Safety of Haloperidol and Penfluridol in Pregnancy: A Multicenter, Prospective, Controlled Study

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Objective: To assess the safety of the butyrophenone neuroleptics haloperidol and penfluridol in pregnancy.

Method: The rate of major anomalies was compared between a cohort of pregnant women counseled for gestational exposure to haloperidol or penfluridol and a control group counseled for nonteratogen exposure. This multicenter, prospective, controlled study was conducted within the European Network of Teratology Information Services (ENTIS) and included women who contacted 1 of 4 teratology information services for counseling between January 1989 and December 2001.

Results: We followed up on the outcomes of 215 pregnancies exposed to haloperidol (N = 188) or penfluridol (N = 27)—78.2% (of 206) were in the first trimester—and compared to outcomes of 631 ENTIS controls. The rate of congenital anomalies did not differ between the haloperidol/penfluridol-exposed group and the control group (6/179 = 3.4% vs. 22/581 = 3.8%, p = .787). No difference was found by limiting the analysis to those exposed to butyrophenones during the first trimester. There were 2 cases of limb defects in the butyrophenone-exposed group (1 after haloperidol and 1 after penfluridol exposure) and none in the controls. A higher rate of elective terminations of pregnancy (8.8% vs. 3.8%, p = .004), a higher rate of preterm birth (13.9% vs. 6.9%, p = .006), a lower median birth weight (3155 g vs. 3370 g, p < .001), and a lower median birth weight of full-term infants (3250 g vs. 3415 g, p = .004) were found in the butyrophenone-exposed group compared to the controls.

Conclusion: This study suggests that haloperidol and penfluridol do not represent a major teratogenic risk. Since a possible association between butyrophenone exposure and limb defects cannot be ruled out with this sample size, a level II ultrasound with emphasis on the limbs should be considered in pregnancies with first trimester exposure.

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Haloperidol and penfluridol are butyrophenone neuroleptics used in pregnancy for psychotic disorders and for hyperemesis. Despite the introduction of atypical antipsychotics, haloperidol still has a central role in the treatment of schizophrenia.[1] Penfluridol is a highly lipophilic oral neuroleptic with a slow release of drug from the tissues, resulting in a long duration of activity.[2] A general rule to follow in pregnancy is to prefer medications that have been on the market for a longer period and, therefore, have a better-known fetal safety profile. Animal reproductive studies on haloperidol have been inconsistent.[3–10] In human pregnancies involving early first trimester exposure to haloperidol, there have been 2 isolated reports of limb defects.[11,12] The first[11] described an infant with phocomelia born to a woman who had taken haloperidol 1.5 mg/day from the 28th through the 38th day of gestation along with several other drugs. The second[12] described an infant with multiple upper and lower limb anomalies, aortic valve defect, and death, born to a woman who had taken haloperidol 15 mg/day during the first 7 weeks of pregnancy. Additional exposures in the latter case included methylphenidate 30 mg/day, phenytoin 300 mg/day, tetracycline, a decongestant, and general anesthesia. A causal relationship could not be established on the basis of those anecdotal reports. Human studies on the use of butyrophenone neuroleptics in pregnancy are scant. Van Waes and van de Velde[13] studied 100 pregnancies in which haloperidol 0.6 mg was administered twice daily for vary-

ing periods in pregnancy for hyperemesis gravidarum. Not a single malformation was found in 94 newborns examined. In a retrospective study of 31 infants with severe reduction deformities born over a 4-year period, none of the mothers remembered taking haloperidol.[14] Major birth defects, of which 2 were cardiovascular defects and none were limb reduction defects, were reported in 3 (5.4%) of 56 infants whose mothers were given prescriptions for haloperidol during the first trimester of pregnancy in a study of Michigan Medicaid recipients.[15] There are no studies on penfluridol in pregnancy.

Our primary objective was to prospectively evaluate the rate of major anomalies after pregnancy exposure to haloperidol or penfluridol compared to the rate in a control group exposed to nonteratogens. Secondary endpoints of interest were pregnancy outcome, birth weight, gestational age at delivery, and neonatal effects.

METHOD

The European Network of Teratology Information Services (ENTIS) is an organization of counseling services in regard to environmental exposures during pregnancy.[16] Our multicenter, prospective, controlled cohort study enrolled pregnant women who (or whose physician or midwife) contacted one of 4 teratology information services (TISs) seeking counseling in regard to gestational exposure to haloperidol or penfluridol between the years 1989 and 2001. The 4 participating centers were the Israeli TIS (Jerusalem, Israel), Beratungsstelle für Embryonaltoxikologie (Berlin, Germany), TIS (Bilthoven, The Netherlands), and Servizio di Informazione Teratologica (Padova, Italy). The butyrophenone-exposed group was compared to an ENTIS control group of women who had been counseled during pregnancy in regard to exposures known to be nonteratogenic from the 4 participating centers. In order to increase the power of our study, we tried to reach a 1:3 ratio between the exposed (haloperidol or penfluridol) and control groups.

Details of exposure were collected during pregnancy, and before pregnancy outcome was known, using a structured questionnaire (available from the authors by request). Oral consent to participate was given at initial contact. In addition, the following information was recorded: maternal demographics, medical and obstetric histories, exposure details (dose, duration, and timing in pregnancy), and concurrent exposures. After the expected date of delivery, follow-up was conducted by a telephone interview and/or mailed questionnaire with the woman, her physician, or her midwife to obtain details on the pregnancy outcome, gestational age at delivery, birth weight, and congenital anomalies. This offspring follow-up was performed between the neonatal period and 6 years of age. However, in most cases, it was carried out within the first 2 years of life.

The primary outcome of interest was the rate of major anomalies, that is, those offspring having a structural abnormality that has serious medical, surgical, or cosmetic consequences. In the case of multiple births, each live-born offspring was included in the analysis. Secondary endpoints were the rates of live birth, miscarriage, pregnancy termination, stillbirth, ectopic pregnancy, and premature births (≤ 37 weeks); gestational age at delivery; and birth weight. Gestational age in the present study is defined as the number of weeks after the last menstrual period.

Statistical Analysis

Categorical data were compared by χ^2 test or Fisher exact test. Continuous data did not follow normal distribution and were compared using the Mann-Whitney test (for 2 groups). The data are expressed as ratios or percentages for categorical data. Continuous data are presented using median with interquartile range. Relative risk and power calculation were performed using Epi Info 2000 software (Centers for Disease Control and Prevention, Atlanta, Ga.). Linear and logistic regression was performed post hoc to analyze the relative contribution of various predictors to differences in dependent variables. Significance was set at $p \leq .05$.

RESULTS

A total of 215 pregnancies with exposure to the butyrophenones haloperidol or penfluridol were prospectively followed up by the 4 participating centers (101 in Jerusalem, 55 in Berlin, 54 in Bilthoven, and 5 in Padova). Follow-up rate in the butyrophenone-exposed group ranged between 63% and 100%, depending on the center. In 161/206 pregnancies (78.2%), the exposure to butyrophenones was at least in the first trimester of pregnancy (9 cases excluded for lack of data on timing of exposure). The medication was taken throughout pregnancy in 94/196 pregnancies (48.0%) (19 cases excluded for lack of data on duration of treatment). In 188 pregnancies the exposure was to haloperidol (136 [72.3%] in the first trimester) and in 27 to penfluridol (25 [92.6%] in the first trimester). The control group included 631 pregnancies exposed to nonteratogens from the 4 participating centers (313 in Berlin, 216 in Jerusalem, 88 in Bilthoven, and 14 in Padova).

The median daily oral dose of haloperidol was 5 mg (2.25–10 mg), the median parenteral dose of haloperidol was 100 mg/4 weeks (50–100 mg), while the median oral dose of penfluridol was 20 mg/week (20–40 mg). The reported indications for the butyrophenone treatment in our cohort were psychosis (33.5%), schizophrenia (10.7%), depression (9.3%), bipolar disorder (4.2%), schizoaffective disorder (1.4%), anxiety (1.4%), panic attacks (0.9%), hyperemesis gravidarum (0.5%), borderline personality

Table 1. Maternal Characteristics and Obstetric History in Women Exposed to Haloperidol or Penfluridol (butyrophenone group) and the European Network of Teratology Information Services Control Group

Variable	Butyrophenone Group (N = 215)[a]	Controls (N = 631)[a]	p Value
Age, median (interquartile range), y	32 (28–36)	30 (27–33)	< .001
Pregnancies, N (%)			
1	61/170 (35.9)	200/594 (33.7)	.592
2–4	88/170 (51.8)	339/594 (57.1)	.219
≥ 5	21/170 (12.4)	55/594 (9.3)	.235
Live-born children, N (%)			
None	74/166 (44.6)	242/588 (41.2)	.430
1–3	79/166 (47.6)	324/588 (55.1)	.087
≥ 4	13/166 (7.8)	22/588 (3.7)	.027
Past miscarriages, N (%)			
None	136/161 (84.5)	488/584 (83.6)	.782
1	21/161 (13.0)	65/584 (11.1)	.501
≥ 2	4/161 (2.5)	31/584 (5.3)	.134
Past elective terminations of pregnancy, N (%)			
None	142/161 (88.2)	527/585 (90.1)	.486
1	16/161 (9.9)	42/585 (7.2)	.247
≥ 2	3/161 (1.9)	16/585 (2.7)	.778
Gestational age at first contact, median (interquartile range), wk	10 (8–16)	10 (7–18)	.677
Cigarettes smoked/d, N (%)			
None	117/157 (74.5)	509/562 (90.6)	< .001
≤ 5	6/157 (3.8)	20/562 (3.6)	.876
> 5	34/157 (21.7)	33/562 (5.9)	< .001

[a]Group Ns for each item are less than the total group Ns due to incomplete data.

Table 2. Pregnancy Outcomes in Women Exposed to Haloperidol or Penfluridol (butyrophenone group) and the European Network of Teratology Information Services Control Group

Variable	Butyrophenone Group (N = 215)	Controls (N = 631)	p Value
Live births, N	179[a]	577[b]	
Delivery, N (%)	176 (81.9)	570 (90.3)	.001
Miscarriage, N (%)	19 (8.8)	35 (5.5)	.105
Elective termination of pregnancy, N (%)	19 (8.8)	24 (3.8)	.004
Ectopic pregnancy, N (%)	1 (0.5)	1 (0.2)	.444
Stillbirth, N (%)	0 (0.0)	1 (0.2)	1.000
Major anomalies, N (%)	6/179[c] (3.4)	22/581[c] (3.8)	.787
Major anomalies in live births with first trimester exposure, N (%)	4/128[c] (3.1)	22/581[c] (3.8)	1.000
Gestational age at delivery, median (interquartile range), wk	40 (38–40)	40 (39–41)	.024
Birthweight, median (interquartile range), g	3155 (2800–3500)	3370 (3030–3700)	< .001
Preterm birth, N (%)[d]	22/158 (13.9)	37/534 (6.9)	.006
Birthweight of full-term infants, median (interquartile range), g	3250 (3000–3590)	3415 (3140–3750)	.004
Cesarean section, N (%)[d]	38/149 (25.5)	65/400 (16.3)	.014

[a]3 twin pairs.
[b]7 twin pairs.
[c]Includes elective terminations of pregnancy due to prenatal diagnosis of defects: none in the butyrophenone group and 4 in the control group.
[d]Group Ns for item are less than the total group Ns due to incomplete data.

(0.5%), suicide attempt (0.5%), substance abuse (0.5%), and Tourette syndrome (0.5%). In 36.1% of the cohort, the indication for therapy was not specified. Additional psychotropic medications were taken by 75.1% of the women. Concomitant anticholinergic medications were used by 31.6% (68/215) of the women (biperiden by 43, trihexyphenidyl by 20, dexetimide by 4, and orphenadrine by 1).

A comparison of maternal characteristics and obstetric history between the butyrophenone-exposed and control groups is presented in Table 1. The women in the haloperidol/penfluridol-exposed group were older than those in the control group, and a higher proportion of them had 4 children or more. A higher proportion of women in the butyrophenone-exposed group reported smoking more than 5 cigarettes per day compared to the control group (21.7% vs. 5.9%, $p < .001$). There were no significant differences between the groups in number of pregnancies, history of miscarriages, history of elective terminations of pregnancy, or gestational age at first contact.

A comparison of pregnancy outcome between the groups is presented in Table 2. There was a higher rate of elective terminations of pregnancy in the butyrophenone-exposed group compared to the control group. There was no difference in the rate of major anomalies between

Table 3. Major Congenital Anomalies in the Offspring of Women in the Haloperidol/Penfluridol-Exposed Group

	Details of Exposure				
Type of Anomaly	Butyrophenone, dose	Gestational Period	Drug Delivery Method	Additional Exposures	TIS Location: Follow-Up/ Comments
Severe bullous emphysema, lung hypoplasia	Haloperidol, 10 mg/d	From wk 34	Oral	Chlorprothixen from wk 32	Berlin, Germany: lobectomy on d 3, assisted ventilation
Absent left fourth finger, common wrist (carpus) of left first and second fingers	Haloperidol, 12.5 mg, every 4 wk	During wk 0–35	Parenteral	None	Berlin, Germany
Cystic hygromas	Haloperidol	During 2 wk in the second trimester	Oral	Metoclopramide, meclizine, clonazepam, oxazepam (first trimester), fluvoxamine (third trimester)	Bilthoven, The Netherlands
Upper limb reduction defect and foot deformity	Penfluridol, 20 mg/wk	During wk 0–13	Oral	None	Bilthoven, The Netherlands
Carbamazepine syndrome, developmental delay, congenital heart defect	Haloperidol, 150 mg/mo	Throughout pregnancy	Parenteral	Carbamazepine throughout pregnancy	Jerusalem, Israel
Ventricular septal defect, genu varum	Haloperidol, 10 mg/d	During wk 0–30	Oral	Perphenazine ongoing from wk 5	Jerusalem, Israel: spontaneously closed

Abbreviation: TIS = teratology information service.

the groups either when the whole butyrophenone-exposed cohort was compared or when the subgroup exposed to haloperidol or penfluridol only in the first trimester of pregnancy was compared to controls. The gestational age at delivery was lower, the median birth weight was 215 g lower, and there was a 2-fold increase in the rate of preterm births in the butyrophenone-exposed group compared to the control group. A reduction of 165 g in birth weight was found in the butyrophenone-exposed group when the analysis was confined to full-term infants. A higher proportion of women in the butyrophenone-exposed group delivered by Cesarean section (25.5% vs. 16.3%, $p = .014$). There were no significant differences in the rate of miscarriages, ectopic pregnancies, or stillbirths between the groups.

In order to evaluate the relative contribution of various predictors to the differences in birth weight and rate of preterm births, linear regression analysis was performed for the first, while logistic regression analysis was performed for the latter. The following predictors were entered into the model for birth weight: gestational age at delivery, maternal age, smoking status, duration of treatment (in the butyrophenone-exposed group), parity, butyrophenone exposure, alcohol consumption, and the TIS from where the data were obtained. Gestational age at delivery was the most important significant predictor contributing to the difference in birth weight (R^2 change = 37.1%, $p < .001$). Smoking status (R^2 change = 1.1%, $p = .015$), duration of butyrophenone treatment (R^2 change = 0.8%, $p = .036$), and parity (R^2 change = 0.7%, $p = .043$) were significant but much less important predictors. The other predictors mentioned were not significant. Butyrophenone exposure, maternal age, and smoking status were entered into the model in an attempt to assess whether they contributed to the higher rate of preterm births. Butyrophenone exposure (Exp[B] = 0.476, $p = .030$) and smoking status (Exp[B] = 2.851, $p = .009$) were significant predictors, while maternal age was not. The model was significant ($p = .042$), but the 2 significant predictors were not very useful ($R_L^2 = 0.028$ [butyrophenone exposure], $R_L^2 = 0.018$ [smoking status]) at predicting the outcome variable, which was rate of preterm births.

The list of congenital anomalies in the butyrophenone group is presented in Table 3. It is of interest to note that there were 2 limb defects, one after exposure to haloperidol throughout pregnancy and the other, a limb reduction defect, after first trimester exposure to penfluridol. There were no limb defects in the control group.

The prevalence of neonatal effects was 5.0% (9/179). The details of the reported neonatal effects are provided in Table 4. In the case with respiratory problems, the underlying bullous pulmonary emphysema might have been the cause. In the majority of cases with neonatal effects possibly associated with psychotropic medication use late in pregnancy, the use of additional medications was reported.

DISCUSSION

This multicenter, prospective, controlled cohort study followed up 215 pregnancies exposed to haloperidol or penfluridol. Both the butyrophenone-exposed group and their controls had malformation rates within the expected baseline risk for the general population. The study suggests that butyrophenones do not represent a major teratogenic risk in humans. A sample size of 179 butyrophenone-exposed live births with a ratio of 1:3.2 to the control

Table 4. Neonatal Effects Possibly Associated With Butyrophenone (haloperidol or penfluridol) Use Late in Pregnancy

Reported Effect	Additional Medications	Gestational Age at Delivery, wk	Birthweight, g	Comments
Hyperexcitability	Diazepam, chlorprothixen, biperiden	NA	NA	
Transient hyperexcitability/ muscular hypotonia	Diazepam, biperiden	Preterm: 34	1500	Haloperidol blood level 9.1 μg/L (toxic level > 10 μg/L)
Respiratory problems	Chlorprothixen	37	2900	Bullous pulmonary emphysema
Hypertonia, irritability, arrhythmia	Diazepam	39	3860	
Jitteriness	Lithium	41	2750	
Restlessness, feeding problems	Promethazine, fluoxetine	37	3275	
Restlessness	None	40	3800	
Feeding problems	Clonazepam, biperiden, risperidone, lithium	40	3340	
No cry at birth, lethargy	Chlordiazepoxide, fluoxetine	35	NA	Neonatal intensive care unit for 10 d

Abbreviation: NA = data not available.

group and a power of 80%, assuming a baseline risk of 3% for major anomalies, enables detection of a 2.9-fold increase in the overall rate of major anomalies (with 95% confidence interval). Our results are consistent with most previous studies that found no association between haloperidol exposure during pregnancy and teratogenic risk in humans.[13–15]

In contrast to the above-mentioned studies,[13–15] 2 isolated case reports[11,12] suggested an association between limb defects and early first trimester exposure to haloperidol. Animal studies to date have not supported this specific association. Two of the defects in the present study were limb defects, 1 after first trimester exposure to haloperidol and 1 (limb reduction defect) after penfluridol. In order to detect an increase in the incidence of low frequency defects, a larger sample size is required. Larger studies, preferably of retrospective case-control design, are warranted to verify the possible association between limb defects and butyrophenones in pregnancy.

Reduced birth weight and a 2-fold increase in the rate of preterm birth were found in the butyrophenone-exposed group. The birth weight reduction was partly explained by an earlier gestational age at delivery and a higher rate of preterm births. The reduction in birth weight was still noticeable when comparing full-term neonates only. The most important predictor explaining 37.1% of the difference in birth weight between the butyrophenone-exposed group and the control group was gestational age at delivery. Smoking status, butyrophenone-exposure, and parity predicted 1.1%, 0.8%, and 0.7% of the difference in birth weight. Duration of butyrophenone treatment did not play a significant role.

We lacked or had incomplete data on several maternal characteristics (e.g., nutrition, socioeconomic status, ethnic origin) and placental factors (e.g., chronic placental abruption, oligohydramnios), all potentially affecting neonatal birth weight. The presence of a psychotic disorder is likely to affect both nutritional status and compliance with prenatal care. Low birth weight and preterm birth have been previously linked with other psychiatric conditions such as depression.[17,18] Women with schizophrenia are more likely to have obstetric complications,[19,20] to deliver infants with intrauterine growth restriction, or to deliver preterm infants.[21,22]

Decreased prenatal and postnatal body weight have been previously reported in animal studies in the offspring of mice or rats treated during pregnancy with 2.5 or more times the maximum human dose of haloperidol.[10,23,24] Animal studies suggest a growth stunting effect of haloperidol through a direct drug effect on a dopamine D_1-like recognition site and not related to reduced maternal food intake.[18] In our study, butyrophenone exposure and smoking status were significant but not very useful predictors for preterm birth. We did not have data on 2 important risk factors for preterm birth: history of previous preterm birth and premature rupture of membranes.

A higher rate of elective terminations of pregnancy in the butyrophenone-exposed group could be related to many factors, e.g., the underlying disease, lifestyle, and fear of medication effect on pregnancy outcome.

In most cases where neonatal effects associated with drug use late in pregnancy were reported, concurrent medications, e.g., benzodiazepines, were taken. Benzodiazepines are known to be associated with the "floppy infant syndrome"[25] on the one hand and neonatal withdrawal syndrome[26] on the other hand.

The present multicenter, prospective, controlled cohort study, despite its limitations (i.e., reliance on self-reported drug exposure and maternal interview as a source for outcome data in most cases, variation in timing of follow-up, combining data from 4 TISs and 2 chemically related compounds, and limited power for specific rare defects), is a valid approach to the question of the safety of butyrophenones in human pregnancy. The same procedure applied to both arms of the study, and the prospective nature of the study minimized the potential biases.

Human pregnancy experience with anticholinergic drugs in the literature is limited. In our study, concomitant

anticholinergic medications were used by 31.6% of the women. Our data also suggest that anticholinergic drugs do not represent a major teratogenic risk.

In summary, this study supports that butyrophenones do not represent a major teratogenic risk in humans. The study was powered to find a 2.9-fold increase in the overall rate of major anomalies. A possible association between limb defects and butyrophenones cannot be ruled out. Therefore, it may be advised to perform a level II ultrasound, with emphasis on the limbs, in pregnancies with first trimester exposure to butyrophenones.

Drug names: biperiden (Akineton), carbamazepine (Carbatrol, Tegretol, and others), chlordiazepoxide (Librium and others), clonazepam (Klonopin and others), diazepam (Diastat, Valium, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), meclizine (Antivert and others), methylphenidate (Metadate, Ritalin, and others), metoclopramide (Reglan and others), orphenadrine (Norflex and others), oxazepam (Serax and others), perphenazine (Trilafon and others), phenytoin (Dilantin and others), promethazine (Promethacon, Phenergan, and others), risperidone (Risperdal), tetracycline (Sumycin, Bristacycline, and others).

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