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Research Submission

Maternal Butalbital Use and Selected Defects in the National Birth Defects Prevention Study

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Background.—Butalbital is a barbiturate contained in combination products with caffeine and an analgesic prescribed for the treatment of migraine and tension-type headaches. Controversy exists as to whether butalbital should continue to be prescribed in the United States because of the potential for abuse, overuse headache, and withdrawal syndromes. Butalbital crosses the placenta but there is limited information about potential teratogenicity.

Objective.—To evaluate associations between butalbital and a wide range of specific birth defects.

Methods.—The National Birth Defects Prevention Study is an ongoing, case–control study of nonsyndromic, major birth defects conducted in 10 states. The detailed case classification and large number of cases in the National Birth Defects Prevention Study allowed us to examine the association between maternal self-reported butalbital use and specific birth defects. We conducted an analysis of 8373 unaffected controls and 21,090 case infants with estimated dates of delivery between 1997 and 2007; included were birth defects with 250 or more cases. An exploratory analysis examined groups with 100 to 249 cases.

Results.—Seventy-three case mothers and 15 control mothers reported periconceptional butalbital use. Of 30 specific defect groups evaluated, adjusted odds ratios for maternal periconceptional butalbital use were statistically significant for 3 congenital heart defects: tetralogy of Fallot (adjusted odds ratio = 3.04; 95% confidence interval = 1.07–8.62), pulmonary valve stenosis (adjusted odds ratio = 5.73; 95% confidence interval = 2.25–14.62), and secundum-type atrial septal defect (adjusted odds ratio = 3.06; 95% confidence interval = 1.07–8.79). In the exploratory analysis, an elevated odds ratio was detected for 1 congenital heart defect, single ventricle.

Conclusions.—We observed relationships between maternal periconceptional butalbital use and certain congenital heart defects. These associations have not been reported before, and some may be spurious. Butalbital use was rare and despite the large size of the National Birth Defects Prevention Study, the number of exposed case and control infants was small. However, if confirmed in additional studies, our findings will be useful in weighing the risks and benefits of butalbital for the treatment of migraine and tension-type headaches.

Key words: butalbital, headache, migraine, birth defect

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BACKGROUND

Butalbital is a short- to intermediate-acting barbiturate that can produce central nervous system depression ranging from mild sedation to general anesthesia.[1] Combination products containing butalbital with caffeine and an analgesic, acetaminophen, aspirin, or codeine are prescribed for the treatment of migraine and tension-type headaches. In a study of patterns of prescription medication use in the management of headache in the United States, 17% of survey respondents reported use of a butalbital-containing product.[2] Nevertheless, recently published guidelines do not recommend butalbital-containing products for treatment of migraine headache,[3] and some European countries have banned its use because of the well-known potential for abuse, overuse headache, and withdrawal syndromes.[1]

Butalbital, similar to other barbiturates, suppresses neuronal responses by enhancing γ-aminobutyric acid (GABA) binding to $GABA_A$ receptors.[1] Studies of other barbiturates, in particular the antiseizure medication, phenobarbital, indicate a teratogenic effect.[4,5] A suggested mechanism is through bradyarrhythmias, hemodynamic changes, and hypoxia caused by blockage of ion channels in the embryonic heart.[4] In an analysis of drug registry data based on relatively small numbers of exposed cases, an excess of heart defects was observed (4/51 infants exposed to the higher dose of phenobarbital).[5] Risks to the fetus from maternal butalbital use have been little studied and have not been taken into account in the controversy as to whether butalbital should continue to be prescribed in the United States. Two previous studies of maternal butalbital use did not find significant associations with birth defects.[6,7]

Investigators with the National Birth Defects Prevention Study (NBDPS), a large ongoing case–control study of risk factors for birth defects, periodically conduct screens of the study database to detect signals for increased risks between medication components and specific birth defects. In 1 such screen, an association was observed between periconceptional (defined as 1 month preconception through the third month of pregnancy) butalbital use and pulmonary valve stenosis. This finding prompted us to conduct a formal analysis of self-reported butalbital use and a wide range of specific birth defects using NBDPS data.

METHODS

The NBDPS is a multisite population-based case–control study that began in 1997.[8] Infants with 1 or more of over 30 different categories of major structural defects (cases), excluding those attributed to a known chromosomal abnormality or single-gene condition, were ascertained through birth defects surveillance systems in 10 states (AR, CA, GA, IA, MA, NC, NJ, NY, UT, and TX). Each study site obtained institutional review board approval for the NBDPS; informed consent was provided by all participants. The authors had full access to all the data in the study. Population-based data were collected from either the entire state or selected regions of the state. Control infants were liveborn infants without birth defects randomly selected from hospital records (AR, CA, NY, TX), birth certificates (IA, MA, NC, NJ, UT), or both (GA: hospital record, 1997-2000; birth certificate, 2001-1007) in the same time period and geographic areas as the cases.

Included in the present study were births with an estimated date of delivery (EDD) from October 1997 through December 2007. Control infants and infants with birth defects for which 100 or more cases were available for study were included. The main analysis comprised birth defects with greater study power (250 infants or more). To avoid missing strong effects in small case groups, we also conducted an exploratory analysis of birth defects with 100-249 infants. We excluded infants with a maternal history of type 1 or type 2 diabetes diagnosed before pregnancy because pre-existing diabetes is associated with increased risk of a variety of birth defects.[9,10] Participation rates were 69% and 66% for eligible case and control mothers, respectively.

Case inclusion criteria have been described by Yoon et al.[8] Clinical geneticists reviewed and classified each case infant as having isolated or multiple birth defects (2 or more major unrelated defects).[11] To reduce etiologic heterogeneity within case groups, we excluded infants classified as having a complex sequence (a group of defects that are believed to be pathogenetically related, but for which the primary defect is not apparent).

Only structural heart defects confirmed by echocardiography, cardiac catheterization, or autopsy were included in the NBDPS. Patent ductus arteriosus and patent foramen ovale, which are often related to preterm birth, were not included. Congenital heart defect (CHD) cases were further categorized as simple, associations, or complex.[12] Most of the heart phenotypes analyzed in this study were simple CHDs (defined as a single CHD or CHD "entity") or common CHD associations (eg, coarctation of the aorta + ventricular septal defect [VSD]). Cases recorded as "atrial septal defect (ASD) not otherwise specified" were viewed as probably ASD secundum type and were counted as such in the main analysis. Certain study sites did not ascertain cases during the entire study period for oral clefts and pulmonary valve stenosis, and muscular VSDs were included for only the first year of data collection for sites participating in 1997-1998. When we analyzed those birth defects, cases and controls were excluded for the study sites and years for which case ascertainment was incomplete, ie, analyses of muscular VSDs were restricted to the first year of data collection for sites participating in 1997-1998.

For classification of noncardiac birth defects, microtia included dysplastic ear pinna and stenosis or atresia of external auditory canal. Oral clefts were classified into 2 groups that are generally recognized as having different etiologies: cleft lip with or without cleft palate (CL/P) and cleft palate only.[13] Infants with intestinal atresia limited to the duodenum were not counted as small intestinal atresias for this analysis; only ileal, jejunal, and multiple intestinal atresias or stenoses were included. Infants with esophageal or small intestinal atresia that occurred as a component of a VATER/VACTERL association of defects (at least 3 of the following: vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) were included in the study and were classified as having multiple defects. Only second and third degree hypospadias cases were included because of concerns about incomplete ascertainment of first-degree hypospadias. The control group was restricted to male infants for the analysis of hypospadias.

Between 6 weeks and 24 months after the EDD, trained interviewers used a computer-assisted telephone interview to collect information about demographic characteristics, pregnancy history, and various health conditions and exposures before and during pregnancy from mothers of cases and controls. A pregnancy calendar mailed in advance of the interview was used to help participants more accurately report timing of exposures. Study mothers were asked about all medications taken during the period from 3 months preconception through the end of pregnancy. Self-reported information was collected on timing, frequency, and duration of medication use. The Slone Epidemiology Center Drug Dictionary was used to code all reported medications. Maternal periconceptional butalbital exposure was defined as any use of a medication containing butalbital from 1 month preconception through the third month of pregnancy.

Information on certain medications was queried through specific questions about conditions such as seizure disorder, diabetes, and hypertension as well as an "other disease" question ("did you have any other diseases or illnesses that we haven't already talked about, such as . . . "). Medication use was also queried through questions on specific medications including an open-ended question asking, "Between three months prepregnancy and delivery did you take any medications, remedies, or treatments that we haven't already talked about? For example . . . " Butalbital was primarily reported in response to the open-ended medication question.

Only case and control mothers reporting no butalbital use from 3 months preconception through delivery were counted as nonexposed (those reporting use only outside of the periconceptional period were excluded from analysis of periconceptional butalbital exposure). Case and control mothers for whom information on timing of butalbital use was missing were excluded from analysis. Because butalbital use was not specifically queried in the interview, we also excluded nonexposed case and control mothers who did not complete the medication questions.

Covariates considered in this analysis included the following maternal characteristics: age at delivery (<20, 20-24, 25-29, 30-34, 35+), parity (primiparous, multiparous), race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, other), education (less than high school, high school, college), prepregnancy

body mass index (weight in kg/height in m^2; <18.5, 18.5 to <25, 25 to <30, 30+), mother's state of residence at the time of infant's birth, and dichotomous variables for gestational diabetes and hypertension during pregnancy. We also considered folic acid-containing vitamin supplement use (1 month before pregnancy through month 1, later in pregnancy/none) and periconceptional exposure to the following: cigarette smoking (yes, no), maximum number of alcoholic drinks on 1 occasion (none, 1-3, 4+), and family history of the same birth defect in a first-degree relative.

Bivariate analyses were conducted to assess potential confounding. Variables associated with exposure among control mothers were included in multiple logistic regression models. Family history of the same birth defect in a first-degree relative was included in all adjusted models. For birth defect case groups with 5 or more exposed cases, adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. For birth defects with 3 or 4 exposed cases, crude ORs and exact CIs were calculated. ORs are not shown for birth defect phenotypes with fewer than 3 exposed cases. Analyses using the same models were restricted to isolated birth defects only. All analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA).

To determine whether any associations between butalbital and birth defects were due either to other active ingredients in butalbital products or to confounding by indication, we evaluated 2 additional exposure groups. First, we calculated effect estimates for "other ingredients in butalbital products," defined as periconceptional exposure to any combination products containing acetaminophen, aspirin, caffeine, and/or codeine that do not contain butalbital but are also prescribed for tension headaches or migraines, eg, Excedrin extra strength, Excedrin migraine, and Tylenol with codeine. In addition, we calculated effect estimates for periconceptional exposure to any triptan (selective serotonin agonist) antimigraine medication: sumatriptan, zolmitriptan, naratriptan, rizatriptan, frovatriptan, almotriptan, and eletriptan to examine whether other factors related to migraine or tension-type headaches may have contributed to our findings. Triptan medications were chosen for this evaluation of confounding by indication because they are prescribed specifically for treatment of migraine headaches. The analysis plan (birth defect case groups and statistical models) used in analysis of butalbital exposure was applied to the analysis of exposures to combination products not containing butalbital and to the analysis of triptan medications; infants with maternal exposure to butalbital were excluded from these analyses.

We conducted several sensitivity analyses to examine factors that might influence our effect estimates. First, if "as needed" or "once or twice per year" butalbital use was reported for the entire interval from 3 months preconception through delivery, exposure was flagged as uncertain. Infants with uncertain exposures were removed from a subanalysis. Second, women who use butalbital-containing medications may use additional medications to prevent or treat headaches. Divalproex sodium, sodium valproate, topiramate, gabapentin, and venlafaxine are among the medications prescribed for migraine prophylaxis in the United States,[14] and opioid medications are used to treat acute episodes. To evaluate whether associations with butalbital might be accounted for by "coexposures" to other medications commonly prescribed for headache prevention or treatment, we conducted a subanalysis excluding all infants with maternal periconceptional exposure to divalproex sodium, sodium valproate, topiramate, gabapentin, venlafaxine, opioid medications, triptan medications, and other analgesic combination products not containing butalbital. Third, because butalbital use was much more common among mothers residing in Massachusetts than among mothers residing in any of the other states in the study, we conducted a stratified analysis (Massachusetts/all other states) to determine whether findings were different for Massachusetts residents.

RESULTS

Mothers of 21,750 case infants with birth defect types evaluated in the present analysis and 8492 control infants with EDD from 1997 through 2007 were interviewed for the NBDPS. The interval between EDD and interview varied by outcome category, with average intervals ranging from 9.1 to 13.6

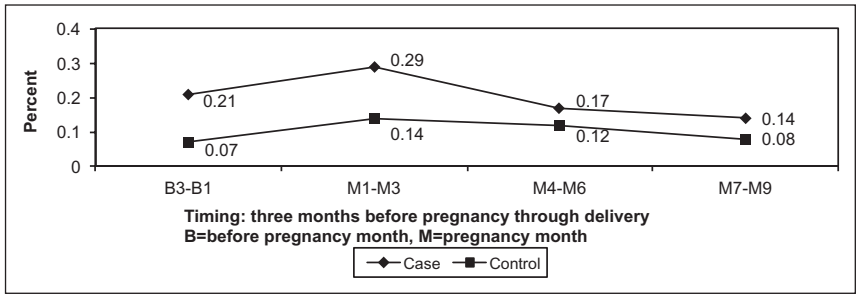

Figure.—Self-reported butalbital use among case and control mothers prepregnancy and by trimester, National Birth Defects Prevention Study, 1997-2007.

months (average = 10.6 months) among the birth defects included in the present analysis and 8.5 months for controls. Infants with incomplete maternal medication data (164 case infants, 61 control infants) and those with maternal history of type 1 or type 2 diabetes diagnosed prior to the index pregnancy (464 case infants, 51 control infants) were excluded from study. An additional 32 cases and 7 controls with butalbital exposure only before or after the periconceptional period were excluded from the analysis of periconceptional butalbital exposure which included 21,090 case infants and 8373 control infants.

The proportion of case mothers and control mothers reporting butalbital use prepregnancy and by trimester is shown in the Figure. Among 102 mothers reporting use of butalbital any time during the period 3 months prepregancy through delivery, 11 (10.8%) reported using butalbital at least once per day for 3 months or more. A total of 73 case infants and 15 control infants were exposed to medications containing butalbital during the periconceptional period. Butalbital is usually contained in combination products containing caffeine and an analgesic. The other medication components and trade names of butalbital-containing products reported in the NBDPS are listed in Table 1.

Table 2 displays the distribution of selected characteristics of control mothers by periconceptional exposure to butalbital. Butalbital use was less common among young mothers and mothers who were obese or who smoked cigarettes. Butalbital use was more common among non-Hispanic white mothers, those with a high school or greater education, those who consumed alcohol, and those who used folic acid-containing supplements.

Table 3 lists the number of exposed and non-exposed infants in each of the birth defect categories evaluated in this study. Along with exposures to butalbital, numbers of infants exposed to other ingredients in butalbital products and to triptan medications are presented. The main analysis included 12 cardiac and 18 noncardiac birth defect categories with 250 or more case infants. None or only 1 of the cases was exposed for 12 of the 30 large case groups, representing fewer than expected exposed cases for many of those birth defects. ORs are presented in Table 4 for the 10 birth defects included in the main analysis for which there were 3 or more case infants with periconceptional butalbital exposure. The ORs for periconceptional butalbital exposure ranged from 1.61 to 5.73 and were statistically significant for 3 CHDs: tetralogy of Fallot (adjusted OR = 3.04; 95% CI = 1.07-8.62), pulmonary valve stenosis (adjusted OR = 5.73; 95% CI = 2.25-14.62), and secundum-type ASD (adjusted OR = 3.06; 95% CI = 1.07-8.79). An

Table 1.—Other Active Ingredients and Trade Names of Butalbital-Containing Products, NBDPS, 1997-2007

Other Components	Trade Names
Acetaminophen	Phrenilin®
Acetaminophen, Caffeine	Anolor®, Esgic®, Fioricet®, Medigesic®
Acetaminophen, Caffeine, Codeine	Fioricet® with Codeine
Aspirin, Caffeine	Fiorinal®
Aspirin, Caffeine, Codeine	Fiorinal® with Codeine

Table 2.—Selected Characteristics Mothers of Control Infants (N = 8373) by Self-Reported Periconceptional Exposure to Butalbital, National Birth Defects Prevention Study, 1997-2007

	Nonexposed N = 8358		Exposed N = 15	
	N*	%	N*	%
Maternal age (years)				
12-19	867	10.4	0	0.0
20-34	6328	75.7	13	86.7
35+	1163	13.9	2	13.3
Race/ethnicity				
White non-Hispanic	4935	59.1	14	93.3
Black non-Hispanic	938	11.2	1	6.7
Hispanic	1940	23.2	0	0.0
Other	542	6.5	0	0.0
Education (years)				
≤12	3414	41.3	3	20.0
12+	4853	58.7	12	80.0
Prepregnancy BMI				
<30	6685	83.5	14	93.3
30+ (obese)	1324	16.5	1	6.7
Gestational diabetes				
No	8000	95.9	15	100.0
Yes	342	4.1	0	0.0
High blood pressure				
No	7584	90.7	14	93.3
Yes	774	9.3	1	6.7
Smoking†				
No	6764	81.6	13	86.7
Yes	1528	18.4	2	13.3
Alcohol (max per occasion)†				
0	5206	63.3	5	33.3
1-3	2008	24.4	6	40.0
4 +	1012	12.3	4	26.7
Folic acid supplement use‡				
Yes	4366	53.1	10	71.4
No	3862	46.9	4	28.6

*Numbers vary due to missing values.
†During the period from 1 month prepregnancy through the third month of pregnancy.
‡Yes = any use 1 month prepregnancy through pregnancy month 1.
BMI = body mass index (weight in kg/height in m^2).

exploratory analysis of smaller birth defect categories (100-249 cases) examined 6 noncardiac and 9 cardiac case groups (Table 3). There were no exposed cases for the majority of the smaller case groups; however, 3 exposed cases were observed for 1 CHD, single ventricle (OR = 14.05; exact 95% CI = 2.57-50.54).

When separate analyses were conducted for infants with isolated defects, ORs for the birth defects included in Table 4 were similar to those for all case infants with a few exceptions. The largest shifts in the ORs were for the associations between periconceptional butalbital use and anorectal atresia and secundum ASD, both of which were closer to the null; the OR for secundum ASD was no longer statistically significant. The ORs for isolated defects are provided in the supplementary material at: http://www.interscience.wiley.com/. . ./.

Analysis of Other Ingredients in Butalbital Products.—Self-reported exposure to combination products containing acetaminophen, aspirin, caffeine, and/or codeine that do not contain butalbital was more common than butalbital use, with 137 case infants and 44 control infants exposed during the periconceptional period. For birth defect categories with 250 or more case infants, only 2 statistically significant associations were observed: with CL/P and hypoplastic left heart syndrome. The 3 CHDs significantly associated with butalbital exposure in the main analysis were not associated with exposure to other ingredients in butalbital products; fewer than expected exposed cases were observed for all 3. For comparison to butalbital, estimates are presented in Table 5 for case groups included in Table 4 for butalbital exposure. No infants with single ventricle were exposed to combination products not containing butalbital.

Analysis of Triptans Medications.—A total of 75 case infants and 34 control infants were exposed to triptan medications during the periconceptional period. No statistically significant associations were observed between self-reported periconceptional triptans use and the large birth defects case groups. Estimates were below the null or not calculated because of small numbers of exposed cases for all CHDs with the exception of secundum ASD, for which a nonsignificant elevation in the OR was observed. However, among the smaller birth defects case groups, 3 exposed cases were observed for single ventricle (OR = 6.32; exact 95% CI = 1.22-20.53). As above, estimates are presented in Table 5 for case groups included in Table 4 for butalbital exposure.

Table 3.—Maternal Self-Reported Periconceptional Butalbital and Other Migraine Medication Use, National Birth Defects Prevention Study, 1997-2007

		Other Migraine Medications	
Birth Defects Group Non-malformed controls	Butalbital Exposed/Nonexposed 15/8358	Other Ingredients in Butalbital Products* Exposed/Nonexposed 44/8266	Triptans Exposed/Nonexposed 34/8312
Congenital heart defects			
Main Analysis (250 + cases)			
Heterotaxy	0/247	0/247	1/246
Tetralogy of Fallot	5/829	4/820	3/825
d-Transposition of the great arteries	3/455	2/451	0/454
Hypoplastic left heart syndrome	3/448	6/439	0/447
Coarctation of the aorta	2/441	5/434	0/441
Aortic valve stenosis	1/248	3/241	1/247
LVOTO associations†	0/357	3/353	1/355
Pulmonary valve stenosis	7/761	2/754	2/758
RVOTO associations†	2/280	0/279	1/279
Perimembranous VSD	4/996	6/980	3/992
Secundum atrial septal defect	5/1431	5/1416	8/1423
Septal associations†	1/599	2/594	1/598
Exploratory Analysis (100-249 cases)			
DORV-TGA	0/103	0/102	0/103
AVSD	0/146	3/141	1/145
TAPVR	0/199	0/194	0/199
Pulmonary atresia	1/128	0/128	0/126
Muscular VSD	0/158	1/155	0/158
Single ventricle	3/119	0/119	3/116
Noncardiac birth defects			
Main Analysis (250 + cases)			
Anencephaly	0/431	3/425	2/429
Spina bifida	0/923	6/914	3/919
Hydrocephaly	0/367	4/361	2/365
Congenital cataracts	2/250	2/247	1/249
Anotia/microtia	0/486	4/479	0/484
Cleft palate only	4/1171	3/1159	6/1164
Cleft lip ± cleft palate	6/2224	23/2186	7/2215
Esophageal atresia	2/524	4/517	3/521
Small intestinal atresia	0/345	2/340	1/344
Anorectal atresia	4/748	6/737	1/747
Hypospadias	7/1643	12/1620	4/1638
Longitudinal limb deficiencies	0/332	2/324	1/331
Transverse limb deficiencies	2/517	4/513	3/514
Craniosynostosis	2/1054	6/1042	4/1049
Diaphragmatic hernia	1/619	6/611	1/617
Omphalocele	1/309	2/306	1/308
Gastroschisis	2/955	6/946	2/953
Amniotic band sequence	2/250	1/246	1/249
Exploratory Analysis (100-249 cases)			
Encephalocele	0/160	0/159	0/160
Dandy-Walker malformation	1/125	1/124	0/125
Holoprosencephaly	0/116	1/115	2/114
Anophthalmos/microphthalmos	0/163	1/160	0/163
Glaucoma/anterior chamber defects	1/135	1/133	0/135
Choanal atresia	1/110	1/109	1/109
Duodenal atresia/stenosis	0/159	0/159	0/159
Biliary atresia	2/132	0/132	2/129
Bilateral renal agenesis or hypoplasia	0/122	0/122	0/122

*Combination products containing acetaminophen, aspirin, caffeine, and/or codeine that do not contain butalbital.

†LVOTO associations include coarctation of the aorta + aortic stenosis; coarctation of the aorta + VSD; coarctation of the aorta + VSD + ASD. RVOTO associations include pulmonary valve stenosis + VSD and pulmonary valve stenosis + ASD. Septal associations are VSD + ASD.

ASD = atrial septal defect; AVSD = atrioventricular septal defect; DORV-TGA = double outlet right ventricle, transposed great artery type; LVOTO = left ventricular outflow tract obstruction; RVOTO = right ventricular outflow tract obstruction; TAPVR = total anomalous pulmonary venous return; VSD = ventricular septal defect.

Table 4.—Associations Between Self-Reported Maternal Periconceptional Butalbital Use and Selected Birth Defects, National Birth Defects Prevention Study, 1997-2007

	Any Periconceptional Butalbital Use			Excluding Periconceptional Use of Other Medications Used to Treat Migraines*		
	Exposed/Nonexposed†			Exposed/Nonexposed†		
Birth Defects Group	Cases	Controls	OR (CI)‡	Cases	Controls	OR (CI)‡
Congenital heart defects						
Tetralogy of Fallot	5/801	14/8094	3.04 (1.07-8.62)	2/799	11/8120	1.85 (0.20-8.49)
d-Transposition of the great arteries	3/455	15/8358	3.67 (0.68-13.05)	1/444	11/8120	–
Hypoplastic left heart syndrome	3/448	15/8358	3.73 (0.68-13.25)	3/425	11/8120	5.21 (0.93-19.82)
Pulmonary valve stenosis	7/729	13/7649	5.73 (2.25-14.62)	6/696	9/7419	5.71 (1.88-17.36)
Perimembranous VSD	4/996	15/8358	2.24 (0.54-7.04)	3/966	11/8120	2.29 (0.41-8.70)
Secundum atrial septal defect	5/1392	14/8094	3.06 (1.07-8.79)	2/1375	11/8120	–
Noncardiac birth defects						
Cleft palate only	4/1171	15/8222	1.87 (0.45-5.89)	3/1122	11/7986	1.94 (0.35-7.36)
Cleft lip ± cleft palate	6/2176	14/7964	1.73 (0.65-4.57)	5/2096	10/7730	2.01 (0.67-5.99)
Anorectal atresia	4/748	15/8358	2.98 (0.72-9.38)	4/723	11/8120	4.08 (0.95-13.82)
Hypospadias	7/1593	7/4099	1.61 (0.55-4.69)	7/1537	4/3966	2.98 (0.85-10.45)

*Infants whose mothers reported periconceptional exposure to divalproex sodium, sodium valproate, topiramate, gabapentin, venlafaxine, opioid medications, triptan medications and other analgesic combination products not containing butalbital were excluded from this analysis.

†The number of exposed controls varies according to the years and study centers, and in the case of hypospadias, infant sex (male infants only) and whether covariates are included in the model. Both cases with isolated anomalies and those with additional defects are included.

‡For case groups with 5 + exposed cases, estimates were adjusted for mother's state of residence at the time of infant's birth, age, race/ethnicity, education, and periconceptional smoking, alcohol use and folic acid use; asymptotic confidence intervals were calculated. Crude odds ratios with exact 95% confidence intervals are presented for defects with 3-4 exposed cases. Estimates are not presented for analyses based on <3 exposed cases.

– = not calculated for phenotypes with <3 exposed cases; CI = confidence interval; OR = odds ratio; VSD = ventricular septal defect.

Sensitivity Analyses.—Seven mothers (all of case infants) reported "as needed" or "once or twice per year" use of butalbital for the entire interval from 3 months preconception through delivery. Following exclusion of these infants from analysis, the OR for pulmonary valve stenosis remained significantly elevated (4.86; 95% CI = 1.81-13.01) and the ORs for CL/P and perimembranous VSD were reduced to 0.99 (95% CI = 0.61-4.29) and 1.68 (95% CI = 0.31-5.95), respectively. None of the other estimates presented in Table 4 changed nor did the estimate for single ventricle change.

Exclusion of infants whose mothers reported periconceptional exposure to divalproex sodium, sodium valproate, topiramate, gabapentin, venlafaxine, opioid medications, triptan medications, and other analgesic combination products not containing butalbital shifted estimates for some case groups farther from the null and others closer to the null (see Table 4). Estimates for tetralogy of Fallot and secundum ASD were substantially reduced. The point estimate for pulmonary valve stenosis was essentially unchanged but the CI was somewhat wider. The estimate for single ventricle remained very elevated (19.26; 95% CI = 3.40-74.08).

An analysis stratified by study site (Massachusetts/all other sites combined) produced elevated ORs for each stratum for all case groups included in Table 4 with 2 exceptions: CL/P and perimembranous VSD. For these case groups, the

Table 5.—Associations Between Self-Reported Maternal Periconceptional Exposure to Other Ingredients in Butalbital Products or Triptan Medications and Selected Birth Defects, National Birth Defects Prevention Study, 1997-2007

Birth Defects Group	Other Ingredients in Butalbital Products*			Triptan Medications		
	Exposed/Nonexposed†			Exposed/Nonexposed†		
	Cases	Controls	OR (CI)‡	Cases	Controls	OR (CI)‡
Congenital heart defects						
Tetralogy of Fallot	4/820	44/8266	0.88 (0.31-2.49)	3/825	34/8312	0.89 (0.17-2.84)
d-Transposition of the great arteries	2/451	44/8266	–	0/454	34/8312	–
Hypoplastic left heart syndrome	6/426	44/8003	2.67 (1.10-6.45)	0/447	34/8312	–
Pulmonary valve stenosis	2/754	44/7804	–	2/758	32/7850	–
Perimembranous VSD	6/947	44/8003	1.20 (0.51-2.84)	4/996	34/8312	0.74 (0.14-1.74)
Secundum atrial septal defect	5/1377	44/8003	0.83 (0.32-2.17)	8/1384	33/8051	1.83 (0.82-4.09)
Noncardiac birth defects						
Cleft palate only	3/1159	44/8130	0.48 (0.09-1.50)	6/1123	32/7922	1.17 (0.47-2.92)
Cleft lip ± cleft palate	23/2138	44/7873	1.92 (1.14-3.22)	7/2167	32/7922	0.84 (0.37-1.92)
Anorectal atresia	6/710	44/8003	1.70 (0.72-4.05)	1/747	34/8312	–
Hypospadias	12/1570	27/4049	0.87 (0.42-1.79)	4/1638	18/4223	0.53 (0.14-1.74)

*Combination products containing acetaminophen, aspirin, caffeine and/or codeine that do not contain butalbital.
†The number of exposed controls varies according to the years and study centers, and in the case of hypospadias, infant sex (male infants only) and whether covariates are included in the model. Both cases with isolated anomalies and those with additional defects are included.
‡For case groups with 5 + exposed cases, estimates were adjusted for mother's state of residence at the time of infant's birth, age, race/ethnicity, education, and periconceptional smoking, alcohol use and folic acid use; asymptotic confidence intervals were calculated. Crude odds ratios with exact 95% confidence intervals are presented for defects with 3-4 exposed cases. Estimates are not presented for analyses based on <3 exposed cases.
– = not calculated for phenotypes with <3 exposed cases; CI = confidence interval; OR = odds ratio; VSD = ventricular septal defect.

majority of, or all, exposed cases were from the Massachusetts site.

DISCUSSION

In our main analysis, we observed associations between self-reported periconceptional exposure to butalbital and specific conotruncal, left ventricular outflow tract obstruction, right ventricular outflow tract obstruction, and septal heart defects, with ORs of 2.2-5.7, 3 of which were statistically significant. Our exploratory analysis of smaller birth defect case groups revealed a high OR for single ventricle heart defect. An association between butalbital and pulmonary valve stenosis was noted in an NBDPS screen of medication components and was the strongest association noted in the main analysis. This association in particular persisted in each subanalysis we conducted. If this estimate represents a true increase in risk, based on an estimated prevalence of 6.69 infants with pulmonary valve stenosis per 10,000 live births,[15] an OR of 5.73 would translate to a potential increase in risk from 1 infant with pulmonary valve stenosis per 1495 live births to 1 in 261 live births among women exposed during the periconceptional period.

Butalbital was a rare exposure in our study. This is reassuring given the U.S. Headache Consortium recommendation that "[b]ased on concerns of overuse, medication-overuse headache, and withdrawal, the use of butalbital-containing analgesics should be limited and carefully monitored.[1] Nevertheless, we noted evidence of butalbital overuse. Silberstein and McCrory recommend that butalbital should be used for no more than 2-3 treatment days per week.[1] Butalbital was used at least once per day for 3 months

or more by 11% of mothers reporting any use of butalbital.

Previous studies either did not report results for specific types of birth defects or did not separately examine butalbital exposure. In the Collaborative Perinatal Study, no association was detected with first trimester exposure to butalbital. Four infants with major birth defects were observed among 112 pregnancies with first trimester exposures.[6] In 1124 first trimester exposures in the Michigan Medicaid surveillance study, no significant associations were detected (53 observed/45 expected).[7] Neither of these studies had adequate sample size to evaluate risks of specific types of birth defects. In a case–control study using the Hungarian Congenital Abnormality Registry data, relationships between headache, medication use, and risks of selected birth defects were evaluated.[16] Migraine headache in the second or third month of pregnancy was significantly associated with limb deficiencies (OR = 2.5, 95% CI = 1.1-5.8) while other headaches were not. This study did not evaluate the use of butalbital-containing products separately.

We considered alternative explanations for an association between butalbital exposure and CHDs. If factors related to migraine headaches play a role in the etiology of CHDs, confounding could have occurred. For example, migraine headaches have been associated with vascular disease and with vascular events during pregnancy,[17] though the exact role in migraine etiology is unclear. Vascular abnormalities, whether a cause of headache or not, might influence risk of CHDs in offspring. In our study, high blood pressure during pregnancy was not reported more frequently among mothers who used butalbital. Other vascular abnormalities would have to have been strongly linked to butalbital use and to CHDs to explain our findings. Another example is the possibility that a right to left cardiac shunt (usually through a patent foramen ovale) plays a role in some types of migraine headaches.[18] If a familial risk for CHDs was also linked to risk of migraine headaches, we would expect to observe a similar pattern of outcomes among infants exposed to maternal triptans use. Our analysis of triptan medications did not reveal a pattern of increased ORs for CHDs similar to that observed for butalbital. Confounding by indication is not supported as an explanation for the associations we observed with CHDs in our main analysis unless the types and severity of headaches for which butalbital is prescribed differ from those treated with triptans (eg, if butalbital was prescribed for more severe migraine headaches). However, in the exploratory analysis of smaller case groups, elevated ORs were observed for single ventricle among both butalbital and triptans users. Although it was a criterion for exclusion from analysis, maternal pregestational diabetes was much more common among infants with single ventricle compared with control infants and compared with infants with other types of birth defects. The relationship between diabetes and migraines is not well understood; however, there is evidence of an association between insulin-resistance and migraine headaches.[19] It is possible that untreated/undiagnosed insulin resistance is a confounding factor in the analysis of migraine medications and single ventricle. Given the small number of infants with single ventricle exposed to either butalbital or triptans, our findings may also be explained by chance.

We did not find evidence that the other active ingredients in butalbital products are responsible for the associations observed for butalbital-containing products. Other ingredients in butalbital products (in combination products also used for migraine and tension headaches) were associated with 1 noncardiac defect and with left ventricular outflow tract obstruction defects but not with any other type of CHD whereas butalbital products were associated with various conotruncal, right ventricular outflow tract obstruction, and septal defects as well as single ventricle, and with nonsignificant elevations for certain left ventricular outflow tract obstruction defects. An NBDPS analysis by Feldkamp et al of single-ingredient-acetaminophen use and a range of birth defects observed patterns of associations that are not similar to those we observed for butalbital. No significant associations were observed with CHDs; all ORs for CHDs were less than 1.5.[20] Similarly, an NBDPS analysis of maternal caffeine consumption and CHDs found only a few nonsignificant positive associations and no association with pulmonary valve stenosis.[21]

If our results were due to coexposures to other migraine medications, we would have expected that exclusion of infants whose mothers reported those medications would have caused most of the positive ORs to move closer to the null. The ORs became more unstable but did not change in a predictable way, suggesting that coexposures are not responsible for our findings.

Strengths and Weaknesses.—The strengths of our study include the clinically well-characterized case groups resulting from clinical geneticists' classification of case infants using pathogenetically uniform case definitions.[11] The overall study design excluded case infants with known chromosomal or single-gene defects, which can increase homogeneity and improve the opportunity to identify risk factors. The NBDPS provides access to large sample sizes for most types of birth defects and standardized interviews reduce bias. Case and control mothers are asked to remember their exposures in a similar way. Recall bias is always a concern in case–control studies of birth defects that rely on retrospective reporting of medication use during pregnancy. However, we observed significant associations for only a small proportion of the defect categories studied, and there were no exposed cases for 8 of 30 case groups in the main analysis. Because we know of no reason why mothers of infants with CHDs would tend to recall exposure to butalbital differently than mothers of infants with other birth defects, we believe that recall bias did not strongly influence our results. Nevertheless, inability to recall exposures up to 36 months prior to interview may have resulted in underreporting or inaccurate reporting of exposure. Selection bias is a possibility because nearly one third of eligible cases and controls did not participate in the NBDPS. Besides introducing potential bias, nonparticipation could affect the generalizability of our findings. An analysis by Cogswell et al showed that for maternal age, previous livebirths, maternal smoking, and diabetes, control participants were similar to their base populations but differed somewhat by maternal race/ethnicity and education.[22]

Butalbital use was a rare exposure, and because we examined specific birth defect phenotypes, the number of exposed case and control infants was small, despite the large size of the NBDPS. We had poor power to detect associations for the smaller birth defect case groups, and the many birth defects case groups tested contributes to the likelihood that some of our findings may be spurious. Although ORs were not generated for all case groups because of small numbers of exposed cases, a total of 30 associations were evaluated for the main analysis of large birth defect case groups. Approximately 1.5 statistically significant associations would be expected by chance alone based on a 5% type I error rate and we observed 3; all 3 were increased ORs for CHDs.

Uncontrolled confounding by unmeasured factors that distinguish butalbital users from nonusers may also have played a role. Those with migraines or tension headaches because of life stress may use butalbital for its anxiety-reducing properties.[23] And women who overuse butalbital may have other lifestyle characteristics that could affect the risk of birth defects in their offspring.

CONCLUSIONS

We observed an association between self-reported periconceptional maternal butalbital use and certain CHDs including pulmonary valve stenosis. Given the small number of exposed cases upon which our findings are based, and the lack of previous studies examining specific birth defects, our findings should be interpreted cautiously. However, if confirmed, a potential teratogenic effect would add to the list of other well-known drawbacks to butalbital-containing medications including the potential for abuse, overuse headache, and withdrawal syndromes and would be useful in weighing the risks and benefits of butalbital in the treatment of migraine and tension-type headaches for women of childbearing age.

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