The role of entacapone in the management of Parkinson's disease

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Catechol-O-methyltransferase (COMT) inhibition is an important advance in the treatment of Parkinson's disease. This consensus statement provides guidelines for the optimal use of the only currently available COMT inhibitor, entacapone (Comtess®, Orion Pharma (UK) Ltd, Newbury, Berkshire).

Catechol-O-methyltransferase (COMT) inhibitors are a recently introduced, novel class of drugs which extend the duration of effect of levodopa, the gold standard for the symptomatic treatment of Parkinson's disease (PD). The only currently available COMT inhibitor in Europe is entacapone (Comtess®, Orion Pharma (UK) Ltd, Newbury, Berkshire), which was licensed for sale in the European Union in September 1998. Between the launch of entacapone and March 1999, worldwide clinical experience reached approximately 20 000 patient years.

Based on a review of this experience with entacapone, the authors of this consensus statement, all of whom have considerable experience in the management of PD, have provided guidelines for the optimal use of this drug, and highlighted the role that COMT inhibition can play in the treatment of many PD patients. This statement was developed from a round-table meeting of 29 PD specialists from across the UK held in June 1999.

THE RATIONALE FOR COMT INHIBITION

Levodopa is the most effective treatment for the symptoms of PD. However, long-term levodopa treatment is associated with diminishing efficacy and the emergence of motor complications, such as fluctuations and dyskinesia (Koller and Hubble, 1990). These motor complications, which are experienced by about 50% of patients after about 5 years of levodopa therapy, worsen and become more complex over time, and increasingly become a major source of disability for the patient.

The long-term problems of levodopa therapy are thought to be triggered by the progressive degeneration of presynaptic striatal dopaminergic terminals, which results in a reduced capacity of these terminals to buffer fluctuations in plasma levodopa (Fabbrini et al, 1988). This causes the patient to become increasingly reliant on stable, therapeutic levels of plasma levodopa. Increasing the oral dosage of levodopa may improve the fluctuating response to medication, but may cause intolerable side-effects, such as dyskinesias, hallucinations and confusion.

An alternative approach to stabilizing plasma levels of levodopa is to inhibit its metabolism. When administered alone, levodopa is peripherally metabolized to dopamine by dopa decarboxylase (DDC). Therefore, to prevent the side-effects of nausea, vomiting and hypotension caused by peripheral dopamine and to increase the amount of levodopa reaching the brain, levodopa is now routinely administered with a DDC inhibitor (DDCI), either carbidopa or benserazide. Despite this, only 5–10% of the orally administered levodopa dose reaches the striatum to be decarboxylated to dopamine. Following DDC inhibition, most of the loss of levodopa is the result of action of the COMT enzyme in the periphery (intestinal mucosa and red blood cells).

Entacapone is a selective, reversible, peripherally acting inhibitor of COM, which, when administered concomitantly with levodopa+ DDCI, reduces the peripheral metabolism of levodopa by COMT. This action lengthens the elimination half-life of levodopa, resulting in more sustained plasma levodopa levels without changes to the peak plasma levodopa concentration (C_{max}) or the time taken to reach this peak concentration (t_{max}) (Ruottinen and Rinne, 1996). Entacapone treatment thus allows more levodopa to reach the brain (*Figure 1*). Furthermore, repeated dosing with entacapone reduces daily peak–trough variations in plasma levodopa levels (Nutt et al, 1994).

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CLINICAL EFFICACY OF ENTACAPONE

The clinical efficacy of entacapone has been investigated in two large-scale, double-blind, placebo-controlled trials (Parkinson Study Group, 1997; Rinne et al, 1998). Over 350 patients with Parkinson's disease and end-of-dose motor fluctuations were stabilized with levodopa+DDCI treatment during the initial study phase. Following this period, patients entered a 24-week double-blind phase, and were randomized to receive either placebo or entacapone 200 mg with each levodopa+DDCI dose. Efficacy was assessed from home diaries in which patients indicated the amount of 'on' and 'off' time they experienced.

The studies showed that entacapone treatment increased daily 'on' time by about 1 hour and allowed levodopa dosage to be reduced by 100 mg/day (equivalent to a one-dose reduction). These differences were all statistically significant compared with placebo. In addition, there was a significant improvement in the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al, 1987) total scores in the entacapone-treated patients.

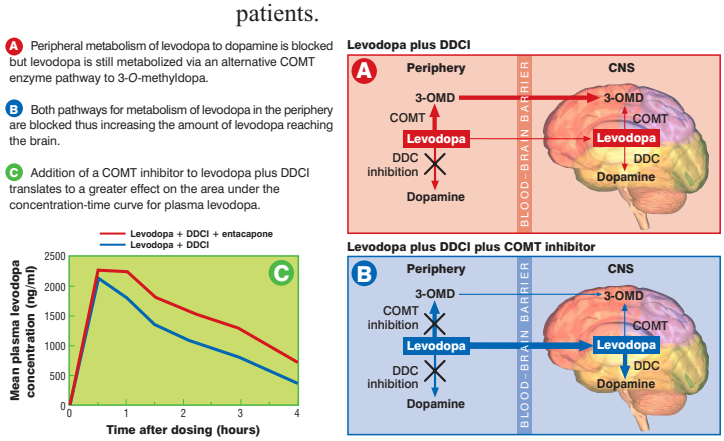

Figure 1. The rationale for COMT inhibition. COMT = catechol-O-methyltransferase; 3-OMD = 3-O-methyldopa; DDC = dopa decarboxylase; DDCI = dopa decarboxylase inhibitor.

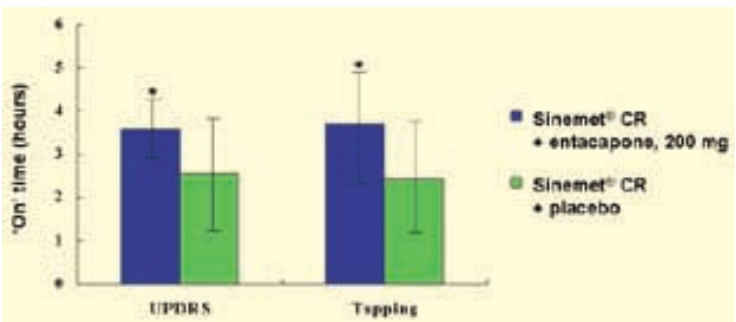

*Figure 2. Entacapone significantly increased 'on' time when administered as an adjunct to a controlled-release formulation of levodopa (Sinemet® CR, DuPont Pharmaceuticals Ltd, Stevenage, Hertfordshire), as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) and by finger tapping. *P<0.05 vs Sinemet® CR + placebo. From Piccini et al (2000).*

Data from a separate study show that entacapone is also effective when given as an adjunct to controlled-release (CR) formulations of levodopa (Piccini et al, 2000). After a single dose of Sinemet® CR (DuPont Pharmaceuticals Ltd, Stevenage, Hertfordshire), entacapone significantly increased 'on' time (defined as a 20% improvement in baseline scores) by just under 1 hour over an 8-hour period, as assessed by both UPDRS and finger tapping (*Figure 2*).

INITIATING ENTACAPONE TREATMENT

Entacapone dosage

Entacapone is used as an adjunct to levodopa to prolong the effect of levodopa. Without levodopa, entacapone has no antiparkinsonian effect. The pharmacokinetic profile of entacapone matches that of levodopa, and as such, for optimal effect a 200 mg dose of entacapone is taken concurrently with each levodopa dose. The majority of patients who are experiencing wearing-off phenomena — and so will benefit from entacapone — will be taking between three and four doses of levodopa per day. Entacapone is not taken between levodopa doses.

Entacapone in patients with motor fluctuations

At present, the key criterion for starting entacapone is whether the levodopa-treated patient is experiencing a fluctuating motor response to medication. In early PD, nearly all patients benefit from levodopa and the clinical response to a single dose of levodopa is sustained, lasting for more than 4 hours. Once the benefit from an individual dose of levodopa wears off before the next dose is due, patients are considered to be experiencing end-of-dose motor fluctuations ('early wearing off'). Asking patients proactively whether they are experiencing symptoms attributable to early wearing off (rather than waiting for them to present with problems) is valuable, as it indicates those patients who will derive maximum benefit from the addition of COMT inhibition. Aside from adding entacapone, there are a number of other therapeutic options for patients experiencing early wearing off and more complex forms of motor fluctuations:

- Changing the levodopa dose regimen (increasing the dose and/or frequency of levodopa, or using smaller but more frequent doses)
- Using CR levodopa
- Adding a dopamine agonist
- Adding a monoamine oxidase B inhibitor such as selegiline.

Table 1 compares the addition of entacapone with these different treatment options. The chosen treatment regimen should be tailored to the individual patient.

In the early stages of PD, adequate control of symptoms is usually provided by levodopa 200–400 mg/day in three to four divided doses. When a three to four times daily dose of levodopa is no longer adequate in controlling symptoms, adjunctive therapy such as entacapone should be added considered at this stage in preference to increasing either the dose or dose frequency of levodopa. The advantages of using entacapone as a first-line adjunct in preference to a dopamine agonist include:

- A rapid clinical improvement — the benefits of entacapone are usually apparent with the first dose
- Entacapone may cause fewer psychiatric complications in the elderly or cognitively impaired than adjunct dopamine agonist therapy. Furthermore, entacapone may be used instead of agonists to treat motor fluctuations in patients with a past history of neuropsychiatric problems.

Early use of adjunct entacapone

Repeated dosing with entacapone reduces variations in plasma levodopa levels (Nutt et al, 1994), which may reduce the risk of levodopa-related adverse events. Entacapone may, therefore, have a role as an adjunct to levodopa+DDCI from the beginning of levodopa therapy. However, controlled clinical studies of entacapone in de novo patients are needed to test this hypothesis.

Alleviating dopaminergic side-effects

The most common side-effects of entacapone treatment are central dopaminergic effects, caused by the increased availability of levodopa in the brain. These dopaminergic side-effects may be alleviated by decreasing the levodopa dose frequency (and/or the levodopa dose size). Such adjustments of the levodopa dosage may have to be made within the first days or weeks after initiating entacapone. However, levodopa dosage should not be adjusted before entacapone is started in anticipation of possible dopaminergic side-effects: levodopa dosage adjustments should be made in response to the clinical condition of the patient.

Educating the patient and carer

The key to patient concordance or compliance is patient education. It is important to explain at the start of treatment that dopaminergic side-effects may occur, and that these may necessitate an adjustment of the levodopa dosage within the first few days or weeks. Carers are sometimes concerned about the size of the entacapone tablet, but patients themselves often find the size an advantage as they can feel the tablet on their tongues, which makes it easier to swallow. No soluble or

TABLE 1
Adding entacapone to levodopa therapy compared with other adjunct treatment options

Treatment option	Comments
Adding entacapone	Increases 'on' time
	Smoother plasma levodopa levels may reduce risk of further levodopa-related adverse events
	Dopaminergic side-effects can be reduced by lowering the levodopa dosage and frequency
	Does not delay onset of switching 'on'
	Simple and convenient dosing regimen. Requires no titration; benefits quickly felt, often with the first dose
	Acts by extending the duration of action of the gold standard, levodopa; maximizes period over which levodopa works effectively
	Few psychiatric or cardiovascular side-effects associated with levodopa
Changing the levodopa dose regimen	Increases 'on' time
	Generally results in greater fluctuations and unpredictability of plasma levodopa levels
	Increased risk of side-effects with increased levodopa dosage
	Compensatory reductions in dose size may result in dose failures
Using controlled-release levodopa	Increases 'on' time
	Generally results in greater fluctuations and unpredictability of plasma levodopa levels. Large-scale, 5-year studies to date have found no difference in the incidence of motor fluctuations or dyskinesias between early patients randomized to immediate- or controlled-release levodopa (Block et al, 1997; Dupont et al, 1996)
	Increased risk of side-effects with increased levodopa dosage
	Patients may complain of slow onset of switching 'on', prolonged dyskinesias, and may suffer occasional dose failures
	Difficult to titrate in severely fluctuating patients
Adding a dopamine agonist	Increases 'on' time
	Levodopa-sparing
	Direct stimulation of dopamine receptors in the brain and the periphery results in more severe dopaminergic side-effects — postural hypotension, psychosis, nausea and vomiting are all common
	Complicated dosing regimen. Initial titration is slow, taking weeks to reach optimal dose. Tolerance may occur
	Does not extend the duration of action of levodopa, but directly stimulates dopamine receptors
	Psychiatric complications (hallucinations) may be a problem, particularly in the elderly. Caution required in disturbances of peripheral circulation and coronary insufficiency, which are common problems in the elderly
Adding selegiline	Increases 'on' time
	Levodopa-sparing. Inhibits central metabolism of dopamine
	Exacerbates dopaminergic peripheral and central side-effects. One study has reported increased mortality in patients receiving selegiline as an adjunct to levodopa+DDCI (Lees, 1995)

DDCI = dopa decarboxylase inhibitor

liquid formulation is available (entacapone solutions are impractical as they stain the lips, mouth and hands yellow). If a patient reports no benefit from entacapone, the doctor should check that the patient is taking entacapone with each levodopa dose and at the same time as the levodopa dose rather than between levodopa doses.

Concomitant use with antidepressants

So far there have been two single-dose studies with antidepressants in healthy volunteers: no interactions were observed between either entacapone and imipramine or entacapone and moclobemide (Illi et al, 1996a, b). However, there is still only limited clinical experience of the use of entacapone with monoamine oxidase-A inhibitors, tricyclic antidepressants and noradrenaline reuptake inhibitors such as desipramine, maprotiline and venlafaxine. Therefore, the current summary of product characteristics states that the use of entacapone with these drugs is not recommended. As antidepressants are often prescribed to PD patients, further studies with antidepressants are needed to clarify which should be recommended for use with entacapone.

Targeted dosing

Some patients at a relatively early stage of disease progression may experience early wearing off clearly associated with a particular dose of levodopa. In these patients, clinical observation suggests that entacapone may convey clinical benefits for the patient when taken only with that particular dose of levodopa. There have been no formal clinical studies to determine if this treatment strategy is advantageous in the long-term, and it is likely that such patients will require more frequent doses of entacapone as their disease progresses. This strategy also reduces the potential benefits from achieving continuous dopaminergic stimulation — namely a reduction in later complications.

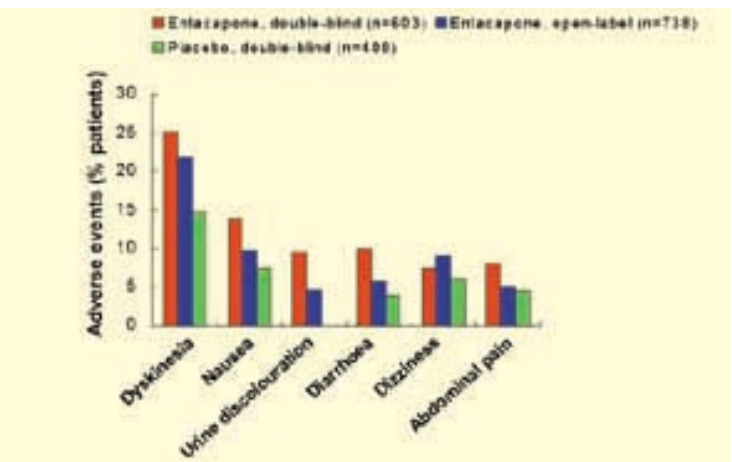

Figure 3. Incidences of the most frequent adverse events in controlled phase III trials and long-term follow-up studies. The most common adverse events were central dopaminergic effects (dyskinesia and nausea). From Adis International Ltd (1999).

SAFETY PROFILE

Over 1600 patients have received entacapone in clinical studies, including 800 patients who have been treated for over 1 year (Orion Pharma, data on file, 1999). The results of these clinical trials indicate that, as well as being effective as an adjunct to levodopa+DDCI treatment, entacapone is generally well tolerated (Parkinson Study Group, 1997; Rinne et al, 1998). Clinical safety studies have not found any evidence that entacapone causes liver toxicity or disabling, explosive diarrhoea. Following the launch of entacapone, there have been 19 800 patient years of exposure to the drug worldwide; this post-launch experience confirms the safety and tolerability profile found in clinical trials.

Adverse effects

These are mostly mild or moderate and generally occur at the onset of treatment. In controlled phase III trials and long-term follow-up studies, the most common side-effects were dyskinesia and nausea (*Figure 3*). These central dopaminergic side-effects can usually be controlled by reducing the levodopa dose frequency (and/or the levodopa dose size). Relatively few patients withdrew from the controlled phase III studies because of adverse events: 14% of entacapone-treated patients compared with 9% of the placebo group.

Excretion of entacapone in the urine may cause a red-brown discolouration, but this has no clinical significance. Up to 10% of patients may experience mild diarrhoea which can most commonly be ameliorated with simple symptomatic measures. Entacapone treatment does not appear to be associated with disabling, explosive diarrhoea.

There have been no reports of neuroleptic malignant syndrome or rhabdomyolysis associated with entacapone usage in clinical studies to date. These clinical studies included about 500 patients in whom entacapone was withdrawn abruptly as part of the study protocols.

Haematology

In controlled phase III studies, mild but clinically significant decreases in haemoglobin (more than 2 g/dl) were observed in 1.8% of patients. Anaemia, when present, is microcytic and may be caused by chelation of iron by entacapone in

the bowel. Patients who are anaemic should be monitored carefully if they are given entacapone.

Liver function

In clinical trials, the incidence of significantly raised liver enzymes was similar in the entacapone and placebo groups. Five entacapone-treated patients were found to have abnormal liver enzymes, but all subsequently continued entacapone treatment without any further derangement of liver function, and in two of these patients liver function spontaneously normalized. To date there is no evidence that entacapone is hepatotoxic, therefore regular liver function tests are not required. Extensive toxicological studies with entacapone have been performed in rats, dogs and monkeys, and also suggest that hepatic toxicity is not a class effect of COMT inhibitors.

CONCLUSION

Levodopa remains the most effective symptomatic treatment of PD. The first significant step taken to improve the pharmacokinetics of levodopa was the introduction of peripheral DDCIs, which are now routinely administered as adjuncts to levodopa. The introduction of a peripheral COMT inhibitor such as entacapone is the second significant step in extending the clinical efficacy of levodopa. Controlled clinical studies of entacapone in de novo patients are needed to test whether entacapone has a role as an adjunct to levodopa from the start of levodopa therapy.

At present, the key indication for initiating entacapone is in patients with end-of-dose motor fluctuations. When a three to four times daily dose regimen of levodopa is not sufficient for controlling symptoms, adjunctive treatment such as entacapone should be considered in preference to increasing either the levodopa dose or dose frequency.

Entacapone significantly increases 'on' time when given as an adjunct to either immediate-release or CR levodopa. Entacapone is effective and generally well tolerated in both elderly and younger fluctuating patients, and should be considered for all PD patients who have an appropriate disease profile. The dosing regimen is simple and convenient, and the benefits are quickly felt, often with the first dose. HM

Conflict of interest: The authors have acted as advisers to Orion Pharma.

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KEY POINTS

- Entacapone extends the duration of action of levodopa, which remains the most effective treatment for the symptoms of Parkinson's disease.
- Entacapone, when given as an adjunct to levodopa, significantly increases 'on' time in patients with Parkinson's disease.
- A 200 mg dose of entacapone is taken with each levodopa dose.
- The key indication for initiating entacapone is in patients with end-of-dose motor fluctuations (early wearing off).
- When a three to four times daily dose regimen of levodopa is not sufficient for controlling symptoms, adjunctive treatment such as entacapone should be considered in preference to increasing either the levodopa dose or dose frequency.
- Entacapone should be tried as a first-line adjunct in preference to a dopamine agonist in the elderly or cognitively impaired, or when a quick result is desired.
- Entacapone has a simple dosing regimen and is generally well tolerated.
- Preclinical and clinical data show suggest that entacapone has no liver toxicity.