Tolcapone and Hepatotoxic Effects

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Four patients with Parkinson disease have recently been described in whom severe hepatic dysfunction developed in association with tolcapone therapy. These reports led to the introduction of a “black box” warning and more intensive monitoring requirements in the United States. A review of these cases and all clinical trials indicates that liver dysfunction did not develop in any patient who had received monitoring of liver function according to the original prescribing information. Virtually all instances of liver enzyme abnormality and clinical liver dysfunction occurred within 6 months of initiating treatment. To assess the current role of tolcapone therapy in Parkinson disease, a panel of neurologists and hepatologists was convened. Consensus was reached with respect to the following: (1) Tolcapone is an effective agent in the treatment of patients with fluctuating Parkinson disease. (2) The risk of developing irreversible liver injury is negligible with appropriate monitoring. (3) It may be possible to reduce the frequency of monitoring after 6 months of treatment. (4) The requirement that tolcapone be withdrawn if liver enzymes are elevated above the upper limit of normal on a single occasion is unnecessarily restrictive. It was concluded that tolcapone, when used as an adjunct to levodopa, is an effective anti-parkinsonian agent and that less frequent monitoring after 6 months, with an action limit of 2 to 3 times the upper limit of normal, is sufficient to ensure safety in patients who are deriving benefit from the drug.
brain availability of levodopa. In general, these effects could be controlled by a 20% to 30% decrease in the levodopa dose. Diarrhea was the most common nondopaminergic adverse event, and necessitated discontinuing treatment in approximately 5% of patients. A 3-fold increase in liver transaminase levels was noted in 1% to 3% of tolcapone-treated patients, and the original prescribing information recommended that biochemical liver function tests (LFTs) be monitored every 4 weeks during the first 3 months of treatment and every 6 weeks during the next 3 months. As of October 1998, approximately 60,000 patients worldwide had been treated with tolcapone for a total of 40,000 patient-years.

Although tolcapone was generally well tolerated in clinical trials, 4 cases of serious hepatic dysfunction have been described in postmarketing surveillance reports, with 3 of these resulting in death.9-11 These reports have led to the drug being withdrawn from the market in some countries (in Europe and Canada) and the introduction of more intensive monitoring requirements and a black-box warning in the United States.12 This article reviews the preclinical and clinical evidence of liver dysfunction associated with the use of tolcapone and the opinions of an expert panel of neurologists and hepatologists who were assembled by Roche Laboratories, Inc, Nutley, NJ, to consider the role of tolcapone in the management of PD based on current information.

LIVER DYSFUNCTION AND TOLCAPONE

Preclinical Testing

Preclinical testing for toxic effects was performed in animals exposed to tolcapone. Studies in mice (18 months in duration) revealed slight to moderate hepatic necrosis in plasma bilirubin levels, but this was thought to be related to drug interference with the assay, and the results were thought to be artifactual. No evidence of serious hepatic dysfunction was recognized in any of the preclinical studies.

Clinical Trials

Tolcapone was evaluated in 1535 patients during a period of approximately 6 months in phase IIIa studies. A greater than 3-fold increase above the upper limits of normal in levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) was detected in 1.3% and 3.7% of patients receiving tolcapone in doses of 100 mg TID and 200 mg TID, respectively. Female patients were more frequently affected than male patients by a ratio of 3:2. Elevated liver enzyme levels occurred within 6 weeks to 6 months after starting tolcapone and resulted in the therapy being stopped in 0.3% and 1.7% of patients in the 100- and 200-mg dose groups, respectively. Liver enzymes returned to baseline levels within 1 to 3 months in approximately 50% of patients who continued to receive tolcapone and generally returned to normal within 2 to 3 weeks after therapy was discontinued. Approximately one third of patients with abnormal LFTs had diarrhea, but not all patients who had diarrhea had elevated LFTs. Diarrhea and jaundice were reported to have developed in 1 patient who participated in the clinical trials and subsequently died. No liver biopsy or postmortem study was performed, and the death was thought to be due to a cardiac cause. More than 4000 patients have been observed in controlled clinical trials, and no cases of serious liver dysfunction have been attributed to tolcapone.

POSTMARKETING SURVEILLANCE REPORTS

Since the introduction of tolcapone to the market in Europe in late 1997 and to the United States in March 1998, there have been 4 reports of serious liver dysfunction in tolcapone-treated patients, with 3 of these resulting in death.

Patient 1 was a woman aged 74 years who was described in Lancet.10 She received a diagnosis of PD in 1978 and was treated with levodopa-benserazide, 125 mg TID, and amantadine hydrochloride, 100 mg twice daily (BID). Other medications included tlefine, amiloride hydrochloride–hydrochlorothiazide, and oxazepam. In March 1998, she complained of hypotension with falls, and amantadine was discontinued. On March 25, 1998, she started receiving tolcapone, 100 mg BID. Liver function tests were not obtained, but results had been normal in May 1997 (AST, 18 U/L; ALT, 21 U/L; and γ-glutamyltransferase [GGT], 10 U/L). In May 1998, the patient complained of malaise, dizziness, falls, hypotension, and palpitations with a brief loss of consciousness. On June 3, hypotension and malaise worsened. Jaundice, hepatomegaly, edema of the legs, and numerous hematomas were noted. She was hospitalized, and the following laboratory test results were obtained (reference range from this laboratory not available): AST, 2541 U/L; ALT, 2904 U/L; lactate dehydrogenase [LDH], 1548 U/L; alkaline phosphatase, 177 U/L; GGT, 311 U/L; total bilirubin, 367 µmol/L [21.5 mg/dL]; ammonia, 102 µmol/L [142.9 µg/dL]; and international normalized ratio, 1.7. Abdominal ultrasound findings suggested hepatic steatosis with biliary cysts and a contracted gall bladder. Results of screening tests for hepatitis A, B, and C viruses were negative (more specific details were not available). Tolcapone therapy was stopped, and the dosage of levodopa-benserazide was reduced (dosage was not specified). A liver biopsy performed on June 9 showed slight to moderate hepatocellular necrosis with a lobular inflammatory infiltrate largely composed of plasma cells and eosinophils. There was no evidence of liver fibrosis. The patient deteriorated and died on June 17, 1998. An autopsy was not performed.

Patient 2 was a 73-year-old woman with a history of PD, osteoporosis, diverticular disease, colon polyps, hysterectomy, weight loss, decreased appetite, aortic regurgitation, staphylococcal infection of the back, septicemia, and chronic depression with anxiety. There was no history of hepatic dysfunction, and results of LFTs performed in September 1997 were within normal limits. Medications included levodopa-carbidopa, omeprazole sodium, lorazepam, conjugated estrogens, megestrol acetate, paroxetine hydrochloride, trazodone...
PATIENT 3 was a 74-year-old woman with a history of PD since 1985, atrial and ventricular ectopy, and osteoarthritis. There was no history of antecedent liver dysfunction or drug allergies. Medications included levodopa-carbidopa, 25/100 tablets, 8 times per day; trihexyphenidyl hydrochloride, 2 mg 4 times daily; pergolide mesylate, 1 mg TID; clonazepam, 0.25 mg BID; baclofen, 10 mg BID; ibuprofen, 400 mg TID; entericoated aspirin, 325 mg/d; medroxyprogesterone acetate, 2.5 mg/d; and conjugated estrogen vaginal cream (vitamin K), lactulose, digoxin, spironolactone, and albuterol. Levodopa-carbidopa and trihexyphenidyl therapies were initiated in May 1998, and the patient noted dark urine. No LFTs were performed. On approximately September 15, the patient experienced nausea, vomiting, and dark urine; again no LFTs were performed. The patient was hospitalized on October 2 with nausea, vomiting, a 9-kg (20-pound) weight loss, and jaundice. Results of laboratory tests (normal reference values, units, and more specific details were not provided) included AST level of 1254, total bilirubin level of 209 µmol/L (12.6 mg/dL); and ALT level, of 1436 (reference range, 0-55), alkaline phosphatase level of 64 (reference range, 8-42), ALT level of 1436 (reference range, 8-39 U/L); and LDH level, of 5756 U/L; total bilirubin level rose to 732 µmol/L (42.8 mg/dL). A liver biopsy was not performed. The patient died on October 29, 1998. Autopsy findings included jaundice, massive ascites, pulmonary edema with bilateral pleural effusions, and a massive degree of necrosis of the liver with superimposed autolysis. Results of microscopic studies are not presently available.

Patient 4 was a 66-year-old woman with PD and a history of gall bladder disease with a cholecystectomy performed in 1995. There was also a history of allergies to sulfa and amoxicillin, but no history of previous liver disease. In 1997, results of LFTs were reportedly normal. Concomitant medications included regular and sustained-release levodopa-carbidopa, levothyroxine sodium (Synthroid), and lansoprazole (Prevacid). Tolcapone therapy, 200 mg TID, was initiated in May 1998, and the patient noted dark urine. No LFTs were performed. On approximately September 15, the patient experienced nausea, vomiting, and dark urine; again no LFTs were performed. The patient was hospitalized on October 2 with nausea, vomiting, a 9-kg (20-pound) weight loss, and jaundice. Results of laboratory tests (normal reference values, units, and more specific details were not provided) included AST level of 1254, total bilirubin level of 6.9, seronegative findings for hepatitis B surface and core antigens and hepatitis A and C antibodies, and international normalized ratio of 1.65. Results of testing for antinuclear antibodies were positive at 1:320, with a speckled pattern suggestive of autoantibodies to extractable nuclear antigens. Computed tomographic scan of the abdomen suggested hepatic cirrhosis with splenomegaly secondary to portal hypertension. Tolcapone therapy was discontinued, and during the next 3 days the AST level fell to 678. A liver biopsy was performed on October 8, and findings included diffuse portal infiltrates with lymphocytes, plasma cells, and piecemeal necrosis. There was no evidence of cirrhosis. Pytonadione (vitamin K) and fresh frozen plasma were given, and the patient started receiving oral prednisone, 40 mg/d. She improved and was discharged home on October 10, 1998.
FDA-MANDATED LABELING REVISIONS FOR PRESCRIBING TOLCAPONE

Based on the reports of serious liver dysfunction in 4 patients taking tolcapone, regulatory authorities in the United States mandated labeling revisions for prescribing tolcapone and issued a black-box warning.11,12 The major features of the US revision as of November 1998 are as follows:

- Before prescribing tolcapone, physicians should be thoroughly familiar with details of the prescribing information.
- Tolcapone should not be used by patients until their physician has provided them with a complete discussion of the risks and the patient has signed a written informed consent.
- Tolcapone should only be used in patients with PD who are experiencing symptom fluctuations and are not responding satisfactorily to, or are not appropriate candidates for, other adjunctive therapies.
- Tolcapone therapy should be withdrawn if patients do not show substantial benefit within 3 weeks of initiation.
- Tolcapone should not be used in patients who exhibit clinical evidence of liver disease or who have had 2 ALT or AST values greater than the upper limits of normal.
- For patients starting treatment with tolcapone, ALT and AST values should be determined at baseline and monitored every 2 weeks for the first year, every 4 weeks for the next 6 months, and every 8 weeks thereafter.
- Tolcapone therapy should be discontinued if even a single ALT or AST level exceeds the upper limits of normal, or if clinical signs and symptoms suggest the onset of hepatic failure (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, and right upper quadrant tenderness).

COMMENT

Tolcapone initially was approved in the United States and Europe as an adjunct to levodopa in the management of PD and became widely used, particularly in patients with fluctuating PD. Clinical trials indicate that tolcapone is associated with a dose-related increased incidence of abnormal LFT findings, and for this reason, monitoring was recommended during the first 6 months of therapy. In clinical trials, LFT monitoring was used routinely, and clinical features of hepatic dysfunction attributable to tolcapone were not observed in any of 4000 patients. However, postmarketing surveillance studies noted 4 reports of severe liver dysfunction in patients receiving tolcapone. The time course of damage and the pattern of histopathologic involvement suggest a drug-induced hepatitis, most likely due to tolcapone. However, because the patients were receiving multiple medications, it is not possible to exclude completely the role that other drugs might have played in the development of the liver dysfunction. In addition, patient 4 recovered with prednisone treatment and may have had an autoimmune hepatitis. Should liver dysfunction recur following discontinuation of prednisone therapy, it would argue against the notion that tolcapone was a contributing factor. It is also possible that the number of cases reported to the manufacturer underestimates the true incidence of tolcapone-related hepatitis.

There are several noteworthy features about these patients. Liver dysfunction developed in all 4 patients within 6 months of initiating treatment with tolcapone. There have been no cases of serious liver dysfunction that are known to have developed after this time. Indeed, increases in LFT results observed during clinical trials also largely occurred within the first 6 months of tolcapone therapy. Also, in each of these 4 patients, the recommended guidelines for monitoring liver function were not followed. In 3 patients, no monitoring was performed at all. In addition, tolcapone continued to be prescribed in 2 patients even after clinical evidence of hepatic dysfunction developed. Although it is not known if early withdrawal of tolcapone in the event of an increase in liver enzymes can prevent the occurrence of severe hepatic dysfunction, no case has been reported when the recommended monitoring schedule was followed. It thus appears that tolcapone-induced liver dysfunction occurs within the first 6 months after introduction and may be prevented by rigorous monitoring and immediate drug withdrawal if liver enzyme abnormalities are detected.

As with any medication, the risk-benefit ratio of using tolcapone must be considered. To assess the impact of the new findings of liver dysfunction on the usefulness of tolcapone in the management of PD, a panel of 12 movement disorder neurologists and 4 hepatologists was convened to review this information and to make recommendations. Consensus among members of the panel was reached with regard to the following positions:

1. Tolcapone, as an adjunct to levodopa, is an effective agent in the treatment of patients with fluctuating PD.
2. With appropriate monitoring, tolcapone can be used safely as an adjunct to levodopa in patients with PD who derive benefit from the drug and are free of liver dysfunction. Further, it is probably not necessary to restrict the drug to only patients in whom all other therapies have failed. It is our opinion that with the new monitoring schedule, the risk for development of irreversible liver injury is virtually negligible.
3. Although we consider it appropriate to monitor transaminase levels at regular intervals during tolcapone treatment, virtually all instances of liver enzyme abnormalities and clinical liver dysfunction appear to occur within 6 months of initiation of treatment. Therefore, it may be possible to reduce the frequency of monitoring after this time. We recommend that a registry be established to gather long-term data on liver function, adverse events, and clinical status in tolcapone-treated patients. If it can be confirmed that liver enzyme abnormalities and liver dysfunction only occur within the first 6 months of treatment, then consideration should be given to revising the monitoring schedule.
4. The requirement that tolcapone therapy be withdrawn if liver enzyme levels are elevated above the upper limit of normal on even a single occasion may be unnecessarily restrictive. This is a greater standard than has been imposed on other drugs with a known risk of hepatic dysfunction.
totoxic effects such as troglitazone, valproic acid, carbamazepine, or phenytoin sodium. Many drugs known to be extremely safe in clinical practice can cause a small increase in liver enzyme levels without posing a risk for clinically significant liver disease. Further, the need to monitor enzyme levels frequently (26 times in the first year) may lead to insignificant enzyme elevations simply because of the variability associated with repeated testing. Limiting the use of tolcapone to this degree will markedly restrict the number of patients who can take the drug. It is our opinion that an action limit of 2 to 3 times the upper limit of normal is a more reasonable criterion for discontinuation of the drug, given its clinical benefit.

CONCLUSIONS

It is the opinion of the panel that tolcapone, when used with levodopa, is an effective drug for the treatment of motor fluctuations in patients with PD. Based on post-marketing surveillance reports, there are concerns that the drug can induce hepatotoxic effects. The mechanism responsible for the liver dysfunction is not known, and it remains to be determined if it is a class effect or due to the tolcapone molecule itself. Entacapone, a less potent COMT inhibitor, is also being evaluated as a treatment for PD, and to date has not been associated with liver dysfunction. The labeling revisions for prescribing tolcapone stress safety and, in our opinion, with the new monitoring guidelines, the risk for irreversible liver injury is negligible. These guidelines are, however, exceptionally restrictive and will lead to many patients stopping the therapy unnecessarily. In addition, the requirement of such frequent laboratory monitoring is so onerous that many physicians and patients will choose not to use the drug at all. Our analysis of the safety data leads us to believe that a less demanding schedule of blood monitoring, especially after 6 months of treatment, will provide equivalent security. We further believe that the threshold for initiating therapy is too high and for discontinuing it is too low. We recommend that the guidelines be reviewed periodically based on ongoing safety information, and suggest that less frequent monitoring after 6 months with an action limit of 2 to 3 times the upper limit of normal will likely be sufficient to ensure safety in patients who are deriving benefit from the drug.

Accepted for publication May 19, 1999.

The Tasmar Advisory Panel was supported by Roche Laboratories Inc, Nutley, NJ.

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