COMT Inhibitors for Parkinson’s: Tolcapone Revisited

Often overlooked due to safety concerns, this older medication can still play an important role in clinical practice.

The COMT inhibitors, tolcapone and entacapone, are useful adjuncts in treating Parkinson’s disease that were first approved by the FDA in 1997 and 1998 respectively. A combined preparation of carbidopa, levodopa and entacapone, marketed as Stalevo, was released in 2004. For the patient suffering from end-of-dose failure and motor fluctuations, this group of agents can provide a significant improvement in functional on-time with resultant improvement in the ability to carry out activities of daily living.

Of the two agents, tolcapone is the more potent but has been associated with rare, life-threatening hepatotoxicity, which has markedly restricted its use. Nonetheless, the neurology community has probably been overly reluctant to employ this very useful agent due the perceived hazards of the drug, when there is a population of patients who would significantly benefit from its use.

The enzyme inhibition strategy is not a new story in the treatment of Parkinson’s, as Cotzias first proposed the use of a peripheral l-aromatic acid decarboxylase inhibitor, carbidopa, in the early 1970s. L-aromatic acid decarboxylase is one of the two enzymatic pathways for the metabolism of levodopa in the periphery. The other enzyme that metabolizes levodopa in the periphery is catechol-o-methyl transferase (COMT).

Cotzias’ pharmaceutical trick with carbidopa markedly reduced the peripheral conversion of levodopa to dopamine, increasing the bioavailability of levodopa within the central nervous system by 70 to 80 percent. Consequently, the tolerability and efficacy of levodopa was markedly improved with dramatic benefit to the quality of life of our Parkinson’s disease patients. Analogously, tolcapone and entacapone act peripherally by inhibiting levodopa metabolism via catechol-o-methyl transferase (COMT) to 3-O-methylated. Through this mechanism, COMT inhibitors promote greater availability of an administered dose of levodopa for entry into the central nervous system (Figure 1).

In and of themselves, COMT inhibitors have no major central nervous system effect and therefore have no primary therapeutic efficacy in the treatment of Parkinson’s. More specifically, these agents increase the half-life of levodopa and increase the area under the pharmacokinetic curve for an administered dose of levodopa. Based upon these pharmacokinetic parameters, tolcapone is approximately twice as potent as entacapone.

In the pivotal clinical trials of tolcapone in patients with motor fluctuations, the average “off” time was decreased by over three hours per day and the maintenance dosage of levodopa was decreased by approximately 20 percent. The main ill effect of the agent was significant worsening of dyskinesias and the induction of explosive diarrhea. In these trials, some insignificant elevations of serum transaminases were noted, except for one patient who was forced to withdraw from the study secondary to liver enzyme elevations. In the study of stable responders, the tolcapone group experienced a significant improvement of the ability conduct activities of daily living and a meaningful reduction of their daily levodopa requirements at either 100 or 200mg three times per day.

The pivotal preclinical trials of an entacapone demonstrated about a one-hour reduction per day of “off” time as compared with placebo. Levodopa requirement was reduced by approximately 12 percent. The side effect profile of entacapone was superior with less troublesome issues with diarrhea and less apparent liver enzyme elevations. Entacapone also induced some exacerbation of dyskinesias, but not as severely as noted with tolcapone. Unfortunately, there has been no systematic clinical trial comparing the two COMT inhibitors.

Putting it Into Practice

Trials with either of the COMT inhibitors have not clarified for us their role in patients with a stable response to levodopa or their potential role upon the introduction of levodopa therapy.

It is clear from the above data that tolcapone is the more effective COMT inhibitor but, due to the hepatotoxicity concerns, this agent’s use has been severely restricted, becoming unavailable to all patients in the European Union and unavailable for new patients in Canada. Fortunately, the drug remains available in the United States, but with a very ominous “black box” warning, which necessitates frequent liver function testing upon initiation of therapy and continued monitoring throughout the entire course of therapy. It has been recently reintroduced to the European Union market.

In light of these concerns, is there a place for tolcapone in our pharmacologic armamentarium? The answer is a resounding yes. Although there are very limited data concerning the comparative efficacy...
of the two drugs and there are no controlled trials evaluating these issues, the accumulated clinical experience of se-asoned movement disorder specialists sug-gests there is a significant coterie of patients who benefit significantly from this agent as compared with entacapone.

Anecdotally, my own patients who were treated long-term with tolcapone following the clinical trials were all placed on entacapone once the hepatotoxicity con-siderations became known. None of these patients found entacapone as effective as tolcapone and all requested resumption of tolcapone therapy after a reasonable empiric trial of entacapone. This entire group has continued tolcapone, in spite of the necessity for regular monitoring of liver function studies. This anecdotal experience has been confirmed systematically only to a limited degree, as will be dis-cussed in a presentation to be delivered by Stewart Factor’s group from Albany Medical Center at the movement disorders meeting in New Orleans in March 2005.

So, when should we be considering the use of tolcapone as a COMT inhibitor in the treatment of our patients? Given the safety concerns surrounding this agent, it should not be used in patients with any impairment of hepatic function or taking exogenous agents, such as alcohol or other pharmaceuticals that might impair hepatic function. The patients must also understand the necessity of intensive monitoring of their liver function studies, particularly during the early months of this therapy, and must sign a consent form acknowledging their understanding of this require-ment, as recommended by the pharmaceu-tical manufacturer and FDA. Though less than a concern, this agent’s proclivity to induce diarrhea and alter urine color must be clearly disclosed.

Once these issues have been addressed, for those patients with unsatisfactory alle-viation of motor fluctuations and end-of-dose failure with other pharmaceutical options, particularly entacapone, tol-capone becomes a very reasonable and effective alternative that should be offered to our patients with all of these caveats in mind. To do less is to deprive a small but significant patient population of this effective drug’s benefits. **PN**

Additional information can be found in the presentation by Stewart Factor, MD on the WE MOVE web site at www.mevne.org/library/disease/pdf_par_orm.html, from which portions of this article are derived.

**Figure 1. Diagram of Levodopa Metabolism**

- **AADC**
- **L-Dopa**
- **COMT**
- **3 0-methyl-dopa**
- **MAO**
- **Dopamine**
- **3 methoxytyramine**
- **homovanillic acid**
- **BBB**

**Figure courtesy of WE MOVE.**