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Commentary

Opioid Antagonists: Will they Solve all of the Problems Associated with Opioid Agonists?

observation of possible symptoms of opioid overdose. Vague signs such as extreme sleepiness, breathing problems, or even “pinpoint” pupils may prompt a family member or close friend to whip out this life-saving device and spring into action!



<http://evzio.com/hcp/index.php>

Physicians employed in operating and emergency rooms have utilized opioid antagonist for almost half a century for the treatment of opioid overdose. The prototype antagonist remains naloxone hydrochloride, which actually received FDA approval back in 1971. Why after so many years on the market is this medication now being formulated in the form of an easy to use “auto-injector” that was designed for non-medical professionals to be able to utilize at a moment’s notice? Could this wonder product, being hailed as the best possible safety tool available for life threatening opioid emergencies actual make heroes out of lay people? [1].

Will marketing and providing to the family and caregivers of chronic pain patients prevent the epidemic of opioid medication related deaths of people in our country? What else can be done by physicians and the U.S. Food and Drug Administration (FDA) to reduce the unbelievable statistic of a death every 36 minutes from an opioid overdose in the United States? With upwards of 17,000 Americans dying yearly from prescription opioid overdose, accidentally or intentionally via suicide& deliberate misuse, and constantly consuming more and more of these powerful painkillers-the million dollar question remaining to be answered is: will a new drug formulation device in the hands of laypeople really make a dent in this crisis that in recent years has actually surpassed car accidents as the leading cause of accidental death? [2].

This new formulation Evzio contains naloxone in a new useful device: an “auto-injector” that was recently approved for the emergency treatment of suspected opioid overdose. The FDA and physicians see Evzio as a new “tool” to combat opioid abuse/misuse related deaths. It will work in a manner similar to the epinephrine pen which is marketed for the acute treatment of anaphylaxis. (EVZIO contains a speaker that provides voice instructions to guide the user through each step of the injection).When activated, an automatically inserted needle delivers 0.4 mg of naloxone hydrochloride injection intramuscularly or subcutaneously and afterwards fully retracts the needle into its housing [3].

Caregivers will be expected to utilize this medication after an

For Evzio to be effective, it will have to be prescribed and probably paid for by either the patient or the prescription insurance company. Will the prescriber be willing to address the risk of opioid overdose to their patients on high-dose opioids or just those with known substance abuse or those with a history of addiction or past stays in detox programs? Are we really naïve enough to believe that only those people that are prescribed these powerful medications are at risk? The numbers of “users” who acquire these pain killers from friends, relatives and illegal “dealers” is unknown but surely an enormous and unacceptable number that clearly has overwhelmed the ability of law enforcement to eliminate.

I am all for prescribers suggesting Evzio to all their chronic pain patients on high-dose opioids. The need for an explanation on the risk of respiratory depression and death is crucial even if the prescriber does not suspect abuse of opioids. Unintentional overdose is a common term used by physicians and medical examiners after patients consumed dozens of medications, often at extremely high doses-many not even prescribed or acquired legally. Sounds a lot like suicide? Unfortunately these are reported as “accidental” and continue to be counted the same as a car accident of falling off a building. For these and many other and unclear reasons most autopsy reports will not even suggest that a patient was attempting to take their life-without a suicide note!

This brings us back to the question of will this medication actually be used by a family member if they see someone on their couch breathing shallow?

It is unbelievable how much positivity is being reported with naloxone! Reports of it being without risk or side effects have suggested that the medication can be used by Good Samaritans who happen to be bystanders positioned around the country with open arms and

equipped with the life-saving antidote and unwavering willingness to assist doctors and reduce society concerns of opioid death. Caregivers must be educated about what to expect AFTER giving naloxone... sweating, goose-bumps, increased heart rate, agitation, withdrawal symptoms, and the lack of efficacy for overdoses of other medications that may be onboard including benzodiazepines, etc.

It is also very important to remain aware that most opioids will last longer than naloxone-so good luck encouraging patients to head on down to the emergency room for additional doses of naloxone, and further care including management of withdrawal symptoms.

Any physician, paramedic or researcher with experience injecting naloxone into an unconscious patient, unresponsive due to large doses of opioids on board, is well aware of dramatic increases in both blood pressure (BP) and heart rate (HR) upon its pharmacological response. It is not surprising that rapid “withdrawal-like” symptomatology after IM or IV opioid antagonist treatment, including an unpleasant increase in severe anxiety, palpitations, and hypertensive changes will make this “marketed” and “inferred” safe and easy treatment a very difficult and even potentially dangerous situation for these non-medical professional bystanders who are only trying to help revive someone who may be unresponsive in their humble and untrained opinion.

Safety and complications from treatment apparently are not being advertised as an issue with this newly marketed naloxone- injector according to evzio.com:

“No clinically significant safety findings”

“No serious adverse events”

“No volunteer discontinuation or withdrawal”

This is not really that surprising since “real- world- use” implies “out of a hospital settings” with obvious reduced availability of heart rate or blood pressure monitoring devices or even medical professionals that could use them properly and death that occurred despite utilization of the naloxone-injector could be easily determined to be due to “late” administration of this anecdote.

With drug companies downplaying any cardiovascular complications or even side effects being associated with naloxone, it will be interesting to watch for sympathomimetic-catecholnergic surge with a corresponding rapid pulse following naloxone administration. Myocardial Infarction/Stroke complications can and will occur-especially in patients with risk factors including smoking history, obesity, sedentary lifestyle (from their chronic pain) or hypertension, hyperlipidemia and tachycardia.

The development of a severe hypertensive response after the administration of the opiate antagonist naloxone was evaluated in one study that characterized the potentially dangerous role of blocking or antagonizing opioids and the potential alteration in the regulation of blood pressure in patients. One individual studied showed significant mean arterial pressure changes with a rise from a baseline of 107 mmHg to 147 mmHg 145 min after naloxone injection and infusion. After stopping naloxone, his blood pressure rapidly returned to baseline. Thus, endogenous opioids appear to regulate

blood pressure in some hypertensive patients and opiate antagonists must be administered with caution to these individuals [4].

It is shocking that despite evidence of cardiovascular side effects in studies, few warnings have been provided about untoward side effects that could manifest as dramatic changes in vital signs following administration by lay people.

This is not the first time that naloxone has been suggested as a panacea. Since naloxone is needed as rapidly as possible in an operating room situation-intravenously use to reverse opioid overdose is the most preferred route. Over the years, countless researchers have tinkered with oral formulations for both treatment and reduction of associated opioid agonist complications. A slowed gastrointestinal-related complication has plagued man since the first use of opioid agonists, and continues to contribute to both the unpleasantness and even immobility of chronic pain patients. It is not uncommon for patients on large doses of chronic and powerful opioids to require multiple daily doses of stimulant cathartics and stool-softeners in an effort to have regular bowel functions. The ineffectiveness of laxatives to target the underlying cause of opioid-induced inhibition of gastric motility and the resulting chronic associated constipation have led to the development of treatments that utilize opioid receptor antagonists including naloxone and methylnaltrexone to target receptors in the gut preferentially.

Methylnaltrexone marketed under the name Relistor provides peripherally-acting-opioid antagonism that has the ability to reverse constipation in patients using opioid-agonists without affecting analgesia or even precipitating withdrawals. A permanently charged tetravalent nitrogen atom in its design prevents the crossing of the blood-brain barrier. This predominant antagonist effects counteracts troubling opioid-induced side effects such as itching and constipation, all while not minimizing opioid effects in the brain responsible for analgesia.

RELISTOR is marketed as a prescription medication indicated for the treatment of opioid-induced constipation (OIC) in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied. The usual dose schedule for RELISTOR is once every other day, as needed, but no more than once in a 24-hour period [5].

It has been suggested that naloxone, when given orally, has negligible bioavailability but may actually counteract opioid-induced constipation by blocking the action of opioid medications locally in the gut. Because of a sophisticated understanding of pharmacokinetic properties, naloxone activity in the gastrointestinal tract presumably occurs before almost complete metabolism by the liver to the medications necessary reduction to negligible drug activity in the Central Nervous System (CNS) where opioid (pain) receptors are located. Central effects of the oral naloxone are minimized by utilizing sparse doses that benefit colon transit time and minimize complications that would impair analgesia.

Utilizing this research, a new modified-release combination product containing the strong opioid oxycodone plus the opioid

antagonist naloxone is being researched for the treatment of “severe pain, which can be adequately managed only with opioid analgesics”. It is believed that this combination has unique characteristics that “naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut”. If research proves claims of “superior GI [gastrointestinal] tolerability compared to previous treatment in a clinical practice study” to be accurate, it will be just a matter of time before more and diverse opioids will be reformulated with a combined agonist/antagonist formula [4].

The marketing of oxycodone/naloxone tablets, and other fixed dose combination products including previously marketed pentazocine-naloxone and morphine/ naltrexone utilized agonist/antagonist has been attempted in an effort to prevent reactions from crushing or injecting these combination products. Naloxone was considered a wonderful deterrent to tampering with oral pain medications in an effort to prevent a patient from crushing and injecting an oral opioid with the hope of getting a “greater high or euphoria rush”.

The providing of warnings by physicians and pharmacists were thought to reduce the incidence of severe and potentially lethal misuse-reactions. Unfortunately, the morphine/naltrexone formulation was withdrawn not due to any failure by the science of the formulation including any insignificant amount of sequestered naltrexone reaching systemic circulation, but because of reports of potentially fatal reaction upon patient tampering and the subsequent release of naltrexone blunting the euphoria of opioids and precipitating dangerous opioid withdrawal sequelae in opioid-dependent patient. Suboxone (buprenorphine and naloxone) has become a very popular treatment for opiate addiction and while abuse is still possible, it appears to have less euphoria and reduced analgesia effects compared with full-opioid agonists.

Naltrexone basically has the same pharmacological effects as naloxone, but it is longer acting and does possess potent pharmacologic effects when used orally. Naltrexone is often utilized prophylactically to maintain abstinence from opioids and administered by specially trained medical supervision under anesthesia to provide rapid detoxification in addicted patients wishing to bypass the unpleasant withdrawal syndrome. Naltrexone for Opiate Dependence has not proven to be a breakthrough in allowing patients to remain free of opioids. Patients cannot be started on this preventative treatment until they have already been opioid free for at least a week due to its ability to precipitate an opioid withdrawal in opioid-tolerant patient.

VIVITROL® (naltrexone for extended-release injectable suspension) is a long-acting opioid antagonist that was approved by the FDA in 2006. It has been used as a treatment for alcohol dependence and to prevent relapse to opioid dependence after opioid detoxification. The recommended dose is 380 mg intramuscularly once a month.

Due to its powerful antagonistic properties, its use does have potential dangerous consequences with its use. The blocking of

exogenous opioid effects could result in the necessity to utilize potentially life-threatening opioid doses to sufficiently overcome the competitive receptor blockade due to its unique pharmacological properties: it is injected into a muscle, and cannot be removed from the body, its duration (lasts for one month). Since the medication blocks the effects of opioid-containing medicines that might otherwise be prescribed for a patient for pain, cough, or diarrhea, a patient may be limited in their ability to receive any opioid agonist benefits if needed in the case of an emergency or severe illness.

In addition, hepatotoxicity is a known consequence with oral or injectable naltrexone use. If symptoms or lab values indicate any potential liver damage or hepatitis including stomach area pain lasting more than a few days, yellowing of the whites of eyes, dark urine or even tiredness would necessitate a medical judgment to discontinue treatment would seem prudent.

Stopping overdoses is obviously not enough to combat the current enormous multifactorial problem of opioid misuse and abuse. Recent government pressures have also been focused on rescheduling hydrocodone-based products in an effort to reduce the quantities available for illegal or even legally prescribed use to the more restrictive Drug Enforcement Administration (DEA) schedule/class “II”. Currently refills and telephoned prescriptions are available for the less restrictive class III-V opioid-based medications, with the proposed rescheduling to class-II, refills and telephoned prescriptions will no longer be allowed under the law. This of course does not reduce the amount of opioids prescribed, abused or diverted-it just makes prescribers of class-II more cognizant of its restrictive nature and requires more work for writer (physician), dispenser (pharmacist/nurse), and patient (potential chronic pain patient or possible abuser of medications).

Pharmacist and Physicians for the most part do not support these rescheduling measures due to the proposed increase in record keeping requirements and additional roadblocks to filling what has been considered useful and first-line for the treatment of mild, moderate and moderately severe pain. With a potential switch from its long-time position as a class III controlled substance to the class II location, concerns about what forces-if any will prevent physicians from leap-frogging their patients to the more powerful morphine, methadone, hydromorphone, oxymorphone, or even oxycodone products?

Another potential solution includes pharmacy manufactures and researchers designing and creating more abuse-deterrent opioid formulations as another strategy suggested by the medical community and government theorist. Risk Evaluation and Mitigation Strategies (REMS) which include FDA Mandated med-guides together with Prescription Drug Monitoring Programs (PDMP) have done very little possibly due to little cohesiveness between prescribers and pharmacists to address this problem and work toward the creation of a successful strategy to combat abuse and misuse.

Nature gave man opioid agonists and scientists have created antagonists to combat them. Which will prove the most powerful in



the end? These antagonists sure are providing an interesting subplot to the battle against opioid agonists. Sometimes in medicine it is hard to determine what characteristics describe the antagonist hero (naloxone) and that of the protagonist villain (Opioids)? Is the hero (naloxone) really going to protect humanity from a powerful enemy (Opioids)? Is pain no longer the evil bad guy? Are the prescribers, pharmacists and drug pushers the enemies now? Are patients really just non-competitors in this scenario and unable to stay out of “harm’s way” or utilize powerful pain management treatments safely due to unmanageable side effects or life-threatening dangers? We will see!

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