CLINICAL PHARMACOKINETICS OF ALPRAZOLAM EXTENDED RELEASE: A SUMMARY

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ABSTRACT

A new extended-release formulation of alprazolam (alprazolam XR) has been developed to facilitate less-frequent dosing than is required with the conventional formulation (alprazolam compressed tablet [CT]). During a study involving chronic dosing of alprazolam XR 6 mg once daily and alprazolam CT 1.5 mg four times daily, the extent of absorption and peak concentrations were comparable, whereas the trough concentration was higher with the latter formulation. During chronic dosing of alprazolam XR 3 mg twice daily and alprazolam CT 1.5 mg four times daily, the extent of absorption, peak concentrations, and trough concentrations were comparable. The administration of a high-fat meal in conjunction with alprazolam XR 1 or 3 mg did not affect the extent of absorption, but the peak concentration increased by 12% and 26%, respectively. A similar concentration profile was observed when alprazolam XR 3 mg was administered at night as opposed to the morning. Mean maximum sedation scores on the Nurse Rated Sedation Scale (0–4) are comparable with a 3-mg dose of alprazolam XR (2.12 ± 0.485) and a 1.5-mg dose of alprazolam CT (2.74 ± 0.485). During chronic dosing, tolerance to sedation occurs to the same extent with both formulations. The only difference in pharmacokinetic profiles is the slower absorption of alprazolam XR compared with alprazolam CT. In view of the fact that distribution, metabolism, and elimination are comparable, the half-life and extent of accumulation during chronic dosing are the same for both formulations.

INTRODUCTION

Alprazolam is a triazolobenzodiazepine compound that is metabolized to 4-hydroxy and α-hydroxy metabolites (Figure 1). Although these metabolites have pharmacologic activity in in vitro and animal models,[1,2] they are not important from a clinical standpoint because their combined concentrations constitute <15% of the parent compound concentration.[3,4] Only parent compound concentrations are important for evaluating alprazolam pharmacokinetics and pharmacodynamics.

Relationships between drug concentration and therapeutic response are an important component of the assessment of clinical utility. In a double-blind, placebo-controlled, fixed-dose study, the probability of response to the conventional immediate-release formulation of alprazolam (alprazolam compressed tablet [CT]) was examined in 90 patients with
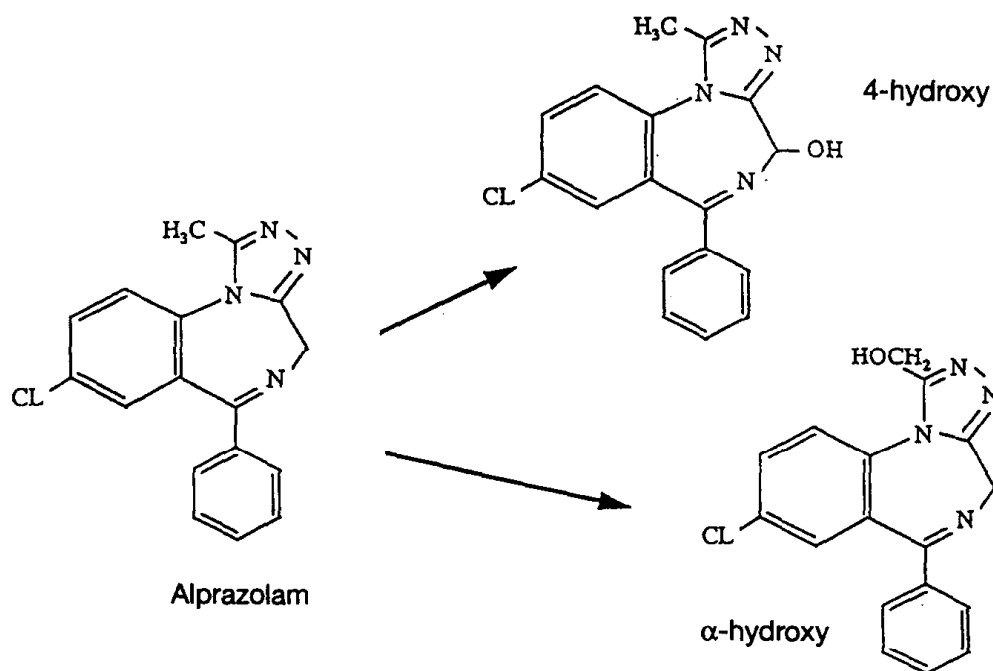
Figure 1. Chemical structures of alprazolam and its metabolites.

panic disorder.[5] The patients were randomized to receive either placebo or alprazolam CT 2 or 6 mg/d in three or four divided doses. Major response was defined as a >75% reduction, moderate response as a 25% to 75% reduction, and no response as a <25% reduction in the number of panic attacks. During a 6-week treatment period, the probability of a patient being classified as a major responder increased with increasing alprazolam concentration—from approximately 5% at 15 ng/mL to approximately 75% at 48 ng/mL (Figure 2). In another double-blind, placebo-controlled study, alprazolam doses were adjusted to achieve maximum therapeutic benefit in 219 patients with panic disorder.[6] Maximum improvement in the Hamilton Anxiety Rating Scale and the Hamilton Depression Rating Scale was observed at alprazolam CT concentrations of 20 to 39 ng/mL.

Recently, an extended-release formulation of alprazolam (alprazolam XR) was developed to facilitate less-frequent dosing. The comparative pharmacokinetic and pharmacodynamic profiles of the extended-release and conventional formulations have important implications for the treatment of anxiety and panic disorder.

PHARMACOKINETICS OF ALPRAZOLAM XR VERSUS ALPRAZOLAM CT

Single-Dose Studies

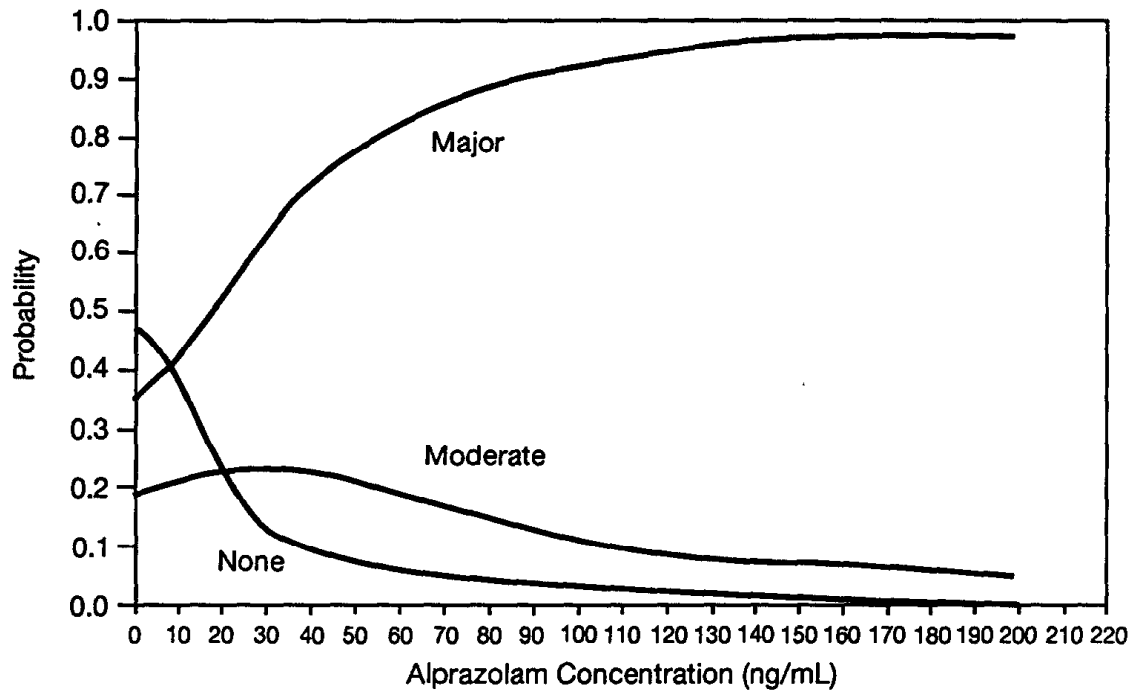Figure 3 shows plasma concentration versus time profiles following a

Figure 2. Probability of a patient being classified as a major responder, moderate responder, or nonresponder as a function post distribution of alprazolam plasma concentration at the patient's last evaluation. (Reprinted with permission from Antal et al.[5])

single oral dose of alprazolam XR (3 mg) and alprazolam CT (1.5 mg) in 17 healthy volunteers.[7] With alprazolam XR, the rate of absorption was slower and the peak concentration was relatively flat, occurring 6 to 12 hours after administration of the dose. The maximum concentration was slightly higher with alprazolam XR than with alprazolam CT, but it occurred much later.

Table I provides details on the pharmacokinetic parameters underlying these observations. At the 3-mg dose of alprazolam XR, the area under the curve (AUC, or extent of absorption) was approximately twice that associated with the 1.5-mg dose of alprazolam CT. However, after correction for dose (AUC_D), the extent of absorption was similar, indicating that patients receiving either formulation would be exposed to comparable amounts of alprazolam. The difference between the maximum concentrations was only approximately 16%, even though the alprazolam XR dose was twice that of the conventional formulation. Clearance was the same with both formulations, indicating that the extended-release tablet did not alter drug metabolism or elimination. The difference between volumes of distribution (although statistically significant) was relatively small in magnitude, and both values were within the range associated with alprazolam CT tablets.[8] The half-lives of the two formulations were similar. Overall, then, only the absorption rate was different with alprazolam XR
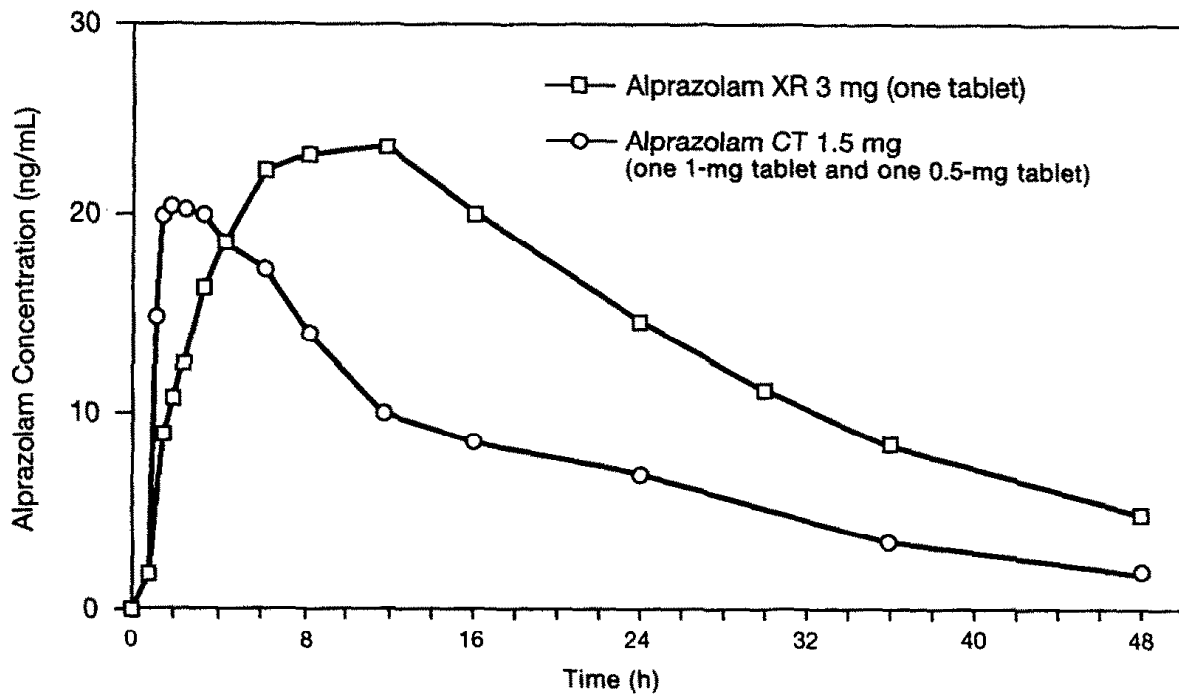
Figure 3. Mean alprazolam plasma concentrations following the administration of single oral doses of an immediate-release formulation of alprazolam (alprazolam compressed tablet [CT]) and an extended-release formulation of alprazolam (alprazolam XR) in 17 healthy male and female volunteers (mean age, 32 years; mean weight, 71 kg).

compared with alprazolam CT. Drug distribution and elimination were not altered.

Figure 4 shows the results of a study in which 21 healthy volunteers received alprazolam XR in single doses of 2, 4, 8, or 10 mg according to a

Table I. Alprazolam pharmacokinetic parameters resulting from the administration of single oral doses of the conventional immediate-release formulation of alprazolam (alprazolam compressed tablet [CT]) or the extended-release formulation of alprazolam (alprazolam XR) in 17 healthy volunteers. Values are expressed as mean ± SD.

Parameter	Alprazolam CT 1.5 mg	Alprazolam XR 3 mg	ANOVA P Value
AUC (ng × h/mL)	359 ± 154	757 ± 421	0.0001
AUC_D (ng × h/mL)*	359 ± 154	378 ± 210	0.9080
C_{max} (ng/mL)	21.7 ± 5.15	25.1 ± 6.89	0.0445
T_{max} (h)	1.82 ± 1.07	9.88 ± 4.09	0.0001
Cl_o (mL/min/kg)	1.12 ± 0.377	1.12 ± 0.429	0.9632
Vd/F (L/kg)	0.964 ± 0.171	1.16 ± 0.162	0.0005
$t_{1/2}$ (h)	10.0	12.4	–

ANOVA = analysis of variance; AUC = area under the (concentration vs time) curve; AUC_D = dose-corrected AUC; C_{max} = maximum concentration; T_{max} = time to maximum concentration; Cl_o = apparent oral clearance; Vd/F = apparent volume of distribution; $t_{1/2}$ = elimination half-life, harmonic mean.
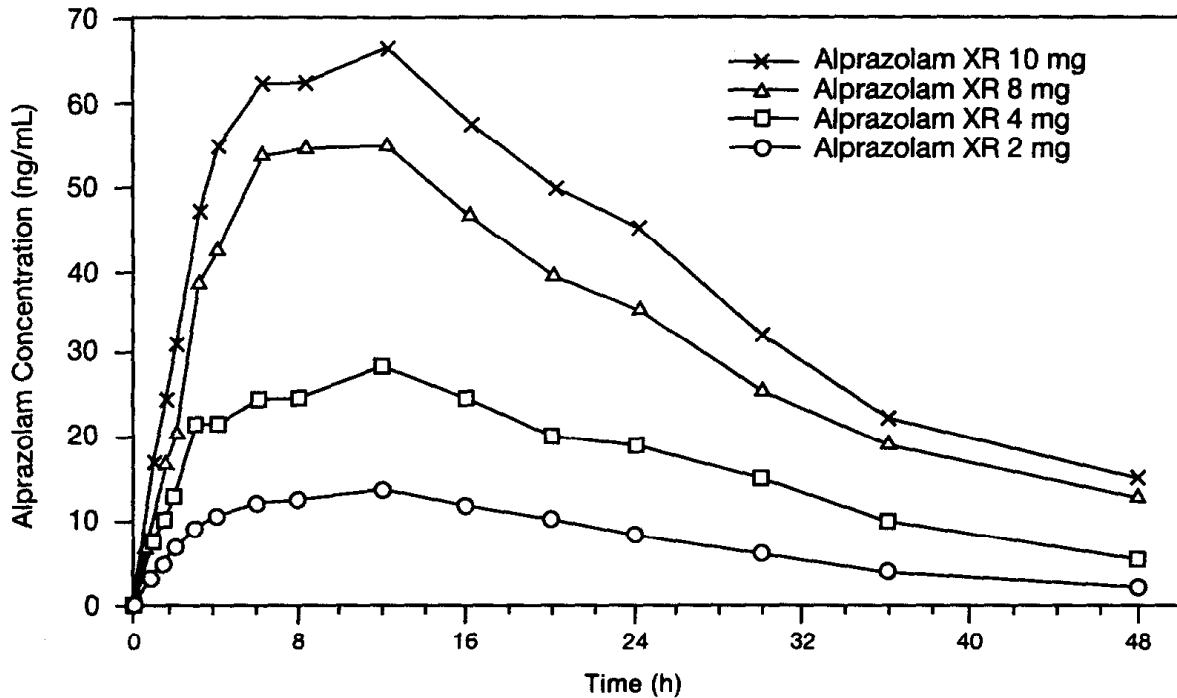* Normalized to a 1.5-mg dose.

Figure 4. Mean alprazolam plasma concentrations following the administration of single oral doses of an extended-release formulation of alprazolam (alprazolam XR) 2 to 10 mg in 21 healthy male volunteers (mean age, 28 years; mean weight, 77 kg).

four-treatment crossover design.[7] The plasma concentration versus time profiles associated with these doses reflected the extended-release characteristics of the formulation and also demonstrated a proportional increase in concentration with increasing dose. Examination of the pharmacokinetic data in Table II revealed that the extent of absorption (AUC) and max-

Table II. Alprazolam pharmacokinetic parameters resulting from the oral administration of four different single doses of extended-release alprazolam (alprazolam XR) tablets to 21 healthy volunteers. Values are expressed as mean ± SD.

Parameter	Dose				ANOVA P Value
	2 mg	4 mg	8 mg	10 mg	
AUC (ng × h/mL)*	443 ± 190	920 ± 475	1800 ± 636	2142 ± 611	0.0001
C_{max} (ng/mL)*	15.1 ± 4.02	31.5 ± 10.3	62.8 ± 11.1	70.5 ± 13.2	0.0001
T_{max} (h)	11.0 ± 3.50	9.76 ± 3.13	9.48 ± 3.43	9.38 ± 3.77	0.4681
Cl_o (mL/min/kg)	1.08 ± 0.272	1.05 ± 0.253	1.05 ± 0.276	1.07 ± 0.246	0.6283
Vd/F (L/kg)	1.19 ± 0.196	1.22 ± 0.175	1.21 ± 0.148	1.26 ± 0.111	0.2366
$t_{1/2}$ (h)	12.8	13.3	13.1	13.6	–

ANOVA = analysis of variance; AUC = area under the (concentration vs time) curve; C_{max} = maximum concentration; T_{max} = time to maximum concentration; Cl_o = apparent oral clearance; Vd/F = apparent volume of distribution; $t_{1/2}$ = elimination half-life, harmonic mean.
* Means for all doses are significantly different from one another.

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