INTRODUCTION

Parkinson’s disease (PD) still has to be treated with dopaminergic drugs and levodopa is the most effective drug in the treatment of PD. However, levodopa therapy presents two basic problems: its poor central availability (only about 1% of an oral levodopa dose reaches the brain) and its short elimination half-life (about one hour). Combination with a dopa-decarboxylase inhibitor (DDCI), which is the formulation currently used, significantly reduces the peripheral metabolism but, when the association is assumed, it is not able to prevent the metabolic switch by cathecol-o-methyltransferase (COMT). COMT rapidly converts levodopa into 3-0-methyldopa (3-OMD), which competes with levodopa for entry into the brain. Consequently, still only 5-10% of the administered levodopa dose reaches the striatum (1). COMT is abundant in the periphery, especially in the liver, kidney and gastrointestinal mucosa and is present in smaller amounts in the CNS; blocking this metabolic pathway of levodopa induces an increase in its elimination half-life while at the same time keeping plasma levodopa levels constant and not affecting the peak plasma levodopa levels or the time to reach the peak. This is the rationale behind the use of COMT inhibitors in PD and the advantages as regards motor function are based, in particular, on extending the length of “on” time, on improving wearing off phenomenon and on reducing “off” time (2).

Recent reports have cited continuous dopaminergic stimulation as an important current concept in the therapy of PD, which could guar-
antee a more suitable stimulation of dopaminergic receptors than the pulsatile kind typical of levodopa (3). Although dopamine (DA) agonists can fulfill this need, in most new patients they are not able to adequately compensate for symptoms for any more than 2-5 years, if used alone (4,5). Thus the use of levodopa remains beneficial, also added to DA agonists, for most PD symptoms and the question of prolonging levodopa’s short half-life continues to be quite a high priority.

COMT inhibitors were developed about 40 years ago with compounds such as gallates and tropolone, which lacked selectivity and were relatively toxic. Subsequently, in the late 1980s, a second generation yielded potent and selective oral formulations of these compounds, nitrocatechol-type derivatives, tolcapone and entacapone, reversible inhibitors of COMT activity (6,7). These compounds are rapidly adsorbed after oral administration (Cmax 0.5 to 2 hours). The bioavailability of entacapone is around 35%, whereas that of tolcapone is 60%. Both have shown high protein binding (>97%) and are rapidly excreted (t1/2 1.5 to 3 hours after oral administration) and metabolised mainly in the liver. Entacapone is eliminated mainly via the biliary route, whereas only 40% of tolcapone is excreted in faeces and a minor part is eliminated by the kidney. Tolcapone and entacapone dose-dependently inhibit COMT activity in erythrocytes and reduce 3-OMD formation from levodopa, improving the bioavailability of levodopa, increasing its entry into the brain, and enhancing its half-life (2,8). Their ability to improve the pharmacokinetics of levodopa (7), by increasing the area under the curve (AUC) while keeping Cmax unchanged, resulted in less fluctuating plasma levels of levodopa, when patients were given multiple doses of a COMT inhibitor (7). This means more stable levels of levodopa and more constant DA receptor stimulation both with standard and controlled-release formulations (9). The clinical benefits of COMT inhibitors have been observed both in fluctuating (10,11) and in stable (12,13) patients through the improvement of daily activities and motor scores and reduced levodopa requirement, when compared with placebo-treated patients.

The aim of this paper is to review the safety of COMT inhibition by evaluating the clinical efficacy vs safety profiles of tolcapone and entacapone.

ENTACAPONE

Entacapone is a potent, peripherally-acting, tight-binding COMT inhibitor; it dose-dependently and reversibly inhibits the enzyme COMT.

Entacapone use versus placebo has been documented in more than 1,300 patients in phase III studies, i.e. the Nomecomt (14), Seesaw (15), Filomen (16) and Celomen (17) studies.

The Nomecomt and Seesaw studies gathered 376 patients in fluctuating phase who received, in addition to levodopa, DA agonists and/or selegiline; the drug/placebo ratio was 1/1. The Filomen study was performed on 326 patients (218 treated with entacapone and 108 with placebo) and followed similar therapeutic patterns. Finally, the Celomen study investigated 301 patients (197 treated with entacapone and 104 with placebo). The dosage of entacapone ranged from 400 to 2000 mg/day, 2 to 10 tablets/day, with a mean dose of 900 mg/day.

Overall, these phase III placebo-controlled parallel studies indicate that entacapone is able to enhance the effect of levodopa in patients in whom this effect was deteriorating; it increases levodopa availability to the brain and allows a levodopa dose reduction of 10-20% and an “on” time increase of 10-15% with a corresponding decrease in “off” time.

The side effects reported in these studies led to discontinuation of the treatment in 7-13% of subjects treated with the active drug. The side effects were often related to the doses of levodopa and entacapone; their severity was not definitely correlated with age, sex, or the concomitant use of DA agonists or selegiline. They were essentially of two kinds: those associated with the potentiation of levodopa and those characteristic of entacapone. The first included induction or increase of dyskinesia, hallucinations, nausea, vomiting and postural hypotension; the most frequent were dyskinesia and nausea, reported by 25-30% and 15-20% of the
subjects, respectively. However, they were mild to moderate and could be managed by levodopa dose reduction; this meant that discontinuation of the treatment was quite rare. The adverse events apparently characteristic of entacapone were gastrointestinal disorders and urine discoloration. Gastrointestinal symptoms were abdominal pain, constipation and diarrhoea, occurring in percentage 9-13% of subjects. Diarrhoea was reported in few cases and was only seldom severe, leading to a withdrawal rate of 1-3%. The discoloration of urine (which is due to the colour of entacapone and its metabolites) is a predictable and innocuous adverse event.

There has been no indication that entacapone is associated with rhabdomyolysis, hyperthermia or neuroleptic malignant syndrome. Preclinical toxicology studies showed no evidence of liver damage; liver enzyme levels were not elevated in comparison to placebo in clinical trials, and in no patient out of a total of over 100,000 exposed to entacapone in clinical studies or in post-marketing surveillance was liver toxicity reported.

TOLCAPONE

Tolcapone is a selective, reversible, oral active inhibitor of COMT, which acts both in the brain and in peripheral tissues such as the gut and liver (18,19). In the clinical trials more than 1,500 patients were enrolled in phase II and III studies to evaluate tolcapone as an adjunct to levodopa therapy; 50-60% of the patients also received selegiline and/or DA agonists.

Phase III studies included double-blind placebo controlled trials performed both on stable (12,20) and fluctuating (11,21,22) patients with PD. The studies on stable patients included 360 patients; 121 received placebo and 239 tolcapone at different doses, ranging from 300 to 1200 mg/day in 3 administrations. The studies on patients with motor fluctuations enrolled 517 patients, of whom 150 received placebo and 367 tolcapone at doses ranging from 150 to 1200 mg/day, in three administrations.

All these studies showed a reduction of 80-190 mg/day in the levodopa dose, depending on the various study designs. The daily “off” time was reduced by 0.9 - 1.7 hours.

Tolcapone was well tolerated: the majority of adverse events were dopaminergic. The drop-out rate, considering the various studies and the various tolcapone doses, ranged from 6 to 24%.

The main side effects were dyskinesia, reported by 15% of patients treated with 100 mg tid and 27% of the subjects who received 200 mg tid, and nausea, experienced by the 2 and 5%, respectively; both these effects were managed by the reducing levodopa dose. Non-dopaminergic events included diarrhoea, reported by the 5% of the subjects treated with 100 mg tid and 6% of those treated with 200 mg tid, respectively. Diarrhoea was the most frequent non-dopaminergic effect leading to drop out. In these cases it was severe, explosive and tended to occur after 6-8 weeks of treatment and, in view of the latency, was probably unrelated to COMT inhibition in the gut. Another non-dopaminergic adverse event was elevated liver transaminase levels, found in 1.7% of the subjects treated with 100 mg tid and in 3.1% of those treated with 200 mg tid. These raised levels occurred mainly within 6-16 weeks of starting treatment and liver enzyme levels returned to baseline within 2-3 weeks of discontinuation. Elevations were not associated with clinical symptoms. On the basis of these findings, specific recommendations were initially given, consisting of the monitoring of patients prior to treatment and liver enzyme levels returned to baseline within 2-3 weeks of discontinuation. Elevations were not associated with clinical symptoms. On the basis of these findings, specific recommendations were initially given, consisting of the monitoring of patients prior to treatment and every 4 weeks during the first six months of treatment and discontinuation if liver transaminase levels were 5 times the upper limit of normal (ULN) or if any indication of liver injury was observed. But on September 19, 1998, the Lancet (23) published a case of fulminant hepatitis in a female in Switzerland. She was aged 74 years, had a 20-year history of disease and had been treated with levodopa/benserazide, amantadine and other medications. Shortly after, another female (aged 73 years), who had been treated with levodopa/carbidopa and lorazepam, died of the same cause in the USA, followed by a third in Canada. The latter subject, aged 74, had been treated with levodopa/carbidopa and pergolide.
In the first two cases quite marked transaminase elevations (50 and 100 times ULN) had occurred after 9 and 15 weeks of treatment, respectively. In the third case the liver transaminase levels were up to 7 times the ULN after 9 weeks of treatment (24). These events, which occurred after 60,000 patients had received tolcapone (25) led to the withdrawal, in November 1998, of marketing authorisation for the drug in the EU and in Canada. It has remained available in 30 countries including Switzerland and the US, but a rigorous serum alanine aminotransferase (ALT) monitoring regimen is recommended. Worldwide, the liver function must be monitored every two weeks during the first year of use and periodically thereafter. Furthermore, the drug must be discontinued if liver enzyme levels rise above the normal levels even on a single occasion. In a retrospective predictor analysis of patients enrolled in clinical trials (pre- and post-marketing), risk factors for developing liver injury in combination with tolcapone seem to be female gender, pre-existing liver disease (elevated liver enzymes), comedication with hepatobiliary liabilities (i.e. ethanol) and gastrointestinal comorbidities (i.e. diarrhoea, constipation). As regards female gender as a risk factor, it has to be noted that oestrogens are metabolised by COMT, increasing the potential for drug interaction with hormones. However, the three patients who died were females aged between 73 and 74 years, with presumably low levels of oestrogens, which would thus seem to leave open the question of gender risk for tolcapone toxicity.

Monitoring of adverse hepatobiliary events (from February 1997 to May 2001) by the pharmaceutical company producing tolcapone highlighted a low incidence of such events. Of the 14,000 patients treated in the period June 2000 - May 2001, there were only 10 reports.

Finally, the time of onset of liver injury generally ranged between 6 weeks and 6 months, with no case occurring before 3 weeks. Providing the subject was monitored and treatment withdrawn, asymptomatic liver transaminase elevation was not found to progress to significant liver injury, (which is what happened in the fatal cases).

CONCLUDING REMARKS

The COMT inhibitors are the only conceptually new, effective pharmacological class of antiparkinsonian agents to emerge in recent years. The problem of their safety is therefore crucial as they could be quite widely used and the future development of a new triple therapy deriving from the association of levodopa with a dopa-decarboxylase inhibitor and a COMT inhibitor could be theoretically conceiviable and of practical interest.

From a clinical point of view tolcapone seems to be more effective than entacapone on UPDRS motor and off time scores and levodopa requirement, as shown by the comparison of the data from the clinical studies.

A crucial problem is the possible hepatic toxicity of these compounds. Neither drug caused hepatotoxicity in preclinical toxicity testing. However, in clinical trials of tolcapone, liver chemistry tests were found to be more than three times the ULN in a low percentage of patients. After the suspension of the market authorisation in the European Union further safety profile studies have also been performed on entacapone in rats, dogs and monkeys and these have confirmed that hepatic toxicity appears unique to tolcapone and is not a class effect (26).

Pre-clinical studies have suggested that a possible mechanism of tolcapone toxicity could be its ability to induce the uncoupling of oxidative phosphorylation, a process involved in energy production in mitochondria. In experimental models tolcapone causes a decrease in the mitochondrial ATP/ADP ratio and an increase in body temperature and the levels of liver enzymes, in a fashion similar to 2,4-dinitrophenol (DPN), which is a classical uncoupler of oxidative phosphorylation (27).

Other data indicate a broad separation between the therapeutic concentrations of tolcapone and those affecting mitochondrial function (28).

But the mechanism of liver damage has not been clarified. Metabolic mechanisms could be relevant, at least in some drug interactions. For instance, one difference between entacapone and
tolcapone is that the former is only glucoronidated while the latter is also methylated and oxidised (29). But in any case the problem of liver toxicity, despite concerning few cases, is a serious factor limiting the use of tolcapone, while the data on entacapone suggest that it is not likely to cause hepatotoxicity.

At the present time, from a clinical point of view, tolcapone could benefit a sub-population of patients who cannot tolerate other adjunct medications to levodopa or have not experienced benefit from entacapone. Restrictive prescription, combined with stringent liver enzyme monitoring, seems to enable tolcapone to be used more safely, but even so a very strong clinical motivation is today necessary to justify its use. Only the development of an easy clinical test to predict possible individual toxicity could today allow the safe reintroduction of this very effective drug into general use, also considering that entacapone does not apparently present any hepatotoxicity.

The current trend suggested for treating PD would be to begin with a long-acting dopamine receptor agonist and associate levodopa combined with a COMT inhibitor (30). The possibility of having at one’s disposal more drugs of the same class, with different pharmacological characteristics could be advisable to tailor treatment to individual patients’ needs, while waiting for more effective and definitive therapies.

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