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Pharmacokinetic and Pharmacodynamic Studies Following the Intravenous and Oral Administration of the Antiparkinsonian Drug Biperiden to Normal Subjects

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Summary. The pharmacokinetics and pharmacodynamics (changes in pupil size and salivary flow) of biperiden following a single oral and intravenous dose were investigated in six normal subjects.

After the injection plasma concentrations declined biphasically, with half-times of 1.5 h for the rapid phase and 24 h for the terminal phase. Clearance and apparent volume of distribution were high ($12\,ml \cdot min^{-1} \cdot kg^{-1}$ and $24\,l \cdot kg^{-1}$ respectively). Absorption was rapid but the systemic availability was incomplete (33%), probably due to first-pass metabolism.

Central nervous system (CNS) adverse effects and changes in pupil size were observed after both routes of administration while salivary flow was affected only by the injection.

Key words: biperiden; pharmacokinetics, pharmacodynamics

Biperiden (Akineton) is a centrally active anticholinergic drug used for the treatment of Parkinson's disease and for the relief of extrapyramidal symptoms caused by neuroleptic drugs. Although it has been used for a long time studies on its kinetics and on the possible plasma concentration-effect relationship have been hampered by the lack of a suitable analytical technique. This problem has been overcome recently by Le Bris and Brode [1], who used a highly sensitive, specific, capillary gas-chromatographic method to measure plasma concentrations of the drug after a single oral dose [2]. In the present study we have used the same method to evaluate biperiden kinetics after both intravenous and oral administration in normal volunteers. In order to obtain an estimate of anticholinergic effect, salivary flow and pupillary size were also determined.

Materials and Methods

Subjects and Protocol

Six healthy male volunteers, aged 23-27 years, body weight 60-84 kg, received in random order and on two occasions separated by a one-week interval single 4 mg doses of biperiden lactate (equivalent to 3.10 mg of the base), given intravenously over 5 minutes, and biperiden hydrochloride (2 × 2 mg tablets, equivalent to 3.59 mg of the base), given orally with 50 ml water. The drug was administered after an overnight fast and no food or drinks were allowed for 3 h after administration. Blood samples were taken into heparinized tubes for up to 32 h after dosing, and the plasma was kept frozen at −20 °C until analysis.

Pharmacodynamic Measurements

Salivary flow was determined at various intervals by inserting under the tongue and between the cheeks and gums nine dental rolls (three for each of three consecutive two-min periods). The first three rolls were discarded and the last six, previously weighed in their sealed container, were weighed again in their container to calculate salivary flow (g/min). Pupillary size was determined at the same intervals using a specially designed pupillometer after adaptation to photopic (8.5 log units p.s.b.) ambient illumination [3].

Determination of Plasma Biperiden

Plasma biperiden concentrations (expressed as the base) were determined by capillary gas-liquid chromatography [1].

Pharmacokinetic and Statistical Analyses

Kinetic analysis on intravenous data was performed according to a two-compartment model, as previous-

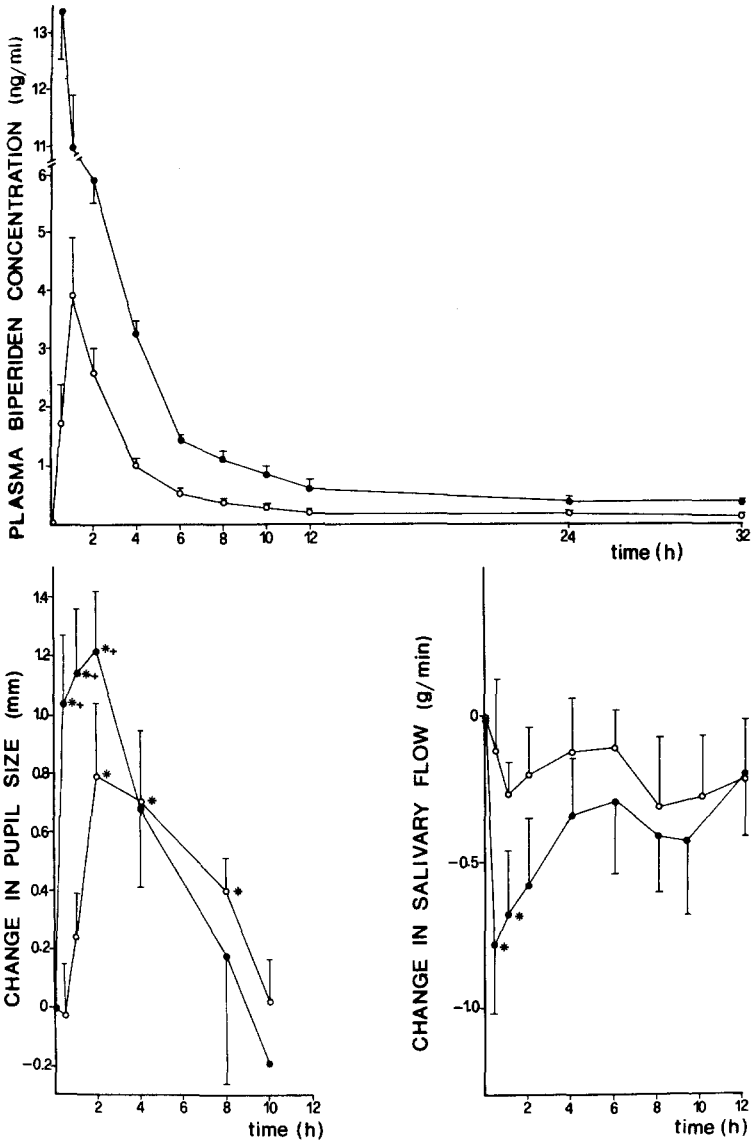

Fig. 1. Plasma biperiden concentrations and changes in pupil size and salivary flow after a single intravenous (●—●) and oral (○—○) dose of biperiden. Values are means ± SEM in six subjects. * $P<0.05$ (vs baseline); + $P<0.05$ (vs oral formulation)

ly described [4]. AUCs were calculated by the trapezoidal rule. Clearance and apparent volume of distribution (V_{area}) were calculated by model independent analysis [4]. Systemic availability was calculated as the ratio between oral and intravenous AUCs, corrected for the minor difference in dose.

Statistical analysis was done using Student's *t*-test for paired data.

Results

The mean plasma biperiden concentrations after intravenous and oral administration are illustrated in Fig. 1. Following the injection plasma concentrations showed a biphasic decline with half-times of about 1.5 h for the rapid (α) phase and 24 h for the terminal (elimination)phase (Table 1). The apparent volume of distribution (V_{area}) and clearance were $24 \pm 4.1 \cdot kg^{-1}$ and $11.6 \pm 0.8\ ml \cdot min^{-1} \cdot kg^{-1}$ respectively.

After oral intake plasma biperiden concentrations were at all times lower than those observed after the injection: peak concentrations ($4.1 \pm 0.9\ ng \cdot ml^{-1}$) occurred within 0.5-2 h and thereafter declined with an initially rapid biphasic pattern and an elimination half-time (21.0 ± 3.1 h) similar to that found after intravenous administration. The systemic availability was $33 \pm 5\%$.

Intravenous administration of biperiden was associated with a marked increase in pupil size, which at 0.5, 1, and 2 h was significantly greater than that seen after oral dosing (Fig. 1). The ocular effects of the oral formulation were less prominent, pupil diameter being significantly increased at 2, 4, and 8 h.

Table 1. Pharmacokinetic variables (means ± SEM) after a single intravenous dose of biperiden

Intercept of the distribution phase (A)	18.4	±3.6 [ng ml^{-1}]
Rate constant of the distribution phase (α)	0.527	±0.074 [h^{-1}]
Half-time of the distribution phase ($t_{½\alpha}$)	1.5	±0.2 [h]
Intercept of the elimination phase (B)	1.0	±0.2 [ng ml^{-1}]
Rate constant of the elimination phase (β)	0.0348	±0.0078 [h^{-1}]
Half-time of the elimination phase ($t_{½\beta}$)	24.3	±3.9 [h]
Rate constant from central to peripheral compartment (K_{12})	0.191	±0.027 [h^{-1}]
Rate constant from peripheral to central compartment (K_{21})	0.0599	±0.013 [h^{-1}]
Rate constant of elimination from central compartment (K_{el})	0.311	±0.050 [h^{-1}]
Area under the concentration-time curve (AUC)	62.8	±2.6 [ng ml^{-1}h]
Volume of central compartment (V_1)	2.6	±0.4 [l kg^{-1}]
Volume of distribution at steady-state (V_{ss})	11.5	±1.8 [l kg^{-1}]
Volume of distribution (V_{area})	24.0	±4.1 [l kg^{-1}]
Plasma clearance (CL)	11.6	±0.8 [ml min^{-1} kg^{-1}]

No significant changes in salivary flow were seen after oral administration, while a reduction in flow was observed at 0.5 and 1 h after the injection.

Discussion

Since plasma biperiden concentrations after intravenous administration had never been determined, no information was available about important kinetic variables such as apparent volume of distribution, clearance, and systemic availability. In our subjects the concentrations of the drug after injection showed an initial rapid decline, followed after approximately 6–8 h by a slower phase. Since sampling was restricted to 32 h it was not possible to ascertain whether the last experimental points reflected the actual terminal phase; it should be noted, however, that the half-time of the slow phase was similar to that calculated previously for up to 48 h after an oral dose [2]. The large apparent volume of distribution indicates marked tissue penetration, while the high clearance is likely to reflect extensive metabolic elimination, no unchanged biperiden being excreted via the kidney [5]. In view of the high metabolic clearance a large first-pass effect would be anticipated. By assuming a blood/plasma ratio of 0.65 [2] the hepatic extraction ratio can be estimated to be 0.87 [6], which should correspond to an oral availability of 13%. Using Gibaldi's equation Hollmann et al. [2] also predicted extensive first-pass removal with a systemic availability of 29%, which is closer to the experimental value (33%) we have found. The overall kinetic profile of oral biperiden in our subjects was also in good agreement with that reported recently in an ethnically different group [2].

After the injection significant effects on pupil size were apparent at 0.5, 1, and 2 h, and were frequently accompanied by reports of dizziness, malaise, and mild disorientation. After oral dosing ocular effects, more marked than those described by Hollmann et al. [2], could be demonstrated at between 2 and 8 h, and subjective CNS symptoms were less prominent than after the injection. While the time of subjective symptoms after both routes of administration was roughly parallel to the plasma concentration, ocular effects reached their peak with some delay and persisted when plasma concentrations had already declined considerably: the dissociation between the time courses of ocular effects and plasma concentrations, however, was less marked than that reported previously [2]. As far as salivary flow is concerned a significant effect could be detected only after the injection and was relatively minor. The latter finding may be explained by a lower sensitivity of this measurement in assessing anticholinergic activity or, alternatively, by a predominantly central action of this compound.

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