COMT inhibition with tolcapone does not affect carbidopa pharmacokinetics in parkinsonian patients on levodopa/carbidopa (Sinemet®)

Karin M. Jorga¹ & David J. Nicholl²

¹Department of Clinical Pharmacology, F. Hoffmann-La Roche Ltd, Basel, Switzerland and ²Department of Neurology, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK

Aims Tolcapone is a novel catechol-O-methyltransferase (COMT) inhibitor used as an adjunct to levodopa/carbidopa or levodopa/benserazide therapy to improve treatment of Parkinson's disease. The aim of the current study was to investigate the potential effect of tolcapone on the pharmacokinetics of carbidopa.

Methods This was an open-label study in 12 parkinsonian patients receiving optimal levodopa/carbidopa therapy and tolcapone 200 mg three times daily for 6 weeks. Blood samples were taken at baseline (i.e. before the first tolcapone intake) and after 1–2 weeks and 6 weeks so that carbidopa pharmacokinetics before and during tolcapone treatment could be assessed.

Results No changes in any pharmacokinetic parameters of carbidopa were observed. The mean AUC(0,τ) and C_{max} values at baseline were 0.39 µg ml⁻¹ h and 0.14 µg ml⁻¹, respectively. During tolcapone treatment these values were on average 0.35 µg ml⁻¹ h (AUC(0,τ), week 1–2), 0.34 µg ml⁻¹ h (AUC(0,τ), week 6 and 0.13 µg ml⁻¹ (C_{max}, weeks 1–2 and 6). t_{max} remained unchanged (approx. 2 h).

Conclusions These results indicate that tolcapone does not affect carbidopa elimination and that no interaction of any clinical relevance occurs between tolcapone and carbidopa.

Keywords: levodopa/carbidopa, Parkinson's disease, COMT inhibition, pharmacokinetics, tolcapone

Introduction

In current Parkinson's disease treatment practice, the dopamine precursor levodopa is combined with an inhibitor of aromatic amino acid decarboxylase (carbidopa or benserazide) to reduce peripheral metabolism of levodopa and increase its clinical benefit. However, with this combination, the metabolism of levodopa is shunted towards the 3-O-methylation pathway catalysed by catechol-O-methyltransferase (COMT) and metabolism to 3-O-methyldopa (3-OMD) predominates [1, 2]. As a potent, reversible, orally active inhibitor of COMT, tolcapone (3,4-dihydroxy-4'-methyl-5-nitrobenzophenone) has recently been approved for adjuvant therapy in parkinsonian patients treated with levodopa preparations. The addition of COMT inhibition by tolcapone is aimed

at reducing further the peripheral metabolism of levodopa to optimize its pharmacokinetics and to improve the clinical response to levodopa [3, 4].

The effect of tolcapone on levodopa plasma concentrations and the resulting clinical benefits have been established in several studies [5–8]. When combined with levodopa/carbidopa, tolcapone increases the half-life and area under the plasma concentration–time curve (AUC) of levodopa without affecting peak levodopa concentrations; the formation of 3-OMD is also substantially reduced [5, 6]. Results of early clinical trials have confirmed that this improved pharmacokinetic profile leads to better symptom control and improvements in the 'wearing-off' phenomenon in patients with Parkinson's disease [7, 8].

Until now the influence of tolcapone on the pharmacokinetics of carbidopa, the decarboxylase inhibitor given in combination with levodopa, has not been investigated. Carbidopa [(–)-L-α-hydrazino-3, 4-dihydroxy-α-methylbenzenepropanoic acid monohydrate] is a catechol

Correspondence: Dr K. M. Jorga, Department of Clinical Pharmacology, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland. Tel: 41 61 688 1449, Fax: 41 61 688 1043, E-mail: karin.jorga@roche.com.

Received 4 March 1998, accepted 1 June 1999.

compound and is possibly metabolized by COMT [9, 10]. Its metabolism might thus conceivably be affected during COMT inhibition. The effect of tolcapone on carbidopa pharmacokinetics was therefore assessed under therapeutic conditions directly in parkinsonian patients optimally treated with levodopa/carbidopa.

Methods

Twelve parkinsonian patients (seven men, five women; mean age 61.5 years, range 51–72 years) participated in this open-label pharmacokinetic study after giving written informed consent. Ethics committee approval was obtained and the study was conducted in conformity with the principles of the Declaration of Helsinki and its amendments. The patients were being optimally treated with levodopa/carbidopa (Sinemet®, MSD/Du Pont, Rahway, NJ, USA), with a mean daily levodopa intake of 525 mg (range 350–1000 mg). They had been treated with levodopa/carbidopa for at least 1 year and were enrolled in an open-label long-term study of the efficacy and safety of tolcapone. Levodopa/carbidopa and other antiparkinsonian regimens (selegiline in seven patients; procyclidine and bromocriptine each in one patient) had been stable for at least 4 weeks before study entry and were not changed during the 6 week treatment period.

Patients received tolcapone 200 mg three times daily orally. The first dose was given with the first daily dose of levodopa/carbidopa; subsequent doses were given at 6 h intervals thereafter. Blood samples (10 ml) were taken on three occasions: before the first administration of tolcapone (baseline) and after 1–2 weeks and 6 weeks of treatment. On each occasion, patients fasted overnight and blood samples were collected just before, and 0.5, 1, 2, and 4 h after the first daily dose of levodopa/carbidopa. A further sample was taken just before the second dose. If the second dose of levodopa/carbidopa was taken more than 6 h after the first dose, additional blood samples were collected up to the second intake at 6, 8, and 10 h. Most patients ($n=9$) took levodopa 100 mg as the morning dose (range 75–200 mg); the first daily carbidopa dose was 25 mg in 10 patients (one patient took 19 mg and one took 20 mg).

Plasma carbidopa concentrations were analysed after protein precipitation by gradient ion-pair high-performance liquid chromatography with fluorescence detection. Protein precipitation was achieved with perchloric acid and chromatographic separation was performed with a 125 × 4 mm i.d. Kromasil 100RP18 column (5 µm), and with a 10 × 4 mm i.d. Hypersil ODS (5 µm) precolumn in gradient ion-pairing mode with phosphate buffer/acetonitrile mobile phases (A=95/5, B=80/20, v/v). The final mobile phases were both adjusted to an apparent pH of 3.0 and both mobile phases

contained identical final concentrations of EDTA (0.5 mM) and octanesulphonic acid (5 mM). The eluent was monitored by fluorescence detection at $\lambda_{\text{exc}}=280$ nm and $\lambda_{\text{em}}=320$ nm. The assay was fully validated for the calibration range of 0.05–10 µg ml⁻¹. The limit of quantification was 0.0425 µg ml⁻¹. The interassay precision at the lower end of the calibration range (0.05 µg ml⁻¹) was 4.2% and the accuracy was 2.4% at this concentration. Over the whole concentration range the average value for precision was 2.1% and the accuracy was within $\pm 3\%$ at all concentration levels.

Pharmacokinetic parameters were determined by non-compartmental methods [11]. Maximum plasma concentration (C_{max}), time to its occurrence (t_{max}) and minimum plasma concentration (C_{min}) were read directly from the individual plasma concentration/time data and AUC over one carbidopa dosing interval ($\text{AUC}(0,\tau)$) was determined by linear-trapezoidal summation. For the calculation of $C_{\text{max}}-C_{\text{min}}$, values below the limit of quantification were assigned to zero.

The pharmacokinetic data were evaluated using descriptive statistics. 95% Confidence Intervals were calculated for the parameter means for each assessment day as well as for the change in carbidopa $\text{AUC}(0,\tau)$ from baseline. No formal hypothesis testing was performed.

Results

No changes were seen in any of the pharmacokinetic parameters of carbidopa after initiation of treatment with tolcapone (Table 1). The carbidopa $\text{AUC}(0,\tau)$ during tolcapone treatment (week 1–2 and week 6) was on average 94% of that at baseline (95% confidence intervals week 1–2: 77–112%; week 6: 73–115%), indicating that, when tolcapone is coadministered with levodopa/carbidopa, the carbidopa steady state AUC is not significantly changed. The median carbidopa $\text{AUC}(0,\tau)$ for all patients

Table 1 Pharmacokinetic parameters of carbidopa before and during treatment with tolcapone 200 mg three times daily in parkinsonian patients treated with levodopa/carbidopa.

	Baseline	Weeks 1–2	Week 6
C_{max} (µg ml ⁻¹)	0.14 ± 0.06 (0.11–0.17)	0.13 ± 0.03 (0.11–0.15)	0.13 ± 0.07 (0.09–0.17)
$C_{\text{max}}-C_{\text{min}}$ (µg ml ⁻¹)	0.11 ± 0.06 (0.08–0.14)	0.11 ± 0.03 (0.09–0.13)	0.12 ± 0.07 (0.08–0.16)
t_{max} (h)	2.1 (1.0–4.1)	2.1 (1.0–4.1)	2.2 (1.0–4.0)
$\text{AUC}(0,\tau)$ (µg ml ⁻¹ h)	0.39 ± 0.25 (0.25–0.53)	0.35 ± 0.18 (0.25–0.45)	0.34 ± 0.22 (0.22–0.46)

Data are median (range) for t_{max} and means $\pm$ s.d. (95% confidence interval) for all other parameters, ($n=12$).

was $0.28 \mu\text{g ml}^{-1} \text{ h}$ at baseline, $0.31 \mu\text{g ml}^{-1} \text{ h}$ at the week 1–2 assessment and $0.30 \mu\text{g ml}^{-1} \text{ h}$ at the week 6 assessment and the individual patient data confirm that there is no evidence for an effect of tolcapone on carbidopa concentrations (Figure 1, illustrated for $\text{AUC}(0, \tau)$). The maximum increase in carbidopa plasma concentration during a dose interval ($C_{\text{max}} - C_{\text{min}}$) and the absolute C_{max} were also unaffected. Carbidopa t_{max} was highly variable (range 0.5–4 h). This was independent of tolcapone treatment and might be a reflection of the limited number of samples available for each dosing interval.

Discussion

Tolcapone is a new pharmacological treatment for patients with Parkinson's disease who are receiving levodopa in combination with a decarboxylase inhibitor (benserazide or carbidopa). An evaluation of any pharmacokinetic interaction between tolcapone and carbidopa in humans was essential because carbidopa is a catechol compound that is potentially metabolized by COMT [9, 10], so inhibition of COMT might interfere with metabolism of carbidopa.

Our study was designed to mimic the clinical situation, where patients on levodopa/carbidopa treatment would receive tolcapone as adjunct to their existing therapy. Any clinically relevant metabolic interaction between tolcapone and carbidopa would have been indicated by an increase in carbidopa $\text{AUC}(0, \tau)$ and $C_{\text{max}} - C_{\text{min}}$ values resulting from COMT inhibition by tolcapone and by the consequent decrease in carbidopa metabolism. Because no systematic change was observed in any of these measures, it appears likely that the COMT pathway plays only a minor role in the elimination of carbidopa and that plasma carbidopa concentrations are not influenced by tolcapone coadministration. Although the metabolism of carbidopa is not fully understood, evidence suggests that the loss of the hydrazine functional group represents the major metabolic pathway for carbidopa [10].

Figure 1 Area under the plasma concentration–time curve of carbidopa before and during treatment with tolcapone 200 mg three times daily. Each line represents data from an individual patient.

The absorption characteristics of carbidopa reflected by t_{max} and C_{max} were also unchanged during tolcapone treatment, indicating that the absorption of carbidopa is unaffected by concomitant administration of tolcapone. In contrast to our findings, results from an interaction study between another COMT inhibitor, entacapone, and carbidopa showed that entacapone can interfere with the absorption of carbidopa. This leads to decreases in carbidopa C_{max} and AUC values, particularly after high entacapone doses [12]. The decrease in carbidopa concentrations due to entacapone led to an increased conversion of levodopa to dopamine and a lower levodopa bioavailability, an effect that is not expected with tolcapone.

The lack of interaction between tolcapone and carbidopa is important, considering the potential complications that could arise from an increase (potential toxicity) or decrease (potential loss of efficacy) in carbidopa concentrations. The present study has confirmed that tolcapone has no clinically relevant influence on the pharmacokinetics of carbidopa. Whether tolcapone interacts with the other decarboxylase inhibitor, benserazide, remains to be investigated.

References

- 1 Reilly DK, Rivera-Calimlim L, van Dyke D. Catechol-O-methyltransferase activity: a determinant of levodopa response. *Clin Pharmacol Ther* 1980; **28**: 278–286.
- 2 Nutt JG, Woodward WR, Beckner RM, *et al.* Effect of peripheral catechol-O-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. *Neurology* 1994; **44**: 913–919.
- 3 Männistö PT, Kaakkola S. Rationale for selective COMT inhibitors as adjuncts in the drug treatment of Parkinson's disease. *Pharmacol Toxicol* 1990; **66**: 317–323.
- 4 Kaakkola S, Gordin A, Männistö PT. General properties and clinical possibilities of new selective inhibitors of catechol O-methyltransferase. *Gen Pharmacol* 1994; **25**: 813–824.
- 5 Jorga KM, Sedek G. Effect of the novel COMT-inhibitor tolcapone on L-dopa pharmacokinetics when combined with different Sinemet formulations. *Neurology* 1995; **45**: A291.
- 6 Davis TL, Roznoski M, Burns RS. Acute effects of COMT inhibition on L-dopa pharmacokinetics in patients treated with carbidopa and selegiline. *Clin Neuropharmacol* 1995; **18**: 333–337.
- 7 Kurth MC, Adler CH, Saint Hilaire M, *et al.* Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. *Neurology* 1997; **48**: 81–87.
- 8 Waters CH, Kurth M, Bailey P, *et al.* Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. *Neurology* 1997; **49**: 665–671.
- 9 Vickers S, Stuart E, Bianchine J, *et al.* Metabolism of carbidopa [(–)-L- α -hydrazino-3, 4-dihydroxy- α -methylbenzenepropanoic acid monohydrate], an aromatic amino acid decarboxylase inhibitor, in the rat, dog, rhesus monkey, and man. *Drug Metab Dispos* 1974; **2**: 9–22.

- 10 Vickers S, Stuart E, Hucker H. Further studies on the metabolism of carbidopa, (–)-L- α -hydrazino-3,4-dihydroxy- α -methylbenzenepropanoic acid monohydrate, in the human, rhesus monkey, dog, and rat. *J Med Chem* 1975; **18**: 134–138.
- 11 Gibaldi M, Perrier D. *Pharmacokinetics* 2nd edn. New York: Marcel Dekker 1982.
- 12 Ahtila S, Kaakkola S, Gordin A, *et al.* Effect of entacapone, a COMT inhibitor, on the pharmacokinetics and metabolism of levodopa after administration of controlled-release levodopa-carbidopa in volunteers. *Clin Neuropharmacol* 1995; **18**: 46–57.