An Opioid-benzodiazepine Interaction: Benzodiazepines as Opioids?

There has been a rise in emergency room (ER) visits in the state of Florida, and the Centers for Disease Control and Prevention (CDC) in Atlanta have reported an increase in deaths that have been attributed to benzodiazepines being added to an opioid regimen.

Such a dose of the benzodiazepine given to a opioid-naive participant would have no adverse effect. A mechanism is proposed for this interaction.

The importance of the "opioid crisis" in the United States has been emphasized by the formation of a Commission by the President to report on it and to present recommendations as to how to deal with it. The report was published in November 2017.[1] However, it deals primarily with the effects of doses of particular opioids, for example, fentanyl, rather than combinations of drugs.

This commentary describes an unusual effect of benzodiazepines in participants taking opioids. The benzodiazepine behaves as an opioid in this setting, depressing respiration and giving the participant an opioid "high." This effect may need to be considered in the management of opioid-addicted patients. An overview of the clinical significance of this unusual drug-drug interaction and a mechanism for the effect is provided.

A recent paper by Jann described the seriousness of the interaction of benzodiazepines with opioids in terms of morbidity and mortality.[2] Using data from the American Association of Poison Control Centers, only 253 (0.3%), of the 82,156 cases of benzodiazepine poisoning reported in 2011, died. Despite this good safety record, benzodiazepines added to patients taking opioids have been lethal on occasion. It has been suggested that this interaction is a cause for the recent rise in Florida ER visits.[3]

The increases in death rates in Florida for individual drugs have been published. However, data for the effects of drug combinations are harder to obtain. From the 2016 Annual Report of the "Drugs Identified in Deceased Persons by Florida Medical Examiners," it is possible to infer that the emergence of alprazolam as having a major presence in deceased persons is due to a drug interaction. This report points out that alprazolam is rarely the sole cause of death.[4]

The CDC in Atlanta in 2012 had reported that there had been approximately 27,000 deaths involving prescription medications nationwide in 2007.[5] Opioids are a major contributor to these deaths.

The CDC subsequently published a guideline in April 2016 for the prescribing of opioids for chronic pain. One key recommendation was to "avoid concomitant administration of opioids and benzodiazepines whenever possible."[6]

One study investigated the pharmacodynamics of diazepam in opioid-dependent patients.[7]

The physiological parameters (pulse, blood pressure, SpO_2, and respiratory rate) were minimally affected with a therapeutic dose of diazepam. However, subjective effects (sedation, reaction time, and Digit Symbol Substitution Test) were increased. High doses of diazepam in these patients caused significant impairment of psychological performance.

A review of opioid and benzodiazepine abuse has been published.[8] The authors are from the Division of Substance Abuse of the New York Psychiatric Institute. They reviewed the efforts to explain why patients using opioids supplement them with benzodiazepines. They felt that the published evidence did not support a pharmacokinetic interaction. They favored a pharmacodynamic explanation. This was based on the response of the methadone-maintained patients, when they were queried as to why they took diazepam. The responses varied "to get high," "have a good time," and "produce an intense-exciting experience." However, none of the responses corresponded to the response of naive participants given benzodiazepines. These findings were similar to those seen in methadone-treated patients given diazepam (20 and 40 mg).[9]

While diazepam given to naive participants had no effect on pupillary constriction, in methadone-treated patients, diazepam showed further pupillary constriction over that attributed to methadone alone.[10] Diazepam is behaving as an opioid in this setting.

A retrospective analysis of claims data obtained from Truven Health Analytics, Ann Arbor, MI, USA, was made.[11] It included claims data for 35 million beneficiaries. The primary outcome was an ER visit or inpatient admission for opioid overdose. The key-independent variable was concurrent use of a benzodiazepine. In this cohort of privately insured patients, the concurrent use of a benzodiazepine in an opioid-treated patient increased 80% from 2001 to 2013.

The Food and Drug Administration (FDA) has also commented on the rise in opioid-related deaths and is in general agreement with the position of the CDC,[12] although the FDA did not comment on the increased morbidity and mortality from the combination of opioids and benzodiazepines.

Mechanism

Preclinical data have suggested that chronic administration of morphine to mice causes changes in the opioid receptor in the animal. A study by Lopez *et al*. showed that chronic administration of morphine to mice augmented the benzodiazepine receptor binding *in vivo* but not *in vitro*.[13]

The activation of the μ-opioid receptor by the binding of morphine causes structural changes in the μ-opioid receptor. These structural changes have been well studied for the activation of other G-protein-coupled receptors (GPCR).[14] There is a good understanding of how the binding of an opioid to a pocket in the receptor then causes changes. In this situation, a receptor to which a benzodiazepine can bind is created.[15] However, the signal that is generated by the binding of the benzodiazepine to the μ-opioid receptor is that of an opioid.

Activation of the μ-receptor is responsible for the analgesia of opioids. An X-ray crystal structure of the murine opioid receptor (μ-OR) bound to the morphinan agonist BU72 and a G-protein mimetic camelid antibody fragment showed how the three conserved amino acids lie in the core of the μ-OR. An earlier publication from this group identified other compounds, with which the μ-OR could interact.[16] The structural work conducted by this group is impressive, particularly the characterization of the μ-OR as being quite flexible. General reviews of GPCR emphasized the role of "binding pockets" in their structures.[17,18]

Conclusion

The explanation for the opioid-like profile of benzodiazepines given to patients taking opioids, therefore, follows. The structure of μ-OR is distorted by the presence of the opioid. This distortion creates a new pocket in the GPCR, into which the benzodiazepine now fits. This creates a signal. However, the signal is from the μ-OR and therefore is that of an opioid not a benzodiazepine.

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