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# In Utero Exposure to Fluoxetine HCl Increases Hematoma Frequency at Birth

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STANFORD, M. S. AND J. H. PATTON. *In utero exposure to fluoxetine HCl increases hematoma frequency at birth.* PHARMACOL BIOCHEM BEHAV **45**(4) 959–962, 1993.—The present study was undertaken to determine if fluoxetine HCl (Prozac, Dista Products Ltd., Liverpool, UK) might cause adverse vascular effects, such as hematomas, in rats exposed in utero. Gravid Sprague–Dawley rats were administered 5.62 mg/kg fluoxetine HCl by oral gavage beginning on day 7 of gestation and ending the day of birth. A control group received distilled water by oral gavage during gestation. At birth, offspring of both groups were assessed for visible adverse vascular effects. Fluoxetine HCl-exposed offspring showed a statistically higher frequency of skin hematomas when compared to water controls. This result is consistent with known adverse effects of fluoxetine and lends support to a recently published report that attempted to link fluoxetine HCl use to bleeding episodes in eight patients being treated for obsessive-compulsive disorder. The results of this study suggest caution in the prolonged use of this medication during pregnancy and in patients with predisposing conditions that may increase the chances of bleeding.

Fluoxetine Prenatal drug effects Serotonin Vascular effects

FLUOXETINE HCl (Prozac, Dista Products Ltd., Liverpool, UK) is an antidepressant drug chemically unrelated to the tricyclic antidepressants. Its antidepressant action appears to be linked to its selective inhibition of serotonin [5-hydroxytryptamine (5-HT)] reuptake in the CNS (10). More traditional tricyclic antidepressants, which have some serotonergic action, have been shown to adversely affect the developing fetus in varying ways (2,3). Presently, the only study of in utero exposure to fluoxetine HCl appearing in the literature is that of Montero, De Ceballos, and Del Rio (6). In that study, 2.5 mg/kg fluoxetine HCl was administered daily via the gravid mother's drinking water beginning on day 6 of gestation and ending on the day of birth. Offspring were sacrificed at 25 days of age and [$^3$H]imipramine binding assays were performed using cortical tissue. The results revealed a 30% decrease in the density of [$^3$H]imipramine binding sites in the cortex of 25-day-old offspring exposed in utero to fluoxetine HCl compared to controls. The results of Montero et al. (6) are consistent with the known effects of fluoxetine HCl on 5-HT and suggest that this medication crosses the placental barrier in concentrations sufficient to effect the fetus.

Adverse vascular effects of fluoxetine in adult humans have been reported and include bruises, metrorrhagia, cerebrovascular accidents, hemoptysis, melena, hematemesis, hematuria, and vaginal bleeding after drug withdrawal (9). These adverse vascular effects are explainable in the context of fluoxetine's effect on 5-HT and 5-HT's role in circulation and platelet function. Serotonin is known to be associated with both vasoconstriction and vasodilation and is present in high concentrations on platelets (4). Work by Horng and Wong (5) demonstrated that fluoxetine HCl inhibits 5-HT uptake by platelets in both rat and human blood plasma. More recently, Yaryura-Tobias, Kirschen, Ninan, and Mosberg (11) reported eight cases of excessive bleeding in patients being treated for obsessive-compulsive disorder with fluoxetine. The combined results of these studies raise concerns about the long-term use of this medication during pregnancy and in patients who have preexisting problems that may predispose them to bleeding episodes. The present study was undertaken to determine if exposure to fluoxetine HCl in utero has adverse vascular effects on neonates.

## METHOD

### *Subjects*

Adult, male and nulliparous female Sprague-Dawley (Baylor University Inbred Strain) rats were used as the breeding stock in this study. All animals were adapted to the laboratory longer than 1 month and housed in polycarbonate group cages (four to six per cage) in a temperature-regulated (22 ± 1°C) and light-controlled (12 L : 12 D cycle with lights on at 1500 h) colony room. During breeding, the female to male ratio

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TABLE 1

DESCRIPTIVE STATISTICS FOR WEIGHTS AND BIRTHS

| | Water | | Fluoxetine | |
|---|---|---|---|---|
| Group/Day | Mean | SD | Mean | SD |
| Dam weights* | | | | |
| 1st day of gavage | 263.6 | 18.0 | 260.6 | 22.4 |
| Day of birth | 298.9 | 18.1 | 285.4† | 21.1 |
| Pup weights* | | | | |
| Day 0 (birth) | 5.6 | 0.6 | 5.4 | 0.6 |
| Births | | | | |
| Live pups | 10.5 | 3.4 | 8.8 | 4.3 |
| Stillborn pups | 2.2 | 2.4 | 2.6 | 3.6 |

*Weights given are in grams.
†Significantly different from water controls ($p < 0.05$).

was 1 : 2. Dams were weighed and orally gavaged daily between 1500 and 1630 h.

*Drug Treatment*

All dams were orally gavaged with distilled water for 2 weeks prior to breeding to habituate them to the gavage technique. After breeding, dams were randomly assigned to one of two groups, fluoxetine (25 dams) or water control (18 dams). Daily treatment for the fluoxetine group consisted of 5.62 mg/kg fluoxetine HCl administered into the stomach by oral gavage. The drug was prepared such that there was 5.62 mg fluoxetine HCl in 1.0 ml distilled water (dose = 0.001 ml drug solution per gram body weight). Prenatal treatment for the water control group consisted of daily administration of distilled water, by oral gavage, in a volume consistent with their weight (amount = 0.001 ml water per gram body weight). The fluoxetine HCl dose and route of administration used were suggested by J. Buelke-Sam (personal communication, June 1991). The dose used is approximately five times the maximum recommended human dose (recommended human dose range: 20–80 mg/day) (9). Treatment for both groups began on day 7 of gestation and continued until the day of birth (day 0).

*Dam and Pup Care*

Dams were weighed daily and received ad lib food (Purina Rat Chow) and tapwater. After breeding, dams were housed two per cage until day 17 of gestation, at which time they were separated into individual cages.

*Evaluation of Hematomas*

All pups were visually examined on the day of birth for the presence of hematomas. The examiner was not blind to drug administration. Each pup was scored as either 1 (hematoma present) or 0 (no hematoma present). A positive hematoma score was given for a discolored area under the skin that contained extravasated blood.

## RESULTS

Descriptive statistics for all weight and birth data appear in Table 1. Analysis of dam weights on the first day of gavage (day 7 of gestation) revealed no significant difference between the fluoxetine and water control groups, $F(1, 41) = 0.22$, $p > 0.05$. Dam weights for the two groups did differ significantly on the day of birth, $F(1, 41) = 4.78$, $p < 0.05$.

Analysis of pup weights on the day of birth (day 0) showed

TABLE 2

PERCENTAGES AND RAW HEMATOMA DATA FOR THE WATER CONTROL GROUP

| Dam No. | Live Birth Hematomas | Stillborn Hematomas | Total Hematomas | Stillborn Births | Live Births | Total Litter Size |
|---|---|---|---|---|---|---|
| 001 | 0 | 0 | 0 | 3 | 13 | 16 |
| 003 | 0 | 0 | 0 | 1 | 13 | 14 |
| 004 | 1 | 0 | 1 | 1 | 10 | 11 |
| 005 | 0 | 0 | 0 | 5 | 12 | 17 |
| 006 | 0 | 0 | 0 | 2 | 10 | 12 |
| 007 | 2 | 0 | 2 | 2 | 13 | 15 |
| 009 | 0 | 0 | 0 | 6 | 11 | 17 |
| 010 | 0 | 0 | 0 | 1 | 12 | 13 |
| 432 | 0 | 0 | 0 | 1 | 12 | 13 |
| 452 | 0 | 0 | 0 | 0 | 14 | 14 |
| 456 | 0 | 0 | 0 | 1 | 9 | 10 |
| 471 | 1 | 0 | 1 | 1 | 11 | 12 |
| 475 | 0 | 0 | 0 | 0 | 8 | 8 |
| 487 | 0 | 0 | 0 | 2 | 16 | 18 |
| 492 | 0 | 0 | 0 | 9 | 7 | 15 |
| 494 | 0 | 0 | 0 | 3 | 7 | 10 |
| 497 | 0 | 0 | 0 | 1 | 1 | 2 |
| 499 | 0 | 0 | 0 | 0 | 11 | 11 |
| Totals | 4 | 0 | 4 | 39 | 190 | 228 |
| Percentages | 1.8 | 0.0 | 1.8 | 17.1 | 83.3 | |

TABLE 3

PERCENTAGES AND RAW HEMATOMA DATA FOR THE FLUOXETINE HCl GROUP

| Dam No. | Live Birth Hematomas | Stillborn Hematomas | Total Hematomas | Stillborn Births | Live Births | Total Litter Size |
|---|---|---|---|---|---|---|
| 020 | 8 | 1 | 9 | 1 | 14 | 15 |
| 022 | 2 | 0 | 2 | 6 | 3 | 9 |
| 023 | 1 | 0 | 1 | 1 | 7 | 8 |
| 024 | 4 | 0 | 4 | 4 | 12 | 16 |
| 025 | 1 | 0 | 1 | 1 | 10 | 11 |
| 028 | 2 | 0 | 2 | 1 | 13 | 14 |
| 029 | 1 | 0 | 1 | 3 | 9 | 12 |
| 031 | 1 | 0 | 1 | 0 | 14 | 14 |
| 431 | 2 | 0 | 2 | 1 | 8 | 9 |
| 435 | 4 | 0 | 4 | 1 | 11 | 12 |
| 451 | 3 | 0 | 3 | 0 | 5 | 5 |
| 458 | 4 | 0 | 4 | 0 | 13 | 13 |
| 459 | 4 | 0 | 4 | 0 | 10 | 10 |
| 464 | 4 | 0 | 4 | 1 | 11 | 12 |
| 469 | 1 | 0 | 1 | 3 | 7 | 10 |
| 470 | 0 | 3 | 3 | 10 | 1 | 11 |
| 473 | 5 | 2 | 7 | 3 | 13 | 16 |
| 477 | 2 | 0 | 2 | 1 | 12 | 13 |
| 479 | 0 | 0 | 0 | 1 | 5 | 6 |
| 482 | 1 | 0 | 1 | 0 | 13 | 13 |
| 485 | 3 | 0 | 3 | 2 | 12 | 14 |
| 486 | 0 | 5 | 5 | 12 | 1 | 13 |
| 489 | 4 | 1 | 5 | 3 | 11 | 14 |
| 493 | 0 | 13 | 13 | 13 | 0 | 13 |
| 495 | 2 | 0 | 2 | 0 | 4 | 4 |
| Totals | 59 | 25 | 84 | 68 | 219 | 287 |
| Percentages | 20.6 | 8.7 | 29.3 | 23.7 | 76.3 | |

no significant difference between the two groups, $F(1, 66) = 1.89$, $p > 0.05$. Offspring used in the pup weight analysis were a group of 68 offspring (35 fluoxetine, 33 water control) randomly selected for biochemical analysis. Results of the biochemical analysis are not discussed here.

The number of live and stillborn offspring for the two groups were compared to determine if fluoxetine HCl exposure effected birth number and/or fetal viability. Analyses demonstrated that the two groups did not differ in either the number of live births, $F(1, 41) = 1.22, p > 0.05$, or the number of stillborn births, $F(1, 41) = 0.24, p > 0.05$.

All offspring were visually inspected at birth for the presence or absence of visible skin hematomas. Raw data and percentages of hematomas appear in Table 2 for the water control group and Table 3 for the fluoxetine HCl group. $\chi_2$ analysis of these data by single pups revealed a significantly higher frequency of skin hematomas in the fluoxetine HCl group when compared to water controls ($\chi^2$ 65.9, $p < 0.001$). In an attempt to control for any possible litter effects, the same data were analyzed by litter. This analysis confirmed the previous analysis in that there was a significantly higher frequency of litters having skin hematomas in the fluoxetine HCl group when compared to litters in the water control group ($\chi^2 = 24.5$, $p < 0.001$). Hematomas were similar in appearance across all fluoxetine HCl and water control offspring. The hematomas appeared as purplish-red marks under the skin approximately 2 mm in diameter. Hematomas were most prevalent in three areas on the fluoxetine HCl-exposed offspring: middorsal-scapular area of the back, the end of the snout, and on the paws.

## DISCUSSION

The results of this study suggest that exposure to fluoxetine HCl in utero is associated with a high frequency of skin hematomas on the day of birth in rats. The difference in dam weights on the day of birth can possibly be attributed to the known anorectic effects of fluoxetine (1). Although fluoxetine-treated mothers were significantly lower in weight on the day of birth, this difference did not appear to affect pup weights, which did not differ between the two groups.

As discussed above, the hematomas were similar in appearance across all offspring and most prevalent in three areas on the exposed pups: middorsal-scapular area of the back, the end of the snout, and on the paws. Within the fluoxetine-exposed group, 29.3% of pups displayed hematomas compared to 1.8% of water control pups. A 1.8% rate of spontaneous hematomas is well within published norms for sporadic vascular malformations in several strains of laboratory rats (7,8). Visible hematomas on living pups were absorbed within 3-5 days and no further adverse vascular effects were observed.

We suggest that exposure to fluoxetine HCl in utero affects serotonergic aspects of vascular activity and thus causes ex-

posed offspring to be highly susceptible to bruising and hematomas during the birth process. This would account for the concentration of hematomas in three specific areas. All of these areas are highly susceptible to trauma during birth or soon afterward. Once high circulating levels of fluoxetine HCl and its metabolites have cleared the pups' systems, animals do not appear to have any further problems with bruising or bleeding. These results are consistent with known adverse effects of fluoxetine (9) and with the observations of Yaryura-Tobias et al. (11), who reported eight cases of fluoxetine-induced bleeding in patients being treated for obsessive-compulsive disorder.

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