

Short Communication

Barbiturates, Smoking, and Bladder Cancer Risk¹

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Abstract

Phenobarbital treatment has been observed to be negatively associated with bladder cancer risk in a few studies. It has been suggested that phenobarbital may induce drug-metabolizing enzymes that detoxify the bladder carcinogens found in cigarette smoke. We examined the relationship of barbiturate use to bladder cancer risk and the potential modifying effect of cigarette smoking in a large cohort of Kaiser Permanente Medical Care Program members with computerized pharmacy prescriptions and smoking information. Newly diagnosed bladder cancers were identified among individuals in the study cohort by linkage with data from cancer registries. The overall standardized incidence ratio associated with barbiturate use was 0.71 [95% confidence interval (CI), 0.51–0.99]. Among current smokers, former smokers, and never smokers, the standardized incidence ratios were 0.56 (95% CI, 0.23–1.16), 0.68 (95% CI, 0.27–1.40), and 1.04 (95% CI, 0.48–1.98), respectively. Although our estimates were imprecise, the finding of an inverse association between barbiturate treatment and bladder cancer risk only among current and former cigarette smokers is consistent with the hypothesis that treatment with these medications induces drug-metabolizing enzymes that deactivate bladder carcinogens found in cigarette smoke.

Introduction

Olsen *et al.* (1) observed a negative association between phenobarbital use and bladder cancer risk among 8004 patients treated at an epilepsy center in Denmark. The relative risk was 0.6 (95% CI,³ 0.3–0.9). A study linking computerized pharmacy records from 1969 to 1973 for a cohort of 143,574 members of a Northern California health maintenance organization to cancer registry information collected through 1984 also showed an inverse relationship between phenobarbital use and bladder cancer risk (2). The SIR was 0.44 ($P < 0.05$).

Olsen and colleagues (3, 4) proposed and investigated the hypothesis that treatment with phenobarbital may induce drug-

metabolizing enzymes that detoxify bladder carcinogens, such as 4-aminobiphenyl, that are found in cigarette smoke. They compared levels of 4-aminobiphenyl DNA adducts in hemoglobin among epileptic patients who were being treated chronically with phenobarbital to the DNA adduct levels among individuals treated with other anticonvulsants. Among smokers, adduct levels were lower in the phenobarbital-treated group. No difference in adduct levels was observed for nonsmokers.

We have updated and reanalyzed our health maintenance organization data to confirm the inverse association of phenobarbital or barbiturates in general with bladder cancer risk and to determine whether our data might support a modification of this relationship by cigarette smoking status.

Materials and Methods

Our initial cohort included 143,574 Kaiser Permanente health plan members with computerized pharmacy prescriptions. Between July 1969 and August 1973, all prescriptions filled at the outpatient pharmacy for the San Francisco Kaiser Permanente facility were stored on a computer. We identified subjects for whom computerized smoking information was also available because they had received a MHC. The MHC is a voluntary, comprehensive health evaluation used by members and their physicians for routine checkups. The Kaiser Permanente membership is similar to the general population but tends to be somewhat more educated. In addition, members who received the health checkup were, on average, slightly older, more educated, and more likely to be black (5). If a member had more than one MHC, the last MHC between 1964 and 1973 was used. We examined the use of phenobarbital alone, as well as the use of any barbiturates [these primarily included three single preparations (pentobarbital sodium, phenobarbital, and secobarbital sodium) and two barbiturate mixtures (butabarbital, phenobarbital, and secobarbital; and amylal and secobarbital)]. As in our earlier study (2), newly diagnosed bladder cancers were identified among individuals in the study cohort by linkage with data from the internal Kaiser Permanente cancer registry and the Northern California Cancer Center, which is part of the Surveillance, Epidemiology, and End Results Program. Members with bladder cancer diagnosed prior to the beginning of follow-up were excluded. Otherwise, all cases of primary bladder cancer were part of our analysis, including those identified by death certificates. Follow-up began at the time of their first prescription of the drug(s) of interest in the pharmacy database and ended at the diagnosis of bladder cancer, departure from the Kaiser Permanente Medical Care Program for any reason (including death), or December 1992, whichever occurred first. SIRs were calculated as the ratios of the number of new cases of cancer observed in users of the drugs under consideration to the number expected. Expected numbers were obtained by calculating standard incidence density rates for cancer in the entire cohort (by sex and 10-year age interval) and applying these rates to the age- and sex-specific distribution of follow-up time for users of the drug(s) of interest. Ninety-five % CIs were calculated by applying the Poisson distribution to the observed number of cases.

Information about barbiturate exposure among the study cohort was also obtained from the MHC standardized medical

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³ The abbreviations used are: CI, confidence interval; SIR, standardized incidence ratio; MHC, multiphasic health checkup.

history questionnaire, which included the item "In the past year have you often taken any phenobarbital or barbiturates?" The correspondence between self-reported barbiturate exposure and the pharmacy database was extremely poor. For example, only 34% of the 1,749 individuals in the pharmacy database who answered "yes" had received one or more barbiturate prescriptions during the previous year. We believe that the pharmacy data are a more objective and reliable measure of barbiturate exposure than self-report, and the results presented here are based on barbiturate use as determined by the drug-dispensing data. The questionnaire-related findings are available from the authors upon request.

Results

There were a total of 10,368 individuals in our pharmacy database who had been prescribed barbiturates between 1969 and 1973 and who were at risk for primary bladder cancer. As of 1992, 34 cases of bladder cancer had been diagnosed among these barbiturate users. The SIR was 0.71 (95% CI, 0.51–0.99). Restricting the study group to those with smoking information reduced the number of barbiturate users to 5142. The SIRs for current smokers and former smokers were 0.56 (95% CI, 0.23–1.16) and 0.68 (95% CI, 0.27–1.40), respectively, whereas the SIR for never smokers was 1.04 (95% CI, 0.48–1.98). When exposure was restricted to individuals with at least two prescriptions of any barbiturate, the number of users was substantially reduced, but the pattern of risk remained largely the same. However, when exposure was restricted to the use of phenobarbital, the pattern previously involving no reduced risk among the never smokers disappeared, but the numbers of cases in each smoking category were quite small (Table 1).

Discussion

Cigarette smoking is an established risk factor for bladder cancer, with smokers experiencing a risk that is ~2–3 times that of nonsmokers (6). Two bladder carcinogens contained in cigarette smoke, the aromatic amines 4-aminobiphenyl and 2-naphthylamine, are believed to be likely smoking-related causative agents of bladder cancer (7). Hemoglobin adduct levels of several aromatic amines, including 4-aminobiphenyl and 2-naphthylamine, have been found to be correlated with smoking patterns (6).

The carcinogenic potential of 4-aminobiphenyl and other bladder carcinogens is thought to be regulated by a complex system of metabolizing enzymes involved in the oxidation and detoxification of drugs and other xenobiotic compounds (e.g., cytochrome p450 enzymes, *N*-acetyltransferases, and glutathione *S*-transferases; Ref. 6). The activity of these metabolizing enzymes may vary by genotype and, for cytochrome p450 enzymes and glutathione *S*-transferases, by induction from environmental exposures (6–8). It is well established that barbiturates, such as phenobarbital, are potent inducers of certain cytochrome p450 enzymes and glutathione *S*-transferases (8, 9). However, it is unclear the extent to which barbiturates may be important inducers of specific enzymes involved in the activation of aromatic amines found in cigarette smoke to their carcinogenic forms and/or the enzymes involved in detoxifying these compounds.

The inverse association of phenobarbital and barbiturates use with risk of bladder cancer was confirmed, but the small number of bladder cancer cases in specific smoking categories resulted in risk estimates that were unstable and the associations observed may have been the result of chance alone. Nevertheless, our barbiturate data, showing a risk reduction only among current and

Table 1 SIRs for the association of barbiturates and bladder cancer, stratified by smoking status

	No. of users	No. of exposed cases	SIR ^a	95% CI
Barbiturates				
1+ prescriptions	10,368 ^b	34	0.71	0.51–0.99
Current smokers	1,901	7	0.56	0.23–1.16
Ex-smokers	1,120	7	0.68	0.27–1.40
Never smokers	2,121	9	1.04	0.48–1.98
2+ prescriptions	4,658 ^b	17	0.65	0.38–1.04
Current smokers	881	3	0.45	0.09–1.32
Ex-smokers	561	4	0.69	0.19–1.77
Never smokers	1,046	6	1.24	0.46–2.70
Phenobarbital				
1+ prescriptions	5,850 ^b	13	0.50	0.27–0.85
Current smokers	1,009	3	0.45	0.09–1.33
Ex-smokers	578	4	0.79	0.21–2.01
Never smokers	1,222	3	0.59	0.12–1.73
2+ prescriptions	2,444 ^b	7	0.52	0.21–1.07
Current smokers	433	2	0.60	0.01–1.66
Ex-smokers	277	2	0.72	0.01–2.01
Never smokers	567	2	0.79	0.01–2.19

^a Standardized for age and sex.

^b Not restricted to individuals with information on smoking status.

former cigarette smokers, are consistent with the hypothesis that treatment with these medications induces drug-metabolizing enzymes that detoxify bladder carcinogens found in cigarette smoke. A reduction in an already small number of cases may explain why we did not observe this same pattern of risk when exposure was restricted to treatment with phenobarbital. Additional studies are needed to further examine the potential modifying effect of treatment with barbiturates on the association of smoking and bladder cancer risk. Because barbiturate use is associated with a decreased risk of bladder cancer, such studies are apt to suffer from a paucity of cases, especially when the treated patients are further subdivided by smoking status.

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