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ORIGINAL COMMUNICATION

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The effect of tolcapone on levodopa pharmacokinetics is independent of levodopa/carbidopa formulation

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Abstract Clinical pharmacology studies have shown that the catechol-*O*-methyltransferase inhibitor tolcapone increases the bioavailability area under the plasma concentration-time curve (AUC) and the plasma elimination half-life ($t_{1/2}$) of levodopa. The objective of the study was to evaluate the pharmacokinetics of levodopa and 3-*O*-methyldopa (3-OMD) after coadministration of tolcapone 200 mg with levodopa/carbidopa in the following doses: 100/10 mg, 100/25 mg, 200/20 mg, 200/50 mg, 250/25 mg (all immediate-release) and 200/50 mg (controlled-release). Thirty healthy male volunteers were divided into four groups: three groups of 8 and one group of 6. Participants in the first three groups received two formulations of levodopa/carbidopa. Each dose was administered on two occasions, once with tolcapone 200 mg and once with placebo (four-way crossover). In the fourth group, one formulation was given on two occasions, once with tolcapone 200 mg and once with placebo (two-way crossover). Dosing days were separated by a 7-day washout. The effect of tolcapone on levodopa and 3-OMD pharmacokinetics was found to be similar with all levodopa/carbidopa formulations. The absorption of levodopa was unaffected by tolcapone in all treatment groups and the maximum plasma concentration (C_{max}) remained unchanged. When tolcapone was given with the immediate-release formulations, levodopa AUC increased by 60–90% and levodopa $t_{1/2}$ by 20–60%. With tolcapone and the controlled-release formulation, AUC increased by 80% and $t_{1/2}$ by 60%. With all levodopa/carbidopa formulations, 3-OMD C_{max} decreased by 80% and AUC by 70% with tolcapone. The tolerability of all treatment combinations was similar. We conclude that adjunctive treatment with tolcapone should have similar levodopa-potentiating clinical effects, regardless of the levodopa/carbidopa formulation.

Key words Catechol-*O*-methyltransferase inhibition · Levodopa/carbidopa · Parkinson's disease · Pharmacokinetics · Tolcapone

Introduction

The dopamine precursor levodopa is the mainstay of symptomatic treatment for Parkinson's disease [1]. To prevent its peripheral degradation, levodopa is administered with a dopa decarboxylase inhibitor (DCI; carbidopa or benserazide). However, levodopa is still metabolized in the periphery to 3-*O*-methyldopa (3-OMD) by catechol-*O*-methyltransferase (COMT), so only 5–10% of orally administered levodopa reaches the central nervous system [17].

Furthermore, response fluctuations that develop in more than 50% of parkinsonian patients who receive levodopa/DCI for more than 5 years are believed to result

Table 1 Study design for levodopa/carbidopa treatment[a]

Group	Levodopa/carbidopa dose (ratio, formulation)	
	Study days 1 and 8	Study days 15 and 22
I (n=8)	Levodopa 100 mg, carbidopa 10 mg (10:1, immediate-release)	Levodopa 100 mg, carbidopa 25 mg (4:1, immediate-release)
II (n=8)	Levodopa 200 mg, carbidopa 50 mg (4:1, immediate-release)	Levodopa 200 mg, carbidopa 20 mg (10:1, immediate-release)
III (n=8)	Levodopa 200 mg, carbidopa 50 mg (4:1, immediate-release)	Levodopa 200 mg, carbidopa 50 mg (4:1, controlled-release)
IV (n=6)		Levodopa 250 mg, carbidopa 25 mg (10:1, immediate-release)

[a] Participants were given tolcapone once and placebo once with each levodopa/carbidopa formulation. The days on which they received tolcapone or placebo were randomized

at least partially from fluctuating plasma concentrations of levodopa [12]. Various pharmacological strategies have been developed to improve the peripheral pharmacokinetics of levodopa/DCI. Sustained-release preparations can prolong the duration of effect of each levodopa dose; however, the time to onset of effect can be increased by delay of levodopa absorption [2]. Adjunctive treatment with deprenyl or dopamine agonists and subcutaneous apomorphine injections or infusions is also often used to provide more constant dopaminergic stimulation [6, 14, 17].

More recently, clinical studies have shown that the second-generation COMT inhibitor tolcapone (3,4-dihydroxy-4'-methyl-5-nitrobenzophenone) can significantly improve the pharmacokinetics and prolong the therapeutic effects of levodopa. Doses of 200 mg three times daily were well tolerated in healthy volunteers when coadministered with levodopa/DCI [5], and levodopa bioavailability and plasma half-life increased up to twofold, while 3-OMD plasma concentrations decreased by 70% [3, 5]. Furthermore, in Parkinson's disease patients with fluctuations, single doses of tolcapone 200 mg extended the antiparkinsonian action of levodopa by nearly 70% [15]. In all of those studies, tolcapone was combined with an immediate-release formulation of levodopa 100 mg and DCI 25 mg.

The objective of the present study was to evaluate, under COMT inhibition by tolcapone, the pharmacokinetics of levodopa when given as various levodopa/carbidopa formulations differing in ratio (4:1 and 10:1), levodopa dose (100, 200 and 250 mg) and release characteristics (immediate and controlled). The tolerability of these combinations was also assessed.

Methods

Participants

Thirty male volunteers were enrolled in the study; they were aged between 20 and 46 years and were within –20% to +15% of their ideal body weight (defined in the Metropolitan Life Insurance Tables, 1983). Participants were assessed as being healthy on the basis medical history; physical examination; vital signs, including a 12-lead electrocardiogram (ECG), and clinical laboratory determinations. Men who had had gastrointestinal-tract surgery that might interfere with drug absorption or who had received regular treatment with any medication during the 3 months before the start of the study were excluded. No medication other than tolcapone and levodopa/carbidopa was permitted during the study.

Study design

The study was performed on 4 days, each separated by a 1-week washout period, as shown in Table 1. Participants in groups I–III were randomized to receive two formulations of levodopa/carbidopa (unblinded), each on two occasions, once with tolcapone 200 mg and once with matching placebo (blinded, in random order). These participants received four treatment combinations altogether (four-way crossover design). Six men in group IV were given only one levodopa/carbidopa dose (250/50 mg), once with tolcapone and once with placebo (two-way crossover).

Levodopa/carbidopa and tolcapone or placebo were given simultaneously on each occasion. All treatments were given orally, after an overnight fast, and the fast was continued until 4 h after dosing.

The levodopa formulations were those available for prescription at the time of the study and were tested at doses usually prescribed to parkinsonian patients. The tolcapone dose of 200 mg was selected because it yielded the maximum effect on levodopa pharmacokinetics in earlier studies [8] and because it was previously found to be well tolerated, with and without levodopa/DCI [3, 5].

The study was performed according to the Declaration of Helsinki and its amendments. The protocol was approved by the Ethics Committee of the study centre. All of the men gave their written informed consent to participate.

Assessments

Pharmacokinetics

Two 6-ml blood samples were collected from each participant into polypropylene tubes containing ethylenediaminetetracetic acid (EDTA) as anticoagulant just before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 48 h after test medication intake. Within 15 min of collection, the blood samples were centrifuged at 4°C to separate plasma from erythrocytes. Plasma from one set of samples was stored in the dark at –70°C pending evaluation of levodopa and 3-OMD concentrations; the second set of samples was stored, after the addition of 100 µl stabilizer solution containing 0.1 mmol/l sodium metabisulphite, in the dark at –20°C pending determination of tolcapone concentrations.

Table 2 Variability in tolcapone pharmacokinetics (%)[a] (C_{max} peak plasma concentration, t_{max} time to C_{max}, *AUC* area under the plasma concentration-time curve, $t_{1/2}$ elimination half-life)

	Total	Intrasubject	Intersubject
C_{max}	31.2	19.6	24.4
t_{max}	50.9	31.3	40.1
AUC	21.8	13.5	17.2
$t_{1/2}$	60.6	42.8	42.9

[a] Data are coefficients of variability

Plasma concentrations of tolcapone were determined using high-pressure liquid chromatography (HPLC) with ultraviolet light according to a method described previously [16]. The limit of quantification of this assay was 0.05 μg/ml, and the interassay coefficient of variation was less than 4.0% in the concentration range of 0.05–2.7 μg/ml tolcapone.

Plasma concentrations of levodopa and 3-OMD were determined by HPLC with electrochemical detection. The method involved filtration of plasma samples by centrifugation using a 10-kDa cutoff filter. The filtrate was diluted with mobile phase [citric acid monohydrate 60 mmol/l, heptanesulphonate 0.25 mmol/l, EDTA 67 μmol/l and 10% methanol (pH 4.65)] at a ratio of 1:3, 1:60 or 1:300, depending on the expected concentration; 15 μl of each solution, representing 5.00, 0.25 and 0.05 μl plasma, respectively, was then loaded onto the HPLC system (comprising an 8 mm×10 cm C18 radial compression column) and eluted at 1 ml/min. Levodopa and 3-OMD were finally quantified by colometric detection using two electrodes set at +0.1 V and –0.3 V. Quantification, using authentic external standards, was by the peak-height ratio method.

Tolerability

Adverse events were assessed from spontaneous reports and by observation and questioning on admission, just before each test medication intake and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 48 h thereafter. The investigator rated the intensity of adverse events as mild, moderate or severe and assessed the potential relationship to the study medication before the study was unblinded. Supine and standing blood pressure, pulse rate and body temperature were measured at intervals throughout each study period and at the final follow-up assessment; an ECG was also performed at this point. Laboratory data were evaluated from haematology, serum chemistry, electrolyte tests and urine analysis using blood and urine samples taken from participants on admission to each study period and completion of each period.

Evaluations

Pharmacokinetics

The primary pharmacokinetic–pharmacodynamic parameters for levodopa, 3-OMD and tolcapone were calculated from plasma concentration-time data. The maximum plasma concentration (C_{max}) and the time to C_{max} (t_{max}) for all compounds were read directly from the individual plasma concentration-time data. The remaining pharmacokinetic parameters were calculated by non-compartmental methods. The elimination rate constant (λ_z) was obtained by log-linear regression analysis of the terminal portion of the curve. The corresponding elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$. The area under the plasma concentration-time curve (AUC) was calculated by conventional linear-trapezoidal summation and extrapolation to infinity.

The effect of tolcapone on C_{max}, AUC and $t_{1/2}$ of levodopa and 3-OMD was evaluated by dividing the value of a parameter obtained with COMT inhibition by the value with placebo.

Tolerability

Adverse events and clinical laboratory data were evaluated descriptively and tabulated by treatment group. Individual vital signs data were screened for values outside the predetermined normal ranges defined in the study protocol, that is, systolic blood pressure from 90 to 200 mmHg, diastolic blood pressure from 55 to 110 mmHg, pulse rate from 40 to 120 beats/min and body temperature from 35.0 to 37.5°C. Mean vital signs were screened for trends. Clinical laboratory values were compared with the normal ranges supplied by the analysing laboratory.

Statistical analyses

Pharmacokinetic parameters of levodopa and 3-OMD and tolerability data were summarized using descriptive statistics divided by levodopa/carbidopa treatment. Tolcapone pharmacokinetic data from all participants were pooled. A statistical analysis of variance (ANOVA) model, including the fixed factors of participant and dose, was used to test for dose proportionality of the dose-normalized pharmacokinetic parameters of levodopa and 3-OMD with the immediate-release formulations. For comparison of the effect of tolcapone on the different pharmacokinetic parameters, 95% confidence intervals were calculated for the parameter ratios, and statistical significance was concluded at a 5% level. Pharmacokinetic parameters for tolcapone were obtained on two separate occasions from participants in groups I–III. With these data, intra- and intersubject variability of tolcapone pharmacokinetics were calculated by ANOVA, including the factors subject and treatment day, assuming no effect of period and cotreatment.

Results

Pharmacokinetics of tolcapone

No differences in tolcapone pharmacokinetics were observed between the different levodopa/carbidopa treatment groups, indicating that the pharmacological properties of tolcapone were not affected by levodopa/carbidopa treatment. This justified the decision to pool the pharmacokinetic parameter data. Tolcapone was rapidly absorbed, with an average t_{max} of 3 h. C_{max} was approximately 6 μg/ml, and AUC was on average 21 h·μg/ml. The mean plasma elimination $t_{1/2}$ was 2.2 h.

The crossover study design, whereby the majority of participants received the same dose of tolcapone on 2 treatment days with different levodopa/carbidopa formulations, allowed us to evaluate the inter- and intrasubject variability in tolcapone pharmacokinetic parameters; these are summarized in Table 2.

Pharmacokinetics of levodopa

The pharmacokinetic parameters of levodopa during coadministration with tolcapone or placebo are summarized in Table 3.

In participants receiving placebo with levodopa/carbidopa in a 10:1 ratio (immediate-release), with levodopa doses of 100, 200 or 250 mg, the pharmacokinet-

Table 3 Levodopa pharmacokinetics during coadministration of various doses of levodopa/carbidopa and tolcapone or placebo[a] (*CR* controlled-release formulation)

	Levodopa/carbidopa dosage (mg)					
	100/10 (n=8)	100/25 (n=8)	200/20 (n=7)	200/50 (n=16)	200/50 CR[b] (n=7)	250/25 (n=6)
C_{max} (μg/ml)						
With tolcapone	1.1 (0.4)	1.4 (0.3)	2.1 (0.7)	2.1 (0.5)	1.3 (0.5)	2.7 (1.1)
With placebo	1.1 (0.2)	1.7 (0.7)	2.0 (0.5)[c]	2.3 (0.8)	1.2 (0.4)	2.7 (1.2)
t_{max} (h)						
With tolcapone	1.4 (0.6)	1.0 (0.5)	1.3 (0.9)	1.5 (0.9)	3.6 (1.4)	1.8 (1.0)
With placebo	0.8 (0.3)	1.5 (1.4)	1.4 (1.1)[c]	1.3 (0.8)	2.2 (0.9)	1.3 (1.0)
AUC (h·μg/ml)						
With tolcapone	3.9 (1.6)	4.9 (1.0)	7.4 (2.5)	8.0 (1.9)	7.6 (2.6)	8.6 (1.4)
With placebo	2.0 (0.3)	2.9 (0.7)	4.9 (1.3)[c]	5.0 (0.9)	4.5 (0.9)	6.1 (2.8)
$t_{1/2}$ (h)						
With tolcapone	2.9 (0.6)	2.9 (0.8)	2.2 (0.3)	2.4 (0.4)	2.2 (0.3)	2.5 (0.3)
With placebo	2.1 (0.4)	1.9 (0.4)	1.6 (0.3)[c]	2.1 (0.6)	1.4 (0.3)	1.8 (0.3)

[a] Data are means (SD)
[b] All others are immediate-release
[c] n=6

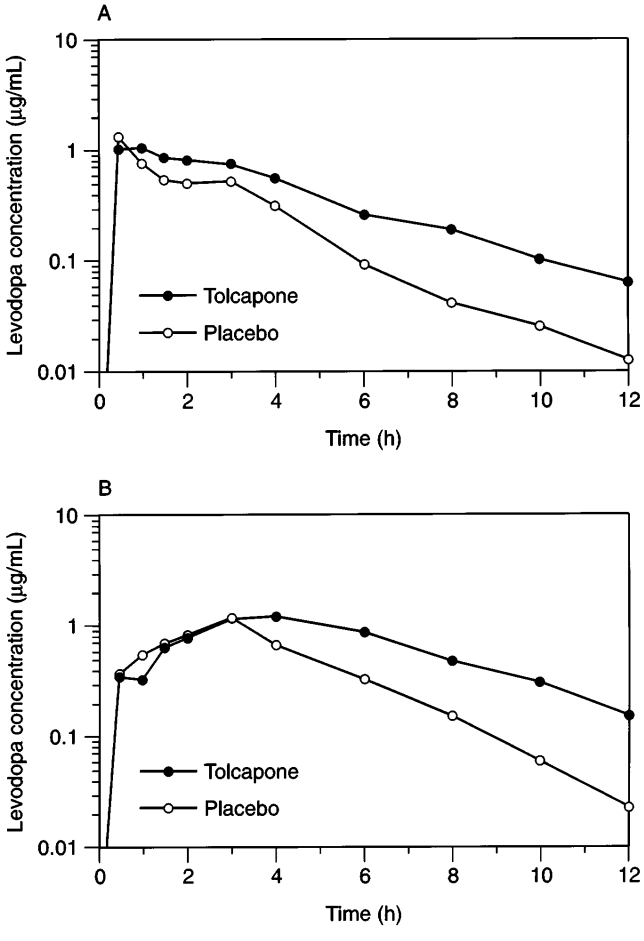

Fig. 1A,B Levodopa plasma concentration profiles after administration of tolcapone 200 mg or placebo with (**A**) levodopa/carbidopa 100/25 mg immediate-release (data from other immediate-release formulations are similar to this representative curve) and (**B**) levodopa/carbidopa 200/50 mg controlled-release. Data are means

ics of levodopa were linear (Table 3). C_{max} and AUC increased roughly proportionally with dose, $t_{1/2}$ was independent of dose and t_{max} was slightly longer with levodopa 200 and 250 mg than with 100 mg. With placebo and levodopa/carbidopa in a 4:1 ratio, with levodopa doses of 100 or 200 mg, the increase in levodopa C_{max} was less than dose-proportional, although AUC increased in a linear fashion and $t_{1/2}$ and t_{max} were independent of dose (Table 3). Comparison of levodopa pharmacokinetics after a single dose of levodopa/carbidopa 4:1 or 10:1 and placebo showed that levodopa C_{max}, t_{max} and $t_{1/2}$ were independent of carbidopa intake; only levodopa AUC was lower after administration of levodopa/carbidopa 100/10 mg than after 100/25 mg. When two tablets of each formulation were taken, differences in levodopa AUC were no longer detectable.

Coadministration of placebo and levodopa/carbidopa 200/50 mg (controlled-release) resulted in a shorter levodopa $t_{1/2}$ than with the other levodopa/carbidopa formulations (Table 3). When the controlled-release formulation was compared with the 200/50 mg immediate-release formulation, levodopa C_{max} was 50% less and t_{max} occurred later, although levodopa bioavailability was approximately 90% of the immediate-release formulation.

Mean plasma concentrations of levodopa during coadministration of levodopa/carbidopa and tolcapone or placebo can be seen in Fig. 1. When tolcapone 200 mg was coadministered, statistically significant increases in levodopa AUC were observed with all levodopa/carbidopa formulations except 250/25 mg, although the mean increase in AUC seen with this formulation was similar to the effect on other formulations (Fig. 2). The increase in levodopa AUC with tolcapone was 60–90% and no difference in relative AUC increase was detected between for-

mulations. The increase in levodopa $t_{1/2}$ with tolcapone was 20–60% ($P<0.05$ for all formulations; Fig. 2). Average levodopa C_{max} from all formulations did not change with coadministration of tolcapone; the confidence intervals for the C_{max} ratios included the value 1.0 for all formulations (Fig. 2). Administration of tolcapone affected levodopa t_{max} only for the controlled-release formulation, with the mean t_{max} increasing by 1.4 h. This apparent delay in t_{max} was caused not by interference with levodopa absorption, because the initial phase of the profile was similar for tolcapone and placebo (Fig. 1), but by a prolongation of the plateau around C_{max}.

Pharmacokinetics of 3-OMD

The pharmacokinetic parameters of 3-OMD are summarized in Table 4. When different levodopa/carbidopa formulations were given with placebo, 3-OMD C_{max} and AUC increased approximately dose-proportionally when the levodopa/carbidopa ratio remained the same. However, both parameters were influenced by the amount of carbidopa in the dose: 3-OMD C_{max} was on average 0.23 μg/ml lower with carbidopa 10 mg than with 25 mg; no difference was seen between carbidopa 20 and 50 mg. A stronger trend was seen for 3-OMD AUC, with differences between carbidopa 10 and 25 mg and between carbidopa 20 and 50 mg. 3-OMD t_{max} and $t_{1/2}$ were independent of both levodopa and carbidopa dose. No significant differences in 3-OMD pharmacokinetics were seen between the controlled-release formulation (levodopa/carbidopa 200/50 mg) and the immediate-release formulation (two tablets of levodopa/carbidopa 100/25 mg) when given with placebo.

Evaluating the effect of tolcapone using the ratio method (parameter with COMT inhibition divided by parameter without COMT inhibition) showed that, with COMT inhibition by tolcapone 200 mg, 3-OMD C_{max} was reduced by an average of 80% and AUC by an average of 70% with all levodopa/carbidopa formulations.

Tolerability

All reported adverse events were mild or moderate, with no significant differences within or between treatment groups; these results suggest that all treatment combinations were well tolerated. Two participants withdrew from the study because of intercurrent illness (fever in one, fever and vomiting in the other), which was not considered by the investigator to be caused by test medication. A third participant, who received trial medication on day 1 only, withdrew for personal reasons. These participants were not replaced.

Overall, a higher incidence of adverse effects with tolcapone than with placebo was found only in participants receiving the levodopa/carbidopa controlled-release formulation. The observed difference was exclusively owing to

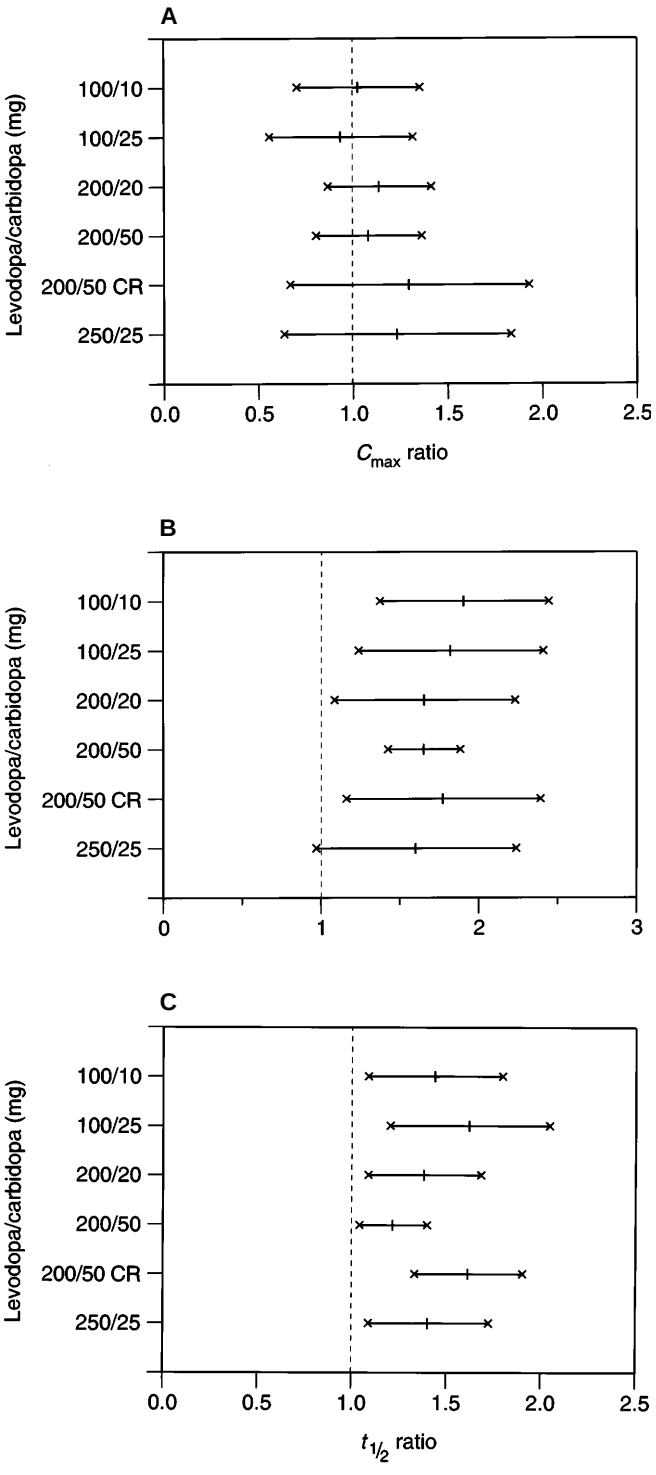

Fig. 2A,B,C Pharmacokinetic parameter ratios of levodopa after administration of different levodopa/carbidopa formulations. **A** Peak plasma concentration (C_{max}); **B** area under the plasma cocentration-time curve (AUC); **C** half-life ($t_{1/2}$). Data are means and confidence intervals (*CR* controlled-release formulation)

Table 4 3-*O*-methyldopa (3-OMD) pharmacokinetics during coadministration of various doses of levodopa/carbidopa with tolcapone or placebo[a] (*CR* controlled-release formulation)

	Levodopa/carbidopa dosage (mg)					
	100/10 (n=8)	100/25 (n=8)	200/20 (n=7)	200/50 (n=16)	200/50 CR[b] (n=7)	250/25 (n=6)
C_{max}(μg/ml)						
With tolcapone	0.2 (0.1)	0.2 (0.0)	0.3 (0.1)	0.2 (0.1)	0.2 (0.0)	0.2 (0.0)
With placebo	0.5 (0.1)	0.7 (0.3)	1.3 (0.3)[c]	1.3 (0.3)	1.3 (0.4)	1.3 (0.3)
t_{max}(h)						
With tolcapone	7.5 (2.3)	7.6 (2.9)	7.0 (4.0)	8.3 (3.6)	10.0 (1.6)	4.8 (3.0)
With placebo	4.9 (1.3)	6.5 (2.6)	5.3 (2.1)[c]	5.1 (2.0)	7.7 (1.8)	5.5 (1.8)
AUC (h·μg/ml)						
With tolcapone	6.3 (1.6)	7.5 (1.7)	8.2 (2.1)	9.1 (3.4)	7.9 (3.4)	8.7 (3.2)
With placebo	12.8 (2.1)	19.9 (6.4)	28.9 (8.9)[c]	32.4 (10.4)	28.9 (8.2)	32.5 (6.7)
$t_{1/2}$(h)						
With tolcapone	36.1 (18.8)	30.8 (8.8)	17.8 (2.1)	20.0 (4.6)	20.8 (8.2)	22.6 (9.8)
With placebo	17.3 (3.4)	16.2 (4.8)	13.2 (1.7)[c]	14.1 (3.5	13.3 (2.4)	13.8 (3.2)

[a] Data are means (SD)
[b] All others are immediate-release
[c] n=6

urine discoloration, which is a known side effect of tolcapone. This was the most frequently reported adverse event and occurred in nine participants who received tolcapone and in one who received placebo. Ten cases of central nervous system disorders (somnolence, headache or light-headedness) were reported by participants receiving tolcapone and six cases by those who received placebo; incidences between levodopa/carbidopa treatment groups were similar. Gastrointestinal system disorders (nausea, vomiting, abdominal discomfort, hiccups or dyspepsia) were the next most frequently reported adverse events (eight cases by participants who received tolcapone and four cases by those who received placebo).

Incidences of adverse events between levodopa/carbidopa treatment groups were similar, except for slightly higher numbers in the six participants who received levodopa/carbidopa 250/25 mg: three of these experienced gastrointestinal adverse events when taking tolcapone (nausea in one, nausea and vomiting in one and abdominal discomfort in one), compared with none receiving placebo.

No pattern of abnormal laboratory values or vital signs was observed that suggested a relationship to treatment with tolcapone. All ECGs recorded during the study were reported as normal.

Discussion

In previous pharmacokinetic interaction studies of tolcapone and levodopa/carbidopa, combinations of single or multiple doses of tolcapone and single or multiple doses of an immediate-release levodopa/carbidopa 100/25 mg formulation were used. The present study is the first in which the pharmacokinetics of levodopa in levodopa/carbidopa formulations with different release characteristics and dosage ratios have been evaluated under COMT inhibition by tolcapone.

The effect of tolcapone on levodopa pharmacokinetics was unaffected by levodopa/carbidopa formulation characteristics. Levodopa AUC increased by 60–90% with tolcapone and $t_{1/2}$ increased by 20–60%; these increases were consistent with previous findings [3, 4]. Nevertheless, despite these general elevations in levodopa concentration, levodopa C_{max} did not increase during COMT inhibition, indicating that tolcapone treatment should lead to more sustained levodopa plasma concentrations. The combination of tolcapone and the controlled-release formulation also led to an increase in levodopa AUC (by 80%) and $t_{1/2}$ (by 60%), indicating that the therapeutic effects of this formulation of levodopa would be further potentiated by tolcapone. The apparent delay in levodopa t_{max} with this combination resulted not from any delay in absorption but rather from a prolongation of the C_{max} plateau. This points to greater levodopa absorption with the treatment combination of tolcapone and controlled-release levodopa/carbidopa.

Combining tolcapone with immediate-release levodopa/carbidopa preparations offers a very effective means of stabilizing levodopa plasma concentrations. The combination appears to have advantages over the controlled-release levodopa/carbidopa formulation given alone because the delayed and variable levodopa absorption with this formulation can result in delayed and variable response in some patients [2]. However, combining tolcapone with immedi-

ate-release levodopa formulations yields the benefit of controlled-release therapy (prolongation of levodopa plasma concentrations), while providing rapid and reliable levodopa absorption. In patients who do not require rapid levodopa absorption and who therefore receive controlled-release levodopa therapy, tolcapone could provide the additional benefit of extending levodopa concentrations even further.

The pharmacokinetics of tolcapone were similar to those previously reported when a single 200 mg dose of tolcapone was combined with levodopa/DCI [7, 8]. The levodopa/carbidopa formulation had no effect on tolcapone pharmacokinetics. The intrasubject variability of tolcapone C_{max} and AUC was relatively small (20% for C_{max} and 14% for AUC), indicating a reduced risk of over- or underexposure of a patient to the drug; this should contribute to consistent efficacy and safety in clinical practice.

Tolcapone was well tolerated when combined with all formulations – no serious adverse events were reported, and none of the participants withdrew prematurely for reasons related to tolcapone. Urine discoloration was reported more frequently with tolcapone than with placebo; this is a known, harmless side effect of tolcapone, caused by the intense colour of the compound and its metabolites. Another COMT inhibitor, entacapone, produces the same phenomenon [13]. The incidence of gastrointestinal adverse events increased slightly when tolcapone was combined with levodopa/carbidopa 250/25 mg. Possibly, a single dose of carbidopa 25 mg was not sufficient to prevent dopamine formation because of the high plasma concentrations of levodopa that resulted from the intake of levodopa 250 mg plus tolcapone. The small number of participants (n=6) and the single-dose nature of the study precluded our drawing any conclusions about the clinical relevance of this finding, but it was in agreement with previous observations that the high incidence of nausea and vomiting associated with levodopa/carbidopa 10:1 formulations could be caused by insufficient inhibition of dopa decarboxylase by low carbidopa intake (<75–160 mg/day) [2].

Although the present study was primarily designed to evaluate the effect of tolcapone on levodopa pharmacokinetics, it also yielded interesting findings on the pharmacokinetics of different levodopa formulations in general. Levodopa pharmacokinetics were linear at doses of 100–250 mg, except for the less-than-dose-proportional C_{max} increases observed with the 4:1 formulations; this could be a result of interference with levodopa absorption by the higher carbidopa dose. The large variation in levodopa C_{max} observed with the 250 mg dose in the present study is consistent with the multiple peaks of absorption observed previously at higher levodopa doses [10], thought to result from altered gastric motility caused by large local concentrations of levodopa [2].

As in a previous study [10], a lower levodopa AUC was observed with a single dose of levodopa/carbidopa 100/10 mg (i.e. 10:1 ratio) than with levodopa/carbidopa 100/25 mg (4:1). However, this difference was not found when the levodopa/carbidopa dose was doubled. This suggests that a single dose of carbidopa 10 mg may not have been sufficient to prevent peripheral levodopa decarboxylation, resulting in reduced levodopa bioavailability. The lower 3-OMD C_{max} and AUC observed at low carbidopa doses reflect less levodopa *O*-methylation by COMT. However, during multiple dosing, carbidopa accumulates and a carbidopa dose of at least 75 mg/day should be sufficient to prevent dopa decarboxylation under these conditions [2].

In conclusion, the optimization of levodopa pharmacokinetics seen with tolcapone in previous studies was confirmed for all levodopa/carbidopa formulations, and the observed benefit was not accompanied by any increase in adverse events. Although only single-dose administrations were investigated in the present study, the effect of tolcapone on levodopa pharmacokinetics after multiple administration appears to be highly predictable from single-dose data [3–5, 7, 8, 9]. This suggests that the coadministration of tolcapone with different levodopa/carbidopa formulations in parkinsonian patients should have similarly beneficial clinical effects to those observed when tolcapone is coadministered with an immediate-release formulation of levodopa/carbidopa in a 4:1 ratio [11].

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