Eur J Clin Pharmacol (1984) 27: 619–621

European Journal of Clinical Pharmacology

Biperiden Effects and Plasma Levels in Volunteers*

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Summary. The pharmacokinetics of biperiden was studied and compared with pharmacodynamics (pupil size, accomodation, self-rating mood scale) in 6 healthy volunteers. A single-blind cross-over design was employed with placebo and biperiden (4 mg as commerically available tablets). After a lag time of 0.5 h, biperiden was rapidly absorbed with a half-life of 0.3 h, plasma peak levels of 5 ng/ml being reached after 1.5 h. Biperiden showed good tissue penetration (distribution half-life 0.6 h; ratio of total to central distribution volume 9.6), the terminal half-life time of plasma concentration was 18 h, and the oral clearance was 146 l/h. The pharmacodynamic maximum lagged behind the plasma peak concentration by 1 (self-rating) to 4 h (accomodation).

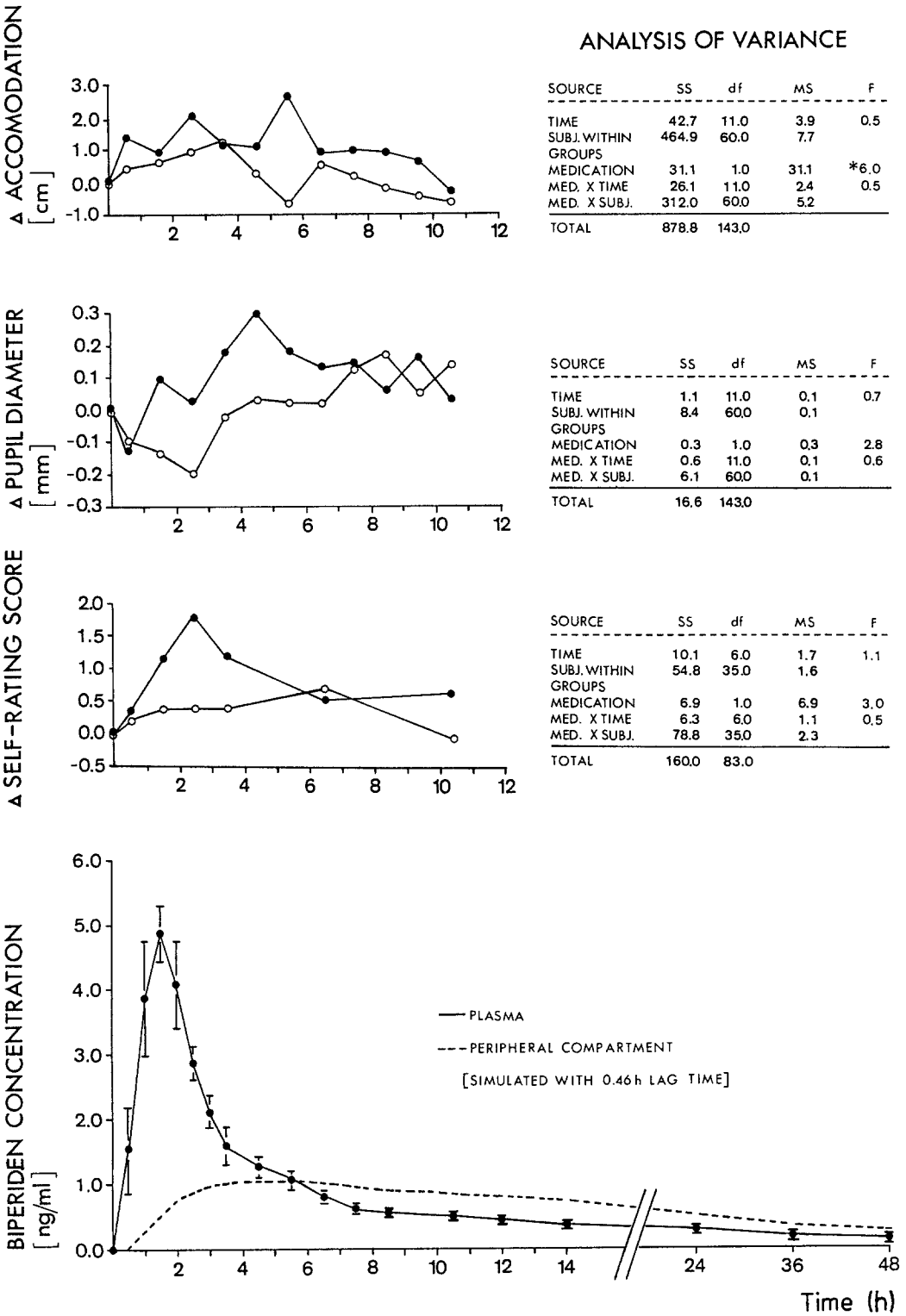
Key words: biperiden; pharmacokinetics, pharmacodynamics, plasma levels

Biperiden (Akineton, Knoll AG Ludwigshafen, FRG) is an anticholinergic drug used for treatment of the Parkinson syndrome [1, 2, scientific information, Knoll AG 1981]. Little is known about its pharmacokinetics because an assay had not been developed due to considerable analytical problems and the low dose used [3, scientific information, Knoll AG 1981]. By improving a procedure of Ottoila [7] a method has been developed which is sufficiently sensitive for a pharmacokinetic study [6, Brode E, Le Bris T, personal communication]. To evaluate the clinical relevance of plasma concentration, in this instance the pharmacodynamic response was also studied; based on pilot observations of our own and from the literature [4, 5], the effects of biperiden on pupil size, accomodation and subjective physicomental state were studied.

Materials and Methods

Six healthy volunteers (20–33 years old) participated in the study. A single-blind, randomized, cross-over study of biperiden and placebo was employed with at least 1 week between treatments. Biperiden 4 mg was administered orally (2 commercial tablets of 2 mg). After a light breakfast baseline values were taken 0.5 h before dosing. Then 12 ml blood samples were taken between 0.5 and 48 h for analysis by capillary gas chromatography [6]. For evaluating pharmacodynamic responses pupil size and accomodation were determined from 0.5 to 10.5 h after dosing. Pupil diameter was measured under controlled conditions of accomodation at an illumination intensity of E = 33 000 lux at eye level. Near point accomodation was tested by means of 5 approaches of a needle. Each volunteer reported on his subjective physicomental state 0.5–10.5 h after dosing by answering a standardized questionaire of 35 items with only negative aspects on a selfrating ordinal mood scale. Under normal standardized conditions a score range of 0–3 (average 0.32) was found (Greger G and Müller-Peltzer; personal communication). 2 h after dosing the volunteers received breakfast, at 6 h lunch and at 12 h dinner. They stayed on the ward under medical supervision until 13 h. For pharmacokinetic evaluation an open 2-compartment model was used, and its parameters were calculated by means of Metzler's computer program NONLIN with $1/C_p^2$ weighting. For evaluation of pharmacodynamic data a 2 fixed-factor model with complete repeated measurements was employed. Analysis of variance was used to test hypotheses by examining differences from baseline values.

* Dedicated to Prof. Dr. Ernst Biekert on the occasion of his 60th birthday



ANALYSIS OF VARIANCE

SOURCE	SS	df	MS	F
TIME	42.7	11.0	3.9	0.5
SUBJ. WITHIN GROUPS	464.9	60.0	7.7	
MEDICATION	31.1	1.0	31.1	*6.0
MED. X TIME	26.1	11.0	2.4	0.5
MED. X SUBJ.	312.0	60.0	5.2	
TOTAL	878.8	143.0		

SOURCE	SS	df	MS	F
TIME	1.1	11.0	0.1	0.7
SUBJ. WITHIN GROUPS	8.4	60.0	0.1	
MEDICATION	0.3	1.0	0.3	2.8
MED. X TIME	0.6	11.0	0.1	0.6
MED. X SUBJ.	6.1	60.0	0.1	
TOTAL	16.6	143.0		

SOURCE	SS	df	MS	F
TIME	10.1	6.0	1.7	1.1
SUBJ. WITHIN GROUPS	54.8	35.0	1.6	
MEDICATION	6.9	1.0	6.9	3.0
MED. X TIME	6.3	6.0	1.1	0.5
MED. X SUBJ.	78.8	35.0	2.3	
TOTAL	160.0	83.0		

Fig. 1. Mean concentrations and pharmacodynamic effects of biperiden (●) vs time (h) compared to placebo (○) using the differences from baseline. The summary of the analysis of variance presents the sum of squares (SS), degrees of freedom (df), mean of squares (MS) and F values (F) for the total variance and its different sources

Results

The essential results are summarized in Fig. 1. Plasma levels could be determined up to 48 h (0.1–0.2 ng/ml), with peak values of 3.9–6.3 ng/ml at 1.5 h. The concentration curve showed a biphasic decline compatible with a 2-compartment model, for which the following parameters (mean) were obtained: lag time 0.46 h, peak level C_{max} 5.1 ng/ml at peak time t_{max} 1.5 h, area under curve AUC 27.2 ng × h/ml, absorption constant k_{abs} 2.18 1/h, elimination constants α and β 1.11 and 0.03 1/h (terminal elimination half-life time $t_{½\beta}$ 18.4h), apparent central and total volumes of distribution V_C/F 419 l and V_B/F 4032 l, apparent total clearance CL/F 146 l/min.

The average accomodation distance was 15.1 cm before placebo and 14.3 cm before biperiden dosing. Thereafter a lengthening was observed from 2–8 h, with a maximum at 6 h. With placebo the values remained significantly lower ($p < 0.05$). The pupil diameter before dosing (biperiden and placebo) was 3.1 mm. After biperiden pupil size was larger than after placebo from 2–7 h ($p < 0.1$), with maximum at 5 h. The time course of the pupillary effect was similar to that of accomodation. The self-rating score was 0.67 before placebo and 0.33 before biperiden, followed by an increase to a maximum at 2.5 h and return to base level after 6 h. After placebo no relevant changes were observed; $p < 0.09$ for the differences vs biperiden. The scores of the volunteers were found within the normal range (0–3) except 1 volunteer at 2.5 h.

Discussion

Biperiden shows rapid absorption which, by analogy with animal data (scientific information, Knoll AG 1981), can be assumed to be almost complete. Total clearance is high and is essentially due to metabolism, for no unchanged biperiden is excreted via the kidney [8]. Thus, with the assumption of linearity all requirements for the use of Gibaldi's equation to calculate bioavailability are met: considering a ratio in blood vs plasma of 0.65 (Brode, E., Le Bris, T. personal communication) it is estimated as 29%. This relatively low value, despite a long terminal half-life, is explained by the great total distribution volume, i.e. good tissue penetration. The long half-life requires estimation of concentration data for at least 48 h. The latter could be obtained only by administering the rather high although therapeutically employed dose of 4 mg (scientific information, Knoll AG 1981), which was also required to produce observable pharmacodynamic effect in volunteers. The earliest pharmacodynamic response recognized was an increase in the self-rating score, which lagged behind the peak plasma level by about 1 h. There were comments of weariness, fatigue, dizziness up to 6 h. As a group the volunteers showed a significant ($p < 0.1$) central nervous reaction, although the intensity of symptoms was mild considering the dosage; at the peak time in only 2 volunteers did they exceed the score values observed in a group of untreated persons. In contrast, ocular effects were observed distinctly later than the peak concentration and CNS symptoms with a maximum at 5–6 h and lasting for up to 6–8 h. An equally prolonged pupillometric effect has been reported after i.v. injection [5]. In view of the different time course of peripheral ocular and CNS signs, it is possible that there might be a special ocular compartment not identical with the CNS. The concentration time curve simulated for the peripheral compartment showed a broad maximum at around 4 h and then it declined slowly (Fig. 1), corresponding to the long elimination half-life and compatible with the prolonged duration of action observed clinically. However, it does not correspond to any of the three pharmacodynamic time curves, possibily for methodological reasons, especially of the self-rating scores, or due to the small size of the ocular compartment.

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Received: July 25, 1984
accepted: August 24, 1984

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