Monoamine oxidase-A: pharmacodynamics in humans of moclobemide, a reversible and selective inhibitor

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- 1 Single oral doses of 300, 450 and 600 mg moclobemide, a monoamine oxidase type A inhibitor, were administered in a cross-over design to eight healthy male volunteers. Plasma concentrations of the parent drug and of two monoamine metabolites (3,4-dihydroxyphenylglycol DHPG from noradrenaline; 5-hydroxy-indoleacetic acid 5HIAA from serotonin) were measured over time.
- 2 A physiological pharmacokinetic-pharmacodynamic model was used to describe MAO-A inhibition as reflected in the alterations of monoamine metabolites. Population values for the model parameters were obtained by a two-stage method allowing for repeated dosing per subject.
- 3 Even at the lowest dose an effect of moclobemide on plasma DHPG and 5HIAA concentrations was detectable in most subjects for up to 24 h. In contrast to DHPG, 5HIAA formation was only partially suppressed by moclobemide (maximum fractional extent of enzyme inhibition $I_{\max}$: 0.57, CV 26%) suggesting the existence of 5HIAA formation pathways independent of those inhibitable by moclobemide.
- 4 Plasma moclobemide concentrations associated with 50% of maximum enzyme inhibition (IC_{50}) were in the range of 100 ($IC_{50,5HIAA}$ at 300 mg) to 400 $\mu\text{g l}^{-1}$ ($IC_{50,DHPG}$ at 600 mg).

Keywords moclobemide pharmacodynamics MAO-inhibition modeling monoamine metabolites 5-hydroxy-indoleacetic acid 3,4-dihydroxyphenylglycol

Introduction

The benzamide derivative moclobemide is a reversible inhibitor of monoamine oxidase with a high selectivity for the type A isoenzyme (MAO-A). It has been shown to modulate central nervous system neurotransmitter disposition and to have therapeutic applications [1, 2, 3]. MAO-A is widely distributed in the body [4]. Direct measurement of its activity is not possible in large populations and under clinical conditions. However, an indirect measure of MAO-A activity is provided by the plasma concentrations of monoamine metabolites which are formed by MAO-A. The time courses of two metabolites, 3,4-dihydroxyphenylglycol (DHPG) and 5-hydroxyindoleacetic acid (5HIAA), following single oral doses of moclobemide have been studied previously [5, 6]. We have used the results published by the latter group to con-

struct a physiological pharmacokinetic-pharmacodynamic model to describe MAO-A inhibition. The ability to measure the sensitivity of patients to inhibition of MAO-A might offer the opportunity for prospective identification of non-responders which is especially pertinent for the treatment of disorders with a slow time course such as depression.

Methods

Clinical studies

Eight young (21–34 years old) male volunteers participated in the studies after giving written informed

consent. The trial was conducted in full conformance with the principles of the declaration of the World Medical Assembly of Helsinki as amended in Tokyo and Venice. It was approved by the Ethics Committee of the University Hospital in Vienna, Austria. Subjects were healthy as assessed by a detailed medical history, physical examination, laboratory tests and an ECG. No medication was taken 14 days prior to start of the trial and alcoholic beverages were prohibited for 24 h before and during a session. The subjects received in a randomized sequence (Latin square design) placebo and single, oral doses of 300, 450 or 600 mg moclobemide on separate occasions always at the end of a standard breakfast. Repeat treatment with each dose was also given as part of a separate investigation. Individual doses were always separated by a 1 week period. Blood samples were taken at frequent intervals following doses. Plasma was separated within 10 min of sampling by centrifugation (4° C, 2000 g) and divided into aliquots for measurement of moclobemide, DHPG and 5HIAA.

Monoamine metabolite concentrations

DHPG was measured by the h.p.l.c. method of Scheinin *et al.* [7] which uses coulometric electrochemical detection. The limit of reliable determination of concentrations of DHPG was 0.4 nmol l⁻¹; inter-day coefficients of variation were below 10% (7.3% at 2.05 nmol l⁻¹; 6% at 5 nmol l⁻¹).

5HIAA was measured by the h.p.l.c. method of Berlin *et al.* [8]. The minimum quantifiable concentration of 5HIAA was 0.5 nmol l⁻¹; in duplicate analyses the inter-day coefficient of variation was below 10%.

Plasma concentrations of moclobemide

A specific h.p.l.c. assay was used to measure plasma concentrations of moclobemide [9]. The minimum quantifiable concentration of moclobemide was 20 µg l⁻¹ (0.5 ml sample volume) with an inter-day coefficient of variation ranging from 7.5% (40 µg l⁻¹) to 3.1% (2400 µg l⁻¹).

Pharmacokinetic and pharmacodynamic models

The absorption and disposition of moclobemide were described in terms of a zero-order input (duration: T_{K0}) into a one- or two-compartment model allowing for a lag time (t_{lag}) before commencement of the absorption process. Elimination was expressed in terms of intrinsic (hepatic) clearance (CL_{int}) from which bioavailability F and elimination clearance (CL) was derived assuming 90 l h⁻¹ for hepatic blood flow. The estimate of distribution volume (V_{ss}) was based on the derived value of F . Because the blood/plasma partition coefficient is close to unity (0.95; [10]) plasma drug concentrations were assumed to be identical to blood drug concentrations.

The MAO-A activity, E , relative to pre-moclobemide activity, was describable in terms of moclobemide

concentration at the enzyme, C_e , using the following model:

$$E(C_e) = 1 - \frac{I_{max} \cdot C_e}{C_e + IC_{50}} \quad (1)$$

where I_{max} is the maximum fractional extent of enzyme inhibition attributable to C_e and IC_{50} is the concentration of moclobemide producing 50% of maximum enzyme inhibition. C_e was assumed to be identical to the predicted plasma concentration of moclobemide.

Physiological model for monoamine metabolite concentrations

The concentrations of DHPG and 5HIAA prior to administration of moclobemide may be assumed to be at equilibrium reflecting the formation of these metabolites (e.g. from MAO-A) and their clearance. The effect of an inhibitor on the formation of a metabolite can be described in terms of a pharmacodynamic model for drug effect and a pharmacokinetic model for the metabolite [11].

The time course of metabolite concentration can be predicted by solving the following differential equation:

$$\frac{dC(m)}{dt} = \frac{(C \cdot CL_m - C(m) \cdot CL(m))}{V(m)} \quad (2)$$

where $C(m)$ is the concentration of metabolite, C is the plasma concentration of the parent monoamine, CL_m is the formation clearance of metabolite from parent, $CL(m)$ is the elimination clearance of metabolite and $V(m)$ is the apparent volume of distribution of the metabolite.

If the change in $C(m)$ following administration of moclobemide is assumed to be due to a change in CL_m secondary to inhibition of MAO-A then the time course of $C(m)$ can be predicted by using $E(C_e(t))$ to modify CL_m as follows:

$$\frac{dC(m)}{dt} = \frac{(C \cdot CL_m \cdot E(C_e(t)) - C(m) \cdot CL(m))}{V(m)} \quad (3)$$

The values for C and CL_m are not directly known but Equation 2 predicts that $C \cdot CL_m$ must equal the product of $C(m)(0)$ and $CL(m)$, where $C(m)(0)$ is the steady-state concentration of metabolite prior to administration of moclobemide. Therefore $C \cdot CL_m$ can be substituted by $C(m)(0) \cdot CL(m)$. Because $V(m)$ is not known Equation 3 can be further simplified by replacing $CL(m)$ with a corresponding rate constant, $k(m)$, i.e. $CL(m)/V(m)$:

$$\frac{dC(m)}{dt} = C(m)(0) \cdot k(m) \cdot E(C_e(t)) - C(m) \cdot k(m) \quad (4)$$

Parameter estimation

Models were defined and parameters estimated using MKMODEL [12]. Differential equations were solved using a variable 4th/5th order Runge-Kutta method [13] with a relative local error tolerance of 10^{-6} . Pharmacokinetic and pharmacodynamic parameters were estimated simultaneously using measured concentrations of moclobemide, DHPG and 5HIAA. The parameter estimates obtained in this way were changed very little when compared with sequential estimation of the pharmacokinetic parameters followed by pharmacodynamic estimation alone with fixed values for the pharmacokinetic parameters. The model for $C(m)$ was parameterized in terms of the apparent elimination half-life of the monoamine metabolites, $t_{1/2}$ (DHPG) and $t_{1/2}$ (5HIAA) by replacing the corresponding $k(m)$ with $\ln 2/t_{1/2}(m)$. The variance of the i th measured value of moclobemide concentration and monoamine metabolite concentration was described using a power variance model:

$$\text{Var}_i = \text{SD}^2 \cdot (\hat{Y}_i^{\text{PWR}} + V_0)$$

where $\hat{Y}_i$ is the model prediction, and where PWR (power coefficient), V_0 (background variance) and SD (standard deviation scale factor) are error model parameters. There was no significant improvement in the fit when PWR was allowed to differ from zero for the monoamine metabolite predictions. Therefore, a homoscedastic model was assumed for the pharmacodynamic parameter estimation.

The extent to which moclobemide could inhibit the formation of DHPG and 5HIAA was examined by comparing models which had I_{max} fixed at 1 for both metabolites (inhibition model 1), or allowed to be less than 1 (model 2), or only allowed to be less than 1 for 5HIAA formation (model 3).

Population parameter estimates

To obtain population parameters (pharmacokinetics: CL_{int} , V_{ss} , t_{lag} , T_{K0} ; CL , F ; pharmacodynamics: DHPG IC_{50} , $C(m)(0)$, $t_{1/2}$ (DHPG), 5HIAA I_{max} , IC_{50} , $C(m)(0)$, $t_{1/2}$ (5HIAA)) the two stage method of Sheiner & Beal [14] was modified to allow for repeated measures in each subject. For each parameter the estimates per subject and dose were used in a three-way analysis of variance (ANOVA; PROC GLM, SAS) with the fixed factors dose and period and with the random factor subject ($\alpha = 0.05$). The least square means were taken as estimates of the population parameters. The within- and between-subject variations were obtained from a variance component estimation (PROC VARCOMP, restricted maximum likelihood method) underlying the same model as in the analysis of variance. For the between-subject variance component the difference of the subject mean square and a multiple of the error mean square was calculated. This difference may become negative and the variance component as well if the between-subject variability is small. In this case the restricted maximum likelihood method uses

zero as estimate of the variance component and re-estimates the within-subject variance.

An attempt was made to use the EM method described by Racine-Poon [15] to obtain improved population parameter estimates. The EM method takes the accuracy and correlation of the individual estimates into account using the covariance matrix associated with individual parameter estimates. However, it does not allow repeat measures (3 doses in each subject) or period effects to be modelled. The individual estimates at each dose had, therefore, to be assumed to be stochastically independent and uninfluenced by period or subject. The SAS code for this method was kindly supplied by Dr Racine-Poon.

In the pharmacokinetic model all but the parameters t_{lag} and T_{K0} were assumed to be log-normally distributed and their logarithms were used in the calculation; similarly log-normal distribution was presumed for the pharmacodynamic parameters IC_{50} and $t_{1/2}$.

Results

Plasma moclobemide, DHPG and 5HIAA concentrations after a single dose in a single subject are shown in Figure 1. Even at the lowest dose (300 mg) the effect of moclobemide on DHPG and 5HIAA was detectable for up to 24 h in most subjects. No trend in the placebo response could be discerned. Comparison of the Schwarz criterion [16] from the tested models favoured a model allowing complete inhibition of DHPG but not for 5HIAA (Table 1). Even at the highest concentration formation of 5HIAA was not totally abolished ($I_{\text{max}} = 0.57$).

The population estimates for the pharmacokinetic parameters are given in Table 2. Estimates of the within-subject and total (i.e. the sum of between- and within-subject components) variability are presented as a coefficient of variation, CV%. The clearance parameter, CL_{int} , was significantly different between the dose levels and decreased with increasing doses. The derived estimates of CL decreased and of F increased but the difference between the average values at the lowest (CL: 33 l h^{-1} ; F 0.62) and highest dose given (26 l h^{-1} ; 0.70) were small. No differences between dose levels were found for t_{lag} , T_{K0} and V_{ss} . There was a period effect associated with CL, CL_{int} and F with a lowest clearance value in period 4 but no other trend in the other study periods.

Table 3 lists the population estimates for the pharmacodynamic parameters using inhibition model 3. Different IC_{50} values were found for inhibition of DHPG formation ($\sim 200\text{--}400 \mu\text{g l}^{-1}$) and 5HIAA ($\sim 100\text{--}250 \mu\text{g l}^{-1}$) formation. The ANOVA revealed significant increases in IC_{50} of DHPG with dose of moclobemide ($P < 0.001$) and a significant period effect ($P = 0.003$); the mean value in period 4 was significantly higher than in any other period. A similar effect trend for an increase in IC_{50} of 5HIAA with dose was seen but this did not achieve statistical

Figure 1 Time course of moclobemide, DHPG and 5HIAA in plasma after a single dose of 300 mg moclobemide (subject 6).

significance. No effect of dose could be discerned on any of the other pharmacodynamic parameters.

In the combined pharmacokinetic-pharmacodynamic model parameters describing the error were estimated as well. The PWR parameter for the moclobemide concentration data was 1.2 ± 0.81 (mean $\pm$ s.d.). V_0 for concentration was fixed at 0.25, implying a standard deviation of 0.5, i.e. one half of the minimum detectable concentration. The standard deviation scale factor for concentration was $16 \pm 31 \mu\text{g l}^{-1}$. The PWR parameter for the DHPG and 5HIAA data was fixed at 0 and V_0 fixed at 1. The standard deviation scale factor for DHPG was $0.27 \pm 0.15 \text{ nm}$, for 5HIAA $1.5 \pm 1.5 \text{ nm}$.

Model parameters in an individual were usually well defined with typical (median) values for the coefficient of variation of the estimation error below 10% of the pharmacokinetic and below 25% for the pharmacodynamic parameters (exceptions: $t_{1/2}$ (DHPG) 176%, $\text{IC}_{50,5\text{HIAA}}$ 61%, $t_{1/2}$ (5HIAA) 46%).

Discussion

We have used a pharmacokinetic-dynamic model to describe the time course of MAO-A inhibition in humans. Although the pharmacokinetic model for the absorption and disposition of moclobemide may be complex, requiring a time-dependent change in elimination processes after multiple doses [17], we have been able to describe the pharmacological effects of moclobemide after a single dose with a time-invariant pharmacokinetic model. The model incorporated the intrinsic hepatic clearance allowing an estimate of extent of bioavailability under the assumption of complete absorption across the gut wall into the portal vein, and that metabolism occurs solely in the liver [17, 18].

DHPG and 5HIAA plasma concentrations following placebo showed a random deviation about the baseline over the entire observation period in all subjects. They contributed nothing further to the estimation of parameters when active drug was given and no attempts were therefore made to model the placebo observations.

Dose-dependence in several parameters was found. A decrease in clearance and increase in bioavailability has previously been noted after single doses of 50–200 mg [19], and when comparing 100 and 150 mg dose administration [20]. An augmentation of this effect was expected for the higher doses used in the present study. It was unexpected to find also a dose-dependence in the IC_{50} value for inhibition of DHPG formation and a similar trend for 5HIAA. The apparent increase in IC_{50} could be due to different subtypes of MAO-A. At low doses of moclobemide a more readily inhibitable form could be mainly responsible for plasma DHPG and 5HIAA production. At higher doses this enzyme subtype may be substantially inhibited and a less sensitive form may then be revealed. Moclobemide's own metabolism appears not to depend on the activity of MAO-A since no metabolic products formed by its interaction with this enzyme have been identified [2]. It is also possible

Table 1 Inhibitory models used to describe the maximum effect of moclobemide on formation of DHPG and 5HIAA

Model number	Description	Schwarz criterion
1	$I_{\max} \text{ DHPG} = 1, \quad I_{\max} \text{ 5HIAA} = 1$	-70.72
2	$I_{\max} \text{ DHPG} = 0.95, \quad I_{\max} \text{ 5HIAA} = 0.57$	-69.67
3	$I_{\max} \text{ DHPG} = 1, \quad I_{\max} \text{ 5HIAA} = 0.57$	-68.29*

* = significantly different from model 1 and 2 by paired Student's *t*-test.

Table 2 PK parameter estimates of combined pharmacokinetic-pharmacodynamic model for MAO-A-inhibition (Model 3)

Parameter	Dose (mg)	Least square means	Modified 2 stage		P values	
			CV % Total	CV % Within	Dose	Period
CL _{int} (l h ⁻¹)	300	52.3				
	450	38.3	34	19	0.001	
	600	37.7				0.023
V _{ss} (l)	300	95.9				
	450	76.1	20 ¹	20	0.089	
	600	77.8				0.257
t _{lag} (h)	300	0.84	90 ¹	90		
	450	0.45	166 ¹	166	0.326	
	600	1.08	70 ¹	70		0.779
T _{k0} (h)	300	1.83	82	73		
	450	2.72	55	49	0.405	
	600	2.52	59	53		0.908
CL (l h ⁻¹)	300	32.6				
	450	26.9	23	13	0.002	
	600	26.4				0.023
F	300	0.62				
	450	0.69	11	6.3	0.001	
	600	0.70				0.030

¹the between-subject variability was small and set to zero to estimate total variability.

that the apparent increase in IC₅₀ is an artefact arising from estimation bias. The extent of inhibition of monoamine metabolite formation was different at each dose and there were fewer observations available at concentrations around the IC₅₀ at the higher doses. However, Monte Carlo simulations at the three dose levels using the mean structural and error model parameters estimated following a 300-mg dose did not reveal a bias or trend in the resulting estimates of model parameters.

The best model predictions for pharmacodynamic observations were obtained when I_{max} for 5HIAA was allowed to be less than 1. It is possible that some of the enzyme activity responsible for 5HIAA formation is due to amine oxidases other than MAO-A [21]. It is of interest to note that patients with Norrie disease, a hereditary deficiency of MAO-A, excrete, in the urine, less than 5% of DHPG expected from plasma noradrenaline concentrations yet they have essentially normal urinary elimination of 5HIAA in relation to platelet serotonin concentrations [22]. This suggests that serotonin can be metabolized to 5HIAA by enzymes other than MAO-A. Further studies of these patients have shown that they possess normal plasma amine oxidase activity [23].

We have allowed the delay between changes in plasma moclobemide concentration and changes in metabolite concentration to be determined by a single parameter—the apparent metabolite half-life. In reality three processes are likely to contribute to any apparent lag of plasma metabolite concentration in relation to plasma moclobemide concentration, namely (i) distribution of moclobemide to the enzyme, (ii) dissociation of moclobemide from the enzyme, (iii)

elimination of the metabolite. The experimental design of our study did not allow us to distinguish these separately. It would be possible to describe the metabolite concentrations by proposing a delay in equilibration of moclobemide between plasma and the enzyme active site [11]. However, such an effect compartment model would imply that plasma metabolite concentrations change immediately in response to changes in MAO-A activity. While a delay in equilibration of moclobemide with the enzyme active site has a reasonable mechanistic basis, e.g. distribution kinetics from plasma to extra-vascular enzyme, the assumption of an instantaneous change in metabolite concentration does not. A delay between changes in moclobemide concentration in the neighbourhood of the enzyme and inhibition of MAO-A activity may arise because of the binding kinetics of moclobemide with the enzyme. If moclobemide concentration close to the enzyme was instantaneously changed to a new constant value then the time course of moclobemide binding to the enzyme would be determined by its dissociation rate. It seems reasonable to speculate that the distribution half-time of moclobemide to extra-vascular enzyme would be of the order of only a few minutes. The elimination half-life of DHPG has been estimated to be 2–5 min in rabbits [24, 25] and 3 min in rats [26]. These figures suggest that the three separate processes that might determine the time course of metabolite concentration changes may be of similar magnitude. The apparent metabolite half-lives we have estimated (DHPG 3–4 min; 5HIAA 10–20 min) would be largely determined by the slowest of these.

Population parameter values were calculated using a two-stage approach modified to take repeated obser-

Table 3 PD parameter estimates of combined pharmacokinetic-pharmacodynamic model for MAO-A-inhibition (Model 3)

Parameter	Dose (mg)	Least square means	Modified 2 stage		P values	
			CV % Total	CV % Within	Dose	Period
DHPG						
I _{max}	300	1.0				
	450					
	600					
IC ₅₀ (μg l ⁻¹)	300	181	56	35	0.001	0.003
	450	253				
	600	399				
C(m)(0) (nM)	300	4.27	13	11	0.167	0.117
	450	3.96	14	11		
	600	3.82	15	12		
t _{1/2} (min)	300	3.78	311 ¹	311	0.956	0.984
	450	4.15				
	600	3.21				
5HIAA						
I _{max}	300	0.57	25 ¹	25	0.973	0.625
	450	0.56	26 ¹	26		
	600	0.57	26 ¹	26		
IC ₅₀ (μg l ⁻¹)	300	102	214	143	0.287	0.603
	450	129				
	600	249				
C(m)(0) (nM)	300	32.2	28	16	0.414	0.687
	450	33.1	28	16		
	600	29.6	31	18		
t _{1/2} (min)	300	17.8	166 ¹	166	0.493	0.451
	450	21.1				
	600	10.2				

¹the between-subject variability was small and set to zero to estimate total variability.

variations per subject and dose effects into account. The expectation maximization (EM) algorithm proposed by Racine-Poon [15] for calculation of population characteristics would have the advantage that it uses not only the individual parameter estimates but also their covariance matrices and, therefore, makes better use of the data. However, it cannot handle repeated measurements and only gives joint estimates for the three dose levels. When the EM method was applied with small values for prior estimates of the covariance matrices (the number of parameters to be estimated times a diagonal matrix with identical values $\sigma^2 = 1$ on the diagonal) the population parameter estimates were similar to those from the ANOVA. However, using different prior estimates ($\sigma^2 = 10$) the coefficients of variation were not stable.

The relatively small number of healthy subjects studied does not allow us to conclude that the extent of maximum inhibition or the sensitivity to inhibition is not an important cause of variability in response. There was relatively little variability among subjects in the maximum possible inhibition ($I_{\max}$) of 5HIAA formation (Table 3). However, there appeared to be wide variability in the sensitivity (IC_{50}) of MAO-A to inhibition particularly for 5HIAA formation. Variance

component estimation revealed that between individual variability was either negligible (in case of $t_{1/2}$ for the two amine metabolites and maximum inhibition $I_{\max}$ for 5HIAA) or contributed in equal parts to overall variability with the between subject component (IC_{50} , $C(m)(0)$). Several factors may have led to the marked variability seen in the pharmacodynamic parameters. In the case of 5HIAA the existence of an additional formation pathway may reduce the sensitivity of 5HIAA concentrations to changes in the MAO-related formation pathway. Furthermore most moclobemide concentrations observed were well above the IC_{50} for DHPG and even more so for 5HIAA formation which made the design of this study sub-optimal for estimating IC_{50} .

In contrast to 5HIAA the formation of DHPG appears to depend entirely on the functional status of the MAO-A. Further studies aiming at identifying potential responders/non-responders to MAO-A inhibitor therapy should therefore focus on DHPG with its more pronounced maximum deviation from baseline upon a test dose of the inhibitor.

We are grateful for helpful discussions with Professor M. Da Prada (F. Hoffman-La Roche Ltd) and his colleagues.

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(Received 29 June 1993,
accepted 7 January 1994)