Selective Serotonin Reuptake Inhibitors in the Context of Hepatitis C Infection: Reexamining the Risks of Bleeding

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Objective: Selective serotonin reuptake inhibitors (SSRIs) are used to treat interferon-associated depression in patients receiving hepatitis C virus therapy. Prior studies have cautioned against the combined use of SSRIs and interferon due to increased risk of hemorrhage. Given the morbidity of depression and its impact on interferon compliance, we sought to reexamine the data.

Method: In a retrospective analysis of our database of hepatitis C virus patients, a consecutive series of 303 patients (receiving treatment between January 2001 and January 2005) were evaluated for any evidence of bleeding. On the basis of our standard practice of care, patients were treated prophylactically with antidepressants for 3 to 4 weeks before beginning combination therapy with interferon and ribavirin. Patients were evaluated every 4 weeks during antiviral treatment with physical examinations and complete blood cell counts with differentials and platelets.

Results: The overall rate of bleeding in our study was 0.3%, representing a single case of hemophilia.

Conclusions: The bleeding risk of SSRIs is lower than previously reported.

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The overall prevalence of hepatitis C virus (HCV) infection in the United States from 1988 through 1994 was 1.8%, corresponding to an estimated 3.9 million persons nationwide.[1] Sixty-five percent of these persons with HCV infection were 30 to 49 years old.[1] The burden of disease associated with HCV infection is expected to increase during the next 10 to 20 years as this cohort reaches an age at which complications of chronic liver disease typically occur. Hepatitis C virus represents a major public health burden. The direct health costs associated with HCV for the period of 2010 through 2019 are expected to total $10.7 billion.[2] The current standard of care for HCV infection is combination therapy with pegylated interferon and ribavirin, a combination that achieves a sustained viral response in more than one half of treated patients.[3] The duration of treatment is determined largely by genotype and varies from 24 weeks for genotypes 2 and 3 to 48 weeks for genotype 1. The goal of treatment is to eradicate the virus and improve liver histology.

Side effects of combined treatment are significant and include fatigue, irritability, depression, delirium, mania, psychoses, anemia, leukopenia, thrombocytopenia, nausea, flu-like symptoms, insomnia, and malaise. Between 10% and 14% of HCV-infected patients in large randomized trials discontinue therapy secondary to adverse effects.[4] Significant depressive symptoms occur in 21% to 58% of patients receiving interferon, with the median time from initiation of interferon therapy to the development of major depressive disorder being 12 weeks.[5,6]

Selective serotonin reuptake inhibitors (SSRIs) are increasingly being used to treat interferon-associated side effects in patients receiving HCV therapy. Paroxetine, in particular, has demonstrated efficacy as a prophylaxis to prevent interferon-associated depression in malignant melanoma.[7] There are no studies in the HCV population addressing the prophylactic use of antidepressant prior to interferon treatment. Hepatitis C virus–infected patients are already at increased risk of bleeding secondary to the development of cirrhosis, portal hypertension, hepatic failure, and the hematologic side effects of interferon. Hematologic side effects are particularly common with combination therapy; bone marrow suppression caused by interferon may result in neutropenia and thrombocytopenia. Ribavirin is directly toxic to red blood cells and is associated with hemolysis, which is dose related but self-limited.[8] Most of the drop in hematocrit occurs in the first month, with the nadir occurring between weeks 8 and 24 of therapy.[9]

Selective serotonin reuptake inhibitors have been associated with spontaneous hemorrhage[10,11] and may have a thrombolytic mechanism of action. Antidepressants have

Table 1. Treatment Guidelines for Treating Anemia in Patients Receiving Combination Interferon and Ribavirin Therapy for Hepatitis C Virus Infection

Blood Level	Action
Hemoglobin > 2.5 g drop from baseline or patient symptomatic	Consider initiation of epoetin alfa
Hemoglobin ≤ 10.0 g/dL	Consider reducing dose of ribavirin
Hemoglobin ≤ 8 g/dL	Transfuse with packed red blood cells
Platelets ≤ 25×10^9/L	Consider dosage reduction of PEG
Platelets < 20×10^9/L	Definitely reduce dose of PEG
WBC ≤ 1.5×10^9/L and/or ANC ≤ 500×10^9/L in noncirrhotic	Dose reduce PEG or start filgrastim (usually the latter)
WBC < 2.0×10^9 /L and/or ANC < 1000×10^9/L in cirrhotic	Dose reduce PEG or start filgrastim (usually the latter)

Abbreviations: ANC = absolute neutrophil count, PEG = pegylated interferon, WBC = white blood cell count.

been associated with decreased cardiovascular disease.[12] At therapeutic doses, serotonin reuptake inhibitors have been shown to block the reuptake of serotonin by platelets leading to a depletion of serotonin after several weeks of treatment.[13,14]

The release of serotonin from platelets seems to be an important step in platelet aggregation. Serotonin depletion could be expected to impair the hematostatic response to vascular injury.[15] A literature search published by Weinrieb et al.[16] in 2003 reported a high incidence (67%) of gastrointestinal bleeding in HCV patients, of whom 79% were taking SSRIs. The authors warned that SSRIs, especially when combined with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), increased the risk of hemorrhage. This article is often cited as evidence of the risk of using SSRIs in the HCV population as a whole. Given the morbidity of depression and its impact on interferon compliance, we sought to reexamine the data.

METHOD

This is a retrospective analysis of our Mayo Clinic Arizona database of HCV patients, based on our standard practice of care. Our HCV program has been using antidepressants prophylactically since 2001. Antidepressants are a required component of the program and they are begun 3 to 4 weeks prior to antiviral therapy. Citalopram and escitalopram are the agents of choice in our program given their limited potential for drug-drug interactions and generally tolerable side effect profiles. Patients who failed to respond to citalopram or escitalopram in the past, despite therapeutic drug trials (40 mg/day of citalopram or 20 mg/day of escitalopram for 4–6 weeks) were initiated on alternative agents: fluoxetine, paroxetine, or sertraline. Provider discretion determined the final antidepressant choice.

Before treatment, all candidates for interferon undergo a 1-hour psychiatric assessment by one of our department psychiatrists to screen for contraindications to treatment. The initial Beck Depression Inventory (BDI)[17] is administered at this time. The most common reason for exclusion is active alcohol or drug use followed by a history of mania. A consecutive series of 303 patients with HCV on SSRI treatment (receiving treatment between January 2001 and January 2005) were evaluated for any evidence of bleeding. Patients were prohibited from using aspirin. Acetaminophen and NSAIDS were allowed as long as patients had normal kidney function. Patients were instructed to alternate acetaminophen and NSAIDs and to space doses no more frequently than 6 to 8 hours apart. The total dose of analgesic could not exceed 2000 mg/24 hours. After beginning treatment with interferon (pegylated alfa-2b 1.5 μg/kg/week; pegylated alfa-2a 180 μg/week; interferon alfa-2b, recombinant 3 MIU 3 times per week; gamma interferon 100 μg 3 times per week; or interferon alfacon-1 15 μg daily—all subcutaneously administered) and ribavirin (weight based: below 75 kg received 1000 mg/day, split morning and evening; 75 kg or above received 1200 mg/day, split morning and evening), hematologic issues such as bleeding, bruising, and anemia were assessed by evaluating patients every 4 weeks with physical examinations and complete blood cell counts with differentials and platelets. Anemia was treated as necessary with combination therapy dosage modification and growth factors and/or blood transfusions (Table 1). Beck Depression Inventory[17] was repeated at each visit throughout treatment. The Mayo Clinic Institutional Review Board approved the study.

RESULTS

The mean ± SD age of our patient population was 48 ± 9 years. Sixty-one patients had 2 or more trials of SSRIs with escitalopram replacing citalopram being the most common switch (27 cases). Men composed 59% of the study population; women composed 41%. The vast majority of our study population was white (91%), followed by Hispanic (5%), African American (2%), and Asian (1%). Genotype 1 composed 71% of the population, with genotypes 2 and 3 the next most common at 17% and 10% of the total population, respectively. Two percent of our population bore genotype 4.

A single case of bleeding occurred among the 303 patients involved in our study. A 53-year-old man with hemophilia and HCV developed a hematoma after falling,

Table 2. Incidence of Bleeding for Various Antidepressants in Patients Receiving Combination Interferon and Ribavirin Therapy for Hepatitis C Virus Infection

SSRI	No. of Courses of Treatment	Maximum Dose, Mean (range)	Duration of SSRI Treatment,[a] Mean (range)	Bleeding Case, N (%)
Citalopram	120	46 mg (10–80)	16.5 mo (3–48)	1 (< 1%)
Sertraline	97	104 mg (25–200)	13.5 mo (5–48)	0 (0%)
Escitalopram	59	24 mg (5–40)	13.6 mo (1–24)	0 (0%)
Paroxetine	14	37 mg (20–60)	13.5 mo (5–48)	0 (0%)
Fluoxetine	13	40 mg (10–80)	19 mo (3–48)	0 (0%)

[a]If genotype 1 or 4, duration of interferon treatment is 48 weeks; if genotype 2 or 3, duration is 24 weeks.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

which was treated with factor VIII and 2 units of packed red blood cells. This patient did consume the NSAID valdecoxib and acetaminophen for pain per our treatment protocol. Interferon, ribavirin, and citalopram 40 mg/day were continued until he completed 48 weeks of treatment as planned.

The overall rate of bleeding in this study was 0.3%. The average treatment course lasted 1 year or longer (Table 2).

CONCLUSIONS

High-dose interferon alpha-2b treatment is associated with increased risk of depression. In light of emerging data that HCV treatment adherence might be associated with improved antiviral outcomes, the appropriate management of neuropsychiatric side effects in patients who have hepatitis C is crucial in ensuring that such patients receive optimum antiviral therapy and experience improved treatment outcomes.[18–20] The utility of antidepressants in treating the mood side effects of interferon has been tainted by concern of increased risk of spontaneous hemorrhage in this hemodynamically vulnerable population. Our study demonstrates that these concerns are overstated.

The risks of bleeding due to SSRIs are not as high as previously reported. The overall rate of bleeding in our study was 0.3%, representing a single case of hemophilia. These are valuable data when determining the risks, benefits, and alternatives of SSRI use for interferon patients, especially for prophylactic purposes. Caution is still warranted for HCV patients with multiple risk factors for bleeding, but the risk is not significant enough to forego prophylactic treatment.

Drug names: citalopram (Celexa and others), epoetin alfa (Procrit), escitalopram (Lexapro and others), filgrastim (Neupogen), fluoxetine (Prozac and others), interferon alfa-2b, recombinant (Intron A), interferon alfacon-1 (Infergen), paroxetine (Paxil and others), pegylated interferon alfa-2a (Pegasys), ribavirin (Rebetol, Ribasphere, and others), sertraline (Zoloft and others), valdecoxib (Bextra).

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