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Subject:	Training on Clinical Study for Alcohol Interaction with Kadian
Show Time As:	Free
Recurrence:	(none)
Required Attendees:	Miller, Scott; Nathalie Leitch; Birtchet, Alan; Shepherd, Michael; Allen, Benjamin; Askew, Richard; Connon, Sandra; Fitch, Shelley; Hepp, Christopher; Hight, Cecil; Rastovski, Cynthia; Romer, Lori; Sontag, John
Attachments:	Effect of alcohol on KADIAN pk.pdf

When: Wednesday, November 04, 2009 11:00 AM-11:30 AM (GMT-05:00) Eastern Time (US & Canada).

~~*~*~*~*~*~*~*~*

Team,
Listed below is the call-in information for our training call on the Clinical "Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of Kadian Capsules". Attached is a copy of the study. Please review the clinical piece prior to our call. You are not to use or disseminate in the field this clinical prior to our training call. I will send a copy of the training deck to you separately, most likely Monday afternoon. As mentioned previously if you cannot make this training call you must attend the call with the East Region on 11/3 at 9am eastern. Thanks.

Mark

Call-in Number: (877) 419-9491
Conf Code: 3178371963
<<Effect of alcohol on KADIAN pk.pdf>>

PLAINTIFF TRIAL EXHIBIT
P-04418_00001

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ELSEVIER

Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of KADIAN (Morphine Sulfate Extended-Release) Capsules

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Abstract: **The recent withdrawal of hydromorphone hydrochloride extended-release capsules (Palladone; Purdue Pharma L.P., Stamford, CT) from the market after pharmacokinetic data revealed a risk of alcohol-induced dose-dumping prompted a re-examination of the risk-benefit profiles of extended-release drugs. Although warnings on concomitant alcohol use are included on opioid product labels, further investigations of extended-release formulations to determine the risk of dose-dumping were recommended by the US Food and Drug Administration. The present study was undertaken to assess the single-dose relative bioavailability of polymer-coated, extended-release morphine sulfate capsules (KADIAN, 100 mg; Alpharma Pharmaceuticals LLC, Piscataway, NJ). This open-label, randomized, 3-way crossover study with an additional index arm, conducted among 32 healthy male volunteers, found no significant evidence of a formulation interaction between KADIAN and alcohol, in vivo. The pharmacokinetics of serum morphine did not differ significantly among subjects taking KADIAN with water (fasted) or with 240 mL 40% alcohol under fasted or fed conditions. Analysis of variance ratios of least-squares means for ln-transformed AUC_{∞} and C_{max} satisfied the criteria (90% confidence intervals within 80%–125%) to declare no drug formulation interaction among the KADIAN regimens dosed with alcohol compared with KADIAN taken with water. There were no serious adverse events or deaths reported during the study.**

Perspective: ***Because of the high rate of alcohol use in the United States, the potential for drug-alcohol interactions is an important clinical concern. Although it is recommended that alcohol not be used while the patient is taking opioids, results of this in vivo study indicate that the risk of alcohol-induced dose-dumping in connection with the use of KADIAN is negligible.***

Key words: *KADIAN, opioid, morphine sulfate extended-release, alcohol, naltrexone, pharmacokinetics.*

Alcohol enhances the effects of opioids on the central nervous system (CNS), and even moderate drinking may pose a risk of potential drug-drug interaction.[20] Results of the 2005 National Survey on Drug Use and Health indicate a high rate of alcohol use among Americans. Sixty-seven percent of those aged 21 to 25 years, and nearly half of those aged 60 to 64 years, had consumed alcohol in the previous month.[13] The Drug Abuse Warning Network (DAWN) reported that concomitant use of alcohol and pharmaceuticals, with or without other illicit drugs, accounted for 13.5% of total drug-related emergency room visits in 2005.[12] The possibility of concomitant use of alcohol with pain medication, including opioids, is a reasonable concern. The dangers of concomitant consumption of alcohol and extended-release opioids have recently attracted attention in the scientific and regulatory arenas.

Extended-release formulations contain enough opioid to provide analgesia over the dosing interval, generally 12 to 24 hours. There are several strategies used in creating extended-release tablets and capsules. Tablet formulations contain opioid enmeshed within a matrix consisting of polymers that are hydrophobic, hydrophilic, or combinations of more than 1 type of polymer.[7-11] On tablet ingestion, the hydrophilic polymer swells in the gastrointestinal (GI) fluid. Drug release can be controlled by the

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rates of diffusion of liquid into the tablet and diffusion of drug into the system, or by the partition coefficients of the drug between the 2 polymer types.[7,9,11] Some tablet formulations may use 2 types of hydrophobic polymer matrices, which enable dual control: One component can be released immediately upon contact with GI fluids, and a sustained-release component can be released by slower diffusion through the matrix pores.[10,11]

Capsule formulations adsorb morphine onto an inert core bead, which is then enclosed within a polymer coating. The chemistry of the polymer (hydrophobicity, pH dependence) surrounding each bead controls the rate of release of active drug.[1,3,4,19] One formulation uses fumaric acid as an osmotic agent and local pH modifier. Inclusion of beads that are not enclosed within a rate-limiting polymer produces immediate-release beads.[2]

After a pharmacokinetic (PK) study in healthy volunteers indicated a potentially fatal interaction between alcohol and hydromorphone hydrochloride extended-release capsules (Palladone; Purdue Pharma L.P., Stamford, CT), the US Food and Drug Administration (FDA) requested the removal of this opioid from the market. In the study, co-ingestion of Palladone with 240 mL (8 oz) of 40% (80 proof) alcohol raised peak plasma hydromorphone concentrations approximately 6-fold, compared with ingestion with water. One subject in this study experienced a 16-fold increase in peak plasma hydromorphone concentrations after ingesting Palladone with 40% alcohol compared with water.[19] Of interest, the in vivo PK study showed that lower concentrations of alcohol, eg, a mixed drink (20% alcohol) or beer (4% alcohol), also led to potentially serious increases in hydromorphone concentrations.[14]

After the withdrawal of Palladone from the market, the FDA recommended that makers of other extended-release formulations conduct investigations to determine the risk of alcohol-induced dose-dumping, whereby alcohol interacts with the extended-release characteristics to yield unintended, rapid drug release in a short period of time.[6,14] In vitro studies conducted with an extended-release formulation of morphine sulfate (AVINZA; King Pharmaceuticals, Inc., Bristol, TN) demonstrated accelerated release of morphine in buffer solutions containing ethanol. As a result, the AVINZA label was revised to warn against consumption of alcohol and use of medications containing alcohol while taking the product.[2,5] Similar information was placed as a Black Box Warning for extended-release oxymorphone hydrochloride (OPANA ER; Endo Pharmaceuticals, Chadds Ford, PA) due to results of an in vivo study examining the effect of alcohol on the bioavailability of a single 40-mg dose in healthy fasted volunteers.[8]

The current study was conducted to assess the single-dose bioavailability of morphine sulfate extended-release capsules (KADIAN; Alpharma Pharmaceuticals LLC, Piscataway, NJ) when dosed with alcohol in the fasted and fed conditions relative to KADIAN administered with water.

Materials and Methods

Objective

The objective of this study was to compare the single-dose relative bioavailability of KADIAN (100 mg) when dosed with alcohol under fasted and fed conditions versus water.

Participants

Participants were opioid-naive, healthy, adult male volunteers (N = 32) with a mean age of 24 years (range, 21–37 years). To be eligible for participation, subjects were required to have a history of moderate alcohol consumption, operationally defined as at least 7 to 21 units of alcohol per week, with 1 alcohol unit equivalent to 12 oz of beer or 1.5 oz of 80-proof (40% alcohol) distilled spirits. The inclusion criteria also specified that subjects were nonsmokers for at least 3 months or light smokers (<10 pack-years), were within 20% of their ideal weight, and had no clinically significant laboratory abnormalities during screening. Exclusion criteria included history of alcoholism or drug abuse; history of no alcohol intake; less than moderate, or excessive alcohol intake; history or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, GI, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease; hypersensitivity to morphine, other opioids, or opioid antagonists; and other physical or laboratory abnormalities considered clinically significant. The protocol for this study was approved by the MDS Pharma Services institutional review board, and informed consent was obtained from each participant.

Study Design

This was an open-label, single-dose, 3-way crossover PK drug interaction study between 100 mg KADIAN and 40% alcohol in the fasted and fed conditions and 100 mg KADIAN with water administered in a randomized fashion. Pharmacokinetics of an immediate-release morphine oral solution (20 mg) without alcohol in the fasted condition, as an index arm, were explored during the fourth period.

Typically, subjects enrolled in PK studies are healthy, opioid-naive, adult volunteers. As such, it is common practice to provide 1 or more oral administrations of the opioid receptor antagonist, naltrexone hydrochloride, before dosing with an opioid to attenuate opioid-induced adverse events (AEs), in particular, vomiting and respiratory depression. Therefore, in this study, naltrexone hydrochloride (50 mg tablet) was administered with 240 mL of water at 12 hours and 2 hours before treatment.

Regimens

Subjects were randomly assigned to begin with 1 of the following regimens:

- Regimen A: KADIAN 100 mg + 240 mL 40% alcohol (four 60-mL shots of 40% [80-proof] alcohol [101 mL

190-proof Everclear (Luxco, St. Louis, MO), 139 mL water]) under fasted conditions
- Regimen B: KADIAN 100 mg + 240 mL 40% alcohol (four 60-mL shots of 40% [80-proof] alcohol) immediately after ingestion of a standard FDA high-fat meal
- Regimen C: KADIAN 100 mg + 240 mL water under fasted conditions

Subjects were required to consume all alcohol (or water) within 20 minutes of dosing.

All subjects who completed the study then received the following regimen during period 4:

- Regimen D: Concentrated oral morphine solution (20 mg/5 mL) 5 mL + 235 mL water under fasted conditions

Procedures

Subjects assigned to regimens A, B, or C were housed at the study center from at least 15 hours before dosing until 36 hours after dosing. They returned for a 48-hour blood sample. Subjects assigned to regimen D were housed until completion of the 24-hour blood sample. At check-in, each subject was screened for alcohol and various controlled substances. In addition, serum aspartate transaminase, serum alanine transaminase, and serum amylase assessments were repeated at each check-in, whereas hemoglobin and hematocrit were assessed at check-in for subjects in regimens C and D.

All subjects were fed according to a standardized meal schedule. For those undergoing the fasted regimens (A, C, and D), food was restricted from 10 hours before dosing until 4 hours after dosing. Subjects assigned to regimen B consumed a standard high-fat breakfast within 30 minutes before dosing. A 7-day washout period separated each regimen.

Pharmacokinetic blood sampling (ie, serum morphine and metabolites) took place before dosing and at the following time intervals after dosing for regimens A, B, and C: 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 7.0, 8.0, 9.0, 10, 12, 18, 24, 36, and 48 hours. For regimen D, blood samples were collected before dosing and at 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, and 24 hours after dosing. An overview of the study design is presented in Fig 1.

Pharmacokinetic Analyses

Pharmacokinetic measurements for serum morphine, morphine-3-glucuronide, and morphine-6-glucuronide included the following parameters: $AUC_{0\text{-}t}$, the area under the serum concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method; AUC_{∞}, the area under the serum concentration versus time curve from time 0 to infinity, calculated as the sum of $AUC_{0\text{-}t}$ plus the ratio of the last measurable serum concentration to the elimination rate constant; percentage of AUC extrapolated; C_{max}, the maximum measured serum concentration over the time span specified; T_{max}, the time of the maximum measured serum concentration; k_{el}, the apparent first-order terminal elimination rate constant calculated from a semilogarithmic plot of the serum concentration versus time curve; and $t_{½}$, the apparent first-order terminal elimination half-life calculated as $0.693/k_{el}$.

Statistical Analyses

Analyses of variance (ANOVA) were performed on the ln-transformed $AUC_{0\text{-}t}$, AUC_{∞}, and C_{max} PK parameters for regimens A, B, and C. Each ANOVA included calculation of ratios of least-squares means (LSMs), the differences between regimen LSMs, and the standard error associated with these differences. LSMs ratios were expressed as a percentage relative to the reference regimen (C). The comparisons of interest were A versus C and B versus C. In addition, A versus D (the oral morphine solution) was compared for investigational purposes. Ninety percent confidence intervals (CIs) for the ratios of the LSMs of regimens A and B, relative to regimen C, were calculated from the ln-transformed AUC_{∞} and C_{max} data. Calculation of these 90% CIs was consistent with the statistical test for bioequivalence. Traditional criteria for bioequivalence recommend that ratios for AUC_{∞} and C_{max} fall within the limits of 80% to 125%.[16-18]

Safety Assessments

Safety and tolerability were assessed by monitoring AEs, clinical laboratory results, vital signs, ECGs, and physical examinations. In addition, alcohol blood tests and alcohol breath tests were performed.

Results

The study population consisted of 32 adult male volunteers, with a mean age of 24 years (range, 21–37 years), mean height of 182 cm (range, 168–193 cm),

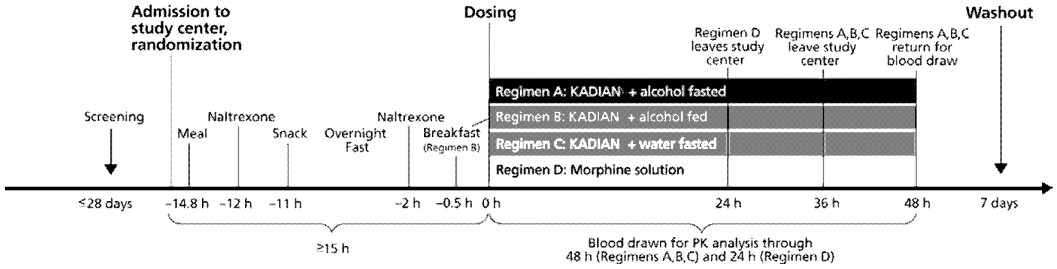


Figure 1. Study design.

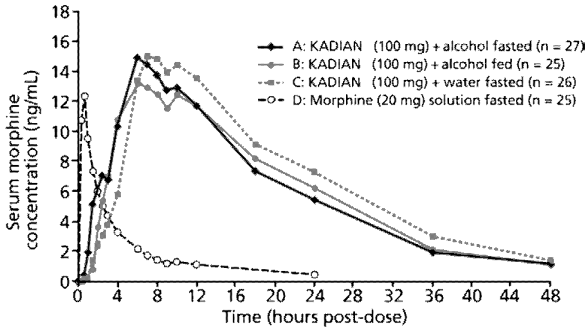


Figure 2. Mean serum morphine concentration-time profiles for all subjects with evaluable data.

and mean weight of 81.0 kg (range, 70.8–99.8 kg). Of the 32 subjects enrolled in the study, PK analyses were performed on data from 27 subjects, as 5 subjects did not complete at least 2 study periods enabling a comparison either of regimens A versus C or B versus C. One subject was included in the PK analysis but excluded from the ANOVA because of a protocol deviation (regimen C was not administered). Seven subjects discontinued the study, 5 due to AEs (3 due to vomiting, 1 due to chest pain, and 1 due to streptococcal pharyngitis), 1 due to a positive urine drug screen for amphetamines, and 1 who withdrew from the study before starting regimen D.

Pharmacokinetic Results

Mean serum morphine concentration-time profiles for all subjects with evaluable data are illustrated in Fig 2. The serum morphine profile after coadministration of regimens A (KADIAN + 40% alcohol fasted) or B (KADIAN + 40% alcohol fed) was comparable to the serum morphine profile after regimen C (KADIAN + water). Peak absorption was reached at a median T_{max} of 8 hours after dosing for all 3 regimens. The serum profile of regimen D (oral morphine solution, 20 mg) is also displayed in Fig 2 for visual comparison with the extended-release morphine time-release profiles.

The FDA Guidance for Industry regarding bioavailability and bioequivalence studies for orally administered drugs recommends that data from subjects taking modified-release products who experience vomiting at any time during the dosing interval (12 hours for KADIAN) can be excluded from statistical analyses.[17]

Eleven subjects who were included in the overall analysis vomited at times ranging from 0.17 to 11.85 hours after administration of regimen A. Five of them also vomited after administration of regimen B, at times ranging from 0.08 to 7.85 hours. No subject vomited after taking regimen C, with the exception of 1 subject who vomited but also had strep throat and was withdrawn from the study. The mean serum morphine concentration-time profile for the group of subjects excluding those who had vomited within 12 hours of dosing was similar to the group that included all subjects. Fig 3 displays the mean serum morphine concentration-time profiles for these subjects.

Both profiles demonstrate that the extended-release characteristics of KADIAN were maintained in the presence of alcohol. A summary of the PK parameters for all subjects with evaluable data, as well as the group excluding patients who had vomited within 12 hours, is presented in Table 1.

Overall mean exposure (AUC) was similar between the KADIAN regimens (A, B, and C), and to regimen D when dose-normalized to 100 mg. Mean C_{max} for regimens A, B, and C were similar and were approximately one-fourth of the dose-normalized C_{max} for regimen D. Median T_{max} was 8.0 hours (range, 2.5 to 18 hours) for all 3 KADIAN regimens. The mean $t_{½}$ for KADIAN was approximately 11 hours.

The ANOVA ratios of LSMs for AUC and C_{max} are presented in Table 2. This table includes all subjects who had PK data for a comparison of interest, either regimens A/C and/or regimens B/C (n = 26 for all subjects; n = 21 for all subjects excluding those who vomited within the 12-hour dosing interval). Comparisons of regimens A/C and B/C 90% CIs for the ratio of geometric means for AUC_{∞} and C_{max} were within the 80% to 125% acceptance range for CI boundaries to declare no drug formulation interaction.

In addition, individual subject C_{max} ratios of regimens A/C versus B/C were calculated. The ratios were similar for most subjects. This trend is depicted in Fig 4. C_{max} ratios ranged from 0.43 to 1.89 (overall median, 1.00), with the exception of 1 subject whose C_{max} ratio was 4.54 for regimen A versus C. For this subject, the serum morphine concentration-time profile after regimen A still showed a time-release pattern consistent with an extended-release formulation. The T_{max} was 6 hours, and C_{max} was approximately 42% lower than the dose-normalized mean C_{max} for regimen D (oral morphine solution), which suggests the extended-release mechanism of KADIAN was not affected. The data also include 1 subject who did not consume the fourth shot of alcohol in regimen A due to an AE (vomiting), but whose PK values fell within the range for those of the other subjects.

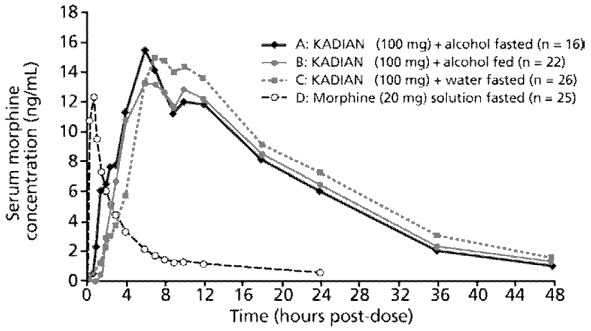


Figure 3. Mean serum morphine concentration-time profiles excluding subjects with emesis within the 12-hour dosing interval.

Table 1. Summary of Serum Morphine Pharmacokinetic Parameters

Parameter	Regimen A KADIAN + Alcohol Fasted	Regimen B KADIAN + Alcohol Fed	Regimen C KADIAN + Water Fasted	Regimen D Dose-Normalized OS + Water Fasted
All subjects with evaluable pharmacokinetic data				
AUC_{0-t}[a] (ng · h/mL)	271.80 (35.5) (n = 27)	279.33 (29.3) (n = 25)	307.2 (32.2) (n = 26)	231.8 (31.6) (n = 25)
AUC_{∞}[a]* (ng · h/mL)	300.68 (39.2) (n = 26)	301.6 (33.7) (n = 25)	337.28 (33.3) (n = 26)	347.8 (27.2) (n = 18)
C_{max}[a] (ng/mL)	16.95 (42.1) (n = 27)	15.71 (30.3) (n = 25)	16.46 (32.9) (n = 26)	68.4 (39.0) (n = 25)
T_{max}[b] (h)	8.0 (4–24) (n = 27)	8.0 (2.5–18) (n = 25)	8.0 (6–18) (n = 26)	0.67 (0.33–1.5) (n = 25)
$t_{1/2}$[c]* (h)	11.8 (4.89) (n = 26)	10.8 (3.20) (n = 25)	11.6 (4.46) (n = 26)	14.3 (8.40) (n = 18)
Excluding subjects with emesis within 12-hour dosing interval				
AUC_{0-t}[a] (ng · h/mL)	283.22 (32.2) (n = 16)	290.37 (21.2) (n = 22)	307.2 (32.2) (n = 26)	231.8 (31.6) (n = 25)
AUC_{∞}[a]* (ng · h/mL)	305.74 (32.3) (n = 15)	311.36 (23.0) (n = 22)	337.28 (33.3) (n = 26)	347.8 (27.2) (n = 18)
C_{max}[a] (ng/mL)	16.96 (35.4) (n = 16)	16.03 (29.1) (n = 22)	16.46 (32.9) (n = 26)	68.4 (39.0) (n = 25)
T_{max}[b] (h)	6.0 (4–24) (n = 16)	8.0 (4–18) (n = 22)	8.0 (6–18) (n = 26)	0.67 (0.33–1.5) (n = 25)
$t_{1/2}$[c]* (h)	9.96 (3.11) (n = 15)	10.5 (2.56) (n = 22)	11.6 (4.46) (n = 26)	14.3 (8.40) (n = 18)

OS = oral morphine solution.

[a]Geometric mean (CV%); [b]Median (range); [c]Arithmetic mean (SD).

*Extrapolated parameters AUC_{∞} and $t_{1/2}$ could not be estimated for some subjects.

The morphine-3-glucuronides and morphine-6-glucuronides were also measured during the study. Mean serum morphine-3- and morphine-6-glucuronide concentration-time profiles are presented in Figs 5 and 6, respectively. Visual inspection of the mean profiles shows that although the mean peak concentrations with concomitant alcohol administration were slightly greater than the reference treatment, concentrations at the end of terminal elimination phase were similar to the reference treatment. The mean profiles suggest that concomitant alcohol administration did not adversely affect morphine metabolism, nor was there any evidence in the terminal phase to suggest the likelihood of metabolite accumulation from multiple dosing with KADIAN and alcohol. Furthermore, ANOVA results for the ln-transformed mean AUC ratios of LSMs provided CIs within 80% to 125% for both metabolites, confirming that the total exposures of both metabolites were not significantly affected by alcohol coadministration.

Table 2. ANOVA Ratios of Least-Squares Means

	Regimen	Ratio of LSMs, %	90% CI (lower; upper)
Subjects with at least 1 comparison of interest (n = 26)			
AUC_{∞}(ng · h/mL)	A/C	89.1	80.3; 98.9
	B/C	89.7	80.7; 99.6
C_{max} (ng/mL)	A/C	102.3	89.5; 116.8
	B/C	98.0	85.5; 112.3
Subjects with at least 1 comparison of interest excluding those with emesis within 12-hour dosing period (n = 21)			
AUC_{∞}(ng · h/mL)	A/C	96.3	89.4; 103.8
	B/C	94.6	88.7; 100.9
C_{max} (ng/mL)	A/C	107.6	93.5; 123.8
	B/C	100.9	89.1; 114.3

Safety Results

There were no reported incidents of respiratory depression during the study, nor were there any serious AEs or deaths. Overall, 27 subjects (84%) experienced at least 1 AE that was possibly or probably related to the administration of multiple drugs: 21 subjects (66%) with regimen A (KADIAN 100 mg + alcohol [fasted]), 19 subjects (59%) with regimen B (KADIAN 100 mg + alcohol [fed]), 7 subjects (22%) with regimen C (KADIAN 100 mg + water [fasted]), and 3 subjects (9%) with regimen D (morphine sulfate 20 mg oral solution [fasted]). Most AEs were mild to moderate, the most frequent being nausea (15 subjects), vomiting (15 subjects), headache (14 subjects), and som-

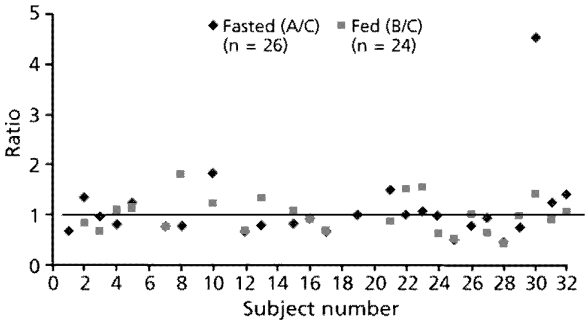
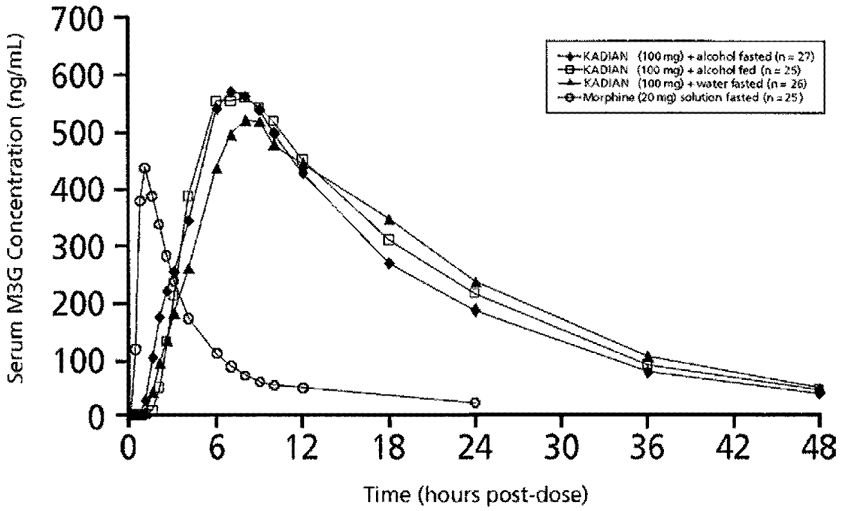


Figure 4. C_{max} ratio of KADIAN + alcohol versus KADIAN + water for each subject.



Abbreviation: M3G, morphine-3-glucuronide.

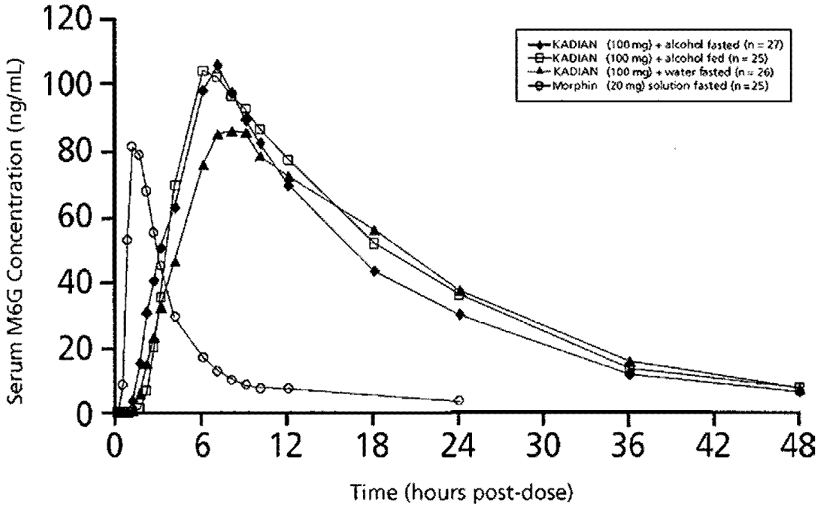
Figure 5. Mean M3G concentration-time profile for all subjects.

nolence (or "feels intoxicated," 12 subjects). The 1 severe AE, chest pain, was deemed unlikely to be related to the study regimen. All AEs resolved before the end of the study. There were no important changes in clinical laboratory results, vital signs, ECGs, and physical examinations. Serum ethanol concentrations were determined to 10 hours post-dose after regimens A and B for safety analysis. The rate and extent of absorption of ethanol was attenuated in the presence of food.

Discussion

No drug interaction between alcohol and KADIAN was observed in this study. Furthermore, since the in vivo data suggest that rate and extent of absorption of morphine from KADIAN dosed with alcohol under fasted or fed conditions was similar to that of KADIAN given with water under fasted conditions, the extended-release mechanism of the KADIAN formulation was not significantly affected by 40% alcohol. The FDA has reviewed data from this study, has concurred that there is no interaction between KADIAN and alcohol in vivo when administered concomitantly, and has not required any changes to the package insert.[15]

It is not yet known why some extended-release opioid formulations are subject to dose-dumping in alcohol and others are not. Potential reasons may relate to the characteristics of the opioid or to the extended-release mechanisms themselves.



Abbreviation: M6G, morphine-6-glucuronide.

Figure 6. Mean M6G concentration-time profile for all subjects.

The KADIAN shell is composed of a combination of pH-independent and pH-dependent water-soluble polymers interspersed within a water-insoluble polymer matrix. This unique combination results in pH-dependent drug release from KADIAN. Although the exact mechanism is not well understood, the poor solubility of the pH-dependent polymer, methacrylic acid copolymer, at low pH, may offer sufficient protection from coingested alcohol while the capsule is in the stomach, where alcohol would be quickly absorbed. The copolymer then gradually dissolves with increasing pH as the capsule moves from the stomach through the GI tract to release the morphine sulfate.

While KADIAN maintained its extended-release profile after co-ingestion with alcohol, consumption of alcohol with any morphine product, whether immediate- or extended-release, is not recommended. All opioids, including KADIAN, may be expected to have additive effects and potentially serious outcomes when used in conjunction with alcohol, other opioids, or illicit drugs that cause CNS depression.[4]

In calling for careful evaluation of the potential for dose-dumping with extended-release dosage forms, the FDA acknowledged that product labeling and other means of informing patients about potential drug-alcohol interactions may not always be effective. The development of extended-release formulations that are not sensitive to alcohol is a goal.[6] Further investigations of social drinking and prolonged moderate alcohol intake may clarify the potential for drug interactions when extended-release formulations are ingested with alcohol.

Acknowledgments

Technical expertise was provided by Alfred Liang, Alpharma Pharmaceuticals LLC. Writing and editorial support for this manuscript was provided by Innovex Medical Communications, Parsippany, NJ.

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