Pharmacodynamics of benserazide assessed by its effects on endogenous and exogenous levodopa pharmacokinetics*

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Aims The objectives of the study were to investigate the pharmacodynamics of the peripheral decarboxylase inhibitor benserazide during multiple-dose regimens.

Methods Two groups of eight healthy male subjects were consecutively treated for periods of 14 days with benserazide 5, 25, 100 mg three times daily and 12.5, 50, 200 mg three times daily, respectively. Plasma levels of levodopa, 3-O-methyldopa (3-OMD) and 3,4-dihydroxyphenylacetic acid (DOPAC) were determined before benserazide treatment and during all benserazide dosing regimens, as existing endogenously and after administration of 250 mg levodopa.

Results Endogenous concentrations of levodopa and 3-OMD increased dose-dependently (from 8 up to 52 $\mu\text{g l}^{-1}$ and from 0.02 up to 0.50 mg l^{-1} , respectively, at doses of 200 mg) with ascending doses of benserazide whereas DOPAC levels remained unchanged. There were no indications of a plateau in the effects of benserazide on the plasma levels of the analytes. The area under the concentration-time curve (AUC) of exogenously administered levodopa increased from 1.2 in the control group to 5.9 $\text{mg l}^{-1} \text{h}$ at benserazide doses of 100–200 mg three times daily. Benserazide caused a dose-dependent increase in the AUC of 3-OMD from 7.4 to 106 $\text{mg l}^{-1} \text{h}$ at doses of 200 mg. Formation of DOPAC was dose-dependently suppressed, with benserazide 5 mg three times daily already halving its AUC.

Conclusions The benserazide-dose response data obtained suggest that even at very high doses extracerebral decarboxylase is not yet completely inhibited.

Keywords: benserazide, levodopa, decarboxylase, pharmacokinetics, pharmacodynamics, Parkinson's disease

Introduction

Treatment with 3,4-dihydroxyphenyl-L-alanine (levodopa) constitutes the cornerstone in the symptomatic therapy of Parkinson's disease [1]. However, oral administration of levodopa as such results in a rapid decarboxylation to dopamine, a reaction catalysed by aromatic L-amino acid decarboxylase [2]. Peripherally circulating dopamine is responsible for a spectrum of side effects of levodopa therapy, *viz.* nausea, vomiting and orthostatic hypotension. Combination therapy of levodopa with an inhibitor of extracerebral decarboxylase such as benserazide (Madopar[®]) or carbidopa (Sinemet[®]) leads to a marked reduction in both the required levodopa dose and the incidence of unwanted effects attributable to the peripheral formation of dopamine [3]. Long-term therapy with levodopa and a decarboxylase inhibitor, however, can lead to fluctuations in clinical response such as dyskinesias, end-of-dose wearing off and the 'on-off' phenomenon [4]. Several approaches

are undertaken to avoid or reduce these complications of long-term therapy [5, 6]. Fractionation of the daily levodopa dose and combination of lower doses of levodopa with a dopamine receptor agonist (e.g. bromocriptine, apomorphine) are commonly employed [6, 7]. A strategy which is still under experimental clinical development is addition of an inhibitor of catechol-O-methyltransferase (COMT) to the combination of levodopa and a decarboxylase inhibitor [8]. COMT inhibitors such as tolcapone and entacapone have been shown to be well tolerated and to enhance the bioavailability of levodopa by reducing its biotransformation to 3-O-methyldopa (3-OMD) [9, 10].

The currently available levodopa/decarboxylase inhibitor formulations contain a fixed combination of both compounds, i.e. levodopa: benserazide 4:1 and levodopa: carbidopa 10:1 and 4:1. The above mentioned strategies to combat side effects of chronic levodopa therapy all imply a reduction of the levodopa and, therefore, also of the decarboxylase inhibitor dose. The effects of low doses of benserazide and carbidopa have not yet been investigated in detail. The influence of relatively high doses of carbidopa on the pharmacokinetics of levodopa has been described previously [11]. The relationship between plasma benserazide or carbidopa concentrations, gut and systemic decarboxylase

* This paper is dedicated to the memory of the late Professor Mosè Da Prada (1934–1995) who for more than 30 years was engaged in research on levodopa and benserazide.

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inhibition and levodopa pharmacokinetics have not been determined [12]. Insufficient inhibition of decarboxylase would lead to an increase in dopamine-related side effects. The objectives of this study were to assess the effects of different dosage regimens of benserazide on levodopa and 3-OMD plasma levels, as existing endogenously and after administration of a fixed levodopa dose. Plasma levels of 3-OMD are an indirect marker for the degree of dopamine formation because in the presence of a decarboxylase inhibitor the metabolism of levodopa is shifted towards 3-OMD [13, 14]. Plasma levels of 3,4-dihydroxyphenylacetic acid (DOPAC), which is formed from dopamine by monoamine oxidase (MAO) B activity, were also measured.

Methods

Subjects

Two groups of eight healthy male Caucasian volunteers, aged 30–54 years and within 20% of their ideal body weight, participated in the study. Ethics Committee approval was obtained from the Roche Clinical Pharmacology Unit Independent Ethics Committee, Welwyn, UK, and all subjects gave their written informed consent before any screening procedures were performed. The study was conducted in full conformity with the principles of the Declaration of Helsinki and its amendments. Volunteers were considered to be healthy on the basis of medical history, results of physical and neurologic examination, and electrocardiographic and routine clinical laboratory determinations. No concomitant medication was allowed during the study. For a major part the study was conducted on an ambulatory basis.

Study design

This was an open-label, parallel-group study. The second group of eight subjects started treatment 1 week after the subjects in the first group. On study days 3–16, 17–30 and 31–44 subjects in group I received treatment with benserazide 5 mg three times daily, 25 mg three times daily and 100 mg three times daily, respectively. On the same study days, subjects in group II received benserazide 12.5 mg three times daily, 50 mg three times daily and 200 mg three times daily, respectively. Doses of up to 1300 mg daily of benserazide have been given to Parkinsonian patients in previous clinical trials [15]. Benserazide in this study was provided in capsules and administered at 08.00, 15.00 and 23.00 h. Endogenous plasma levels of levodopa, 3-OMD and DOPAC were determined in all subjects on days –1, 14, 28 and 42. Levels of levodopa, 3-OMD and DOPAC were also measured following administration of a single oral dose of 250 mg levodopa (provided as a tablet Larodopa®) on days 1, 15, 29 and 43 at approximately 10.00 h. This dose of levodopa was chosen because it is sufficiently high to provide plasma concentrations which can be used for pharmacokinetic evaluation, even in the absence of benserazide. Levels of levodopa, 3-OMD and DOPAC were determined after an overnight fast which continued for 3.5 h after levodopa intake.

Assessments

Tolerability Adverse events were assessed by spontaneous reports, observations, and questioning at regular intervals. The intensity of the adverse events was rated on a three-point scale (mild, moderate, severe). Blood pressure and heart rate and the ECG were recorded and brief neurological examinations performed at frequent intervals on the days of levodopa/3-OMD/DOPAC determinations. Several routine laboratory safety tests on blood and urine were conducted during the study.

Pharmacokinetics Blood samples of 5 ml were collected into tubes containing heparin as anticoagulant via a polyethylene catheter inserted into a forearm vein at 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 10 h after the first dose of benserazide on days 14, 28 and 42. The same series of blood samples was also taken 1 day prior to starting benserazide treatment (day –1). On days 1/2, 15/16, 29/30, and 43/44 blood samples were collected just before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 27, 30 and 33 h after levodopa administration. The blood samples were kept on ice and plasma was separated by centrifugation at 4°C within 2 h of blood collection. Plasma samples were stored at –70°C pending analysis.

Plasma concentrations of levodopa and 3-OMD were determined by high-pressure liquid chromatography (h.p.l.c.) with column switching and electrochemical detection according to a method described previously [16]. DOPAC concentrations were measured by a method involving adsorption to aluminium oxide at pH 8.6, desorption with perchloric acid and quantification by reversed h.p.l.c. with electrochemical detection. Endogenous levels of all compounds could be determined and the lower limits of quantification were $5 \mu\text{g l}^{-1}$ for levodopa and DOPAC and $10 \mu\text{g l}^{-1}$ for 3-OMD. The intra- and inter-assay coefficients of variation were lower than 3% and 4%, respectively, over the concentration range $5\text{--}3000 \mu\text{g l}^{-1}$ for levodopa and DOPAC and $10\text{--}3000 \mu\text{g l}^{-1}$ for 3-OMD, respectively.

Evaluation

Tolerability The adverse events and clinical laboratory data were evaluated descriptively. Clinical laboratory values were compared with the normal ranges supplied by the analysing laboratory. Individual vital signs were screened for values outside the predetermined normal ranges: systolic blood pressure, 80–160 mmHg; diastolic blood pressure, 50–95 mmHg; pulse rate, 40–120 beats min^{-1} . Particular attention was devoted to signs of increased dopaminergic activity, *viz.* dizziness when standing up, nausea and vomiting. Mean vital signs data were screened for trends.

Pharmacokinetics Pharmacokinetic parameters were determined for levodopa, 3-OMD and DOPAC. The endogenous (predose) concentrations were subtracted for calculation of the pharmacokinetic parameters of the exogenous dose [10]. The maximum plasma concentration (C_{max}) and the time to its occurrence (t_{max}) were read directly from the plasma concentration-time data. The terminal elimination rate constant (λ_z) was obtained by log-linear regression analysis of the terminal portion of the curve (exogenous levodopa).

The elimination half-life ($t_{1/2,z}$) was calculated using $\ln(2)/\lambda_z$. For levodopa and DOPAC, only concentrations measured up to 8–10 h after drug intake were used for calculation of λ_z , since concentrations measured thereafter were in the endogenous range. For 3-OMD, concentrations measured from 8 to 33 h after drug intake were used for calculation of λ_z . The area under the concentration–time curve (AUC) was calculated by linear trapezoidal summation and extrapolation to infinity in case of exogenous levodopa administration [17]. The AUC ratios for 3-OMD/levodopa and DOPAC/levodopa following the different benserazide doses were also calculated because these quotients may have more clinical relevance than concentrations of an analyte as such [18, 19].

Statistics In addition to descriptive statistics (mean, s.d., 95% confidence intervals of the differences in mean values versus the control group), statistical analysis was performed to discriminate the mean pharmacokinetic parameters of the three analytes following the different benserazide doses. Multivariate analysis of variance (MANOVA) was applied to investigate whether the values at each ascending dose (5, 25, 100 mg or 12.5, 50, 200 mg) in each subject group differed from the values without benserazide. This repeated measures ANOVA takes into account that data on three benserazide dose regimens were collected in each subject. Differences were considered statistically significant at the $\alpha=0.05$ level.

Results

Tolerability

All 16 subjects completed the study according to the protocol. There was no clear pattern of adverse events which could be attributed to benserazide and/or levodopa. In particular, there were no signs of increased dopaminergic activity such as nausea, vomiting, and orthostatic complaints on days of levodopa intake. Four adverse events were reported to be of severe intensity. Two subjects had a severe

cold during treatment with benserazide 25 mg three times daily. Another subject reported severe diarrhoea for 30 min while on benserazide 100 mg three times daily. Finally, a subject treated with benserazide 200 mg three times daily had a severe headache for 1 day. Influenza and headache events were in several cases treated with paracetamol. There was no pattern of abnormal laboratory values, vital signs (including ECG) or neurological assessments observed during the study to suggest a treatment effect. Some subjects showed low haematocrit values towards the end of the study which could be explained by the amount of blood withdrawn.

Pharmacokinetics

The plasma concentration–time profiles of endogenous levodopa, 3-OMD and DOPAC on study days –1, 14, 28 and 42 are presented in Figure 1. The derived pharmacokinetic parameters ($C_{\max}$ and AUC) are given in Table 1. Ascending doses of benserazide increased endogenous levodopa and 3-OMD levels. $C_{\max}$ and AUC values differed significantly ($P<0.05$) from the control group from 5 mg onwards. The parameters of DOPAC did not differ at any dose from the pretreatment values. On a particular study day the levels of all three compounds were relatively constant.

The concentration–time profiles of levodopa and DOPAC and 3-OMD after a 250-mg dose of levodopa administered on study days 1, 15, 29 and 43 are given in Figures 2 and 3. A summary of the pharmacokinetic parameters of the three compounds at each benserazide dose after exogenous levodopa is given in Table 2. For $C_{\max}$ of levodopa, doses of 12.5 mg and above differed from the control value whereas $t_{\max}$ was not dose-dependent. AUC and $t_{1/2,z}$ of levodopa differed significantly ($P<0.05$) from pretreatment values from 5 mg and 50 mg, respectively, onwards. With respect to DOPAC, only $C_{\max}$ and AUC showed significant ($P<0.05$) differences compared with pretreatment conditions (doses of 5 mg and above). 3-OMD showed the same pattern as DOPAC with regard to $C_{\max}$ and AUC

Table 1 Influence of benserazide on the pharmacokinetics of endogenous levodopa, 3-OMD and DOPAC.

		Benserazide dose (mg three times daily)						
		0	5	12.5	25	50	100	200
Levodopa	$C_{\max}$	7.6 ± 6.4	33 ± 27	20 ± 10	24 ± 6	39 ± 17	50 ± 14	52 ± 18
	($\mu\text{g l}^{-1}$)	(—)	(12–38)	(0–25)	(3–29)	(18–44)	(30–55)	(31–57)
	AUC (0,10 h)	32 ± 16	143 ± 93	123 ± 57	138 ± 37	210 ± 56	319 ± 86	338 ± 121
		($\mu\text{g l}^{-1} \text{ h}$)	(—)	(51–171)	(31–151)	(46–166)	(118–238)	(227–347)
3-OMD	$C_{\max}$	0.02 ± 0.01	0.07 ± 0.03	0.09 ± 0.04	0.17 ± 0.11	0.20 ± 0.05	0.41 ± 0.24	0.50 ± 0.11
	(mg l^{-1})	(—)	(–0.04–0.13)	(–0.02–0.16)	(0.06–0.24)	(0.08–0.26)	(0.30–0.47)	(0.39–0.57)
	AUC (0,10 h)	0.16 ± 0.06	0.53 ± 0.21	0.67 ± 0.27	1.1 ± 0.5	1.6 ± 0.5	2.9 ± 1.3	4.0 ± 1.0
		($\text{mg l}^{-1} \text{ h}$)	(—)	(–0.18–0.9)	(–0.03–1.1)	(0.4–1.5)	(0.9–2.0)	(2.2–3.3)
DOPAC	$C_{\max}$	5.9 ± 3.0	8.5 ± 5.5	12 ± 12	6.9 ± 5.1	8.4 ± 8.0	4.6 ± 1.9	5.5 ± 3.3
	($\mu\text{g l}^{-1}$)	(—)	(–3–8)	(1–11)	(–4–6)	(–3–8)	(–7–4)	(–6–5)
	AUC (0,10 h)	30 ± 10	38 ± 18	40 ± 22	34 ± 22	40 ± 35	26 ± 11	28 ± 15
		($\mu\text{g l}^{-1} \text{ h}$)	(—)	(–9–25)	(–6–27)	(–12–21)	(–7–27)	(–21–13)
							(–21–13)	(–18–15)

Data are presented as means $\pm$ s.d. and within parentheses the 95% confidence intervals of the differences in mean values *vs* the control group ($n=8$, except for 0 mg where $n=16$).

Figure 1 Endogenous plasma levels of levodopa, 3-OMD and DOPAC during benserazide three times daily dosing regimens (○ 0 mg, ● 5 mg, □ 12.5 mg, ■ 25 mg, △ 50 mg, ▲ 100 mg, ▽ 200 mg). Data are presented as means of $n=8$ except for 0 mg where $n=16$.

and, in addition, $t_{1/2,z}$ at 200 mg differed significantly ($P<0.05$) from control. With respect to t_{max} , values for both DOPAC and 3-OMD were not dependent on the benserazide dose regimen.

Figure 4 depicts the AUC ratios of 3-OMD *vs* levodopa and DOPAC *vs* levodopa as a function of the benserazide dose. Both ratios demonstrated a statistically significant dose-dependency.

Discussion

The data reported in this paper constitute a detailed investigation of the pharmacodynamics of benserazide. Although known for more than two decades as a potent inhibitor of peripheral decarboxylase [20], its clinical pharmacology has been sparsely investigated. The main reasons for this lack of data are the complex analysis of benserazide and/or its active metabolite(s) and the absence of a suitable direct marker of decarboxylase activity [3]. By contrast, COMT and MAO-B activity, which are other pivotal enzymes in the metabolism of levodopa, can be relatively easily measured in erythrocytes and thrombocytes, respectively [13, 21]. The availability of a very sensitive assay method enabled the determination of endogenous

plasma levels of levodopa and 3-OMD [16]. This provided an indirect marker of decarboxylase activity which is therapeutically most relevant because levodopa in clinical practice is nearly always combined with benserazide or carbidopa.

Benserazide elicited a dose-dependent increase in endogenous levodopa levels. There were no clear indications that a maximum response to benserazide had been attained at a dose of 200 mg three times daily. Levodopa levels of subjects treated with 50–200 mg three times daily benserazide were at their lowest ($P<0.05$) 6 h after the morning dose of benserazide. This suggests that at least at these doses benserazide does not lead to constant decarboxylase inhibition. Consequently, it is unlikely that benserazide's mechanism of action is completely irreversible [22]. This is in accordance with findings obtained by Da Prada *et al.* [23] who showed that the effect of a single dose of benserazide (1.5 mg kg^{-1}) on endogenous levodopa levels decreased after 3 h following administration. Under physiological conditions decarboxylation activity was found to be rather constant at different times of the day [24]. The slight fluctuations in the extent of decarboxylase inhibition over the day due to benserazide were not reflected in the 3-OMD levels in accord with its long plasma half-life [25,

Figure 2 Plasma levels of levodopa and DOPAC after administration of 250 mg levodopa during benserazide three times daily dosing regimens ($\circ$ 0 mg, $\bullet$ 5 mg, $\square$ 12.5 mg, $\blacksquare$ 25 mg, $\triangle$ 50 mg, $\blacktriangle$ 100 mg, ∇ 200 mg). Data are presented as means of $n=8$ except for 0 mg where $n=16$.

26]. The increase in 3-OMD concentration as a function of benserazide dose indicated that with increasing decarboxylase inhibition the metabolism of levodopa is shifted towards the 3-OMD pathway. Levels of DOPAC, the MAO-B derived metabolite of levodopa, hardly decreased with ascending doses of benserazide. This suggests that endogenously present DOPAC mainly originates from dopamine within the brain.

Benserazide dose-dependently increased the AUC of levodopa when the latter was administered as a 250 mg dose. The difference in response with respect to levodopa AUC between benserazide 100 and 200 mg three times daily was negligible. Relatively high doses are necessary to induce complete inhibition of decarboxylase as has also been demonstrated for carbidopa [27]. Addition of benserazide or carbidopa to levodopa formulations in the ratio 1:4 has generally been shown to increase the latter's systemic exposure by a factor of about two [28]. The more pronounced effects in this study, also at daily benserazide doses of 75–150 mg, can probably be explained by the subchronic treatment with benserazide resulting in a larger extent of decarboxylase inhibition. As reported by other investigators, $t_{\max}$ and $C_{\max}$ after oral levodopa administration showed a marked intersubject variability [14, 29]. The effect

on 3-OMD levels was much more pronounced: 200 mg benserazide three times daily increased the AUC of 3-OMD about 14-fold whereas the AUC of levodopa increased only five-fold. Relatively high doses of carbidopa have also been shown to significantly increase the AUC of 3-OMD without a concomitant effect on levodopa AUC [30]. These divergent effects of decarboxylase inhibitors on levodopa and 3-OMD are difficult to explain because 3-OMD is a poor substrate for decarboxylase [14]. It should, however, be realised that alternative metabolic pathways of levodopa become more prominent when decarboxylase is inhibited. Although benserazide has been reported to be a COMT substrate [31], this study provided no evidence for a COMT inhibitory effect [32]. The role of 3-OMD in the complications inherent to long-term levodopa therapy has not been completely elucidated [33]. 3-OMD is devoid of antiparkinsonian activity but may compete with levodopa for transport across the blood-brain barrier [34, 35]. However, a recently conducted positron emission tomography study questioned competition between levodopa and 3-OMD at clinically relevant concentrations [36]. A high ratio of 3-OMD/levodopa levels has been suggested to reflect a poor response to levodopa therapy [19, 37]. With

Figure 3 Plasma levels of 3-OMD after administration of 250 mg levodopa during benserazide three times daily dosing regimens ($\circ$ 0 mg, $\bullet$ 5 mg, $\square$ 12.5 mg, $\blacksquare$ 25 mg, $\triangle$ 50 mg, $\blacktriangle$ 100 mg, ∇ 200 mg). Data are presented as means of $n=8$ except for 0 mg where $n=16$.

ascending benserazide dose, the 3-OMD/levodopa AUC ratio increased (Figure 4), thus providing a rationale for triple therapy with levodopa, and inhibitors of both decarboxylase and COMT [8].

Patients with Parkinson's disease are treated with a wide range of doses of levodopa/decarboxylase inhibitor. A dosing regimen of levodopa/benserazide 100/25 mg four to five times a day can be considered as average in moderately ill patients without major response fluctuations. Under these conditions decarboxylase is obviously only partially inhibited. Despite peripheral dopamine formation, the tolerability of all treatments in the present study was very good, although one should realise that only single doses of levodopa were given on some separate days. The effect of a low dosing regimen of benserazide (5 mg three times daily) on DOPAC levels was striking. Its AUC was halved and its $C_{\max}$ was reduced to one third of that in the absence of benserazide. Higher doses of benserazide further reduced levels of DOPAC. This indicates that after administration of levodopa the major portion of DOPAC is formed peripherally. The $t_{\max}$ of levodopa, 3-OMD and DOPAC were very similar under the different benserazide regimens and $t_{1/2}$ only increased slightly at doses of 100–200 mg (Table 2). These results, together with the $C_{\max}$ and AUC data, suggest that decarboxylase present in the gastrointestinal tract plays a crucial role in the metabolism of levodopa to dopamine. This is in accordance with the gastric and intestinal mucosa

containing abundant decarboxylase activity [38, 39]. Levodopa and DOPAC had very similar half-lives which could indicate that decarboxylation rather than deamination is the rate-limiting step in the formation of DOPAC. The finding that peripheral decarboxylase inhibitors do not clearly prolong the $t_{1/2}$ of levodopa has been reported previously [28, 40]. Robertson *et al.* showed that carbidopa increased $t_{1/2}$ of oral levodopa only in the elderly [11]. This is in contrast to the effect of the potent COMT inhibitor tolcapone which increased the $t_{1/2}$ of levodopa by up to 90% [10].

The results of this study indicate that lowering of the levodopa/benserazide combination dose, in the context of attempts to limit the adverse effects of long-term levodopa therapy, could result in a reduction of the dose-normalised levodopa exposure. The mechanism underlying this phenomenon is a less complete inhibition of peripheral decarboxylase. No signs, however, were observed which would suggest a parallel poorer tolerability in terms of increased dopaminergic side-effects. Similar or even more marked dose-dependency in the inhibition of decarboxylase is anticipated for levodopa preparations containing carbidopa since this inhibitor is less potent than benserazide [23, 27]. The clinical development of COMT inhibitors should take these possible consequences of lowering the benserazide dose into consideration by the conduct of pharmacokinetic/pharmacodynamic interaction studies with the COMT

Table 2 Influence of benserazide on the pharmacokinetics of levodopa, 3-OMD and DOPAC after exogenous administration of 250 mg levodopa.

		Benserazide dose (mg three times daily)						
		0	5	12.5	25	50	100	200
Levodopa	$C_{\max}$	0.9 ± 0.5	1.4 ± 0.6	1.9 ± 0.7	2.0 ± 0.7	2.6 ± 1.1	2.4 ± 0.6	2.3 ± 1.0
	(mg l^{-1})	(—)	(−0.2–1.1)	(0.3–1.6)	(0.5–1.8)	(1.0–2.3)	(0.8–2.2)	(0.7–2.0)
	$t_{\max}$ (h)	1.0 (0.5–1.5)	1.0 (0.5–2.0)	1.3 (0.5–2.0)	1.0 (0.5–1.5)	1.0 (0.5–1.5)	1.0 (0.5–2.0)	0.5 (0.5–2.0)
	$t_{1/2,z}$	1.2 ± 0.2	1.5 ± 0.4	1.4 ± 0.2	2.2 ± 1.3	1.5 ± 0.2	1.7 ± 0.2	1.7 ± 0.1
	(h)	(—)	(−0.2–0.7)	(−0.3–0.6)	(0.5–1.4)	(−0.1–0.8)	(0.1–0.9)	(0.1–1.0)
	AUC	1.2 ± 0.5	2.7 ± 1.4	3.2 ± 1.7	3.7 ± 0.9	4.7 ± 1.8	5.8 ± 1.6	5.9 ± 1.6
3-OMD	($\text{mg l}^{-1} \text{ h}$)	(—)	(0.4–2.7)	(0.8–3.1)	(1.3–3.6)	(2.3–4.6)	(3.4–5.7)	(3.5–5.8)
	$C_{\max}$	0.27 ± 0.13	0.65 ± 0.29	1.0 ± 0.4	0.96 ± 0.34	1.6 ± 0.6	2.3 ± 0.9	2.4 ± 0.6
	(mg l^{-1})	(—)	(−0.1–0.8)	(0.3–1.2)	(0.3–1.1)	(0.9–1.7)	(1.6–2.4)	(1.7–2.5)
	$t_{\max}$ (h)	4.0 (1.5–24)	6.0 (4.0–10)	3.5 (1.5–6.0)	6.0 (0.5–10)	2.0 (1.0–4.0)	4.0 (1.0–6.0)	2.5 (1.5–4.0)
	$t_{1/2,z}$	19 ± 4	20 ± 5	18 ± 4	20 ± 4	23 ± 11^a	27 ± 10	30 ± 4
	(h)	(—)	(−4–7)	(−6–5)	(−4–7)	(−1–11)	(3–14)	(5–16)
DOPAC	AUC	7.4 ± 3.7	20 ± 9	27 ± 10	32 ± 12	74 ± 62	80 ± 25	106 ± 28
	($\text{mg l}^{-1} \text{ h}$)	(—)	(−10–35)	(−3–43)	(2–47)	(44–90)	(50–95)	(76–121)
	$C_{\max}$	1.5 ± 0.7	0.53 ± 0.16	0.35 ± 0.26	0.42 ± 0.26	0.22 ± 0.10	0.22 ± 0.24	0.11 ± 0.08
	(mg l^{-1})	(—)	(−1.3–−0.7)	(−1.4–−0.9)	(−1.4–−0.8)	(−1.6–−1.0)	(−1.6–−1.0)	(−1.7–−1.1)
	$t_{\max}$ (h)	1.0 (0.5–2.0)	1.3 (0.5–2.0)	1.5 (0.5–2.0)	1.5 (0.5–2.0)	1.5 (1.0–2.0)	1.5 (1.0–2.0)	1.5 (0.5–2.0)
	$t_{1/2,z}$	1.2 ± 0.1	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	1.4 ± 0.4	1.8 ± 0.9	1.8 ± 0.9
DOPAC	(h)	(—)	(−0.3–0.5)	(−0.3–0.5)	(−0.3–0.5)	(−0.1–0.7)	(0.3–1.1)	(0.3–1.1)
	AUC	1.9 ± 0.6	0.95 ± 0.40	0.57 ± 0.29	0.69 ± 0.22	0.54 ± 0.23	0.46 ± 0.28	0.34 ± 0.14
	($\text{mg l}^{-1} \text{ h}$)	(—)	(−1.3–−0.6)	(−1.7–−1.0)	(−1.6–−0.9)	(−1.7–−1.0)	(−1.8–−1.1)	(−1.9–−1.3)

Data are presented as means $\pm$ s.d. and within parentheses the 95% confidence intervals of the differences in mean values *vs* the control group. $t_{\max}$ is presented as median (range); $n=8$, except for 0 mg where $n=16$.

^a $n=7$

Figure 4 AUC ratios of 3-OMD/levodopa and DOPAC/levodopa as a function of the benserazide dose after administration of 250 mg levodopa. Data are presented as means $\pm$ s.e.mean of $n=8$ except for 0 mg benserazide where $n=16$.

inhibitor and different doses/formulations of levodopa/decarboxylase inhibitor.

The clinical part of this study was conducted at the Roche Clinical Pharmacology Unit, Welwyn, UK with Dr G.R. McClelland acting as the principal investigator.

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