Short Communication

A Double-Peak Phenomenon in the Pharmacokinetics of Alprazolam after Oral Administration

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ABSTRACT:

The pharmacokinetics of alprazolam (ALP) after i.v. and p.o. administration in rats were characterized. ALP decayed biexponentially after the i.v. dose (1.25 mg/kg), but the concentration-time profiles after the p.o. doses (7 and 12.5 mg/kg) exhibited a double-peak phenomenon. The presence of two peaks was confirmed by statistical analysis of the serum concentration data of ALP, as well as by observed double peaks in the serum concentration-time profiles of the two active metabolites (α-hydroxyalprazolam and 4-hydroxyalprazolam). An absorption model incorporating a delay site is proposed to describe the data, and the absolute oral bioavailability is estimated to be about 30%. The two peaks were ~80 to 115 min apart, and there was a delay in the absorption of close to 80% of oral ALP, regardless of dose. We hypothesize that the mechanism underlying the double-peak phenomenon is due to reduction in gastric motility caused by the muscle relaxant effect of ALP. This hypothesis is supported by the observed longer delay in the appearance of the second peak at the higher p.o. dose. Enterohepatic recycling is precluded from being the underlying mechanism, because of the presence of double peaks after the p.o. doses but not after the i.v. dose. This is the first reported case of double peaks for oral ALP, and this phenomenon has not been reported for other benzodiazepines. The double-peak phenomenon caused by the hypothesized mechanism may have important therapeutic and drug interaction implications, especially because benzodiazepines are commonly coadministered with other drugs.

Alprazolam (ALP), a triazolobenzodiazepine, is the most widely prescribed benzodiazepine (BZ) and is used as an anxiolytic, antianxiety, and antidepressant agent (Fawcett and Kravitz, 1982; Dawson et al., 1984). In humans, ALP is rapidly and completely absorbed after oral administration, with an elimination half-life of 6 to 16 h and a volume of distribution of 1 l/kg, respectively (Greenblatt et al., 1983; Owens et al., 1984). In rats, ALP was rapidly and completely absorbed after oral administration, with an elimination half-life of 6 to 16 h and a volume of distribution of 1 l/kg, respectively (Greenblatt et al., 1983; Owens et al., 1984). ALP is extensively metabolized in humans; the two active metabolites, α-hydroxyalprazolam and 4-hydroxyalprazolam, are ~60 and 20% as potent as ALP (Sethy and Harris, 1982). In rats, ALP was rapidly eliminated with a terminal half-life of ~40 min (Lau et al., 1997a). Although ALP has been administered orally to rats (Owens et al., 1991; Lau et al., 1997b), there is a lack of information on its oral pharmacokinetics (PK) and bioavailability. This investigation was undertaken to characterize the serum ALP concentration-time profiles after oral ALP doses. The study was designed to be conducted in animals that are of the same species, age, and gender as well as under the same food-limited regimen used in our previous studies for PK of s.c. and i.p. ALP (Lau and Wang, 1996; Lau et al., 1997; Lau and Heatherington, 1997) so that comparison could be made across route of administration.

Here we report a double-peak phenomenon in serum concentration-time profiles of ALP via oral administration. Similar double- and multiple-peak phenomena have been described for many structurally diverse compounds such as acebutolol, veralipride, and danazol after oral doses (Plusquellec et al., 1987; Charman et al., 1993; Piquette-Miller and Jamali, 1997), but such phenomenon has not been reported for BZs.

Materials and Methods

Animals. Four male, albino, Sprague-Dawley rats from Harlan Sprague-Dawley, Inc. (Indianapolis, IN) were used. They were housed individually in a temperature-regulated room with a daily cycle of illumination from 7:00 AM to 7:00 PM. They were reduced to 80% of their initial, adult free-feeding body weights (mean = 381 g; range: 380–382 g) by receiving limited daily food rations (5 g for the first day, 10 g for the next 5 days) and were then maintained at their weights with a daily food supplement (range: 14–16 g). Water was continuously available in the living cages. They were held at these weights for 2 to 3 months before starting the experiment, a time period usually needed for training, establishing baseline, and examining drug dose-response relations for operant behavior. Experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication 85-23, revised 1985).

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that are estimated from the data: \( T_d \), the delay time; and \( N \), the number of delay compartments. Mass entering the delay site passes through each of the \( N \) compartments before entering the central compartment. The mass transfer coefficient between the delay stages and between the delay site and the central compartment is \( k_{1,4} = N/T_d \). Additional parameters in the proposed absorption model are: \( k_a \), a first-order absorption rate constant; \( F \), the bioavailable fraction of a p.o. dose of ALP; and \( f \), the fraction of bioavailable ALP that enters the delay site. The differential equations specifying the model are presented below:

\[
\begin{align*}
\frac{dA_1}{dT} & = - (k_{0,1} + k_{1,2})A_1 + k_{1,2}A_2 + F(1 - f)k_a \cdot A_3 + k_{1,4} \cdot A_{4,N} \\
\frac{dA_2}{dT} & = k_{1,2}A_1 - k_{1,2}A_2 \\
\frac{dA_3}{dT} & = k_{1,4}A_1 - k_{1,4}A_4 + (1 - F)k_aA_3 \\
\frac{dA_{4,N}}{dT} & = A_{4,N-1} - k_{1,4}A_{4,N}
\end{align*}
\]  

(1)

The parameters in the absorption models \((F, f, k_a, N, \text{and } T_d)\) were estimated by numerical optimization using the two-compartment open model parameters previously estimated from the i.v. data. Absorption model parameters are estimated independently for each animal at each p.o. dose level. The \( f \) parameter is constrained to be between 0 and 1 and the number of delay compartments to integer values. Statistical analyses were performed by repeated-measures (RM) one-way ANOVA by using SigmaStat (Jandel, San Rafael, CA). The bioavailability of ALP \((F)\) is also calculated from the i.v. and p.o. areas under the curve (AUCs) of ALP using noncompartmental analysis (Gabrielsson and Weiner, 1997). Additional noncompartmental parameters describing the concentration and location of the two peaks \((C_{1,\text{max}}, C_{2,\text{max}} \text{ and } T_{1,\text{max}}, T_{2,\text{max}})\) and the trough between the peaks \((C_{\text{min}} \text{ and } T_{\text{max}})\) are also reported as observed values.

**Results and Discussion**

The mean serum concentrations \((\pm \text{S.E.})\) of ALP after the i.v. \((1.25 \text{ mg/kg})\) and p.o. doses \((7 \text{ and } 12.5 \text{ mg/kg})\) are shown in Fig. 2. A–C, respectively. ALP decayed biexponentially after i.v. administration, with an initial half-life \((T(1/2)_{\text{int}})\) of 3.22 \(\pm\) 0.72 min and a terminal half-life \((T(1/2)_{\text{term}})\) of 23.1 \(\pm\) 3.85 min. The estimated values of the coefficients in the biexponential equation corresponding to these half-lives are 2.917 \(\pm\) 0.384 nmol/ml and 0.602 \(\pm\) 0.104 nmol/ml, respectively. The microconstants specifying the open two-compartment model (Fig. 1, top) are presented in Table 1. These values closely followed those reported previously (Lau et al., 1997a).

A qualitative visual examination of the data indicated the presence of double peaks in the concentration-time profiles of oral ALP and its two metabolites for each of the four animals regardless of dose (Fig. 2, B and C). Quantitative analysis of ALP serum concentration data for the two p.o. doses is conducted to compare the location \((T_{1,\text{max}} \text{ and } T_{2,\text{max}})\) and magnitude \((C_{1,\text{max}} \text{ and } C_{2,\text{max}})\) of the two peaks, and is presented in Table 1. Although the \( T_{\text{max}} \) for the second peak was significantly greater \((p < 0.01)\) than that for the first, the values of \( C_{1,\text{max}} \) and \( C_{2,\text{max}} \) were similar for both peaks \((p > 0.1)\) at a given dose, as judged by RM one-way ANOVA. However, the values of the \( C_{1,\text{max}} \) and \( C_{2,\text{max}} \) for the 12.5 mg/kg dose were 2-fold greater than...
those for the 7 mg/kg dose. The location ($T_{\text{min}}$) and magnitude ($C_{\text{min}}$) of the concentration in the trough between the two peaks is also presented in Table 1. Although the $T_{\text{min}}$ values were significantly different for the two oral doses, the $C_{\text{min}}$ values were not significantly different.

The goodness of fit of the two absorption models described in Materials and Methods is assessed by using AIC. Analysis of data from each animal, at each p.o. dose level, indicates that the proposed absorption model with a delay site is more appropriate than the conventional first-order absorption model. The mean ($\pm$S.E.) AIC value for the conventional absorption model is 20.108 $\pm$ 0.208 and that for the proposed absorption model is 25.255 $\pm$ 0.367. The mean ($\pm$S.E.) of the parameters in the proposed absorption model are reported in Table 1. The values of $N$ ranged from 3 to 11 and from 9 to 11 for the two oral dose levels.
to 16 for the 7 and 12.5 mg/kg p.o. doses, respectively. The fraction of ALP that experiences delayed absorption ($f \sim 80\%$) estimated by the proposed model is consistent with the observation that the area under the second peak was much larger relative to the first peak regardless of dose. The absolute bioavailability for oral ALP estimated by the proposed model ($F \sim 30\%$) is also consistent with the bioavailability estimated using noncompartmental analysis (Table 1). This bioavailability is considerably lower than that of s.c. ALP (Lau et al., 1997a). The difference in parameter values estimated at the two p.o. dose levels is judged not to be statistically significant ($p > 0.1$) by RM one-way ANOVA (Table 1). Representative ALP profiles predicted by the proposed model after administration of i.v. and p.o. doses for one animal are presented in Fig. 3, A and B.

Similar multiple peak phenomena have been observed for a number of other oral drugs (Plusquellec et al., 1987; Charman et al., 1993; Piquette-Miller and Jamali, 1997); however, this is the first reported case of double peaks in a BZ such as ALP. Several mechanisms have been proposed for the phenomenon: 1) enterohepatic recycling (Veng-Pedersen, 1980), 2) the presence of absorption windows along the gastrointestinal tract (Wagner, 1984), and 3) variable gastric emptying (Oberle and Amidon, 1987). Enterohepatic recycling can be ruled out as a cause of the double peaks in ALP serum concentration-time profiles, because the phenomenon was not observed after i.v. ALP administration, even though the mean serum concentrations were higher than the concentrations after the p.o. doses. In addition, this phenomenon was not observed after i.p. or s.c. ALP administration in rats under the same food regimen (Lau and Wang, 1996; Lau et al., 1997a). Although the double peaks in the serum concentration-time profiles after p.o. doses could be due to differential rates of absorption along the gastrointestinal tract, we hypothesize that the phenomenon is due to reduction in gastric motility caused by the muscle relaxant effect of ALP. BZs (e.g., diazepam, flunitrazepam, midazolam) have been found not only to relax airway muscle by a direct action on airway smooth muscle in guinea pigs (Koga et al., 1992) but also to alter the gastrointestinal motility in conscious dogs (Fargeas et al., 1984). It is likely that gastric emptying played a role in producing the double-peak phenomenon because ALP has been reported to alter the muscle relaxant effect of ALP, which can have important therapeutic and drug interaction implications, especially because BZs are commonly coadministered with other drugs. Further studies are needed to investigate the mechanism underlying the double-peak phenomenon for ALP and other muscle relaxants.

**Fig. 3.** Measured (symbols) and predicted (solid lines) serum ALP concentration-time profiles for a rat after doses of i.v. 1.25 mg/kg (A) and p.o. 7 and 12.5 mg/kg (B).

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References


