Pharmacokinetic-pharmacodynamic analysis of mnesic effects of lorazepam in healthy volunteers

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Aims To describe the pharmacokinetic-pharmacodynamic modelling of the psychomotor and mnesic effects of a single 2 mg oral dose of lorazepam in healthy volunteers.

Methods This was a randomized double-blind, placebo-controlled two-way cross-over study. The effect of lorazepam was examined with the following tasks: choice reaction time, immediate and delayed cued recall of paired words and immediate and delayed free recall and recognition of pictures.

Results The mean calculated EC₅₀ values derived from the PK/PD modelling of the different tests ranged from 12.2 to 15.3 ng ml⁻¹. On the basis of the statistical comparison of the EC₅₀ values, the delayed recall trials seemed to be more impaired than the immediate recall trials; similar observations were made concerning the recognition *vs* recall tasks.

Conclusions The parameter values derived from PK/PD modelling, and especially the EC₅₀ values, may provide sensitive indices that can be used, rather than the raw data derived from pharmacodynamic measurements, to compare CNS effects of benzodiazepines.

Keywords: anterograde amnesia, episodic memory, lorazepam, pharmacokinetic-pharmacodynamic analysis

Introduction

A common side-effect of benzodiazepines, especially described after administration of a single dose to naive subjects [1], is dose-related anterograde amnesia; benzodiazepines with short elimination half-life and rapid onset of action, such as lorazepam, induce the greatest amnesic effects. Sedation and impairment of psychomotor performance are also associated with the use of these compounds [1].

Herein, we describe the pharmacokinetic-pharmacodynamic (PK/PD) modelling of the psychomotor and mnesic effects of a single 2 mg oral dose of lorazepam in healthy volunteers.

Methods

The experimental study design was a randomized double-blind, placebo controlled two-way cross-over study on

12 normal healthy volunteers. The protocol was approved by the local Ethics Committee and all volunteers gave their informed written consent. The study consisted of two 3 day sessions, separated by a 15 day wash-out period. Twelve blood samples were collected before and between 0.25 and 48 h after drug intake. Samples were centrifuged and the plasma separated and stored at -20°C prior to analysis.

Lorazepam plasma levels were measured using a gas chromatography technique with electron capture detection according to the technique of Crevat-Pisano *et al.* [2].

A battery of tests was performed before and after lorazepam administration: choice reaction time (CRT) [3], immediate and delayed cued recall of a list of word pairs [4], immediate and delayed free recall of pictures, and recognition of pictures [5].

All tests were performed at the different blood sampling times excepted the picture recall and recognition tasks which were carried out before lorazepam administration and at 0.5, 2, 6 and 26 h postdosing due to the duration of these tests.

A linear, three-compartment model was used to estimate the pharmacokinetics of lorazepam; the clearance and the distribution volume were calculated according to

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the bioavailability F . The PK/PD modelling of the effects of lorazepam was performed by use of the effect compartment approach and the sigmoid maximum effect ($E_{\max}$) model [6]. The equations were fitted to the data by use of a non linear regression program Siphar (Simed[®], France).

The mean EC_{50} values of lorazepam obtained during the PK/PD modelling of each pharmacodynamic test were compared using the Kruskal-Wallis test.

Results and discussion

Mean ($\pm$ s.d.) pharmacokinetic parameters of lorazepam are as follows: maximum drug concentration ($C_{\max} = 33.4 \pm 4.8$ ng ml⁻¹), area under the curve ($AUC(0, \infty) = 405 \pm 95$ ng ml⁻¹ h), total clearance ($CL/F = 5.4 \pm 1.1$ h⁻¹), volume of distribution ($V_{ss}/F = 111.6 \pm 19.4$ l) and terminal half-life ($t_{1/2} = 16.6 \pm 5.2$ h). These values are in good agreement with published data [7–9].

In accordance with previous studies [1, 10] we show a significant impairment of the tests performed following a single 2 mg oral dose of lorazepam in healthy volunteers (data not shown). We attempted to perform a PK/PD modelling of these data, to characterize the relationship between plasma lorazepam concentrations and the intensity of its effects, and thereby (1) to uncover the most sensitive indices of lorazepam effects and (2) to ascertain whether effects on different tests can be formally separated from each other in terms of concentration necessary to produce a change.

The relationship between plasma concentrations and the intensity of the effects of lorazepam showed a counterclockwise hysteresis as shown in Figure 1a for the delayed cued recall of paired words in one subject. The corresponding PK/PD modelling is illustrated in Figure 1b and c. This analysis was performed for each individual subject and for all significant effects. Table 1 shows the mean ($\pm$ s.d.) pharmacodynamic parameters of lorazepam.

The statistical comparison of the mean EC_{50} values of lorazepam calculated from the modelled tests, showed significantly lower EC_{50} values when comparing [1] the delayed *vs* immediate cued recall tasks (CI95 [–11.485; –1.2682]) the delayed *vs* immediate free recall tasks (CI95 [–6.739; –0.698]) and [3] the recognition trial *vs* the cued (CI95 [–0.323; 9.492]) and free (CI95[1.754, 10.017]) delayed recall tasks, respectively; so, the recognition of pictures appeared to be more altered than the cued and free delayed recall tasks. This observation does not agree with published data [1, 11] which reported that lorazepam is as active on recognition skills as on recall performance. However, the authors have compared the scores of their recall and recognition tests which may indicate that EC_{50} s are more reliable values for statistical analysis than the scores of the different tests and represent

Figure 1 PK/PD analysis of the effect of lorazepam (2 mg orally) on the delayed cued recall of paired words in subject 4. (a) Counter-clockwise hysteresis loop of the delayed cued recall of paired words *vs* lorazepam plasma levels. The arrow denotes the sequence of the observations. (b) Evolution of the delayed cued recall of paired words *vs* predicted effect site lorazepam concentration data. The hysteresis loop was collapsed by accounting for the first-order rate constant ke_0 which determines the equilibration between plasma and effect site. (c) Modelization of the relationship between the delayed cued recall of paired words and the predicted effect site lorazepam concentration data, according to the sigmoid- $E_{\max}$ model. The solid line represents the best fit of the model to the actual data.

Table 1 Mean ($\pm$ s.d.) of the pharmacodynamic parameters of lorazepam determined from the following tasks: CRT, cued immediate and delayed recall of paired words, free immediate and delayed recall of pictures and recognition of pictures. These parameters were: ke_0 , first order rate constant which governs the exit of lorazepam from the effect compartment and also determines the equilibration between plasma and effect site; E_0 , baseline effect; $E_{\max}$, maximal effect; EC_{50} , plasma concentration producing 50% of $E_{\max}$; γ , steepness of concentration–effect relationship; $t_{1/2}$, equilibration half-time between plasma and effect site ($t_{1/2} = \ln(2)/ke_0$).

	CRT	Cued immediate recall of paired words	Cued delayed recall of paired words	Free immediate recall of pictures	Free delayed recall of pictures	Recognition of pictures
ke_0 (h^{-1})	1.27 (0.56)	1.64 (0.86)	1.47 (0.82)	1.70 (0.95)	1.39 (0.77)	1.37 (0.29)
E_0	42.5 (10.1)	6.71 (0.40)	6.33 (0.62)	16.9 (1.77)	17.0 (1.85)	18.6 (4.03)
$E_{\max}$	17.7 (4.75)	−3.97 (1.24)	−5.38 (2.33)	−11.0 (2.04)	−15.4 (2.21)	−4.92 (2.11)
EC_{50} (ng ml $^{-1}$)	13.5 (3.66)	15.1 (6.85)	13.8 (6.80)	15.3 (4.60)	14.8 (5.40)	12.2 (7.15)
γ	4.87 (3.81)	3.93 (4.00)	3.33 (2.61)	5.94 (4.54)	5.55 (5.98)	6.53 (6.47)
$t_{1/2}$ (h)	0.54 (0.18)	0.42 (0.15)	0.47 (1.36)	0.41 (0.22)	0.49 (0.098)	0.51 (0.08)

a more sensitive parameter to estimate CNS effects of lorazepam. No significant differences were found when comparing the EC_{50} values calculated from (1) cued *vs* free immediate recall tasks and cued *vs* free delayed recall tasks, respectively, and (2) the CRT measurements *vs* any of the other tests; so, the free recall tasks and the cued recall tasks on one hand and the sedative and mnesic effects of lorazepam on the other hand, could not be quantitatively distinguished on the basis of the PK/PD parameters of this benzodiazepine.

To our knowledge, the only PK/PD studies of the CNS effects of lorazepam in healthy volunteers [7, 8] used psychomotor and cognitive skills. Both studies reported ke_0 , $t_{1/2}$ and γ -values which are in good agreement with those mentioned here, whereas their EC_{50} values are dramatically higher. The low EC_{50} values calculated in our study may indicate that the psychomotor and mnesic tests performed here are sensitive measurements of lorazepam and of benzodiazepines' CNS effects.

In conclusion, the PK/PD analysis of psychomotor and mnesic effects of benzodiazepines enables one to evaluate the sensitivity of the pharmacodynamic tests to lorazepam. However, its usefulness in predicting the intensity of the effects of different doses remains to be proved.

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