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COMMENTARY

Carlo Colosimo

The rise and fall of tolcapone

On 12 November 1998 the European Agency for the Evaluation of Medicinal Products (EMEA) scientific committee recommended the suspension of the marketing authorization for tolcapone *(Tasmar)* owing to increasing concerns over reports of severe hepatotoxicity. Three cases of acute, unpredictable hepatitis with fatal outcome have been reported so far. Two months before, Assal and coworkers [1] had first described a case of fulminant hepatitis in a Swiss patient possibly related to the use of tolcapone. A 74-year-old woman developed this complication 9 weeks after starting tolcapone as add-on therapy for Parkinson's disease. Despite the lack of postmortem data, a liver biopsy showed severe centrolobular necrosis and a lobular inflammatory infiltrate composed mostly of plasma cells and eosinophils. In the United States another patient under tolcapone died from hepatic necrosis. Following these events the EMEA had mandated on 15 October 1998 the monitoring of liver function before starting tolcapone therapy and every 3 weeks for the first 3 months, then monthly for the next 3 months. Additional liver monitoring using the same schedule was deemed necessary if the dose was increased. The alanine aminotransferase (ALT) threshold for discontinuing treatment was set at three times the upper normal limit. This precaution became inadequate when a third case of fulminant hepatitis related to tolcapone was described in a patient whose liver enzymes were already being closely monitored, and led to the suspension of the marketing authorization for this drug in the European Union.

Since its marketing, approximately 100,000 patients worldwide, approximately half of them in the European Union, have been treated with tolcapone. In the United States the Food and Drug Administration (FDA) has not recommended the suspension of tolcapone but has advised that a revised label be issued for it which indicates that tolcapone should be used as adjunctive therapy only in patients with Parkinson's disease who do not respond satisfactorily to other therapies and with close monitoring of liver function. This and other important safety information were immediately communicated to all physicians. The FDA suggested that serum ALT and aspartate aminotransferase (AST) levels should be determined at baseline and then every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months, and then every 8 weeks thereafter. If the dose is increased from the initial 100 mg t.i.d. to 200 mg t.i.d., liver enzymes monitoring should take place before increasing the dose and then be reinitiated at the frequency above. Tolcapone should be discontinued if ALT or AST exceeds the upper limit of normal, or if clinical signs and symptoms suggest the onset of hepatic failure. The FDA is closely monitoring this matter and may take further action if new reports show that the liver injury rate proves greater than it now appears.

This news was quite remarkable, considering that tolcapone was the first compound of a new class of antiparkinsonian drugs to be marketed, the catechol-*O*-methyltransferase (COMT) inhibitors. These compounds offer the possibility of significantly prolonging the short plasma half-life of levodopa, by blocking its catabolism by COMT [2]. First-generation COMT inhibitors, such as pyrogallol, dopacetamide, and butylgallate, were quite toxic, unspecific for this enzyme, and short-acting, thus leading to disappointing clinical experiences [3]. On the other hand, the new COMT inhibitors were described as potent, highly selective, and apparently nontoxic drugs. Therefore their potential therapeutic role has been fully explored in the past 5 years. Tolcapone and entacapone *(Comtan/Comtess)* are the two compounds which have become available for clinical use. They are chemically related but possess one major difference which is that entacapone inhibits COMT only outside the brain, whereas tolcapone is a reversible inhibitor of COMT both centrally and peripherally.

Seven major double-blind, placebo-controlled studies have tested various doses of tolcapone (from 50 to 400 mg

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C. Colosimo (✉)
Dipartimento di Scienze Neurologiche,
Università La Sapienza,
Viale dell'Università 30,
I-00185 Rome, Italy
e-mail: colosimo@uniroma1.it,
Tel.: +39-06-49914711,
Fax: +39-06-4457705

t.i.d.) over a period ranging from 6 to 52 weeks, in Parkinson's disease patients with fluctuating [4–7] and stable [8, 9] disease. All the doses of tolcapone were well tolerated and similarly effective in reducing *off* time (by 11–32% compared to placebo), and simultaneously levodopa dose (by 12–29% compared to placebo) and dosing frequency. In stable patients the addition of tolcapone to levodopa determined a 13–15% improvement in the motor disability scores in one study [8] but no significant improvement in another [9]. The side effects of tolcapone were consistent with potentiation of levodopa dose (dyskinesia, nausea, postural hypotension), but the drug was generally well tolerated, and no laboratory or electrocardiographic abnormalities were noted. The only exception to this excellent tolerability, was an asymptomatic increase in aminotransferase levels (ALT was more often elevated than AST). These abnormalities were noted in only 1.76% (16 subjects) of the 906 patients treated with tolcapone in the above studies, and they were always reversible with or without the withdrawal of the drug. Consequently this side effect was not considered of significance and tolcapone was launched in the European Union, Canada, and Switzerland in August 1997 and in the United States in early 1998. At the time of marketing suspension in the European Union the drug was available in 38 countries. These data taken together clearly indicate that this uncommon, unfavorable effect could not have been anticipated from the clinical trials. However, the trials were conducted on a relatively low number of patients, compared to the high number of patients who started using tolcapone after it was marketed.

The underlying mechanism of the liver failure induced by tolcapone is still unclear. A severe idiosyncratic reaction, such as that observed with isoniazid or diclofenac, is possible; these rare reactions are usually unpredictable and occur when a series of genetic and environmental factors coincide in a single patient [10]. An immune-mediated or mixed mechanism, such as those observed with halothane and phenytoin, cannot, however, be excluded particularly in light of findings of the only liver biopsy performed [1]. The contribution of liver COMT inhibition and of the complex hepatic catabolism of tolcapone (glucuronization, sulfation, acetylation, and oxidation by cytochrome P450) to the toxic reaction induced by this drug is also unknown [11].

As expected, after tolcapone was banned from the European market, concerns were raised about the possibility of entacapone inducing similar adverse reactions. Entacapone was granted marketing authorization in the European Union in September 1998, and it has subsequently been marketed in most European countries. Given the common structure and mechanism of action of entacapone and tolcapone, the EMEA scientific committee extensively reviewed the safety data for entacapone. The information from preclinical toxicological studies and clinical trials indicates that entacapone does not appear to be hepatotoxic [11–14]. They concluded that the liver toxicity of tolcapone cannot be considered a class effect of COMT inhibitors with a nitrocatechol structure and did not recommend monitoring liver enzymes. However, rare reports of asymptomatic increases in liver enzymes have been made in postmarketing surveillance (EMEA press release, 23 November 1998). Hence, despite the lack of an official statement from EMEA, a strict monitoring of liver function during the first 6 months of therapy with entacapone is advisable, using a schedule similar to the one adopted in the United States for tolcapone. In addition, EMEA notified that entacapone is not recommended for patients with a previous history of neuroleptic malignant syndrome and/or nontraumatic rhabdomyolysis. These rare adverse events have never been reported with entacapone treatment from controlled trials, in which entacapone was discontinued abruptly. Nevertheless, since they have been observed rarely in patients with Parkinson's disease when other medications were withdrawn abruptly or because of severe dyskinesia, prescribers should exercise caution when discontinuing entacapone treatment and even when its dosage is adjusted.

References

1. Assal F, Spahr L, Hadengue A, Rubbici-Brandt L, Burkhard PR (1998) Tolcapone and fulminant hepatitis. Lancet 352:958
2. Colosimo C, De Michele M (1999) Motor fluctuations in Parkinson's disease: pathophysiology and treatment. Eur J Neurol 6:1–21
3. Ericsson AD (1971) Potentiation of the L-DOPA effect in man by the use of catechol-O-methyltransferase inhibitors. J Neurol Sci 14:193–197
4. Baas H, Beiske AG, Ghika J, Jackson M, Oertel WH, Poewe W, Ransmayr G (1997) Catechol-O-methyltransferase inhibition with tolcapone reduces the "wearing off" phenomenon and levodopa requirements in fluctuating parkinsonian patients. J Neurol Neurosurg Psychiatry 63:421–428
5. Kurth MC, Adler CH, St. Hilaire M, Singer C, Waters C, LeWitt P, Chernik DA, Dorflinger EE, Yoo K, and the Tolcapone Fluctuator Study Group I (1997) Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. Neurology 48:81–87

6. Rajput AH, Martin W, Saint-Hilaire MH, Dorflinger E, Pedder S (1997) Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind, placebo-controlled, multicenter trial. Neurology 49:1066–1071
7. Adler CH, Singer C, O'Brien C, Hauser RA, Lew FM, Marek KL, Dorflinger E, Pedder S, Deptula D, Yoo K for the Tolcapone Fluctuator Study Group III (1998) Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. Arch Neurol 55:1089–1095
8. Waters CH, Kurth M, Bailey P, Shulman LM, LeWitt P, Dorflinger E, Deptula D, Pedder S, and the Tolcapone stable study group (1997) Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. Neurology 49:665–671
9. Dupont E, Burgunder JM, Findley LJ, Olsson JE, Dorflinger E, and the Tolcapone in Parkinson's Disease Study Group II (1997) Tolcapone added to levodopa in stable parkinsonian patients: a double-blind placebo-controlled study. Mov Disord 12:928–934
10. Lee WM (1995) Drug-Induced Hepatotoxicity. N Engl J Med 333:1118–1127
11. Bonifati V, Meco G (1999) New, selective catechol-O-methyltransferase inhibitors as therapeutic agents in Parkinson's disease. Pharmacol Ther 81: 1–36
12. Ruottinen HM, Rinne UK (1996) Entacapone prologs levodopa response in a one-month double blind study in parkinsonian patients with levodopa related fluctuations. J Neurol Neurosurg Psychiatry 60:36–40
13. Parkinson Study Group (1997) Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann Neurol 42:747–755
14. Rinne UK, Larsen JP, Siden A, Worm-Petersen J, and the Nomecomt Study Group (1998) Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Neurology 51:1309–1314