CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant, antiobsessive-compulsive, and antibulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and alpha1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion

Systemic Bioavailability: In humans, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/ml are observed after 6 to 8 hours.

The Pulvule, tablet, and oral solution dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food.

Protein Binding: Over the concentration range from 200 to 1000 ng/ml, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS).

Enantiomers: Fluoxetine is a racemic mixture (50/50) of R-fluoxetine and S-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The S-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Metabolism: Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other, unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, S-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to R- or S-fluoxetine. R-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism/Elimination: The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in Metabolism: A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450IID6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-norfluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal.
When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-IID6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including tricyclic and other selective serotonin antidepressants, involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the tricyclic antidepressants) may lead to drug interactions (see DRUG INTERACTIONS).

**Accumulation and Slow Elimination:** The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/ml and norfluoxetine in the range of 72 to 258 ng/ml have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady state levels after prolonged dosing are similar to levels seen at 4-5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

**Liver Disease:** As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared to the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared to the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

**Renal Disease:** In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for two months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable to those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (see PRECAUTIONS, Use in Patients with Concomitant Illness and DOSAGE AND ADMINISTRATION).

**Age:** The disposition of single doses of fluoxetine in healthy elderly subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not
adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥ 60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/ml at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

CLINICAL STUDIES

Depression: The efficacy of fluoxetine HCl for the treatment of patients with depression (≥18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Fluoxetine HCl was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Fluoxetine HCl was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies comparing fluoxetine HCl, 20 mg, and placebo have shown fluoxetine HCl, 20 mg daily, to be effective in the treatment of elderly patients (≥ 60 years of age) with depression. In these studies, fluoxetine HCl produced a significantly higher rate of response and remission as defined respectively by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of <7. Fluoxetine HCl was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between fluoxetine HCl (12%) and placebo (9%).

A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score of ≤7 during each of the last 3 weeks of open-label treatment and absence of major depression by DSM-III-R criteria) by the end of an initial 12-week open treatment phase on fluoxetine HCl 20 mg/day. These patients (N=298) were randomized to continuation on double-blind fluoxetine HCl 20 mg/day or placebo. At 38 weeks (50 weeks total), a statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of major depression for 2 weeks or a modified HAMD-17 score of ≥14 for 3 weeks) was observed for patients taking fluoxetine HCl compared to those on placebo.

Obsessive Compulsive Disorder: The effectiveness of fluoxetine HCl for the treatment for obsessive compulsive disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed fluoxetine HCl doses of 20, 40, or 60 mg/day (on a once a day schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving fluoxetine HCl experienced mean reductions of approximately 4 to 6 units on the YBOCS total score, compared to a 1-unit reduction for placebo patients. In Study 2, patients receiving fluoxetine HCl experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared to a 1-unit reduction for placebo patients. While there was no indication of a dose response relationship for effectiveness in Study 1, a dose response relationship was observed in Study 2, with numerically better responses in the 2 higher dose groups. TABLE 1 provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for studies 1 and 2 combined.

<p>| Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies | Fluoxetine Hydrochloride |
|---|---|---|---|
| Placebo | 20 mg | 40 mg | 60 mg |</p>
<table>
<thead>
<tr>
<th>Worse</th>
<th>8%</th>
<th>0%</th>
<th>0%</th>
<th>0%</th>
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</thead>
<tbody>
<tr>
<td>No Change</td>
<td>64%</td>
<td>41%</td>
<td>33%</td>
<td>29%</td>
</tr>
<tr>
<td>Minimally Improved</td>
<td>17%</td>
<td>23%</td>
<td>28%</td>
<td>24%</td>
</tr>
<tr>
<td>Much Improved</td>
<td>8%</td>
<td>28%</td>
<td>27%</td>
<td>28%</td>
</tr>
<tr>
<td>Very Much Improved</td>
<td>3%</td>
<td>8%</td>
<td>12%</td>
<td>19%</td>
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Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

**Bulimia Nervosa:** The effectiveness of fluoxetine HCl for the treatment of bulimia was demonstrated in two 8-week and one 16-week, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria for bulimia. Patients in the 8-week studies received either 20 mg/day or 60 mg/day of fluoxetine HCl or placebo in the morning. Patients in the 16-week study received a fixed fluoxetine HCl dose of 60 mg/day (once a day) or placebo. Patients in these 3 studies had moderate to severe bulimia with median binge-eating and vomiting frequencies ranging from 7 to 10 per week and 5 to 9 per week, respectively. In these 3 studies, fluoxetine HCl, 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the number of binge-eating and vomiting episodes per week. The statistically significantly superior effect of 60 mg vs placebo was present as early as week 1 and persisted throughout each study. The fluoxetine HCl related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. In each of these 3 studies, the treatment effect, as measured by differences between fluoxetine HCl, 60 mg, and placebo on median reduction from baseline in frequency of bulimic behaviors at endpoint, ranged from 1 to 2 episodes per week for binge-eating and 2 to 4 episodes per week for vomiting. The size of the effect was related to baseline frequency, with greater reductions seen in patients with higher baseline frequencies. Although some patients achieved freedom from binge-eating and purging as a result of treatment, for the majority, the benefit was a partial reduction in the frequency of binge-eating and purging.

**ANIMAL PHARMACOLOGY**

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.