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**H. M. Ruottinen**
**U. K. Rinne**

# COMT inhibition in the treatment of Parkinson's disease

H. M. Ruottinen · U. K. Rinne (✉)
Department of Neurology,
University of Turku,
FIN-20520 Turku, Finland
Tel.: +358-2-2612700
Fax: +358-2-2611709

**Abstract** A new approach in the treatment of Parkinson's disease is the inhibition of catechol-*O*-methyltransferase (COMT) with new generation COMT inhibitors, entacapone and tolcapone. Entacapone acts mainly peripherally whereas tolcapone acts both peripherally and centrally. They induce a dose-dependent inhibition of COMT activity in erythrocytes and a significant decrease in the plasma levels of 3-*O*-methyldopa, indicating their effectiveness as COMT inhibitors. Consequently, they increase the elimination half-life of levodopa and thus prolong the availability of levodopa to the brain without significantly affecting the $C_{max}$ or $t_{max}$ of levodopa. Clinically, the improved levodopa availability is seen as prolonged motor response to levodopa/DDC inhibitor and also as prolonged duration of dyskinesias in Parkinson's disease patients with end-of-dose fluctuations. The dyskinesias are managed by decreasing the daily levodopa dose in Parkinson's disease patients with end-of-dose fluctuations. Both pharmacokinetically and clinically the 200-mg dose of entacapone is the most effective dose compared with placebo. For tolcapone 100 and 200 mg have most often proved to be the optimal doses. Based on the duration of COMT inhibition entacapone is administered with each levodopa/DDC inhibitor dose whereas tolcapone is given three times daily. Both entacapone and tolcapone are well-tolerated. However, there seems to be a trend for tolcapone to induce more often diarrhoea and increase in liver transaminases compared with entacapone. Thus, COMT inhibitors are clinically significant and beneficial adjunct to levodopa therapy in Parkinson's disease patients with end-of-dose fluctuations. Their effects and significance also in the treatment of de novo patients need to be clarified.

**Key words** Catechol-*O*-methyltransferase inhibition · Entacapone · Tolcapone · End-of-dose fluctuations · Parkinson's disease

## Introduction

Levodopa (L-3,4-dihydroxyphenylalanine) is still the most effective therapeutic agent for the treatment of Parkinson's disease (PD). However, levodopa is not an ideal drug. It has a short plasma elimination half-life of 1–2 h [14, 38] owing to its abundant and rapid peripheral metabolism. Only a small fraction of an oral levodopa dose reaches the brain for decarboxylation to dopamine (DA) [35]. In addition, after a few years the clinical responses of many parkinsonian patients become critically dependent on brain levels of levodopa, and end-of-dose fluctuations to levodopa emerge [30, 43]. Decreased storage capacity of DA in the presynaptic dopaminergic neurons or postsynaptic changes may play a pathogenetic role in the

development of motor fluctuations [52]. Various means to extend the effect of levodopa have therefore been developed. One means is to inhibit the levodopa-metabolizing enzymes. Levodopa has two main metabolic pathways: decarboxylation (70%) and O-methylation (10%) [37]. For example, dopa decarboxylase (DDC) is routinely inhibited in levodopa therapy. Another, new means is to inhibit O-methylation, the other main metabolic route of levodopa, by inhibitors of catechol-*O*-methyltransferase (COMT).

COMT (EC 2.1.1.6) is an intracellular enzyme that is widely distributed in the peripheral tissues. The highest levels of activity are in the liver, kidney and intestinal tract [20, 36, 45]. Only a small proportion of levodopa is O-methylated by central COMT in the brain. The substrates of COMT include levodopa, catecholamines (dopamine, noradrenaline and adrenaline), catecholestrogens, and some drugs, e.g. benserazide, carbidopa, dobutamide and isoprenaline [17, 36]. Since the endogenous catecholamines are substrates for COMT, interactions between COMT inhibition and endogenous or exogenous catecholamines are theoretically possible.

In the levodopa treatment of Parkinson's disease, peripheral DDC (EC 4.1.1.28) is almost invariably inhibited, either with benserazide [(±)-DC-seryl-2-(2,3,4-trihydroxybenzyl)hydrazine] or carbidopa [(–)-L-α-hydrazino-3,4-dihydroxy-α-methylbenzenepropanoic acid]. After DDC inhibition, the metabolic profile of levodopa is altered in two ways. Firstly, less levodopa is metabolized to dopamine in the periphery [55], and secondly, more levodopa is shifted to the COMT pathway [13, 32, 55]. DDC inhibitors double the bioavailability of levodopa [55].

COMT enzyme catalyzes the O-methylation of levodopa to yield 3-*O*-methyldopa (3-OMD). 3-OMD has a long elimination half-life of 15–18 h [12, 26], which leads to the accumulation of 3-OMD during chronic levodopa treatment. By inhibiting both the peripheral COMT enzyme and the peripheral DDC, we can further improve the availability of levodopa in the brain for decarboxylation.

Two nitrocatechol-structured compounds from the new generation COMT inhibitors, developed in the late 1980s, are being introduced for the treatment of PD as an adjunct to levodopa/DDC inhibitor: the mainly peripherally acting entacapone [4] and both peripherally and centrally acting tolcapone [5].

## Pharmacokinetics and metabolism of COMT inhibitors

### Entacapone

Entacapone [(*E*)-2-cyano-*N*,*N*-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)propenamide, OR-611, Orion Pharma, Finland] is an effective, selective, reversible and a peripheral COMT inhibitor. The pharmacokinetics and metabolism of entacapone have been investigated both in healthy controls and in PD patients.

Entacapone shows dose-proportional pharmacokinetics over a dose range from 5 to 800 mg in healthy controls [24]. The $C_{max}$ and the area under the plasma concentration-time curve (AUC) of entacapone are dose-related [24, 47]. Entacapone is rapidly absorbed, with a time of maximal concentration ($t_{max}$) of 44 min for a 200-mg dose of entacapone (range from 28 min to 53 min for 5–800 mg, respectively). Its systemic availability is between 29 and 46%. The systemic availability increases with the dose, and the $t_{max}$ tends to be prolonged after increasing entacapone doses [24, 47], suggesting a tendency towards slowed absorption of entacapone with increasing doses. Entacapone is eliminated by metabolic (non-renal) route and is metabolized mainly in the liver. It has a short elimination half-life ($t_{½el}$). The β-phase of the $t_{½el}$ is 0.3–0.5 h and the γ-phase 2.5–3.4 h after i.v. administration in healthy volunteers (Korpela, 1998, personal communication). After oral administration, the $t_{½\beta}$ of entacapone is 0.5–0.7 h (90% of elimination of entacapone) and the $t_{½\gamma}$ 2.4–3.5 h (10% of elimination of entacapone) [24; Gordin 1998, personal communication]. The total plasma clearance of entacapone is 750 ml/min [24]

The main matabolite of entacapone (which itself is an E-isomer) in human plasma is the Z-isomer of entacapone [58]. The AUC of the Z-isomer accounts for only 5% of the total AUC of both isomers [47]. The Z-isomer is as effective a COMT inhibitor in vitro as entacapone, but owing the low plasma levels in humans, the Z-isomer barely contributes to the entacapone-induced COMT inhibition. About 10% of an oral dose of entacapone is excreted into the urine mainly as glucuronides of entacapone and its Z-isomer. Thus, more of entacapone seems to be eliminated by biliary than by urinary excretion [58]. Although entacapone has a catechol-structure, it is a poor substrate for human COMT [4, 58].

### Tolcapone

Tolcapone (3,4-dihydroxy-4′-methyl-5-nitrobenzophenone, Ro 40-7592, F. Hoffmann-La Roche Ltd, Basel, Switzerland) is also an effective, reversible and selective COMT inhibitor, which is considered both a peripherally and centrally acting COMT inhibitor [59].

Tolcapone shows linear and stable pharmacokinetics up to 200 mg t.i.d. The peak concentration of tolcapone is achieved about 2 h (range 1–3.1) after administration of a 200-mg dose of tolcapone [10–12, 19, 54]. The systemic bioavailability of tolcapone has been reported to be much better than that of entacapone [10]. It is rapidly eliminated, with a $t_{½el}$ of 2 h after a single oral 200-mg dose, ranging from 1.7 h for 5 mg to 3.4 h for 800 mg [10, 11, 54]. During multiple dosing of 400–800 mg, some change in clearance of tolcapone is seen, which results in prolongation of $t_{½el}$ up to 19.0 h after an 800-mg dose t.i.d. and accumulation of tolcapone [12, 19]. About 3% of tol-

capone is O-methylated into 3-*O*-methyltolcapone (Ro 40-7591) [8], which has a very poor COMT inhibitory activity in vitro and ex vivo. The $t_{½el}$ for 3-*O*-methyltolcapone is dose-independent, ranging from 30 to 40 h. However, only minor accumulation of 3-*O*-methyltolcapone occurred, owing to suppression of its formation by tolcapone [10–12, 19]. Tolcapone also has two oxidated metabolites present in low concentrations in plasma [8]. Both are equipotent to tolcapone in vitro and in vivo. They barely contribute to the inhibitory effect of tolcapone, since their concentration is less than 3% of that of tolcapone [8]. About 30% of tolcapone is conjugated to glucuronides, which do not inhibit COMT.

## Pharmacodynamics of COMT inhibitors

Activity of S-COMT (S = soluble) in erythrocytes is a pharmacodynamic parameter to assess the effect of COMT inhibitors. Erythrocyte S-COMT activity reflects the activity of COMT in the liver, kidney and lung [6, 57]. Thus, determination of S-COMT activity in erythrocytes is considered an easily accessible method to evaluate systemic COMT inhibition.

### Entacapone

Entacapone has been shown to be an effective inhibitor of COMT both in healthy volunteers [2, 24] and in PD patients [29, 47]. There is a clear and significant correlation between plasma entacapone levels and the inhibition of S-COMT activity in erythrocytes, the correlation coefficient being 0.995 ($P < 0.001$) [24]. The inhibition of S-COMT in erythrocytes, caused by entacapone, is rapid and dose-dependent: with a 200-mg dose the inhibition is 65%, and the highest 800-mg dose of entacapone yields a maximal inhibition of 82%, determined 1 h after entacapone intake without concomitant levodopa [24]. In PD patients 1 h after administration of 200 mg of entacapone and levodopa/DDC inhibitor, the inhibition is 38% [29, 48]. The erythrocyte S-COMT activity recovers within 8 h of the doses of 5–800 mg of entacapone, and within 6–8 h the activity of S-COMT is recovered after a 200-mg dose of entacapone.

### Tolcapone

In healthy controls, single tolcapone doses of 5–800 mg cause a dose-dependent COMT inhibition in erythrocytes: a dose as low as 5 mg causes a 20% inhibition, a 200-mg dose induces an 80% inhibition, whereas an 800-mg dose causes about 90% inhibition for about 4 h [10–12]. Complete recovery of COMT activity occurs at 24 h after the doses of 5–800 mg [10, 60, 61]. Repeated dosing of tolcapone 200 mg t.i.d. during levodopa/carbidopa administration induced around an 80% maximum COMT inhibition in erythrocytes in elderly healthy subjects [19].

## Pharmacokinetic responses to COMT inhibitor as an adjunct to levodopa treatment

### Entacapone

In healthy volunteers, entacapone dose-dependently increases the AUC of levodopa by decreasing the metabolic loss of levodopa to 3-OMD [23]. Largely similar results have been obtained in a study with controlled-release levodopa-carbidopa administered with entacapone to healthy persons [2]. Entacapone seems to improve the bioavailability of levodopa slightly more with standard than with controlled-release levodopa, probably owing to different absorption profiles: entacapone is already almost eliminated before the $C_{max}$ of controlled-release levodopa is reached [2].

Our dose-finding study [47] shows that on a pharmacokinetic basis the most effective entacapone dose is 200 mg compared with placebo in PD patients: the 200-mg dose of entacapone induces the highest increase both in the $t_{½el}$ of levodopa by 39% (25 min) and in the $AUC_{0–4\ h}$ of levodopa by 23% compared with the placebo. Neither the $t_{½el}$ nor the $AUC_{0–4\ h}$ of levodopa increases further with the 400-mg dose of entacapone.

In other studies in PD patients, entacapone also slows the elimination of levodopa from plasma. Entacapone increases the $t_{½el}$ of levodopa significantly by 32–75% (20–56 min) after a 200-mg dose of entacapone [31, 33, 39, 49]. Consequently, the AUC of levodopa increases significantly by 29–48% after a single 200-mg dose of entacapone [21, 33, 39, 48], and by 21–52% after repeated entacapone dosing [21, 22, 29, 39, 48, 49]. The $C_{max}$ and $t_{max}$ of levodopa remained virtually unaffected after the 200-mg dose of entacapone [2, 21, 29, 31, 39, 47–49]. However, there was a trend for the $C_{max}$ to decrease (NS) [22, 33], the $t_{max}$ to be delayed after a 200-mg dose [23, 33, 48], and there was a significant delay in the $t_{max}$ in the studies by Merello et al. [31] and Kaakkola et al. [22]. In one study, the $t_{max}$ even slightly decreased (NS) after 8 weeks on entacapone [39]. Although the $C_{max}$ of levodopa is not increased after a single dose of entacapone, repeated entacapone dosing results in increased interdose trough levodopa concentrations during 1 day and decreased variability in levodopa concentrations [39].

Repeated administration of a 200-mg dose of entacapone along with each levodopa dose decreases the plasma 3-OMD levels by 43–63% [21, 22, 29, 39, 48, 49]. Single doses of entacapone do not usually influence the plasma 3-OMD levels in levodopa-treated patients [21, 33, 48, 49] since the 3-OMD level is rather high and stable in chronic levodopa therapy owing to the long half-life

of 3-OMD [13, 26]. The AUC of 3-OMD is therefore often reduced not after a single dose but after repeated entacapone dosing. The AUC of dihydroxyphenylacetic acid (DOPAC) increases by 77–245% [22, 29, 33, 47, 49] after single and repeated dosing with 200 mg of entacapone. The AUC of homovanillic acid (HVA) decreases significantly by 17–33% both after the first and after repeated dosing with 200 mg of entacapone [21, 22, 29, 31, 47–49]. The increased AUC of DOPAC and the decreased AUC of HVA presumably reflect improved peripheral COMT inhibition.

Selegiline coadministered with levodopa/benserazide and entacapone did not affect the $t_{½el}$ or the AUC of levodopa or the decrease in the AUC of HVA, but selegiline attenuated the entacapone-induced increase in the AUC of DOPAC [29]. Possibly, DA metabolism was shifted towards the COMT-dependent pathway or sulfate-conjugation of DA.

### Tolcapone

Another COMT inhibitor, tolcapone, has induced qualitatively nearly similar changes in pharmacokinetics of levodopa compared with entacapone. The differences are mainly quantitative, tolcapone inducing a longer-lasting COMT inhibition in erythrocytes compared with entacapone. In healthy volunteers, single graded doses of tolcapone (10–800 mg) dose-dependently decrease the AUC of 3-OMD and for levodopa double the $t_{½el}$ and the AUC without virtually affecting the $C_{max}$ or $t_{max}$ [11, 54]. However, higher tolcapone doses of 400–800 mg tend to prolong absorption of levodopa, the delay in $t_{max}$ of levodopa being significant after the 800-mg dose of tolcapone [11, 54]. The maximum, nearly twofold, increase in the $t_{½el}$ and AUC of levodopa is achieved at doses 100–200 mg of tolcapone [11, 54]. Multiple dosing with tolcapone 200 mg t.i.d. increases the $t_{½el}$ of levodopa by 17–68% (18–78 min) and the AUC of levodopa by 33–64% without systematic differences during 1-week dosing in elderly healthy subjects [12, 19]. The 800-mg dose of tolcapone t.i.d. decreases the AUC of 3-OMD by up to 98% and 200 mg t.i.d. by 64-93% [12, 19]. The effect of tolcapone is maintained throughout 1 week's multiple dosing [12, 19].

## Fluorodopa PET response to COMT inhibition

The influences of COMT inhibition on peripheral and central levodopa metabolism have been investigated with positron emission tomography (PET) using 6-[$^{18}$F]fluorodopa ($^{18}$F-dopa). PET can be applied to examining the function of the dopaminergic system in PD and the effect of drug treatment on striatal dopaminergic function. $^{18}$F-dopa qualitatively behaves in vivo very similarly to levodopa, and the striatum handles 6-[$^{18}$F]fluorodopamine ($^{18}$F-dopamine), the decarboxylation product of $^{18}$F-dopa, very similarly to endogenous dopamine.

Peripherally, entacapone induces a significant decrease by 47–66% in the AUC of 3-OMFD, a COMT-dependent metabolite of $^{18}$F-dopa [51]. Correspondingly, entacapone induces a significant increase in the AUC of unmetabolized $^{18}$F-dopa by 28–37% [51] and in the fractions of $^{18}$F-dopa to 2.5– to 3-fold [18, 50, 51, 53]. Thus, entacapone increases the plasma level of $^{18}$F-dopa available for decarboxylation to the brain.

In the brain, the entacapone-induced improved $^{18}$F-dopa availability is seen as increased $^{18}$F-dopa accumulation by 25–45% in the caudate nucleus and by 29–54% in the putamen in healthy controls and early PD patients [18, 50, 51, 53] measured with the occipital influx constant ($k_i^{occ}$), which uses the radioactivity concentration in the reference region (occipital region) as an input function [7, 41]. The $k_i^{occ}$ reflects mainly the level of free $^{18}$F-dopa in the striatum and its decarboxylation to $^{18}$F-dopamine. In levodopa-treated PD patients, the increase in the $k_i^{occ}$ values is 22% in the caudate nucleus and 26% in the putamen after entacapone administration [51], and in PD patients with end-of-dose fluctuations the increase is 14% in the caudate nucleus ($P < 0.05$) but only 2% (NS) in the putamen [50]. The striatal $^{18}$F-dopa accumulation increases in the same proportion as the AUC of unmetabolized $^{18}$F-dopa in plasma in healthy controls and early PD patients. The striatal $^{18}$F-dopa accumulation also increases in levodopa-treated PD patients, but less than the AUC of unmetabolized $^{18}$F-dopa concentration in plasma, as indicated by the smaller increase in their $k_i^{occ}$ values in proportion to the $^{18}$F-dopa availability [51]. The lower increase in the striatal $^{18}$F-dopa uptake in the levodopa-treated and severely diseased, fluctuating PD patients after entacapone administration is presumably owing to decreased overall ability to convert $^{18}$F-dopa to $^{18}$F-dopamine and to store the $^{18}$F-dopamine available.

Thus, the PET findings form a background for clinical response to COMT inhibition with entacapone in the treatment of PD.

## Clinical responses to COMT inhibitor as an adjunct to levodopa therapy

The clinical effects of COMT inhibitors have often been studied using the levodopa test [15]. The clinical response to levodopa/DDC inhibitor is scored frequently, for example with various rating scales [e.g. the Unified Parkinson's Disease Rating Scale (UPDRS) or the Columbia University Rating Scale] [16], global assessment, with tapping and walking test, and often also with the dyskinesia scale, without and with the study medication. A summary of clinical responses to COMT inhibitors as an adjunct to levodopa is presented in Tables 1, 2.

**Table 1** Clinical responses to levodopa after a single 200-mg dose, or after repeated dosing of entacapone 200 mg along with each levodopa dose in Parkinson's disease (PD) patients with end-of-dose fluctuations (*UPDRS* Unified Parkinson's Disease Rating Scale, *St* standard, *CR* controlled-release)

| Study | Study design | Method | Entacapone dosing | Increase in ON-time | Decrease in daily levodopa dose |
|---|---|---|---|---|---|
| Merello et al. 1994 [31] (*n* = 12) | Double-blind, cross-over | Tapping test, walking test, global score | Single dose | 30 min (31%)<br>18 min (25%) | – |
| Nutt et al. 1994 [39] (*n* = 14) | Open, comparative | Tapping test, walking test, global score | Single dose | 28 min (30%)<br>54 min (68%)<br>40 min (71%) | |
| | | Tapping test, walking test, global score | Repeated dosing (8 weeks) | 18 min (20%)<br>44 min (55%)<br>28 min (50%) | 300 mg (27%) |
| Kaakkola et al. 1995 [22] (*n* = 12) | Open, cross-over | Motor UPDRS | Repeated dosing (9 days)<br>St levodopa<br>CR levodopa | <br>50 min (24%)<br>70 min (37%) | – |
| Ruottinen and Rinne 1996 [47] (*n* = 19) | Double-blind, placebo-controlled, cross-over, dose-response | Motor UPDRS, tapping test, walking test | Single dose | 33 min (21%)<br>62 min (81%)<br>48 min (61%) | – |
| Ruottinen and Rinne 1996 [48] (*n* = 12) | Open, comparative | Motor UPDRS | Single dose<br>Repeated dosing (4 weeks) | 54 min (39%)<br>66 min (48%) | 100 mg (11%) |
| Ruottinen and Rinne 1996 [49] (*n* = 23) | Double-blind, placebo-controlled, cross-over | Motor UPDRS, patient's diary | Repeated dosing (4 weeks) | 34 min (24%)<br>2.1 h (23%)/18 h | 140 mg (16%) |
| Lyytinen et al. 1997 [29] (*n* = 12) | Double-blind, placebo-controlled, cross-over (selegiline/placebo) | Motor UPDRS | Repeated dosing (2 weeks) | No change (total motor score decreased by 9%) | |
| Parkinsong Study Group 1997 [40] (*n* = 103) | Double-blind, placebo-controlled, parallel-group | Patient's diary | Repeated dosing (6 months) | ~ 1 h (8%)/24 h | ~ 100 mg (12%) |
| Rinne et al. 1998 [44] (*n* = 77) | Double-blind, placebo-controlled, parallel-group | Patient's diary | Repeated dosing (6 months) | 1.2 h (13%)/18 h | 102 mg (12%) |

## Entacapone

The effects of entacapone have mainly been studied in PD patients with end-of-dose fluctuations. Since the $t_{½\beta}$ of entacapone (~ 1 h in PD patients) [33] is relatively near that of levodopa (1–2 h) after oral administration [12, 14, 19, 38] and there is a good correlation between the COMT inhibition in erythrocytes and the concentration of entacapone in plasma, their coadministration appears rational. Entacapone is therefore given with each levodopa dose.

According to the clinical dose-finding study, the highest and significant increase both in the ON time and in the duration of dyskinesias was achieved with the 200-mg dose of entacapone compared with placebo in PD patients with end-of-dose fluctuations [47] (Table 3). The ON time increased by 33 min (21%), and the duration of dyskinesias by 45 min (32%) after the 200-mg dose of entacapone. The 400 mg of entacapone did not further increase the duration of motor response. The 30-min prolongation in ON time after each levodopa dose can be considered a clinically significant achievement to stabilize end-of-dose fluctuations in disability.

In other clinical studies, the single 200-mg oral dose of entacapone has also significantly prolonged the duration of motor response to levodopa (ON time) by 18–66 min in open studies [22, 39, 49]. In a double-blind 4-week, cross-over study entacapone caused a 34-min (24%) increase in ON time assessed with motor UPDRS scoring during the levodopa test in PD patients with end-of-dose fluctuations [49]. Another double-blind study using a single 200-mg dose of entacapone also provided prolonged ON time by 18–30 min (25–31%) assessed with means other than

**Table 2** Clinical responses to levodopa after a single 100-mg or 200-mg dose, or after 100-mg t.i.d. or 200-mg t.i.d. dosing of tolcapone in PD patients (*NA* not available, *n* refers to the number of PD patients)

| Study | Study design | Method | Tolcapone dosing | Increase ON time | Decrease in daily levodopa dose |
|---|---|---|---|---|---|
| Limousin et al. 1993 [27] | Double-blind, | Motor UPDRS | Single dose: | | |
| ($n$ = 11) | placebo-controlled | | 200 mg | 55 min* (65%) | – |
| Roberts et al. 1994 [46] | Double-blind, | Columbia Motor | Single dose: | | |
| ($n$ = 5) | placebo-controlled | Rating Scale | 100 mg | 54 min (69%) | |
| ($n$ = 10) | | | 200 mg | 15 min (15%) | |
| Davis et al. 1995 [9] | Double-blind, | Patient's diary | Single dose: | | – |
| ($n$ = 4) | placebo-controlled, | | 100 mg | 45 min (19%) | |
| ($n$ = 9) | selegiline 5 mg | | 200 mg | 70 min (28%) | |
| Limousin et al. 1995 [28] | Double-blind, | Motor UPDRS, | Single dose: | | – |
| ($n$ = 10) | placebo-controlled | tapping test | 200 mg | 62 min (65%) | |
| Agid et al. 1997 [1] | Open | NA | Repeated dosing (8 weeks): | | |
| ($n$ = 72) | | | 200 mg × 3 | 2.8 h (44%)/day | 124 mg (17%) |
| Baas et al. 1997 [3] | Double-blind, placebo-controlled | Patient's diary | Repeated dosing (3 months): | | |
| ($n$ = 60) | | | 100 mg × 3 | (21%)/16 h | 109 mg (16%) |
| ($n$ = 59) | | | 200 mg × 3 | (21%)/16 h | 122 mg (18%) |
| Kurth et al. 1997 [25] | Double-blind, placebo-controlled, | Patient's diary | Repeated dosing (6 weeks): | | |
| ($n$ = 40) | parallel-group, dose-finding | | 200 mg × 3 | 0.3 h (4%)/16 h | 200 mg (26%) |
| Myllylä et al. 1997 [34] | Double-blind, placebo-controlled, | Patient's diary | Repeated dosing (6 weeks): | | |
| ($n$ = 38) | parallel-group | | 200 mg × 3 | (34%)/16 h | 80 mg (12%) |
| Rajput et al. 1997 [42] | Double-blind, placebo-controlled, | Patient's diary | Repeated dosing (3 months): | | |
| ($n$ = 69) | parallel-group | | 100 mg × 3 | NA | 166 mg (21%) |
| ($n$ = 67) | | | 200 mg × 3 | NA | 207 mg (24%) |
| Waters et al. 1997 [56] | Double-blind, placebo-controlled, | | Repeated dosing (6 months) | | |
| ($n$ = 98) | parallel-group | | 100 mg × 3 | NA, stable PD | 21 mg (6%) |
| ($n$ = 98) | | | 200 mg × 3 | | 32 mg (8%) |

* approximated from figure

**Table 3** Mean changes in the motor response to levodopa and in the dyskinesias after single graded doses of entacapone compared with placebo in parkinsonian patients with end-of-dose fluctuations ([47] and unpublished results)

| Dose of entacapone | Motor UPDRS | | | Dyskinesias | | |
|---|---|---|---|---|---|---|
| | Change in duration (min) | Change in onset latency (min) | Change in magnitude | Change in duration (min) | Change in onset (min) | Change in magnitude |
| 50 mg | 20 | 9 | –0.79 | 16 | 1 | 0.63 |
| 100 mg | 23 | 10 | –0.13 | 19 | 9 | 0.58 |
| 200 mg | 33* | 12 | –0.66 | 45** | 6 | 0 |
| 400 mg | 27 | 15* | –1.02 | 30 | 17*** | 1.00 |

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, vs placebo

UPRDS scores [31]. The 200-mg dose of entacapone did not significantly change the magnitude, onset, or peak latency of the motor response or dyskinesias, which is in accordance with the virtually unchanged $C_{max}$ and $t_{max}$ [47, 49].

The prolonged motor response presumably to each levodopa dose was reflected as a clinically significant 2.1 h increase in the total daily ON time, as reported by the PD patients with end-of-dose fluctuations in their home diaries [49].

Recent large studies have shown a long-lasting efficacy of entacapone. In long-term studies, the Parkinson Study Group [40] and Rinne et al. [44] reported an in-

crease in daily ON time of 1 h (8%) and of 1.2 h (13%) respectively, in PD patients with end-of-dose fluctuations assessed with patients' home diaries in 6-month double-blind studies. Correspondingly, the mean daily OFF-time was reduced significantly by 1.3 h (–22%) more in the entacapone group than in the placebo group [44]. The global evaluation, the activities of daily living (ADL) subscore of the UPDRS and the mean total motor score of the UPDRS also improved significantly after entacapone [44]. Similarly, in the study by the Parkinson Study Group [40], there was a trend towards improvement in the ADL and mean total motor subscore after entacapone.

Compatibly with the prolonged $t_{½el}$ of levodopa and ON time, entacapone prolonged the duration of dyskinesias [47–49]. The unchanged magnitude and starting time of dyskinesias (Table 1) are also in accordance with the virtually unchanged $C_{max}$ and $t_{max}$ of levodopa. There has been a trend for the magnitude of dyskinesias to increase in some studies [31, 39], and the frequency of dyskinesias increased according to the home diaries [40]. The dyskinesias are controlled by decreasing the mean daily levodopa dose [39, 40, 44, 48, 49].

Entacapone thus results in a reduction of the total daily levodopa requirement [39, 40, 44, 48, 49]. However, despite lower levodopa doses, the mean plasma levodopa levels were higher [39] and the duration of motor response prolonged during entacapone treatment [39, 48, 49]. By slowing the elimination of levodopa, entacapone increased the daily interdose trough levodopa concentrations and reduced variability in daily plasma levodopa concentrations as shown by Nutt et al. [39]. Thus, entacapone not only increases ON time but may also smoothen motor fluctuations in disability and decrease their development.

### Tolcapone

The clinical effects of tolcapone have been investigated not only in patients with end-of-dose fluctuations, but also in non-fluctuating PD patients. The dose-response relationship has not been systematically unambiguous and clear with tolcapone [25, 42, 46]. As far as therapeutic responses are concerned in humans, the inhibition of peripheral O-methylation induced by tolcapone is presumably far more important than central COMT inhibition. Single doses of tolcapone increased the duration of motor response to levodopa/benserazide by 55–62 min (65%; 200 mg) and by 72 min (77%; 400 mg) in fluctuating PD patients assessed on the motor UPDRS scoring during a levodopa test in a double-blind manner [27, 28]. Another single-dose double-blind study showed that 50, 100 and 400 mg of tolcapone significantly extended the clinical response to levodopa/carbidopa assessed with the Columbia Rating Scale [46]. Tolcapone did not affect the magnitude or the onset latency of motor response [27, 28, 46], but higher tolcapone doses of 200 and 400 mg significantly delayed the peak latency by some 30 min [46]. Tolcapone increased the duration and/or magnitude of dyskinesias [9, 27, 28, 46].

During long-term double-blind studies in PD patients with end-of-dose fluctuations, tolcapone 200 mg t.i.d. increased the daily ON time by 0.3–2.1 h (4–34%) according to home diaries [1, 3, 25, 34], but the magnitude of motor response remained unchanged [25, 42]. Correspondingly, the daily OFF time reduced by 1.5 h measured with the Investigator's ON/OFF Rating Scale [25] or by 1.8–4.2 h measured with home diaries [1, 3, 34, 42]. Mean daily levodopa dosages were decreased by 21–32 mg (6–8%) at tolcapone doses of 100–200 mg t.i.d. in stable PD patients [56], and by 109–166 mg (16–21%) at tolcapone dosing of 100 mg t.i.d. [3, 42], and by 80–207 mg (12–26%) at tolcapone dosing of 200 mg t.i.d. in fluctuating patients [1, 3, 25, 34, 42]. Waters et al. [56] reported that fewer patients in the tolcapone group developed motor fluctuations during the study period compared with the placebo group among non-fluctuating PD patients.

## Adverse events

### Entacapone

In general, entacapone coadministered with levodopa/DDC inhibitor has been well tolerated both in healthy controls and in PD patients [2, 21–23, 31, 33, 39]. Mild and transient adverse events, such as dizziness, headache, fatigue, lack of appetite, epigastric pain, nausea, loose stools or diarrhoea, have been reported in some patients. Most adverse effects are due to increased dopaminergic stimulation. Neither supine and standing blood pressure nor heart rate were significantly affected by entacapone treatment, although entacapone tended to slightly decrease the mean systolic supine blood pressure and increase the supine heart rate [22]. Entacapone did not provoke any clinically significant changes in electrocardiograms or on the clinical haematological and biochemical variables. Most patients observed their urine turn temporarily dark yellow or orange, which was owing to the colour of entacapone and its metabolites. Increased dyskinesia was common after entacapone administration but was managed by reducing levodopa doses.

### Tolcapone

Adverse events associated with the addition of tolcapone to levodopa/DDC inhibitor, such as nausea, dyspepsia, vomiting, abdominal pain or cramping and orthostatic hypotension, insomnia, confusion and hallucinations, were also mainly mild and transient. They did not differ substantially from those occasionally occurring when receiving levodopa/DDC inhibitor alone [25, 46]. A higher sensitiv-

ity of women to gastrointestinal side effects at high tolcapone doses coadministered with levodopa/DDC inhibitor has been reported [12, 19]. The most frequently reported adverse event was dyskinesia [3, 25]. Most of the side effects were dopaminergic in nature [3, 25]. Diarrhoea was the most often reported non-dopaminergic side effect, occurring in 25–28% of patients on 200 mg t.i.d. [3, 42] and leading to withdrawal in 8–10% of patients [3, 42]. It usually appeared during the first 3 months of treatment and was resolved after stopping tolcapone [3]. Raised liver transaminases probably related to tolcapone have been reported in a few patients [3, 42], appearing during the first 6 months. The underlying mechanisms of diarrhoea and raised liver transaminases are unclear. No abnormalities were reported in vital sign parameters, electrocardiograms or other laboratory tests.

## Conclusions

COMT inhibitors cause a dose-dependent, reversible inhibition of COMT activity in erythrocytes, tolcapone inducing a longer-lasting inhibition than entacapone. They significantly decrease 3-OMD concentration in plasma, and correspondingly significantly increase the $t_{½el}$ and AUC of levodopa in plasma. The entacapone-induced improved [$^{18}$F]dopa availability in plasma to the brain for decarboxylation is seen as increased striatal [$^{18}$F]dopa accumulation both in PD patients and in healthy control subjects. This forms the background for the therapeutic responses.

Clinically, the prolonged levodopa availability is seen as increased ON time and decreased OFF time both after the first single dose and after repeated dosing in PD patients with end-of-dose fluctuations. The 200-mg dose of entacapone is the most effective dose compared with placebo. For tolcapone doses of 100 mg and 200 mg have most often proved to be the optimal doses. Besides ON time, COMT inhibitors also prolong the duration of dyskinesias, or possibly increase their magnitude or frequency. The dyskinesias are controlled by decreasing the mean daily levodopa dose.

Comparative studies between entacapone and tolcapone are not available. Therefore valid conclusions of their comparison cannot be drawn. However, according to the results published so far, it seems that the beneficial responses of both compounds during long-term studies are rather similar. The requirement of total daily levodopa dose for therapeutic response seems to be decreased on a similar range with both compounds during long-term treatment. In respect to adverse effects, there seems to be a tendency for tolcapone to induce diarrhoea and increases in liver transaminases more often.

In clinical practice, entacapone and tolcapone differ in dosing frequency: 200 mg of entacapone is given along with each levodopa dose, whereas tolcapone is administered at a dose of 100 or 200 mg three times daily. Concomitant dosing of entacapone with each levodopa dose may improve patient compliance and make it easier to control the treatment responses.

COMT inhibitors are thus a clinically significant and beneficial adjunct to levodopa therapy in PD patients with end-of-dose fluctuations. The effects and significance of COMT inhibitors in the treatment of drug-naive de novo PD patients need to be clarified. Only then will it be possible to consider COMT inhibition as a standard treatment for PD, which always has to be initiated together with levodopa.

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