Alcohol and Opioid Interactions: A Critical Review of the Worldwide Literature

Beatrice Setnik, PhD

King Pharmaceuticals

THCI Program on Prescription Opioid Risk Management

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Overview

- Introduction:
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    - Drug Interactions
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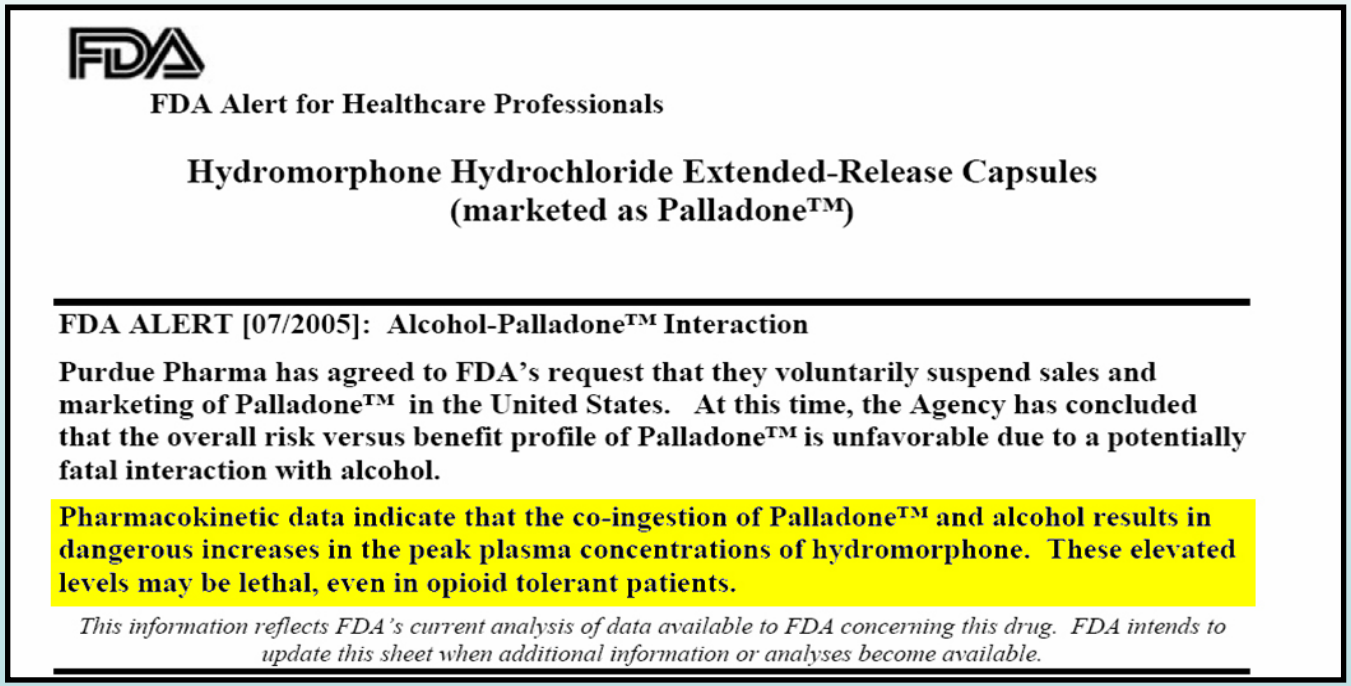
http://www.citizen.org/images/alcohol-prescription-drugs.jpg

Alcohol and Dose Dumping
Palladone™

- Dose Dumping:
  - Unintended, rapid release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified-release dosage form[1]
- July 2005:
  - FDA alerts for the voluntary suspension of sales and marketing of Palladone™[2]



FDA

FDA Alert for Healthcare Professionals

Hydromorphone Hydrochloride Extended-Release Capsules
(marketed as Palladone™)

FDA ALERT [07/2005]: Alcohol-Palladone™ Interaction

Purdue Pharma has agreed to FDA's request that they voluntarily suspend sales and marketing of Palladone™ in the United States. At this time, the Agency has concluded that the overall risk versus benefit profile of Palladone™ is unfavorable due to a potentially fatal interaction with alcohol.

Pharmacokinetic data indicate that the co-ingestion of Palladone™ and alcohol results in dangerous increases in the peak plasma concentrations of hydromorphone. These elevated levels may be lethal, even in opioid tolerant patients.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

[1]Meyer RJ, Hussain AS (October 2005) FDA's ACPS Meeting.

[2] http://www.fda.gov/CDER/Drug/InfoSheets/HCP/hydromorphoneHCP.pdf

Alcohol and Dose Dumping
Avinza®

- October 2005: Avinza® receives black box warning and label change due to an in vitro alcohol-drug interaction

AVINZA® Ⓒ
(morphine sulfate extended-release capsules)
30 mg, 60 mg, 90 mg, 120 mg

R_x Only

WARNING:

AVINZA capsules are a modified-release formulation of morphine sulfate indicated for once daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. AVINZA CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLESAUCE. THE CAPSULE BEADS ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE. PATIENTS MUST NOT CONSUME ALCOHOLIC BEVERAGES WHILE ON AVINZA THERAPY. ADDITIONALLY, PATIENTS MUST NOT USE PRESCRIPTION OR NON-PRESCRIPTION MEDICATIONS CONTAINING ALCOHOL WHILE ON AVINZA THERAPY. CONSUMPTION OF ALCOHOL WHILE TAKING AVINZA MAY RESULT IN THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

Source: http://www.fda.gov/MEDwatch/safety/2005/avinza_PI.pdf

Alcohol and Dose Dumping
Avinza®

- Avinza® label change

Interactions with Alcohol and Drugs of Abuse

Morphine may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

In vitro studies performed by the FDA demonstrated that when AVINZA 30 mg was mixed with 900 mL of buffer solutions containing ethanol (20% and 40%), the dose of morphine that was released was alcohol concentration-dependent, leading to a more rapid release of morphine. While the relevance of *in vitro* lab tests regarding AVINZA to the clinical setting remains to be determined, this acceleration of release may correlate with *in vivo* rapid release of the total morphine dose, which could result in the absorption of a potentially fatal dose of morphine.

Source: http://www.fda.gov/MEDwatch/safety/2005/avinza_PI.pdf

Alcohol and Opioid Interactions
Opana® ER

- June 2006: Opana® ER label includes in vivo alcohol interaction data, contradictory to in vitro results

Ethanol Effect
In Vivo OPANA ER Formulation-Alcohol Interaction

Although in vitro studies have demonstrated that OPANA ER does not release oxymorphone more rapidly in 500 mL of 0.1N HCl solutions containing ethanol (4%, 20%, and 40%), there is an in vivo interaction with alcohol. An in vivo study examined the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of OPANA ER in healthy, fasted volunteers. The results showed that the oxymorphone mean AUC was 13% higher (not statistically significant) after co-administration of 240 mL of 40% alcohol. The AUC was essentially unaffected in subjects following the co-administration of OPANA ER and ethanol (240 mL of 20% or 4% ethanol).

There was a highly variable effect on Cmax with concomitant administration of alcohol and OPANA ER. The change in Cmax ranged from a decrease of 50% to an increase of 270% across all conditions studied. Following concomitant administration of 240 mL of 40% ethanol the Cmax increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the Cmax increased on average by 31% and up to 260% in individual subjects. Following the concomitant administration of 240 mL of 4 % ethanol, the Cmax increased 7% on average and by as much as 110% for individual subjects. After oral dosing with a single dose of 40 mg in fasted subjects, the mean peak oxymorphone plasma level is 2.4 ng/mL and the median Tmax is 2 hours. Following co-administration of OPANA ER and alcohol (240 mL of 40% ethanol) in fasted subjects, the mean peak oxymorphone level is 3.9 ng/mL and the median Tmax is 1.5 hours (range 0.75 – 6 hours).

Co-administration of oxymorphone and ethanol must be avoided.

Oxymorphone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation, coma, or death may result.

Source: http://www.fda.gov/cder/foi/label/2006/021610s001,021611s001lbl.pdf

Background

- The FDA recommends all manufacturers of controlled-release opioids conduct at least *in vitro* studies assessing the risk of alcohol-induced dose-dumping
  - Limited guidance provided on the appropriate design and conduct of these studies
- Pharmacodynamic effects of alcohol–opioid interactions, which have implications for patients safety and misuse or abuse of these agents, have not been well characterized
  - Implications for patient safety, misuse, abuse

Worldwide Literature Search: Objectives

- A global literature review was conducted to better understand
  - Pharmacodynamic effects and safety risks associated with alcohol-opioid interactions and alcohol-induced dose-dumping
  - Study design methodologies considered to characterize this interaction

Search Results

- 16 Clinical trials conducted to date to address alcohol-opioid interactions:
  - Four studies in humans examined dose dumping with extended release opioids
    - Morphine ER[1]
    - Oxymorphone ER[2]
    - Hydromorphone OROS[3] ER[4]
  - Twelve studies in humans examined pharmacokinetic, and/or pharmacodynamic, and safety effects of alcohol and immediate release opioids
    - Morphine IR[5,6]
    - Codeine[7,8]
    - Fentanyl[9]
    - Hydromorphone IR[10]
    - Propoxyphene IR[11,12,13] (dextropropoxyphene/paracetamol)[16]
    - Methadone[14]
    - Meptazinol[12,15]

1. Johnson F et al. J Pain. 2008;9(4):330-336. 2.Fiske W et al. Poster presented at the American Pain Society. 2008. Poster #241. 3. Sathyan G et al. Curr Med Res Opin. 2008 4. FDA Alert for Healthcare Professionals May 2005: Hydromorphone Hydrochloride Extended-Release Capsules (marketed as Palladone™); 5. Setnik B et al. [manuscript in prep]. 6. Sokolowska M et al. The Journal of Pain , 8(4): S39 - S39 . 7. Cudworth AG et al. Br J Clin Pharmacol. 1975;2(1):65-67. 8. Linnoila et al. 1973 Clin Phrramcol Ther 15(4(:368-373 9. Lichtor JL et al. Br J Anaesth. 1991;67(5):579-584. 10. Rush CR. Alcohol Clin Exp Res. 2001; 25(1):9-17. 11. Girre C et al. Eur J Clin Pharmacol. 1991;41(2):147-152 12. Ali NA et al. (1985) Br J Clin Pharmacol 20:631-637 13. Sellers EM et al. (1985) Br J Clin Pharmacol. 19:398-401. 14. Cushman P et al. 1978; Drug Alcohol Dep.3:35-42; 15 Tedeschi G et al. Hum Toxicol. 1984 Feb;3(1):37-43 . 16. Edwards C et al., 1982 Lancet. 2(8294:384

Alcohol & Opioid Interactions: Clinical Trials

Alcohol & Opioid Interactions:

Clinical Trials

Pharmacokinetic Interaction

1. **Cudworth AG, Barber HE, Calvey TN. (1975): The effect of codeine phosphate on the absorption of ethyl alcohol. *Br J Clin Pharmacol.* 2(1):65-67.**

- **Study Design**
  - Randomized, 3-arm parallel, controlled trial in 6 student volunteers (body weight 65.2 kg; range 54.3-86.0 kg)
  - Each subject randomly received one of the following treatments, following an overnight fast, at 30 minute intervals for 2 hours:
    - Water (10 mL)
    - codeine phosphate syrup B.P.C. (10 mL)
    - B.P. syrup (10 mL)
  - Subjects then given ethanol (0.4 g/kg) over 10 minute period
  - PK assessments conducted at 20, 40, 60, 80, 100 and 120 min following ethanol ingestion.
- **Results (N=6)**
  - Ethanol blood concentrations (C_{max}) following codeine pretreatment (29.7 mg/dL) was approximately 20% lower than pretreatment with water (35.0 mg/dL) or syrup (37.0 mg/dL) and was found to be statistically significant (P=0.005)
  - Ethanol AUC between 0-120 minutes was significantly lower for the codeine pretreated group (P≤0.05).
- **Conclusions**
  - ***Pretreatment with codeine phosphate significantly reduced ethanol absorption***
  - ***The concentrations of ethanol in linctuses or syrups containing codeine are unlikely to have any significant effects on the CNS.***

2. Cushman P, Kreek MJ, Gordi E. (1978): Ethanol and methadone in man: A possible drug interaction. Drug Alcohol Dep. 3:35-42.

- **Study Design**
  - Open label, 3-way crossover in 5 stable, methadone maintained males with sporadic, social use of alcohol
  - Subjects were dosed 24 hours following their last methadone dose and received single doses of: regular methadone dose (30-100 mg/day) [M], ethanol alone (35 g) [E] or regular methadone dose + ethanol [ME]
  - PK samples were collected at pre-dose and 2, 4 and 5 hours post dose [M], and 60, 90, 120, 150, 180 and 240 minutes [E, ME]
  - ME treatment: alcohol beverage administered 1 hour following methadone; EtOH administered as 90 mL (100 proof) administered with 1-2 ounces orange juice and ingested within 2 minutes; E treatment, methadone dose withheld until last PK collection (240 minutes)
  - 2-7 day washout period

- **Results**
  - All subjects exhibited fleeting ethanol effects e.g. slurred words, garrulousness, in the E and ME treatment but not the M treatment.
  - Blood Alcohol levels peaked at approximately 60 minutes and ranged from approximately 0.12 – 0.08 g/dL for both E and ME treatments
  - Methadone levels rose and peaked between 3-6 hours following M and ME treatments
  - No systemic differences observed for methadone levels between treatments M and ME

- **Conclusions**
  - ***The addition of a single, acute dose of ethanol did not produce effects on blood methadone levels in methadone maintained subjects***
  - ***Methadone did not appear to produce effects on blood alcohol levels in methadone maintained subjects***

3. Sellers EM, Hamilton CA, Kaplan HL, Degani NC, Foltz RL (1985): Pharmacokinetic interaction of propoxyphene with ethanol. Br J Clin Pharmacol 19:398-401.

- **Study Design**
  - Propoxyphene (65 mg) preceded by 1 hour with EtOH (0.9 g/kg) and administered over 7.5 hours to maintain breath alcohol between 0.08 and 1.0 g/dL (N=6 healthy males)
- **Results**
  - No significant changes in Cmax and Tmax for both propoxyphene and norpropoxyphene ($P>0.05$).
  - AUC 0-8 hours increased for propoxyphene by 31% and decreased for norpropoxyphene by 21%; AUC ratio of propoxyphene:norpropoxyphene decreased by 38% ($P<0.01$)
- **Conclusions**
  - **Ethanol co-administration with propoxyphene results in an increased exposure to propoxyphene levels**

Alcohol & Opioid Interactions: Clinical Trials

Dose Dumping

4. FDA Alert (June 2005): Hydromorphone hydrochloride Extended-Release Capsules (marketed as Palladone™)

- **Study Design**
  - Open label, four-way crossover study in 48 healthy volunteers
  - Subjects received Palladone™ (12 mg) with 240 mL of 0%, 4%, 20% and 40% ethanol in water, in a fed (N=24) and fasted (N=24) state
  - Naltrexone administered prior to dosing
  - Pharmacokinetic assessments conducted

- **Results**
  - Mean Cmax (ratio/0%EtOH) was 1, 2 and 6 in the 4, 20 and 40% ethanol treatment arms. Ranges included an up to 2-fold, 6-fold and 16-fold increase, following the ingestion of 4, 20 and 40% EtOH, respectively.
  - Mean AUC (ratio/0%EtOH) was 1, 1 and 1.3 for the 4, 20, and 40% EtOH treatments, and ranged up to 3.4 fold in the 40% EtOH treatment.
  - In the fed state, mean Cmax ratio following the ingestion of 40%EtOH was 3.5 with a maximum of 6.

- **Conclusions**
  - ***Ingesting Palladone™ with alcohol in clinically relevant amounts resulted in significantly higher peak plasma concentrations of hydromorphone. The effect is more pronounced with increasing concentration of alcohol in a fasted state.***

5. Sathyan G, Sivakumar K, Thippawong J. (2008): Pharmacokinetic profile of a 24-hour controlled-release OROS formulation to hydromorphone in the presence of alcohol. *Curr Med Res Opin.* 24(1):297-305.

- **Study Design**
  - Randomized, open label, four-way crossover study in 48 healthy volunteers
  - Treatments periods separated by 6-14 day washout
  - Subjects received 16 mg OROS hydromorphone with 0%, 4%, 20% and 40% ethanol in orange juice (240 mL) in a fed (Group 1) and fasted (Group 2) state
  - Alcohol was consumed within 30 minutes
  - Naltrexone 50 mg administered 14 and 2 hours prior to dosing and 10, 22, 34, and 46 hours post-dose
  - Pharmacokinetic assessments for up to 48 hours post dosing

- **Results (Group 1 N=20; Group 2 N-19)**
  - Cmax in the fasted state ranged from 1.37 (0% EtOH) to 1.90 (20% EtOH) and from 1.42 (0% EtOH) to 1.64 (4% EtOH) in the fed state, resulting in a 1.3- and 1.1 fold increase, respectively
  - Confidence intervals for AUC were within 80-125% and were higher for all alcohol concentration for C_{max}, relative to 0% ethanol

- **Conclusions**
  - ***Pharmacokinetics of OROS hydromorphone were minimally affected by ethanol and did not result in dose dumping***

6. **Johnson F, Wagner G, Sun S, Stauffer J. 2008: Effect of concomitant ingestion of alcohol on the in vivo pharmacokinetics of KADIAN (morphine sulfate extended-release) capsules. *J Pain*. 9(4):330-336**

- **Study Design**
  - Randomized, double-blind, 4-arm crossover, active controlled trial in 32 adult males (mean age 24, range 21-37 years)
  - Treatments included:
    - Kadian 40 mg + alcohol (40%, 240 mL) (fasted)
    - Kadian 40 mg + alcohol (40%, 240 mL) (fed)
    - Kadian + water (fasted)
    - Morphine IR 40 mg water (fasted)
  - Alcohol consumed within 20 minutes of dosing
  - Pretreatment with naltrexone (50 mg) at 12 and 2 hours pre-dose
  - PK analysis and safety assessments for up to 48 hour post-dose
- **Results (N=27)**
  - Kadian with alcohol (fasted and fed) versus with water resulted in a C_{max} of 16.95, 15.71 and 16.46 ng/mL, respectively compared to morphine IR of 68.4 ng/mL
  - Kadian with alcohol (fed and fasted) versus with water resulted in an AUC of 271.8, 279.33 and 307.2 ng/mL, respectively compared to morphine IR of 231.8 ng/mL
  - Analysis of variance rations for AUC_{∞} and C_{max} satisfied criteria for no drug interaction (90% confidence intervals within 80-125%)
  - No SAEs, AEs experienced by 84% of subjects and included nausea, vomiting, headache, and somnolence.
- **Conclusions**
  - ***There was no drug interaction observed between Kadian (40 mg) and alcohol in a fed and fasted state.***

7. Fiske W, Benedek I, Ahdieh H. (2008): Bioavailability of oxymorphone extended-release tablets following consumption of alcohol or food. Journal of Pain 9(4): 36 - 36 .

- **Study Design**
  - Two part study 1) food effects and 2) alcohol effects
  - Study 2: Randomized, 4-period crossover study in healthy volunteers who received oxymorphone ER (40 mg) with 0%, 4%, 20% and 40% ethanol.
  - Subjects received naltrexone (50 mg)
  - Periods separated by a 7 day washout period
  - PK assessments conducted up to 48 hours post-dose
- **Results (N=6)**
  - Cmax (oxymorphone) increased with increasing ethanol concentrations of 4%, 20%, and 40% (7%, 31%, and 70%, respectively), relative to water
- **Conclusions**
  - ***Increases in Cmax appear to be unrelated to the direct effects of alcohol in the ER tablet because the oxymorphone release in vitro was unaffected by alcohol concentrations of up to 40%***
  - ***Cmax may be increased by an in vivo pharmacokinetic interaction (e.g. gastric emptying, increased splanchnic blood flow).***

Alcohol & Opioid Interactions: Clinical Trials

Pharmacodynamic Interactions

8. Linnoila M, Hakkinen S (1973): Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. Clin Pharamcol Ther. 15(4)368-373.

- **Study Design**
  - Randomized, 7-arm parallel, double-blind, placebo controlled trial in 70 professional drivers (Finnish army) aged 19-22
  - Each subject was randomly assigned to one of 7 groups (N=10/group): 1) no treatment 2) placebo 3) alcohol 0.5 g/kg) 4) diazepam 10 mg 5) diazepam + alcohol 6) codeine 80 mg and 7) codeine 80 mg + alcohol
  - Each subject drove (simulator) for 40 minutes, starting at 30 minutes following dosing
  - During driving performance assessment, 2 emergency situations occurred during each test, where a car drove from the a yard in front of the experimental car
- **Results (N=6)**
  - Placebo increased the inaccuracy of speed estimations
  - Alcohol increased the number of steering wheel reversals and neglected instructions
  - Diazepam 10 mg increased the number of collisions and neglected instructions, but the greatest increase in collisions was after codeine 50 mg ($P<0.001$) compared to the no treatment group
  - The codeine + alcohol group did not show additive effects on performance impairments compared to codeine alone or alcohol alone
- **Conclusions**
  - ***Alcohol (0.5 mg/kg), diazepam 10 mg, and codeine (50 mg), alone or in combination, can increase risks in driving in both emergency situations and monotonous surroundings.***
  - ***Diazepam might have additive or potentiating effects in combination with alcohol.***

9.Tedeschi G, Smith AT, Richens A. Effect of meptazinol and ethanol on human psychomotor performance and mood ratings. Hum Toxicol. 1984 Feb;3(1):37-43

- **Study Design**
  - Double-blind, randomized study in 8 healthy volunteers
  - Meptazinol (200 mg, 3 hourly for 4 doses) or placebo or placebo were administered orally and ethanol (0.8 g/kg) or placebo were given 40 min after the last tablet
  - Peak saccadic velocity (PSV), saccade duration at 30 degrees of amplitude (SD), smooth pursuit velocity (SPV), critical flicker fusion threshold (CFF), choice reaction time (CRT), and visual analogue scales were assessed.

- **Results**
  - PSV ($p < 0.01$), SD ($p < 0.001$) and SPV ($p < 0.01$) were significantly impaired after ethanol, while CFF, CFT and visual analogue scales showed no significant effect ($P > 0.05$)
  - None of the tests were affected by the meptazinol treatment alone. No changes were observed in the ethanol-induced impairment of PSV, SD and SPV when meptazinol was given in combination with ethanol.
- **Conclusions**
  - **Ethanol produced impairing effects on measures of saccadic eye movement, critical flicker fusion threshold and choice reaction time.**
  - **The combination of ethanol with meptazinol did not produce additive changes to these impairments**

10. Ali NA et al. (1985): Comparison of the effects of therapeutic doses of meptazinol and a propoxyphene/paracetamol mixture alone and in combination with ethanol on ventilatory function and saccadic eye movements. Br J Clin Pharmacol. 20:631-637

- **Study Design**
  - Double-blind, double-dummy, six-way crossover study in 6 healthy males
  - Subjects received single doses of meptazinol(200 mg), propoxyphene (65 mg)/paracetamol (650 mg) mixture, or placebo, with and without ethanol (0.8 g/kg), separated by 1 week intervals (fed state)
  - Alcohol was consumed up to 30 minutes following dosing
  - Saccadic eye movements, ventilatory response to hyprecapnia (rebreathing method of Read) and PK sampling conducted at pre-dose and every 30 minutes up to 4 hours following dosing
- **Results**
  - No pharmacokinetic interactions were found between meptazinol, propoxyphene/paracetemol and ethanol ($P>0.05$)
  - Ethanol and in combination with either drug produced significant decreases in saccadic velocity ($P<0.001$), which was not observed for either drug alone ($P>0.05$)
  - Either drug alone, or the combination of meptazinol and ethanol did not produce significant changes in ventilatory response to hypercapnia; propoxyphene/paracetamol with ethanol produced a significant reduction in the slope of ventilatory response at 1.5 and 2 hours post dosing
- **Conclusions**
  - **There were no interactions between meptazinol and propoxyphene/paracetamol with ethanol on pharamcokinetics and saccadic eye movement**
  - **A significant reduction in the slope of ventilatory response to hypercapnia, at 1.5 and 2 hours following dosing, was observed when propoxyphene/paracetamol was combined with ethanol**

11. **Girre C, Hirschhorn M, Bertaux L, et al. (1991): Enhancement of propoxyphene bioavailability by ethanol. Relation to psychomotor and cognitive function in healthy volunteers. *Eur J Clin Pharmacol.* 41(2):147-152.**

- **Study Design**
  - Double-blind, three-way crossover study in 12 healthy males
  - Subjects received one of the following treatments separated by 2 week intervals (fed state):
    - Propoxyphene 130 mg + EtOH (0.5 g/kg) ● Propoxyphene 130 mg ● EtOH (0.5 g/kg)
  - Ethanol administered with plant/fruit juices (Sanbitter) qs 150 mL
  - Pharmacokinetic and pharmacodynamic assessments (objective performance and visual analogue self rating scales) at prior and up to 10 hours (PD) and 31 hours (PK) post dose
- **Results**
  - Propoxyphene treatment resulted in a mean Cmax and tmax of 135 ng/mL and 1.33 hours alone, and 151 ng/mL and 1.63 hours with EtOH, respectively ($P>0.05$)
  - AUC and total clearance of propoxyphene were significantly increased when combined with EtOH versus administered alone (AUC 817 versus 984 ng/mL/h; CL 0.16 versus 0.19 mL/h) ($P<0.05$)
  - Mean plasma EtOH levels were 0.5 and 0.55 g/L with and without propoxyphene, respectively
  - EtOH alone resulted in decreased in flicker fusion threshold ($P<0.05$) and increase in visual reaction time ($P<0.01$); propoxyphene alone resulted in increased visual reaction time ($P<0.001$)and no significant interactions found when administered together
  - EtOH alone or with propoxyphene showed increases in self ratings of drowsy, muzzy, feeble and lethargic compared to propoxyphene alone at 1.25 hours following administration ($P<0.005$); most pronounced increases seen in EtOH alone
- **Conclusions**
  - ***Ethanol enhanced bioavailability of propoxyphene by 25%, probably by reducing first pass metabolism***
  - ***No PD interactions found, EtOH effecgts on physical and mental sedation predominated over the effects of propoxyphene***

12. Lichtor LJ, Zacny J, Apfelbaum JL, et al. (1991): Alcohol after sedation with i.v. midazolam-fentanyl: effects on psyhchomotor functioning. *Br J Anaesth.* 67(5):579-584.

- **Study Design**
  - Randomized, double-blind, four-way crossover study in 12 healthy males (mean age 23; range 21-30 years)
  - Subjects received either midazolam (0.1 mg/kg) followed by fentanyl (2μg/kg), or saline followed by saline, via 30 sec i.v. infusion. 4 hours later subjects received either beverage with no alcohol or 0.7 g/kg alcohol.
  - Pyschomotor and mood assessments at pre-dose and1, 3, 5, and 7 hours post injection and at pre-dose (EtOH) and 1, and 3 hours post-alcohol ingestion.

- **Results**
  - Midazolam-fentanyl alone showed significant changes in eso/exophoria, and increased impairment in the action judgment tester, body sway, fusion flicker, auditory reaction time, divided attention, eye hand coordination, confusion (POMS) ($P < 0.05$)
  - Alcohol alone (mean BAC 0.65 mg/dL) showed significant impairment in visual reaction time, eso/exophoria, and eye-hand coordination ($P<0.05$)
  - No interactions between midazolam-fentanyl were observed.

- **Conclusions**
  - ***Midazolam-fentanyl and alcohol alone, produces impairments on psychomotor performance, however, these effects were not additive under the tested conditions.***

13. **Rush CR. (2001): Pretreatment with hydromorphone, a mu opioid agonist, does not alter the acute behavioral and physiological effects of ethanol in humans. *Alcohol Clin Exp Res.* 25(1):9-17.**

- **Study Design**
  - Randomized, single blind, nine-way crossover study in 9 males and females
  - Subjects received an single oral dose of hydromorphone (0, 1, and 2 mg) followed by ethanol (0, 0.5, and 1 g/kg) administered 1 hour later (30 minutes for consumption) following abstinence from caffeine and solid food for 4 hours prior to dosing
  - Subject-rated, performance-impairing, and physiological effects assessed at pre-dose (drug) and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4 and 5 hours post alcohol ingestion.

- **Results (Group 1 N=20; Group 2 N-19)**
  - Ethanol alone dose dependently produced prototypical subject-rated drug effects (good effects, strong, carefree, high and happy), impaired performance ($P \leq 0.001$) (DSST and Circular lights)
  - Hydromorphone produced few significant subject-rated drug effects but did not impair performance
  - Hydromorphone pretreatment did not significantly alter the effects of alcohol on Subjective drug tests (ARCI, Drug Effects Questionnaire, Adjective Rating Scales, Alcohol Sensation Scale and End of Day Questionnaire, as well as performance tests (Digit symbol substitution, circular lights), physiological assessments (blood pressure) or breath ethanol levels ($P<0.05$)
  - Significant treatment effects found on heart rate ($p<0.02$) where alcohol increased the heart rate and hydromorphone attenuated this increase after the administration of 0.5 g/kg of ethanol but accentuated the increase after administration of 1.0 g/kg ethanol.

- **Conclusions**
  - ***Alcohol alone, produced dose dependent impairments on psychomotor performance, however, these effects were not additive with hydromorphone pretreatment.***

14. Setnik B, Leowen G, Negro-Vilar A, Sellers EM: Pharmacokinetic and Pharmacodynamic evaluations of immediate release morphine in combination with ethanol in healthy subjects. (manuscript)

- **Study Design**
  - Randomized, double-blind, six-way crossover in 24 healthy male moderate alcohol drinkers (7-21 standard drinks/week)
  - Subjects (fasted) received either morphine alone (30 mg), ethanol alone (42.7 g), or morphine (30 mg) with ethanol (11.9, 28.4, 30.8 and 42.7 g) administered as 4% (360 mL), 40% (90 mL), 13% (300 mL), and 20% (270 mL), respectively
  - PK, PD and safety assessments conducted up to 12 hours post-dose
  - Washout between 5 and 9 days
- **Results (N=16)**
  - Ethanol did not have significant effects on morphine plasma levels, and morphine did not have a significant effect on blood alcohol levels ($P<0.05$)
  - Pupil size and blood alcohol levels showed dose dependent changes but did not show significant changes between the morphine alone versus morphine + ethanol, or ethanol alone versus morphine + ethanol treatment, respectively ($P<0.05$)
  - Ethanol produced increased ratings on subjective drug measures (Any effects, bad effects, high and sedation) compared to morphine alone ($P\leq0.0434$), which were not significantly different in the ethanol + morphine treatment ($P>0.05$)
  - Morphine + ethanol (42.7 g) did not produce significant effects on end tidal CO_2, oxygen saturation and choice reaction time ($P\geq0.76$), compared to ethanol alone (42.7 g)
  - No serious or severe AEs reported; 96% of subjects reported mild-moderate AEs most commonly somnolence, feeling drunk, headache, fatigue, nausea, dizziness and vomiting.
- **Conclusions**
  - ***There were no significant interactions found on select PD and safety measures when immediate release morphine was combined with the tested doses of ethanol***
  - ***The combination of morphine and ethanol did not significantly alter the blood levels of either drug.***

15. **Sokolowska M, Sun S, Johnson F, Schuller R, Stauffer J, Romach M, Sellers EM (): The effect of morphine in combination with ethanol on safety, pharmacodynamic (PD) and pharmacokinetic (PK) measures in healthy volunteers. Journal of Pain 8(4):S39 - S39**

- **Study Design**
  - Randomized, double-blind, crossover in 16 healthy, opiate naïve, male moderate alcohol drinkers (7-21 standard drinks/week)
  - Part 1, subjects received: morphine IR (50 mg) alone, ethanol (0.7 g/kg) alone or combined
  - Part 2, subjects who tolerated part 1 received: morphine IR (80 mg) and morphine (80 mg) + ethanol (0.7 g/kg)
  - PK, PD (visual analog scales, pupillometry, capnography, Choice Reaction Time, Digit Symbol Substitution Test, Sternberg Short-Term Memory Test, and Divided Attention Task) and safety assessments conducted up to 8 hours post-dose
  - Washout between 5 and 9 days
- **Results (N=16)**
  - Opiate Naïve subjects who tolerated morphine 50 mg with and without ethanol (0.7 g/kg), administration of morphine 80 mg with and without ethanol, induced side effects of moderate intensity or less
  - Examination of the PD measures indicated that, except for VAS for intoxication, none of the measures were effective in distinguishing between the effects of morphine alone and morphine co-administered with ethanol. Pupillometry was a sensitive measure of the morphine effect, however it was unaltered by ethanol co-administration
  - PK of morphine and its metabolites were generally unaffected by the co-administration of 0.7 g/kg ethanol
- **Conclusions**
  - ***Co-administration of the doses of morphine and ethanol in this study did not appreciably exacerbate the CNS and GI adverse event profiles of morphine***
  - ***Except for one subject with a diastolic blood pressure of 34 mmHg at 6 hours following morphine 50 mg with ethanol, no clinically relevant decreases in vital signs of oxygen saturation were recorded***
  - ***Only limited PD and PK effects were observed and were of minimal clinical importance.***

Conclusions

- Although alcohol alters the pharmacokinetics of certain opioids (propoxyphene; oxymorphone), there were no observed pharmacodynamic or safety effects of alcohol with opioids at the conditions and doses studied
- Limited evidence precludes complete assessment of interaction and safety risks associated with alcohol–opioid co-administration
- Of the limited clinical studies conducted to date, an absence of additive pharmacodynamic, pharmacokinetic and safety effects were noted for select doses of opioids and alcohol. This suggests that additive effects may not occur at such doses and more studies are required to explore various doses and types of opioids.
- Further studies on risks of concurrent alcohol–opioid use in lighter drinkers compared with heavier drinkers and/or drug users are required

Design Considerations

- Objectives
  - Ethanol effects on formulation
  - Drug alcohol interaction
- Drug administration
  - Fed versus fasted
  - Ethanol dose (fixed versus per kg)
  - Dosing duration
- Sample size
  - Often limited sample size
    - May require larger sample size for PD effects
- Endpoints
  - Pharmacokinetic
  - Safety (e.g. vital signs, respiratory function)
  - Pharmacodynamic (e.g. motor impairment, visual impairment, attention)

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