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Abuse Liability Working Group Session: A lethal combination: Clinical trial design considerations to evaluate the nature of opioid and benzodiazepine interactions –

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BZD-Opioid Safety & Abuse Signals

- Rise in deaths and adverse events associated with BZDs misuse and abuse in combination with opioids and/or alcohol
- From 2004 to 2011, rate of nonmedical use-related ED visits involving both opioids analgesics and benzodiazepines increased from 11.0 to 34.2 per 100,000 population (DAWN)
- From 2005 to 2011 an estimated 940,000+ emergency department (ED) visits involved BZDs
- 2014 NFLIS Report: Alprazolam accounted for 53% of tranquilizer and depressants
- Additional reports highlight the dangers of improper use of BZDs: Improperly prescribed to elderly and vulnerable groups (addiction prone individuals); chronic use leading to dependence. [Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry. 2015;72(2):136-42.]

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Benzodiazepines

- Contains approved drug products for approximately 15 benzodiazepines on the US market, not including the Z-drugs (Zolpidem, Eszopiclone, Zaleplon)
- Wide array of indications: used to tx anxiety, alcohol withdrawal syndrome, insomnia, as an anticonvulsant, antiemetic, muscle relaxant, sedative, etc.
- Generally safe and effective when taken as prescribed and directed
- Combinations with opioids or CNS depressants changes the risk benefit balance
- All BZDs listed under Schedule IV by the CSA

Inadequate Label Warnings

- Precautions and Warnings: patients should be ‘cautioned’, ‘advised against’, ‘not recommended’ about the simultaneous ingestion of alcohol
- CNS depressant drugs during treatment with alprazolam tablets”
- Increased risk of suicidal thoughts associated with clonazepam
- No contraindications with opioids listed

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Regulatory Response

1. Title 21, Section 355(o)(4) of U.S. Code empowers the FDA to include new safety information into drug labeling as it comes to light.
2. Increased Rx opioid abuse and accidental overdose in recent years constitutes new safety information.
3. Drug labels communicate the full dangers associated with opioid use.
4. Through revised labels, FDA informed consumers of the potential dangers of combining medications containing opioids with other drugs, such as benzodiazepines.
5. Patients will have more information to ensure use of Rx opioids are safe and effective.
6. Importance of providing information to prevent accidental opioid overdoses.
7. Labels should reflect all information necessary for healthcare providers and patients to make an informed decision on the use of their prescription drugs.

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Literature review

- There is limited literature examining effects of opioids co-administration with CNS depressants
  - One study evaluated co-administration of opioid and benzodiazepine (Zacny et al., 2012)
  - Two studies evaluated co-administration of opioids alcohol (Setnik et al., 2014 and van der Schrier et al., 2017)

Setnik B et al (2014) Evaluation of the safety, pharmacodynamic, and pharmacokinetic effects following oral coadministration of immediate-release morphine with ethanol in healthy male participants. Hum Psychopharmacol.;29(3):251-65
van der Schrier R et al (2017) Influence of Ethanol on Oxycodone-induced Respiratory Depression: A Dose-escalating Study in Young and Elderly Individuals. Anesthesiology.;126(3):534-542
Zacny JP et al (2012) Separate and combined psychopharmacological effects of alprazolam and oxycodone in healthy volunteers. Drug Alcohol Depend.;124(3):274-82.

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Study Results

- Zacny et al showed that alprazolam and alcohol produced stronger effects combined vs alone on a number of measures including psychomotor performance impairment
- Setnik et al demonstrated that morphine increased end tidal CO2, whereas co-administration with ethanol had inconsistent effects
- Van der Schrier et al showed that
  - ✓ Ethanol together with oxycodone causes greater ventilatory depression than either alone, the magnitude of which is clinically relevant.
  - ✓ Elderly participants were more affected than younger volunteers.

Setnik B et al (2014) Evaluation of the safety, pharmacodynamic, and pharmacokinetic effects following oral coadministration of immediate-release morphine with ethanol in healthy male participants. Hum Psychopharmacol.;29(3):251-65
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Criteria for Respiratory Depression

Ventilatory Frequency (Respiratory Rate)

- <10 bpm - 70 study groups used this criterion
- <8 bpm - 46 study groups used this criterion

Oxygen Saturation (SpO_2) – measured by pulse oximetry

- <90% - 24 study groups used this criterion
- <85% - 8 study groups used this criterion

Arterial Partial Pressure of Carbon Dioxide ($PaCO_2$)

- >6.5 kPa - 9 study groups used this criterion
- >50 mmHg - 6 study groups used this criterion

- Cashman JN, Dolin SJ. Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. Br J Anaesth 2004;93(2):212-223.

Partial Pressure of CO_2

- Arterial blood gas analysis
  - Considered the gold standard
  - Invasive
  - Non-continuous
  - Painful
  - Risk of infection and damage to tissue, nerves, vessels

- Transcutaneous electrode
  - Non-invasive
  - Methodological and technical limitations (eg, baseline calibration, improper application of the sensor, increased skin thickness)

- Capnography
  - Standard procedure during general anesthesia
  - Non-invasive

- Huttmann SE, Windisch W, Storre JH. Techniques for the measurement and monitoring of carbon dioxide in the blood. Ann Am Thorac Soc 2014;11(4):645-652.
- Images from https://openi.nlm.nih.gov/detailedresult.php?img=PMC3472870_sensors-12-10980f1&req=4 and http://www.scancrit.com/2013/02/03/nasal-prong-etco2/

Phase I Clinical Trial Experience

Respiratory Depression Endpoints

- $ETCO_2$ (mmHg)

  - Incidence of increased $ETCO_2$ of at least 10 mmHg compared to baseline or a level >50 mmHg (sustained for at least 30 seconds)

- SpO_2 (%)

  - Incidence of reduced SpO_2 to <92% (sustained for at least 30 seconds)

- Respiratory rate (bpm)

  - Incidence of reduced respiratory rate to <10 bpm or a reduction of at least 30% compared to baseline (sustained for at least 30 seconds)

- Cashman JN, Dolin SJ. Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. Br J Anaesth 2004;93(2):212-223.

Phase I Clinical Trial Experience

Medical Interventions

- Verbal stimuli: Call the subject's name loudly. If no response and/or no improvement in respiratory depression, proceed to physical stimuli.
- Physical stimuli: Apply sternal rub and/or apply nail bed pressure. If subject cannot be aroused and/or there is no improvement in signs of respiratory depression, proceed to oxygen administration and prepare for possible naloxone administration (if there is no improvement with verbal or physical stimuli, there is a high likelihood of requiring naloxone administration).
- Oxygen administration: Administer oxygen with a target SpO_2 of 95% to 100%. Prepare naloxone for administration if no improvement in respiratory depression clinical parameters.

For opioid-induced respiratory depression:

- Naloxone administration: Administer naloxone 0.4 mg IV every 2 to 3 minutes to a maximum of 10 mg; titrate until adequate oxygenation/ventilation is achieved.

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Summary

- Opioid and benzodiazepine interactions can be lethal; product labels have been recently revised to include warnings of profound sedation, respiratory depression, coma, and death
- Few clinical trials have been published that have assessed respiratory depression of opioids and benzodiazepines
- Practical considerations need to be given when evaluating respiratory function in a clinical setting