cases diagnosed before 1970 were selected from the 1970 membership roster since earlier rosters had not been maintained. Otherwise, controls were selected from the membership roster of the year of the case's tumor diagnosis.

Two medical record reviewers were assigned the task of reviewing medical charts. The first reviewer confirmed the tumor diagnosis and then masked the charts for both cases and controls on the date 6 months prior to the case's tumor diagnosis The second reviewer noted all prescriptions for barbiturate preparations up until the mask date, thus remaining unaware of the case-control status of each subject. Indications for barbiturate therapy were noted, as was the presence of a variety of potential confounders including epilepsy, headache, head injuries, sleep disorders, behavioral problems, other neurological problems, and other hospitalized events.

For the group of 86 cases with 2 matched controls born at KPMCP hospitals, the second reviewer also reviewed the mothers' prenatal records seeking information on dose and duration of barbiturate exposures, indications for use, other conditions, and use of other medications.

Odds ratios and 95% confidence intervals were derived from matched conditional logistic regression (11) equations.

RESULTS

Gliomas were the predominant tumor, accounting for 170 (72%) of the total. All but 14 of the gliomas were primary tumors of the brain; the remainder included 10 spinal cord tumors and 4 cranial nerve tumors. Craniopharyngiomas and certain types of gliomas occurred more frequently in children <10 years of age, whereas meningiomas, pinealomas, and pituitary adenomas occurred almost exclusively in the second decade of life. Overall, 48% of tumors occurred before 10 years of age. Other than pituitary tumors, which occurred more frequently among females, there was little variation between tumor types by sex or race (Table 1).

Morphological distribution was similar in the subgroup of 86 tumors included in the study of maternal barbiturate exposure (77% gliomas, 1% meningiomas, 1% pinealomas, and 8% pituitary tumors). As expected, these cases tended to be younger at diagnosis than those without maternal records, with 65 (77%) <10 years of age at diagnosis. Distributions by race and sex were also similar to those of the larger group.

Among cases, 55 (23%) had a history of childhood exposure to barbiturates, compared with 72 (15%) controls, yielding a matched pair odds ratio of 1.80 [95% confidence interval (C.I.) = 1.18, 2.74]. There was no case-control difference for *in utero* exposure to barbiturates with 19 (22%) case mothers and 39 (23%) control mothers taking barbiturates during pregnancy (matched pair odds ratio = 0.96; 95% C.I. = 0.47, 1.94) (Table 2).

The most common indication for barbiturate use for both cases and controls was gastrointestinal disorder (38% of case users and 29% of control users). This usually involved a combination preparation administered only once to the patient. Treatment for sleep/emotional disorders (usually temporary) and asthma occurred with similar frequency among case and control barbiturate users and tended to be of short duration. Treatment for seizure disorders also occurred with similar frequency, but case barbiturate users tended to be epileptics with long-term exposure, while control barbiturate users suffered from febrile seizures and were treated infrequently.

Epilepsy was more than 6 times as likely to be the indication for initial barbiturate use among cases than among controls. For this reason, duration of use was more frequently prolonged (>1 week) among cases. Phenobarbital, alone or in combination preparations, was the predominant barbiturate exposure in both cases and controls (Table 3).

Among all subjects, there were 21 children with a history of epilepsy (16 cases and 5 controls). Of these, 86% had been exposed to barbiturates compared with 16% of children without such a history. Of 127 subjects with a history of any childhood barbiturate exposure, those with a history of epilepsy were all exposed for >1 week as compared to only 9% of those without epilepsy. A history of epilepsy was also much more frequent among cases (16 cases, 6.8%) than among controls (5 cases, 1.1%). Thus, epilepsy was both an indication for prolonged barbiturate use and a strong predictor of brain tumor and is,

Table 2 *Distribution of childhood and in utero exposure to barbiturates within matched triplet sets by case-control status*

Controls	Childhood exposure[a]: Case exposed	Childhood exposure[a]: Case not exposed	Childhood exposure[a]: Total cases	In utero exposure[b]: Case exposed	In utero exposure[b]: Case not exposed	In utero exposure[b]: Total cases
Both exposed	2	4	6	6	1	7
One exposed	22	38	60	4	21	25
None exposed	31	140	171	9	45	54
Total	55	182	237	19	67	86

[a] Odds ratio = 1.80; 95% C.I. = 1.18, 2.74 (from conditional logistic regression model with barbiturate exposure entered as a dichotomous variable).
[b] Odds ratio = 0.96; 95% C.I. = 0.47–1.94 (from conditional logistic regression model with barbiturate exposure entered as a dichotomous variable).

Table 3 *Indication, type, and duration of first barbiturate use during childhood by case-control status*

	Cases (n = 55) N	Cases (n = 55) %	Controls (n = 72) N	Controls (n = 72) %
Indication for barbiturate use				
Epilepsy	14	25	3	4
Febrile seizure	3	5	19	26
Sleep/emotional disorder	8	15	14	19
Asthma	8	15	12	17
Gastrointestinal disorder	21	38	21	29
Other/unknown	1	2	3	4
Type of barbiturate				
Phenobarbital	47	85	57	79
Pentobarbital	8	15	11	15
Other/unknown	0	0	4	6
Duration of use (includes subsequent prescriptions)				
≤1 wk	38	69	61	85
1 wk–1 yr	5	9	4	6
>1 yr	12	22	7	10

therefore, a potential confounder of both the overall association and the dose-response analyses.

To control for this confounding, a history of epilepsy was included in a conditional logistic regression model along with a variable for any childhood exposure to barbiturates. This adjustment lowered the odds ratio for childhood barbiturate exposure from 1.80 to 1.41 (95% C.I. = 0.89, 2.21). (The odds ratio associated with a history of epilepsy was 5.07 (95% C.I. = 1.77, 14.48).) The addition of other potential confounders, including history of headache, head injury, sleep, behavioral or neurological disorders, and hospitalization, had negligible effects and they were not included in the final model.

Duration of barbiturate exposure and interval between first barbiturate use and the case's tumor diagnosis (or matched start date for controls) was then analyzed with and without adjustment for a history of epilepsy. In the duration analysis, evidence of a dose-response effect suggested before adjustment (Table 4) was not apparent after adjustment.

While small excess risks appeared to be associated with all time periods from exposure (Table 4) before adjustment for a history of epilepsy, only the period of 3–9 years had excess risk after adjustment. Relative reduction of the odds ratio by adjustment for a history of epilepsy was greater the shorter the time interval.

We attempted to determine whether the association of barbiturate use and tumor diagnosis differed between persons with and those without a history of epilepsy. But, the small number of persons with a history of epilepsy, nearly all of whom were exposed to barbiturates, made it difficult to examine them separately or to assess interaction statistically. However, among 216 triplet sets without epilepsy, an estimated relative risk of 1.31 was still noted (95% C.I. = 0.82, 2.10). Because there were only 6 children exposed to barbiturates for 1 week to 1 year and only 2 for >1 year among the 648 children, further analysis by duration was not warranted.

Risk was examined separately by morphological category of brain tumors (Table 5) and also by age and sex. Increased risk was greater for gliomas, the only category large enough to examine separately, than for the other categories of tumors (combined). Adjustment for epilepsy reduced the risk estimate for gliomas more than that for other tumors combined.

After adjustment for a history of epilepsy was made, the risk seen in younger children (<10 years of age at diagnosis) was slightly lower than that in older children (1.23 *versus* 1.52). The increased risk was confined almost entirely to males both before and after adjustment for a history of epilepsy.

In the study of *in utero* barbiturate exposure, there was no association of trimester of exposure or duration of exposure with case-control status. Essentially no differences were found in the indications or types of barbiturates used between mothers of cases and mothers of controls. Fifty percent of all *in utero* exposure occurred during labor and delivery only. Pentobarbital was more often administered than phenobarbital.

Table 4 *Risk associated with duration of barbiturate use and with interval between first use and tumor diagnosis during childhood*

	Unadjusted model		Model adjusted for epilepsy	
Barbiturate exposure	Odds ratio	95% C.I.	Odds ratio	95% C.I.
Duration of use				
Never used	1.00	Reference	1.00	Reference
<1 wk	1.42	0.88, 2.30	1.44	0.89, 2.32
1 wk–1 yr	2.67	0.71, 9.98	1.53	0.35, 6.72
>1 yr	4.43	1.54, 12.75	0.87	0.14, 5.30
(History of epilepsy)			6.93	1.33, 36.17
Interval between first use and tumor diagnosis				
Never used	1.00	Reference	1.00	Reference
≤2 yr	1.41	0.48, 4.13	0.97	0.31, 3.07
3–9 yr	2.20	1.33, 3.64	1.75	1.03, 2.98
≥10 yr	1.13	0.50, 2.58	0.93	0.39, 2.19
(History of epilepsy)			5.12	1.77, 14.78

Table 5 *Risk due to barbiturate use by type of brain tumor, age, and sex at diagnosis*

		Unadjusted model		Model adjusted for epilepsy	
Stratum	No. of cases	Odds ratio	95% C.I.	Odds ratio	95% C.I.
Morphological type					
Gliomas	170	1.96	1.18, 31.98	1.45	0.84, 2.30
Other tumors	67	1.46	0.67, 3.18	1.34	0.58, 3.10
Age at diagnosis (yr)					
<10	114	1.51	0.76, 3.00	1.23	0.59, 2.57
≥10	123	2.00	1.17, 3.43	1.52	0.85, 2.73
Sex					
Female	120	1.17	0.64, 2.13	0.99	0.52, 1.88
Male	117	2.81	1.51, 5.23	2.07	1.06, 4.03

DISCUSSION

This study contrasts with that of Gold *et al.* (2) in finding no association of *in utero* exposure to barbiturates with subsequent risk of brain cancer. Although our study is also relatively small, the odds ratio was slightly <1.0 and the upper bound of the 95% confidence limit about this odds ratio (1.94) indicates that a doubling of risk, as suggested in the previous study, is unlikely.

The present study measured barbiturate exposure from prenatal medical records rather than from self-report, thereby avoiding the possibility of recall bias and allowing a more complete assessment of exposure. The frequency of barbiturate use in our study was approximately 2–3 times that observed by Gold *et al.* for cases and four to 7 times that observed by Gold *et al.* for controls, suggesting that medical record review yields more complete ascertainment of exposure. The absence in our study of any evidence for a dose-response effect or for a specific period of pregnancy during which risk was increased is further evidence against a causal association. These negative findings for *in utero* exposure to barbiturates are reassuring and provide some confirmation of the negative findings of two small cohort studies (12, 13).

Studies of childhood exposure to barbiturates are more difficult to interpret because barbiturates are frequently used to treat epilepsy, a condition which can be caused by an occult brain tumor. Not surprisingly, a history of epilepsy was strongly associated with childhood exposure to barbiturates, particularly with use for >1 week. Children with epilepsy are more likely to take barbiturates for a prolonged period than children with gastrointestinal disorders or sleep disturbances. Adjustment for a history of epilepsy reduced the overall odds ratio for barbiturate exposure substantially and also eliminated the apparent dose-response effect. This lowering effect was greater for the large group of gliomas than for other central nervous system tumors. Gliomas are the type of brain tumor that has been associated with epilepsy in histopathological studies (10). This lowering effect was also greater the shorter the interval between

first barbiturate use and tumor diagnosis, suggesting that some tumors may already have been formed at the time of barbiturate administration.

Another large study from Kaiser Permanente also suggests that epilepsy could confound studies of antiepileptics and brain cancer. In a cohort of 145,000 pharmacy users, most of whom were adults, we observed a slight, but not statistically significant, increase in incidence of brain cancer among 5,834 recipients of phenobarbital prescriptions, many of whom did not have epilepsy (14–16). The standardized morbidity ratio was approximately 1.6 after 5 years of follow-up ($P = 0.48$) and declined to 1.4 at 13 years of follow-up. No increase in brain cancer incidence was noted in 2,884 users of secobarbital or in 2,186 users of pentobarbital. The incidence of brain cancer was also markedly higher among 954 users of diphenylhydantoin (standardized morbidity ratio = 9.9, $P = 0.04$), a drug used almost exclusively to treat epilepsy. Taken together, these findings are consistent with the hypothesis that the presence of epilepsy in a small subgroup of the phenobarbital users may have led to a non-causal association of barbiturate use with brain cancer.

Despite this evidence of confounding, a small, nonsignificant increase in risk associated with any childhood barbiturate exposure persisted after adjustment for a history of epilepsy. The absence of a dose-response effect and the isolation of the effect to one sex (boys) suggest that this association may be due to chance rather than a causal relation. That an effect was found for very small doses raises questions about the biological plausibility of tumor promotion (see below). Nevertheless, the confidence interval for this estimate included the effect size of 2.0 noted by Gold *et al.* (2).

While near uniformity of exposure to phenobarbital among the small number of epileptics in our study prevented us from examining this group separately, there are at least two reasons to hypothesize the isolation of a carcinogenic effect among epileptics in general. First, the carcinogenicity of phenobarbital in most animal models is thought to be due to a promoting rather than an initiating effect (3, 5). Tumor promotion clearly depends on prolonged exposure (17). Exposure to phenobarbital in the absence of epilepsy may be too brief in many patients to result in a detectable increase in risk. Second, among persons with epilepsy, a portion are likely to have occult brain tumors. Barbiturates may act as promoters of these preexistent lesions, making them more likely to grow and come to clinical attention. If the presence of epilepsy serves as a marker for the presence of these preexisting tumors, it defines a group in which the promoting effect of barbiturates is more likely to be noted.

In conclusion, we found no evidence of an association of *in utero* barbiturate exposure with brain cancer in a case-control study that used medical records rather than maternal recall to determine exposure. An association of childhood barbiturate exposure with brain cancer, of a magnitude similar to that reported previously, was explained, at least in part, by use of barbiturates for epilepsy, itself a strong predictor of brain cancer. After we adjusted for a history of epilepsy, the association was no longer significant and there was no evidence of a dose-response effect. Nevertheless, a small residual increase in risk was apparent whether or not the barbiturates recorded were taken for epilepsy. Our study can therefore not entirely rule out the possibilities that prolonged exposure to barbiturates might either promote the growth of preexistent tumors or initiate tumors *de novo*.

Heretofore, controlled studies of the association of barbiturates with brain cancer in cohorts of epileptics have not been feasible because essentially all persons were treated with phenobarbital. Administration of barbiturates to children with epilepsy has declined in recent years in favor of other medications. More recent cohorts may provide enough epileptics, both exposed and unexposed to barbiturates, to compare with one another. Identification of children with febrile seizures, who sometimes, but not invariably, receive barbiturates, could also provide sufficient numbers of exposed and unexposed subjects for comparison.

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