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The Intentional and Unintentional Side Effects of Loperamide

Loperamide has increasingly been used to combat opioid withdrawal symptoms. During the initial discovery of this over-the-counter-drug in the 1980s, it was originally used to treat diarrhea in small doses. This medication does not cross the blood brain barrier in significant amounts; therefore, it does not cause abnormality in conjunction with central brain activity. Loperamide affects the mu- opioid receptor (MOR) peripherally, specifically in the gut, by decreasing the stomach contractions as its way of relieving cramps and diarrhea. Most opioid agonists, including morphine, have been used for the same initial purpose.

However, Eggleston et. al published an article that evaluated two case studies involving intentional drug abuse and misuse to interact with withdrawal symptoms of substance abuse.2 Ventricular dysrhythmias and prolongation of the QRS duration and QTc interval were reported after oral loperamide abuse in both individuals.2 Furthermore, this anti-diarrheal drug inhibits calcium channels which can increase the likelihood of an overdose. As a result, the prolongation can lead to slower, irregular heartbeats.

Over a 4-year, 4-month period, the eight centers reported only 216 suspected loperamide ingestions. Among these were 182 unintentional exposures and 14 intentional misuses for enhanced therapeutic euphoria effect.1 Exceeding the recommended dosage has been discovered to cause central nervous depression, respiratory depression, and opioid toxicity leading up to death and more fatalities.2

Loperamide works as a mu-opioid receptor agonist that selectively inhibits sodium channels and becomes a promising analgesic medication.4 Additionally, it has the capability to relieve inflammatory pain and causes a blockage of sodium channels, thus resulting in obstruction of the airway and the heart.4 These analgesic alternatives may alleviate opioid withdrawals, but increase dependency due its high accessibility as a low-cost over-the-counter drug. The national poison center found a 71% increase in calls associated with intentional loperamide abuse from 2011 through 2014.2 Despite the risks of substance abuse, it may have the potential of treating patients with pain and lower inflammatory response if used in low dosage.4

Therefore, the public must be aware of the chronic and acute effects of Loperamide and its dangerous exposure in conjunction with opioid withdrawal. Correspondingly, researchers must continue work on providing lower potency alternatives with similar effects. Furthermore, to address this issue, we must understand the possible complications that can result using this medication to interact with opioid withdrawal.

The purpose of the article was to provide two case studies seen in the clinic involving loperamide abuse and the complications following death.2 Emergency Medical Services proceeded with cardiopulmonary resuscitation (CPR), advanced cardiac life support (ACLS), and drug overdose counteraction with naloxone. Both died. The report revealed a twenty-four-year old substance abuser using six boxes of loperamide to avoid drug withdrawal symptoms. An autopsy concluded that he had fluid in the brain and lungs as well as heart complications. A postmortem toxicology analysis of cardiac blood demonstrated a loperamide concentration of of 77 ng/mL (therapeutic range 0.24 to 3.1 ng/mL).2 Similarly, another report revealed a thirty-nine year -old man managing addiction with buprenorphine therapy and collapsed at his residence. The same procedure was executed by the medical team, but he died.

Chronic usage can inhibit calcium channels similarly to opioid receptors, increasing the risk of overdose. A comprehensive postmortem toxicology revealed a femoral blood loperamide concentration of 140 ng/mL.Although these are only two case studies, this has become a widespread problem in the United States. With more reports and case studies taking place, the data will only create similar incidents. Recently, we have heard instances of opioid abuse and loperamide overdose is being exploited on the news, and through social media. It can cause cardiac arrhythmias, ventricular tachycardia, and death. The researchers overlooking the case studies brought attention to the medical profession about a problematic chronic response to the overdoses. Due to the rise of opioid abuse and loperamide abuse, action will soon be taken to regulate the over-the-counter drug similar to other restricted medications. This plays an important role in society as medical professionals and researchers bring public awareness of the effects of loperamide abuse. Furthermore, the scientific community is attempting to conduct more research on the potential long-term effects in rats induced with this anti-diarrheal drug and

the enhancement of hyperglycemia.

In the research article, *Loperamide-induced Cardiac Depression Is Enhanced by*

*Hyperglycemia: Evidence Relevant to Loperamide Abuse*, it was found that Loperamide inhibits Na+ channels causing heart failure leading to cardiac depression enhanced by microangiopathy and hyperglycemia.3  Hyperglycemia expressed the mu-opioid receptor (MOR) which increased binding MOR sites and allowed Loperamide to cause heart problems, which can lead to diabetes. These opioid receptors have been discovered in the heart tissue by using Positron Emission Tomography. The relationship associated with high glucose and hyperglycemia- induced STAT3 caused an increase in the MOR expression. Ethical methods were used appropriately for the care of laboratory animals. Six rats were used in invasive chemotherapy experiments to demonstrate the enhancement of loperamide-induced cardiac depression in anesthetized diabetic rats. To do this experiment, catheters were lodged in the right femoral arteries of the rats. Although loperamide induced cardiac depression in both normal and diabetic rats, nine weeks after inducing diabetic rats, blood glucose in STZ ( streptozotocin) rats was evidently higher than normal rats. Furthermore, it demonstrated the reduction of heart rate and arterial pressure in hyperglycemic diabetic rats. The results of induced STAT3 and enhanced MOR expression of rats produced statistically significant data in measuring glucose levels (p < 0.05, p<0.01 and p<0.001). Validity could have increased if researchers used more laboratory animals to consistently replicate data. The research of the experiment was well conducted in an attempt to control outside variables so that results were strictly due to the manipulation of the independent variable. Researchers concluded that medications such as Loperamide possibly cause cardiac depression in the setting of hyperglycemia. However, there might be some limitations in the generalization of the experiment because the effects of rats might not be the same as on humans. Results would most likely be similar if done on humans, although unethical, it is hard to be certain. However, this experiment can potentially cause cardiac depression to a population that is diagnosed with hyperglycemia.Therefore, more clinical research is crucial in the prevention and reduction of loperamide overdoses. Although its can cause damage to the body, researchers wanted to expand its effects as a possible anti-inflammatory drug.

Loperamide is an antidiarrheal drug that targets mu- opioid receptors, creating an analgesic effect through a non-opioid mechanism.4 It is a Nav1.7 sodium channel expressed blocker in HEK293 cells---- blocking is dose-dependent reversible. However, it did not exert an effect on Nav1.7 sodium channel with the F1737A mutations. To conduct research, a different genetic variant of adult male wild type mice (C57BL/6J) and mu-opioid receptor (MOR) KO mice were purchased from a science laboratory. The involvement of this procedure was done according to ethical research guidelines. In order to control variation, mice were trained before baseline measurements and were adapted to the testing facility. Researchers were curious to investigate the experimental pain in a conscious mouse. The mechanical pain was calibrated by stimulation within ten trials applied to the movement of the hind paw. This demonstrated the amount of paw withdrawal and paw withdrawal frequency causing stronger effects on NAVI.8 channels in ND7123 cells and weaker potency on NAVI.9 channels. More inhibition was observed in the native NavI.8 channels in DRG neurons. The results of the mechanical stimuli measured a statistically significant distribution in white mice and induced mice (p<0.01, p<0.001). White mice showed a decrease in inflammatory pain in correspondence to drug’s activation of mu-opioid receptors. However, this did not take place in KO mice. The results effectively demonstrated that Loperamide has an additive effect on other targets, including muopioid receptors. However, the signaling effect of mu-opioid receptor mechanism is unknown. Researchers were able to demonstrate the strong association that inhibition of Nav1.8 sodium channels could possibly be the main mechanism of Loperamide for pain relief through its effect on the mu-opioid receptor. Naloxone acted as a receptor antagonist that inhibited Loperamide acted as a receptor antagonist that inhibited Loperamide from acting on Nav1.8 channels. This indicates that Na+ channels of opioid receptors both have an effect in pain processing.

Naloxone, a beneficial drug used to treat narcotic overdoses in emergency situations, acts on the same receptors as Loperamide, which are indicated in the opioid-receptor pathway causing a similar effect as opioids. Chronic drug dependence causes heart arrhythmias and possibly myocardial infarctions. This breakthrough of science may include alternative treatments to reduce the potency of sodium channels by using a similar drug to Loperamide for patients. This experiment was conducted very well. The researchers were fully aware of the effects of loperamide and inflammatory pain, but they made sure each mouse had the same dosage each time for control. However, there may have been outside causes of the changes in loperamide administration other that what was expected; it couldn’t be controlled for. A problem found in the study was that it was conducted on rats and assuming effects on humans cannot be fully accurate.

These advances in these studies involving the usage of loperamide will increasingly bring more awareness as researchers continue to understand the chronic and acute effects of this drug. As the opioid abuse becomes a growing problem, it has come to my conclusion that the FDA will most likely attempt to regulate sales to prevent mortality in the United States. After analyzing these articles, I have learned how it can affect opioid abusers, anti-inflammatory response, and cardiac depression enhancing hyperglycemia. Researchers has made great contributions and will hopefully continue further research to prevent further complications by finding alternatives in medicine for the population.

# **Bibliography**

1. Borron, S. W., Watts, S. H., Tull, J., Baeza, S., Diebold, S., & Barrow, A. (2017). Intentional Misuse and Abuse of Loperamide: A New Look at a Drug with “Low Abuse Potential”. *The Journal of Emergency Medicine*. doi:10.1016/j.jemermed.2017.03.018

2. Eggleston W, Clark KH, Marraffa JM. Loperamide Abuse Associated With Cardiac Dysrhythmia and Death. *Annals of Emergency Medicine*. 2017;69(1):83-86.

doi:10.1016/j.annemergmed.2016.03.047.

3. Lo S-H, Niu H-S, Cheng Y-Z, Niu C-S, Cheng J-T, Ku P-M. Loperamide-induced Cardiac Depression Is Enhanced by Hyperglycemia: Evidence Relevant to Loperamide Abuse. *Archives of Medical Research*. 2016;48(1):64-72.

doi:10.1016/j.arcmed.2017.01.008.

4. Wu Y, Zou B, Liang L, et al. Loperamide inhibits sodium channels to alleviate inflammatory hyperalgesia. *Neuropharmacology*. 2017;117:282-291.

doi:10.1016/j.neuropharm.2017.02.010.