Carcinogenicity Studies of Fluoxetine Hydrochloride in Rats and Mice

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ABSTRACT

The antidepressant drug fluoxetine HCl was tested for carcinogenicity in three well designed and controlled studies in Fischer rats and C57BL/6 × C3H F1 mice. The compound was administered to the animals for 24 months at dietary doses of approximately 0, 0.5, 2.0, or 10.0 mg/kg body weight in rats and 1.0, 5.0, or 10.0 mg/kg in mice. The highest dose tested was a maximum tolerated dose for both species as evidenced by clinical signs (rats and mice) and some mortality (mice). There was no evidence of an increased incidence of any type of unusual or commonly occurring spontaneous neoplasm in either rats or mice. There were statistically significant decreases in a few commonly occurring neoplasms. The data reported herein provide convincing evidence that fluoxetine is neither a complete carcinogen nor a tumor promoter.

INTRODUCTION

Fluoxetine hydrochloride, (±)-N-methyl-3-phenyl-3-(a,a,a-trifluoro-p-tolyl)oxy)propylamine hydrochloride, has been shown to inhibit the uptake of serotonin into nerve cells, thereby enhancing serotonergic function in the brain. Serotonin is believed to be a key neurotransmitter in the etiology of human depression, and it is through serotonin reuptake inhibition that fluoxetine is believed to exert its antidepressant effects. In contrast to tricyclic antidepressants, fluoxetine produces specific inhibition of serotonin uptake and the recommended clinical doses of 20–60 mg/day do not affect noradrenergic or dopaminergic neurons.

During the development of this drug, extensive animal toxicology testing was conducted to support the clinical trials and subsequent marketing of the product, Prozac. This report provides a compilation of the results from three 2-year carcinogenicity studies conducted with fluoxetine. One of the studies was conducted using Fischer 344 rats and the other two studies were in C57BL/6 × C3H F1 (hereafter called B6C3F1) mice. These studies were conducted by Lilly Research Laboratories, Indianapolis, IN, in compliance with the Good Laboratory Practices Guidelines of the United States Food and Drug Administration.

The purpose of this report is to communicate the carcinogenicity findings in these studies since they are counter to the recently published work of Brandes et al. (1) which suggests that fluoxetine might be a tumor promoter. Because the focus of the present report is on carcinogenicity, the only detailed data presented are the histopathological diagnoses of neoplasia. Other results of the studies are discussed only as they pertain to the interpretation of potential carcinogenicity.

MATERIALS AND METHODS

Test Animals and Animal Care. All rats and mice were purchased from Harlan Sprague Dawley, Inc. (Indianapolis, IN). Upon receipt, the animals were separated by sex, caged in groups of five to ten animals, and acclimated for 1 week. After acclimation, the animals were distributed randomly to test groups. All animals were 5 to 6 weeks of age at the initiation of the studies.

The animals were housed in ventilated cages constructed of stainless steel sheet metal with Lexan fronts and wire mesh floors. The cages, each measuring 18 x 24 x 18 cm (width x depth x height), were suspended over disposable waste trays that were changed at least weekly. Both rats and mice had free access to Purina Certified Rodent Chow No. 5002 and city water supplied through an automatic watering system. Rats were housed one per cage and mice were housed three per cage. Racks of animals on a given study were housed in separate rooms and each room was maintained at a temperature of 24.5 ± 2.5°C and a minimum relative humidity of 40%. The photoperiod for the rooms was 12 h of light and 12 h of darkness, changing at 6 a.m. and 6 p.m.

All animal handling and housing procedures were conducted in accordance with United States Department of Agriculture guidelines for humane care.

Study Design and Test Article. Each study consisted of a control group and three treatment groups. Each group contained 60 animals/sex. The treatment period was approximately 2 years (range, 727 to 737 days).

The test article, fluoxetine hydrochloride, was administered to the animals via continuously available mash diet. The fluoxetine hydrochloride, prepared by Lilly Research Laboratories, was mixed into the Purina Rodent Chow No. 5002 at concentrations of 0.0, 0.001, 0.0045, or 0.02% for rats and 0.0, 0.001, 0.004, or 0.01% for mice in the control and respective treatment groups. The lots of fluoxetine used in these studies had an assayed purity of approximately 98–99%. Routine sampling of newly mixed, biweekly prepared batches of diet was conducted to assure the stability of the compound, concentration of mix, and homogeneity of mix.

Clinical Observations and Evaluations. All test animals were observed daily for general physical condition and behavior and the observations were recorded. A detailed physical examination was conducted on each animal at weekly intervals to evaluate for abnormal changes in such parameters as condition of pelage, muscle tone, respiration, locomotion, and posture. The animals also were examined for the presence of external palpable tumors. Body weights and food consumption were assessed and recorded weekly in the rat study. In the mouse studies, body weights were measured and recorded weekly for the first 13 weeks and then biweekly for the remainder of the study period. Animals that died during the studies were necropsied as soon as possible and tissues were fixed for subsequent histopathological evaluation.

Necropsy Sampling Procedure. At the scheduled termination of the studies, the animals were fasted overnight. Just prior to necropsy, each animal was anesthetized and blood samples were collected for hematology, clinical biochemistry, and blood levels of fluoxetine and its major metabolite, norfluoxetine. During the necropsies, which were performed by veterinary pathologists, major organs were weighed and tissue samples were collected for fluoxetine/norfluoxetine tissue concentration analysis, phospholipid analysis, and histopathology. Particular attention was directed toward identifying and collecting potentially neoplastic tissue. Tissue samples for histopathology were collected into neutral buffered 10% formalin and were processed routinely for sectioning and hematoxylin and eosin staining.

Statistical Methods for Tumor Data Analysis. A two-tailed Cochran-Armitage trend test (2, 3) was performed to test for linear trends in oncogenesis in benign and malignant tumor bearing animals by sex. Since increased mortality in high-dose female mice was observed at the end of 12 months, the Cochran-Armitage trend test was adjusted for 12-month survival. A positive Z statistic from the Cochran-Armitage test coupled with a small P value (<0.05) suggests a statistically
significant increasing trend in tumor incidence, while a negative $Z$ statistic coupled with a small $P (<0.05)$ suggests a statistically significant decreasing trend in tumor incidence. All statements of statistical significance refer to a two-tailed $P$ value of $<0.05$.

### Table 1 Neoplastic lesions from rats fed fluoxetine HCl for 2 years (R10880/R10980)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Approximate Dose (mg/kg)</th>
<th>Sex</th>
<th>No. of animals</th>
<th>No. evaluated</th>
<th>No. survived (12 mo)</th>
<th>No. survived (24 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
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<td>Benign: hepatocellular adenoma</td>
<td>0 1</td>
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<td>Pancreas</td>
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<td>28 14 19 9 17 4 10</td>
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### Table 2 Neoplastic lesions from mice fed fluoxetine HCl for 2 years (M03081/M03181)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Approximate Dose (mg/kg)</th>
<th>Sex</th>
<th>No. of animals</th>
<th>No. evaluated</th>
<th>No. survived (12 mo)</th>
<th>No. survived (24 mo)</th>
</tr>
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<td>Adrenal</td>
<td>Benign: adenoma</td>
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<td></td>
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<tr>
<td>Malignant: pheochromocytoma</td>
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<td>1 1</td>
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<tr>
<td>Liver</td>
<td>Benign: hepatocellular adenoma</td>
<td>0 0</td>
<td>1 0 0 0 2 0 0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lung</td>
<td>Benign: alveolar/bronchiolar adenoma</td>
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<td>0 0 0 0 1 0 0 0</td>
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<tr>
<td>Malignant: alveolar/bronchiolar carcinoma</td>
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<td>Benign: fibroadenoma</td>
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<tr>
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<tr>
<td>Pancreas</td>
<td>Benign: islet-cell adenoma</td>
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<td>0 0 1 0 0 0 0</td>
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<td>Benign: Angioma</td>
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<tr>
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<td>0 0 1 0 0 0 0</td>
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<td>0 0</td>
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<td></td>
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<td>1 0 0 0 0 0 0</td>
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<td>Systemic neoplasia</td>
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<td>0 0 0 0 1 0 0</td>
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</table>

### RESULTS

On the basis of food consumption measurements, the rats received average daily doses of approximately 0.5, 2.0, or 10.0 mg/kg of body weight for the 0.001, 0.0045, and 0.02% dietary concentrations, respectively. The mice received average daily doses of approximately 1.0, 5.0, or 10.0 mg/kg of body weight for the 0.001, 0.004, and 0.01% dietary concentrations, respectively.

Clinical signs referable to the central nervous system pharmacology of the compound were observed in both rats and mice in the respective highest dose groups. These effects resulted in some mortality, particularly in the mouse studies, during the first 3-4 months of treatment. The loss of these animals early in the studies did contribute to a decrease in the overall 12- and 24-month survival of these groups relative to their respective controls. However, the decreases were not of a magnitude to compromise the validity of the studies. In all groups, the survival at the end of the studies was greater than 50% (Tables 1-3).

Male and female rats in the highest dose group had statistically significantly decreased body weights compared to controls throughout the test period (data not shown). The decreased body weight was associated with decreased food consumption.
Similar effects were not seen in the middle- or low-dose rats or the fluoxetine-treated mice in which the trend was toward increased body weight in all dose groups.

Dose proportional increases in fluoxetine and norfluoxetine were found in tissues and plasma of rats (data not shown). Tissue concentrations were in the order of lung > liver > brain > plasma, with levels of norfluoxetine being generally higher than those of fluoxetine. Similarly, dose proportional increases in levels of the parent compound and metabolite were found in the lungs of the mice. Increased levels of phospholipid were found in tissues and plasma of rats (data not shown).

Increased levels of phospholipid were generally confined to the highest dose groups and were not of major toxicological significance.

The only treatment related histopathological finding of significance in rats was multifocal pulmonary histiocytosis in males and females primarily from the high-dose group. This lesion was considered to be morphological evidence of phospholipid accumulation in pulmonary macrophages. This conclusion was further substantiated by the electron microscopic identification of intracytoplasmic lamellar inclusions indicative of phospholipidosis within affected cells. Treatment related histopathological changes in mice were confined to minimal to moderate fatty change in middle- and high-dose females, and an increase in incidence and prominence of hepatocellular cytomegaly in middle- and high-dose males and high-dose females. There was no increase in the incidence of any type of unusual or commonly occurring neoplasm in either rats or mice as compared to their respective concurrent untreated controls (Tables 1–6). Types of neoplasms that occurred only once in the study are not listed in the tables. These singular occurrences were distributed randomly throughout the study groups. The incidence of fatal neoplasia across the treatment groups was similar, and fatal neoplasms were of the types expected in aging Fischer rats (e.g., mononuclear cell leukemia) and B6C3F1 mice (e.g., lymphosarcoma).

DISCUSSION

Fluoxetine hydrochloride when fed to rats and mice in an ad libitum diet at daily doses of approximately 1–25 times the equivalent daily human dose for depression (20 mg/day) produced no evidence of a carcinogenic response. The doses were

### Table 3 Neoplastic lesions from mice fed fluoxetine HCl for 2 years (M03283/M03383)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>00</th>
<th>01</th>
<th>02</th>
<th>03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate Dose (mg/kg)</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
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<td>No. of animals</td>
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<td>59</td>
</tr>
<tr>
<td>No. evaluated</td>
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<td>59</td>
<td>60</td>
<td>59</td>
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<tr>
<td>No. survived (12 mo)</td>
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<td>54</td>
<td>59</td>
<td>58</td>
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<tr>
<td>No. survived (24 mo)</td>
<td>46</td>
<td>41</td>
<td>38</td>
<td>47</td>
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</tbody>
</table>

**Adrenal**
- Benign: adenocortical adenoma
  - M: 1
  - F: 0

**Duodenum**
- Benign: adenoma
  - M: 0
  - F: 1

**Harderian gland**
- Benign: adenoma
  - M: 2
  - F: 2

**Jejunum**
- Malignant: adenocarcinoma
  - M: 0
  - F: 1

**Liver**
- Benign: hepatocellular adenoma
  - M: 3
  - F: 3
- Malignant: hepatocellular carcinoma
  - M: 13
  - F: 4

**Lung**
- Benign: alveolar/bronchiolar adenoma
  - M: 4
  - F: 2
- Malignant: alveolar/bronchiolar carcinoma
  - M: 1
  - F: 1

**Mammary gland**
- Malignant: adenocarcinoma
  - M: 0
  - F: 2

**Metastatic neoplasms**
- Malignant
  - M: 2
  - F: 2

**Pituitary**
- Benign: adenoma
  - M: 0
  - F: 6

**Skin**
- Malignant: fibrosarcoma
  - M: 0
  - F: 0

**Systemic neoplasms**
- Malignant
  - Lymphosarcoma
    - M: 5
    - F: 14
  - Fibrous histiocytoma
    - M: 1
    - F: 1
  - Histiocytic sarcoma
    - M: 1
    - F: 1

**Testis**
- Benign: interstitial cell tumor
  - M: 0
  - F: 2

**Thyroid**
- Benign: follicular cell adenoma
  - M: 3
  - F: 1

**Uterus**
- Malignant: leiomyosarcoma
  - M: 0
  - F: 1

### Table 4 Statistical analysis on tumor incidence of selected tumors from fluoxetine treated rats (R10880 and R10980)

<table>
<thead>
<tr>
<th>Dose group (mg/kg)</th>
<th>Two-tailed Cochran-Armitage trend test a</th>
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</thead>
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</table>

**Female**
- No. of animals at 12 mo
  - M: 60
  - F: 60
- Pituitary adenoma
  - M: 28
  - F: 19
- Mammary adenoma
  - M: 6
  - F: 5
- Mammary fibroadenoma
  - M: 12
  - F: 8

**Male**
- No. of animals at 12 mo
  - M: 60
  - F: 60
- Pituitary adenoma
  - M: 12
  - F: 14

### Table 5 Statistical analysis on tumor incidence of selected tumors from fluoxetine treated mice (M03081 and M03181)

<table>
<thead>
<tr>
<th>Dose group (mg/kg)</th>
<th>Two-tailed Cochran-Armitage trend test a</th>
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<tbody>
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<td>0</td>
<td>1</td>
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</tbody>
</table>

**Female**
- No. of animals at 12 mo
  - M: 59
  - F: 57
- Lymphosarcoma
  - M: 8
  - F: 11
- Pituitary adenoma
  - M: 2
  - F: 1
- Mammary adenocarcinoma
  - M: 2
  - F: 1

**Male**
- No. of animals at 12 mo
  - M: 59
  - F: 58
- Hepatocellular carcinoma
  - M: 10
  - F: 9
- Pulmonary adenoma
  - M: 9
  - F: 11
- Lymphosarcoma
  - M: 4
  - F: 6

*a Adjusted for 12-month survival."
appropriately chosen with the highest doses being the maximum tolerated as evidenced by the occurrence of marked clinical signs referable to central nervous system activity in both species, pulmonary phospholipidosis in rats, decreased weight gain in rats, and hepatocytic changes in mice. Even though maximum tolerated doses were achieved, the survival of animals in all dose groups was excellent throughout the duration of the studies.

Toxicokinetic and pharmacokinetic studies in rats, mice, and humans have shown that fluoxetine is well absorbed in a dose proportional manner following oral dosing. Furthermore, the metabolism profile and tissue affinity of fluoxetine and norfluoxetine are comparable in all three species.

There was no statistically significant increase in the incidence of any individual type of neoplasm in the studies with either species. However, there were statistically significant decreases in the incidences of pituitary adenomas in male and female rats and mammary adenomas and fibroadenomas in female rats (Table 4). This dose related trend might have been enhanced by the reduced body weights in the high-dose group, but body weight decrease was not a significant factor in rats from the middle- or low-dose groups. In mice, there were statistically significant decreases in hepatocellular carcinomas in males and pituitary adenomas in females from one study (Table 6). These findings were not replicated in the companion mouse study. The reproducibility and biological significance of decreases in tumor incidences can be debated; however, the consistent absence of any type of neoplasm with increased incidence in these data provides compelling evidence that fluoxetine is neither an initiator nor a promoter of carcinogenesis in these animal models.

Recently, Brandes et al. (1) reported data from studies in which two antidepressants, fluoxetine and amitriptyline, were administered to mice that had received transplantable C-3 fibrosarcoma or B16F10 melanoma and to rats that had been fed dimethylbenzanthracene to initiate mammary tumor formation. The report indicates that both drugs enhance the growth of the transplantable and carcinogen-induced tumors. The authors suggest that these data imply potential risk to humans who use antidepressant drugs. This conclusion, in addition to being discordant with the findings in the carcinogenicity studies, is directly contradictory to that of Tutton and Barkla (4). Their data indicate that fluoxetine and another serotonin uptake inhibitor, citalopram, were found to "suppress cell division in dimethylhydrazine-induced colonic tumours in rats, and to retard the growth of 2 out of 3 lines of human colonic tumours propagated as xenografts in immune-deprived mice." Their findings were of sufficient scientific interest to lead them to suggest that these compounds should be studied as antineoplastic agents in humans.

Brandes et al. additionally state that "while undoubtedly of predictive value, standard tests for mutagenesis/carcinogenesis appear to miss the potential of drugs to act as tumor promoters when cancer is already present, or to accelerate the development of malignancy in the presence of chemical or viral initiators." This statement stands counter to the scientific data available from rodent carcinogenicity tests. In fact, the data suggest that many of the positive outcomes of carcinogenicity with nongenotoxic chemicals in these models occur because the compounds are acting as tumor promoters on spontaneously initiated cells (5, 6).

While far from being an ideal model, the 2-year rodent carcinogenicity test is accepted within the scientific and regulatory communities as the most appropriate test which is currently available for evaluating potential carcinogenic effects for human risk assessment (7-9). This model has been shown to detect genotoxic carcinogens and nongenotoxic carcinogens including tumor promoters which affect different target tissues such as liver (phenobarbital, DDT, dioxin, peroxisome proliferators), mammary gland (reserpine), thyroid (propylthiouracil), and urinary bladder (saccharin) (5, 6, 10-12).

Classical tumor promotion assays which involve the use of potent genotoxins to initiate tumor formation are useful and important to apply to questions of basic cancer research; however, they have not been established as having utility in human cancer risk assessment for regulatory purposes (13, 14). The use of the lifetime rodent test, which permits one to evaluate the carcinogenic initiation properties of a chemical as well as its promoter activity on spontaneously occurring neoplasms, remains the most appropriate model for the assessment of the potential for a chemical to produce similar effects on spontaneously occurring neoplasms in humans. Fluoxetine clearly was neither a complete carcinogen nor a promoter in this model.

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Carcinogenicity Studies of Fluoxetine Hydrochloride in Rats and Mice


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