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Short-Term Chloral Hydrate Administration and Cancer in Humans

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Abstract

Objective: Chloral hydrate, used as a hypnosedative in adults and children, has been shown to be genotoxic and carcinogenic in animal studies. We investigated the potential causal association between chloral hydrate exposure and cancer risk in humans.

Methods: Cancer incidence was previously determined via biennial screening analyses of the 215 most commonly used drugs between 1976 and 1998 for a cohort of 143 574 outpatients at Kaiser Permanente who had prescriptions filled between 1969 and 1973. Among users of chloral hydrate, statistically significant elevations in standardised morbidity ratios were observed during various years for cancer at five anatomical sites, including the lung, stomach, prostate, skin melanoma and mouth floor. In this analysis, these associations were investigated using: (i) a dose-response analysis among exposed subjects; and (ii) a two-stage design with exposed and non-exposed persons.

Results: There was evidence of an increasing risk of prostate cancer with increasing number of dispensings of chloral hydrate, which persisted after controlling for benign prostatic hypertrophy, vasectomy and obesity; however, the trend was not statistically significant. There was no evidence of a dose-response relationship between chloral hydrate and risk of any of the other four cancers. In the two-stage design, analyses comparing exposed and unexposed subjects showed no increased risk of cancer after controlling for confounding variables; however, the data were suggestive for prostate cancer, where the increased risk associated with chloral hydrate exposure after adjustment for confounding variables persisted. No dose-response relationship was seen for any of the other four cancer sites.

Conclusions: To our knowledge, this is the first study to examine the relationship between chloral hydrate exposure and cancer risk in humans. There was no persuasive evidence to support a causal relationship between chloral hydrate exposure in humans and the development of cancer. However, statistical power was low for weak associations, particularly for some of the individual cancer sites. Although animal data using much higher doses of chloral hydrate have demonstrated its genotoxicity and carcinogenicity, the effects of chloral hydrate in humans are still uncertain.

Introduction

Chloral hydrate has been used as a hypnosedative since 1869.[1] It is indicated for use in both adults and children, but in paediatric patients it is typically used as a sedative during diagnostic, therapeutic and dental procedures.[1-3] As a hypnotic, chloral hydrate induces sleep without the disruption of rapid eye movement episodes[4] and it is sold as an over-the-counter sleep aid in Europe and Australia.[1,5] Chloral hydrate is also a by-product formed during the disinfection of drinking water[6] and has been detected as an environmental contaminant after the bleaching of softwood pulp.[7]

Recent animal studies have shown chloral hydrate to be genotoxic, causing aneuploidy in eukaryotic microbial organisms, mammalian cells in culture and mammalian germ cells *in vivo*.[8-11] Chloral hydrate may also be carcinogenic, as it is a major metabolite of trichloroethylene (TCE), a general anaesthetic, which was banned in 1977 by the US FDA because of its ability to induce malignancies in rodents.[8,12] TCE is also currently listed by the International Agency for Research on Cancer (IARC) as a probable human carcinogen (Group 2A), based on sufficient evidence in animals and limited evidence in humans.[13] Studies of the potential carcinogenicity of chloral hydrate in mice have demonstrated that it has the ability to induce hepatocellular adenomas and carcinomas.[11,14-20]

Given the above evidence of the genotoxicity and carcinogenicity of chloral hydrate, and its continued use in the clinical arena, the paucity of data regarding its possible carcinogenicity in humans is of concern. Because of the differences in metabolism and predisposing cofactors between species, the rodent data collected thus far do not permit accurate assessment of the potential risks associated with chloral hydrate exposure in humans.[3] To our knowledge, this study is the first to follow a large group of humans exposed to chloral hydrate in order to assess the development of cancer. The current study explores the potential causal association between chloral hydrate exposure and cancer risk.

Methods

Study Population

Cancer incidence was previously determined via biennial screening analyses of the 215 most commonly used drugs and drug groups between 1976 and 1998 for a cohort of 143 574 Kaiser Permanente Medical Care Programme members who had prescriptions filled between 1969 and 1973, and recorded in computer storage.[21-23] These patients comprised both an ethnically and socioeconomically diverse population, who had received both inpatient and outpatient care within this prepaid system. Cancer occurrence was ascertained via the local tumour registry and hospital records of all northern California hospitals in the Kaiser Permanente programme. These records were linked to the pharmacy records by each patient's unique medical record number. Before registry data were complete for the programme, all cancers diagnosed were verified by the review of medical records by a trained medical record analyst.

Drug Screening

The number of new cases of cancer developing at each of the 54 anatomical sites and at all sites combined was determined for the users of each drug or drug group and compared with the number expected in that group based on the experience of the entire cohort. Age- and sex-adjusted standardised morbidity ratios were determined by dividing the number of cancers observed among the users of a certain drug by the number expected. To address the possibility of a drug being prescribed for symptoms related to a cancer before it was diagnosed, lag analyses (after 1 and 2 years) were performed. These analyses required that any cancer case that was counted had to be diagnosed after a specified time interval from the first drug dispensing. Associations with chloral hydrate described in the following paragraphs persisted in lag analyses.

Chloral Hydrate Users

There were 2290 chloral hydrate users within the pharmacy cohort (1.6% of the members), when all doses and varying durations of use of the drug were included. By 1998, there were 285 cancer cases among these chloral hydrate users. Table I sum-

Table I. Cumulative incidence of cancer occurrence among chloral hydrate users by end of follow-up, 1976–98

Site	No. of cases by 1998 (observed/expected)	Year (end of follow-up) in which the difference between the observed and expected no. of cases was significant at the $p < 0.05$ level
Mouth floor	3/0.6	1976, 1984, 1998
Stomach	17/8.2	1980, 1992, 1994, 1996, 1998
Lung	46/36.7	1986, 1988
Skin melanoma	13/9.3	1980, 1982, 1984, 1986, 1988, 1990, 1992
Prostate	37/36.6	1976
Kidney	1/5.1	1988, 1990, 1992
All cancer	285/258.0	1982

marises the cumulative incidence of these various cancers by 1998, at sites where and when a statistically significant departure from expected was ever observed.

Preliminary data in paediatric, adolescent and young adult patients (<25 years of age) who were exposed to chloral hydrate (n = 391) showed that only seven cases of cancer (cervix: n = 2, breast: n = 2, ovary: n = 1, chorioepithelium: n = 1, lymphatic leukaemia: n = 1) occurred between the first computer-recorded dispensing of the drug and the end of 1998. Only two of these cases were diagnosed when the patient was <25 years of age.

Since the number of excess cancers in 1982 was explained by the cancer sites mentioned in table I (mouth floor, stomach, lung, skin melanoma and prostate) and by those that occurred in patients who were adults when they received chloral hydrate, this analysis of chloral hydrate exposure and cancer in humans was restricted to these sites only and to patients aged ≥25 years. Kidney cancer was not examined further since the statistically significant departure was negative.

Dose-Response Analysis

Selection of Cases

Exposed cases were defined as chloral hydrate users within the Kaiser Permanente cohort who developed cancer at the sites associated with a statistically significant risk increase in at least one of the biennial analyses. Only the cases through the last year of statistically significant follow-up were included: mouth floor (n = 3), stomach (n = 17), lung (n = 38), skin melanoma (n = 13) and prostate (n = 14), comprising a total of 85 cases.

Selection of Controls

Controls for the dose-response analysis were defined as chloral hydrate users who did not develop cancer (excluding non-melanoma skin cancer) between the date of the first visit to Kaiser Permanente and an assigned cutoff date, which allotted the same length of exposure history as the case to which the controls were matched. Four exposed controls were individually matched to each exposed case on the basis of age at first prescription of chloral hydrate (during the computerised pharmacy database between 1969 and 1973), sex and the duration of exposure history. If more than four controls per case were available, those controls closest in age to the case were selected. If less than four controls per case were available, then controls were matched on age up to within 5 years of that of the case.

Two-Stage Design

In order to assess potential confounding more fully, additional data were collected on unexposed persons using a two-stage design.[24] Two-stage designs are advantageous when exposure and disease are rare in a study, and collection of confounder information can be very costly. Two-stage sampling designs provide efficient ways to control for the effects of confounding without having to survey the entire study population.

In stage-1, exposure (chloral hydrate vs no chloral hydrate) and disease status (development of any of the five cancers of interest vs no development of any cancer) were determined for all subjects from the original Kaiser Permanente pharmacy cohort. In stage-2, covariate information was collected on a subset of this original population. Typically, the sampling scheme for stage-2 is designed to generate a more precise estimate of risk, since the sub-sample

selected is enriched with both diseased and exposed individuals.[24]

In this two-stage design, the stage-2 sample consisted of the same exposed subjects selected for the dose-response analysis, as well as an additional 85 unexposed cases diagnosed with the cancers of interest and 85 unexposed controls. Unexposed cases were defined as subjects who had never used chloral hydrate and had developed cancer at one of the five cancer sites described earlier, and who were the same age as the exposed case (±2 years) at the first prescription of any drug. Unexposed controls were defined as subjects who had never used chloral hydrate, were the same age as the exposed case (±2 years) at the first prescription of any drug and did not develop any cancer during an equal length of follow-up as the unexposed case. If a prescription for chloral hydrate was found in the chart of an 'unexposed' subject, then a replacement for that subject was selected. In total, about 30 replacements were needed.

Data Collection

Retrospective chart review by trained medical record analysts was performed on each subject using a pre-tested chart review form. Exposure history was collected between the date of the first visit to Kaiser Permanente and the cancer diagnosis date for cases, and an assigned cutoff date for controls, as described earlier. The medical charts generally dated back as far as the early 1950s and follow-up typically lasted through the late 1970s or early 1980s. All pertinent information was recorded, including demographics, medical history (including the cancer diagnosis) and chloral hydrate prescriptions (from both the chart and computer-listed dispensings), including the number of dispensings, indication, strength, frequency, number of pills prescribed, number of refills and excess use. Data regarding potential confounding variables for each cancer type were collected (table II). Quality control measures were instituted with cross-review of every tenth chart by both the chart reviewers and the study coordinator, with tracking of error rates. The error rate for the first week of the study was about 8%, at the midpoint of data collection it was about 3%; from this point onwards the rate decreased until it was approximately about 1% or less at the end of data collection.

Statistical Power and Data Analysis

In the dose-response analysis, the power for detecting an odds ratio of 2.0, based on 85 exposed cases matched to four exposed controls each, was 77%, assuming the probability of high dose (defined as four or more dispensings) at 40% and $\alpha = 0.05$. The power for detecting an odds ratio of 2.5 with the same assumptions was 95%.

No prior power calculations were performed for the two-stage design. Instead, confidence intervals were viewed as an indicator of the study's power.

Descriptive data regarding chloral hydrate use were examined. The dose-response analysis was conducted on exposed subjects only, using conditional logistic regression. Odds ratios (ORs) and 95% confidence intervals for the risk of cancer with an increasing number of dispensings of chloral hydrate were calculated, adjusting for matching variables (age and sex) as well as potential confounding variables. The Cochran-Armitage test for trends was used to assess dose response across categories of chloral hydrate dispensings. Unconditional logistic regression was used to analyse the two-stage sample using the Weinberg and Wacholder method,[25] which accounts for the sampling fraction for each

Table II. List of potential confounding variables by cancer site

Site	Confounding variables/risk factors
Mouth floor	Family history of cancer, cigarette, cigar, pipe smoking, chewing tobacco, use of alcohol
Stomach	Family history of cancer, gastrointestinal bleeding, ulcer, gastritis, hiatus hernia, gastroesophageal reflux disease, previous stomach surgery, cigarette, cigar or pipe smoking, alcohol use, high salt intake, mention of obesity
Lung	Family history of cancer, cigarette, cigar or pipe smoking, chronic bronchitis, emphysema, chronic obstructive pulmonary disease
Skin melanoma	Family history of cancer, excessive exposure to ultraviolet radiation, fair complexion (race/ethnicity), premalignant conditions
Prostate	Family history of cancer, black ethnicity, benign prostatic hyperplasia, vasectomy, obesity, cigarette, cigar or pipe smoking

subject selected for stage-2 using 'offsets' in standard logistic regression. For this analysis, subjects were treated as frequency matched based on 10-year age groups, using sampling fractions for each subject within each age group. Risk of cancer associated with chloral hydrate exposure was examined both dichotomously (i.e. exposed vs unexposed), as well as using a dose-response analysis with zero dispensings as baseline and adjusting for age group, sex and confounding variables. Both the dose-response analysis and the two-stage analysis were performed for all cancers studied, examining both combined and site-specific incidences. Results for lung, stomach and prostate cancer are shown. Because of the large number of confounding variables examined, only those that produced at least a 10% change in odds ratio estimates or that removed the association of chloral hydrate are reported.

All analyses were conducted using the Statistical Analysis Software system (version 8).

Results

At the first prescription of chloral hydrate found in the medical chart, approximately 40% of exposed cases were between the ages of 60 and 69 years and one-fourth were aged ≥70 years (table III). The majority of cases were male and Caucasian. The occupations of those who used chloral hydrate varied widely; however, the most common occupation for both exposed cases and controls was that of 'housewife'.

Overall, exposed controls had a higher mean number of dispensings of chloral hydrate in its capsule form than exposed cases (3.6 [± 3.4] vs 3.3 [± 5.4], $p < 0.0001$, respectively) [table IV]. Prostate cancer cases had the highest proportion of cases with four or more dispensings of chloral hydrate and, thus, the highest mean number of dispensings compared with other exposed cases. The majority of exposed cases and controls used chloral hydrate in its capsule form at a dosage of 500 mg/day, as a hypnotic and for use at home (data not shown).

There was no evidence of a chloral hydrate dose response for all cancers combined or for any individual cancer site (table V). For prostate cancer, some suggestion of an increasing risk with an increasing number of dispensings of chloral hydrate was evident, which persisted after controlling for benign prostatic hypertrophy, vasectomy and obesity. However, all tests for a trend were non-significant.

In the two-stage analysis, elevated risks of cancer were seen when comparing exposed and unexposed subjects overall and by cancer site; however, these risks were either reduced or eliminated when con-

Table III. Demographic characteristics of chloral hydrate users who developed cancer (cases; n = 85) and a sample of other chloral hydrate users (n = 340)

Variable	Cases [no. (%)]	Other chloral hydrate users [no. (%)]
Age at first prescription (chart)		
20–29	0	1 (0.3)
30–39	3 (4)	13 (4)
40–49	10 (12)	44 (13)
50–59	18 (21)	67 (20)
60–69	33 (39)	123 (36)
≥70	21 (25)	90 (26)
Sex		
Male	59 (69)	234 (69)
Female	26 (31)	104 (31)
Ethnicity		
White	67 (79)	265 (78)
Black	9 (11)	38 (11)
Asian	5 (6)	21 (6)
Other	2 (2)	13 (4)
Unknown	2 (2)	3 (0.9)
Occupation		
Housewife	11 (13)	41 (12)
Office worker/secretary	7 (8)	9 (3)
Longshoreman	5 (6)	38 (11)
Postal worker	4 (5)	3 (0.9)
Banker/businessman	3 (4)	1 (0.3)
Clerk/clerical	3 (4)	6 (2)
Waiter/waitress	3 (4)	11 (3)
Custodian/janitor	3 (4)	3 (0.9)
Carpenter/contractor	2 (2)	9 (3)
Bartender	2 (2)	7 (2)
Engineer	2 (2)	9 (3)
Machinist	2 (2)	4 (1)
Nurse/nurse's aide	1 (1)	7 (2)
Painter	1 (1)	7 (2)
Cook/chef	0	16 (5)
Salesclerk	0	9 (3)
Printing/newspaper	0	9 (3)
Electrician	0	6 (2)

Table IV. Distribution of chloral hydrate dispensings by cancer site and case/control status

Total number of dispensings by cancer site	Cases [no. (%)]	Other chloral hydrate users [no. (%)]
Overall	**n = 85**	**n = 340**
1	32 (38)	140 (41)
2–3	30 (35)	110 (32)
4+	23 (28)	90 (27)
Mean (SD)	3.3 (3.4)	3.6 (5.4)
Minimum, maximum	1, 21	1, 53
Median	2.0	2.0
Lung cancer	**n = 38**	**n = 152**
1	17 (44)	64 (42)
2–3	10 (27)	48 (32)
4+	11 (29)	40 (27)
Mean (SD)	2.7 (2.2)	3.6 (5.1)
Minimum, maximum	1, 8	1, 35
Median	2.0	2.0
Stomach cancer	**n = 17**	**n = 68**
1	5 (29%)	29 (43%)
2–3	10 (59%)	26 (38%)
4+	2 (12%)	13 (19%)
Mean (SD)	3.3 (4.7)	2.6 (2.7)
Minimum, maximum	1, 21	1, 18
Median	2.0	2.0
Prostate cancer	**n = 14**	**n = 56**
1	3 (21)	20 (36)
2–3	5 (36)	17 (31)
4+	6 (43)	19 (34)
Mean (SD)	4.3 (3.7)	4.4 (7.9)
Minimum, maximum	1, 13	1, 53
Median	2.5	2.0

founding variables were taken into account (table VI). Although the data were suggestive for prostate cancer, which again showed an increasing risk with an increasing number of dispensings of chloral hydrate after adjusting for benign prostatic hypertrophy, vasectomy and obesity, no dose-response relationship was seen for any of the other four cancer sites.

Discussion

This study, to our knowledge, is the first to examine chloral hydrate use and cancer risk in humans. There was no persuasive evidence to support a causal relationship between chloral hydrate exposure and the development of cancer. With the exception of prostate cancer, which showed some suggestion of an increasing risk of cancer with an increasing number of chloral hydrate dispensings that persisted after controlling for confounding variables, both the dose-response analysis in exposed subjects only and a dose-response analysis in both exposed and unexposed persons did not reveal any trends associating chloral hydrate use with cancer risk. However, statistical power was low for weak associations, particularly for some of the individual cancer sites.

In general, chronic exposure to chloral hydrate does not cause adverse effects in the liver of rats or mice until the exposure approaches 135 and 160 mg/kg/day, respectively.[26] However, in recent studies,[18,19] a marginally significant increase in the combined incidences of hepatocellular adenomas and carcinomas was observed in the low dose group (13.5 mg/kg) of a multidose study of male rats[18] and in the low dose group (17.9 mg/kg/day) of *ad libitum*-fed male rats.[19] Still, there was no indication of dose-response in either study, suggesting that the increase in tumours was not treatment related. In a recent gavage study,[27] chloral hydrate increased terminally adjusted liver tumour incidence in both dietary controlled and ad libitum-fed mice at doses of 25, 50 or 100 mg/kg, but a statistically significant dose response was observed in only the dietary controlled mice.

The current study in humans indicated that, despite chloral hydrate's genotoxicity and carcinogenicity in rodents, its harmful effects may not be evident in humans. It is possible that humans are not exposed to chloral hydrate at the frequency or concentrations required to induce carcinogenesis. The general body of animal studies suggests that the mechanism of carcinogenesis of chloral hydrate in rodents appears to be nonlinear,[12] with very high doses being sufficient to cause mutagenic or clastogenic activity. The recommended dosage of chloral hydrate for use as a sedative in adults is 250mg, three times a day (equivalent to 10.7 mg/kg/day); the recommended dose as a hypnotic is 500–1000mg at bedtime (equivalent to 7–14 mg/kg).[28] Based on the data collected in this study, it appears that most patients who were prescribed chloral hydrate received 500mg only a few times for use in the short-term (e.g. for insomnia), with most patients receiving only 1–3 dispensings in total.

Table V. Odds ratios (OR) and 95% confidence intervals for risk of cancer in relation to number of dispensings of chloral hydrate in exposed cases and controls, overall and by cancer site. Additional characteristics listed were potential confounding variables included in the multivariate analyses

Number of dispensings and confounding variables by cancer site	Cases [no.]	Controls [no.]	OR[a]	95% CI
Overall				
1 (reference)	32	140	1.0	
2–3	30	110	1.2	0.67, 2.0
4+	23	90	1.1	0.61, 2.0
Lung cancer				
1 (reference)	17	64	1.0	
2–3	10	48	0.84	0.34, 2.1
4+	11	40	0.75	0.29, 2.0
Current smoker	24	49	9.0	2.4, 33.4
Ex-smoker	8	41	3.4	0.81, 14.2
Stomach cancer				
Model 1				
1 (reference)	5	29	1.0	
2–3	10	26	2.2	0.55, 9.0
4+	2	13	0.79	0.11, 5.6
Ulcer	11	21	6.4	1.3, 30.2
Model 2				
1 (reference)	5	29	1.0	
2–3	10	26	2.1	0.55, 7.8
4+	2	13	0.81	0.11, 6.3
Bleeding	6	9	8.5	1.6, 45.1
Model 3				
1 (reference)	5	29	1.0	
2–3	10	26	4.5	0.83, 24.6
4+	2	13	0.63	0.08, 5.0
Hiatus hernia	12	18	14.8	2.6, 84.8
Prostate cancer				
Model 1				
1 (reference)	3	20	1.0	
2–3	5	17	2.1	0.42, 10.6
4+	6	19	2.2	0.47, 10.2
Benign prostatic hypertrophy	12	33	3.7	0.78, 17.8
Model 2				
1 (reference)	3	20	1.0	
2–3	5	17	1.9	0.39, 9.6
4+	6	19	3.1	0.59, 15.8
Vasectomy	5	7	4.7	1.0, 22.0
Model 3				
1 (reference)	3	20	1.0	
2–3	5	17	1.9	0.38, 9.1
4+	6	19	1.9	0.42, 8.3
Obesity	7	26	1.1	0.35, 3.4

a Adjusted, in addition, for age and sex. Reference groups were one dispensing of chloral hydrate, never smoked (for smoking), and the absence of each medical condition listed.

Table VI. Odds ratios (ORs) and 95% confidence intervals for risk of cancer in relation to exposure status and number of dispensings of chloral hydrate and additional potential confounding variables included in multivariate analyses of two-stage sample

Exposure status and potential confounding factors by cancer site	Cases [no.]	Controls [no.]	OR[a]	95% CI
Overall				
Model 1				
Exposed	85	340	1.0	0.69, 1.6
Unexposed (reference)	85	85	1.0	
Smoker	73	147	3.6	2.1, 6.2
Ex-smoker	50	102	2.9	1.7, 5.2
Hiatus hernia	61	126	1.8	1.2, 2.7
Model 2				
0 (reference)	85	85	1.0	
1 dispensing	32	140	0.95	0.56, 1.6
2–3 dispensings	30	110	1.2	0.71, 2.1
4+ dispensings	23	90	1.0	0.56, 1.8
Smoker	73	147	3.6	2.1, 6.2
Ex-smoker	50	102	3.0	1.7, 5.2
Hiatus hernia	61	126	1.8	1.2, 2.7
Lung cancer				
Model 1				
Exposed	38	152	0.91	0.48, 1.7
Unexposed (reference)	38	38	1.0	
Smoker	42	60	14.7	5.0, 43.9
Ex-smoker	23	49	8.2	2.7, 25.2
Model 2				
0 (reference)	38	38	1.0	
1 dispensing	17	64	1.1	0.49, 2.3
2–3 dispensings	10	48	0.76	0.31, 1.9
4+ dispensings	11	40	0.86	0.35, 2.1
Smoker	42	60	15.1	5.0, 45.4
Ex-smoker	23	49	8.2	2.6, 25.3
Stomach cancer				
Model 1				
Exposed	17	68	1.1	0.43, 3.0
Unexposed (reference)	17	17	1.0	
Ulcer	19	24	5.0	1.9, 13.1
Model 2				
Exposed	17	68	1.0	0.38, 2.8
Unexposed (reference)	17	17	1.0	
Hiatus hernia	19	21	6.3	2.3, 17.2
Model 3				
0 (reference)	17	17	1.0	
1 dispensing	5	29	0.81	0.21, 3.1
2–3 dispensings	10	26	1.8	0.59, 5.4
4+ dispensings	2	13	0.60	0.10, 3.6

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Table VI. Contd

Exposure status and potential confounding factors by cancer site	Cases [no.]	Controls [no.]	OR[a]	95% CI
Ulcer	19	24	5.0	1.9, 13.3
Model 4				
0 dispensings (reference)	17	17	1.0	
1 dispensing	5	29	0.53	0.13, 2.2
2–3 dispensings	10	26	1.9	0.63, 6.0
4+ dispensings	2	13	0.39	0.06, 2.7
Hiatus hernia	19	21	8.0	2.7, 23.4
Prostate cancer				
Model 1				
Exposed	14	56	1.4	0.50, 4.1
Unexposed (reference)	14	14	1.0	
BPH	20	48	1.6	0.48, 5.3
Vasectomy	11	10	2.8	0.85, 8.9
Obesity	13	28	1.4	0.49, 4.0
Model 2				
0 (reference)	14	14	1.0	
1 dispensing	3	20	0.63	0.13, 3.1
2–3 dispensings	5	17	1.6	0.43, 6.2
4+ dispensings	6	19	2.3	0.62, 8.7
BPH	20	48	1.6	0.48, 5.1
Vasectomy	11	10	3.5	0.99, 12.6
Obesity	13	28	1.6	0.54, 4.5

a Adjusted, in addition, for age (by 10-year age group) and sex. Reference groups were unexposed or zero dispensings of chloral hydrate, never smoked (for smoking), and the absence of each medical condition listed.

BPH = benign prostatic hypertrophy.

Recent data on the differences between species in peroxisome proliferation responses to trichloroacetic acid, a major metabolite of chloral hydrate, are consistent with these findings and show no persuasive evidence to support a causal relationship between (short-term) chloral hydrate exposure and cancer in humans (as far as hepatocarcinogenicity is concerned).[29-31] Nonetheless, the ability of chloral hydrate to induce genotoxic changes in mice suggests that further study of chloral hydrate in humans is warranted. Furthermore, trichloroacetic acid is a weak agonist of the peroxisome proliferator activated receptor (PPAR)-α,[31,32] and PPAR-δ agonists have been shown to promote neoplastic growth in the prostate.[33] These data, as well as the possible association between chloral hydrate exposure and prostate cancer found in this study, indicate that further research may be warranted on the potential relationship between prostate cancer in humans and the use of other drugs that are more potent PPAR-α agonists (i.e. antihyperlipidaemics).

It is possible that the drug-cancer association between chloral hydrate and certain cancers in the initial screening may have been due to chance, particularly because of the multitude of comparisons that were made. Because of the substantial animal data regarding the adverse effects of chloral hydrate, it was important to investigate further. However, this study had its limitations, including the small number of exposed cases, and the resulting low power for weak associations and site-specific statistical analyses. Missing or incomplete data in the medical chart with regard to prescription or dose information also posed a challenge. The calculation of a cumulative dose was attempted for each patient; however, due to uncertainty around these estimates, cumulative dose was not used. This measure may have assessed exposure to chloral hydrate more accurately. With regard to case ascertainment, the

older age at which the majority of patients received chloral hydrate may have limited our ability to capture cancer cases by virtue of time, since both exposure and the general background rate of cancers from all other causes tend to rise fairly steeply with age. Finally, while the computer-listed dispensings can be used to confirm that the patients who were prescribed chloral hydrate actually filled their prescriptions, it is not possible to ensure that the drug was actually ingested. Thus, actual use of chloral hydrate may be uncertain.

Despite these limitations, exposure data were fairly complete and had a high level of accuracy, since the prescription information was collected via Kaiser Permanente's computerised pharmacy database and medical charts. Although this system was available for a timespan of only 4 years, it was still possible to obtain all dispensings from the medical chart (both inpatient and outpatient), which typically corresponded with computer-listed dispensing, as well as other prescriptions from the chart that may have occurred outside this 4-year window. In addition, the length of follow-up was long (between 20 and 30 years).

Conclusion

This study did not find persuasive evidence to support a causal relationship between chloral hydrate exposure in humans and the development of cancer. However, caution should be exercised when prescribing chloral hydrate, and, where possible, alternative drugs should be considered.

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