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Is there a role for vaccines in combatting the opioid epidemic?

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Abstract

Fentanyl is at the center of the opioid crisis in the USA, causing an increasing number of overdoses and deaths. Casey Nevins, Assistant Editor, Vaccine Insights, speaks with Elizabeth Norton, Associate Professor, Tulane School of Medicine, about her work in developing a mucosal vaccination tailored to protect the brain from the effects of fentanyl.

INTERVIEW

Q:

What influenced you to start working with vaccines?

EN:

Like many budding scientists of my generation, I grew up reading The Hot Zone by Richard Preston (a bestselling nonfiction book about viral hemorrhagic fevers) and became interested in infectious disease research. I studied at Emory University for my undergraduate degree and while there, I was fortunate enough to work at the Centers for Disease Control (CDC) in Atlanta, Georgia, researching sepsis in children from Africa. I loved that experience of asking questions and being in the lab to obtain answers. This led me to continue my education and post-doctoral fellowship at Tulane University. There, I investigated mucosal vaccination under the mentorship of John Clements PhD, the former Chair of the Department of Microbiology and Immunology. Since then, I have carried out research on mucosal vaccination as an independent investigator at Tulane.

Q:

What immunotherapeutic advantages does a vaccine targeting fentanyl offer in mitigating the physiological and behavioral effects associated with its abuse?

Contributions: All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

AUTHORSHIP & CONFLICT OF INTEREST

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EN:

For fentanyl substance abusers, the vaccine would stop the effects of the drugs by blocking the molecule from getting into the brain and binding to the body's opioid receptors. This would prevent the effects of fentanyl including respiratory suppression, which in its most severe form results in acute respiratory failure leading to overdose and death. The vaccine would also eliminate the high that comes with taking opioids, which makes the drug less attractive to users. Also, because the vaccine specifically works on fentanyl, it does not stop the effects of other drugs used for pain management. For example, someone could still effectively use morphine after being vaccinated.

By blocking the effects of the drug, you can block a potential reinstatement of craving after an abuser comes off fentanyl with other therapy programs. For individuals with substance abuse, the vaccine is designed to work in parallel with other therapies in order to prevent relapse, overdose, and death.

Other populations protected by a vaccine would be the unintended victims of fentanyl. Fetanyl effects are so potent that material much smaller than the size of a coin (~2 mg) can be lethal. Unintential use includes people taking a powder or pill drug obtained outside of a pharmacy without knowing that it has been laced with fentanyl. Emergency responders like police or military personnel can also come into accidental contact with illicit fentanyl or fentanyl-laced drugs during their routine job duties. A vaccine for this population would also prevent the fentanyl from having any toxic effects on the body.

Q:

What insights or challenges from prior fentanyl vaccine studies have influenced the design and methodology of your investigation [1]?

EN:

Prior studies that have investigated vaccines for drugs of addiction have taught us that we can block the effects of the compound with antibodies to prevent drug intoxication, drug cravings, and re-addiction in the case of relapse. These antibodies can be generated by vaccination with a conjugate antigen, meaning the drug gets chemically attached to a carrier protein. The resulting antigen is immunogenic but lacks any of the original stimulatory ability of the drug when administered to the body.

Previous studies have all focused on making high levels of antibodies after injected vaccination by adding adjuvants to the conjugate antigen. They reasoned that a vaccine that generates the highest titers of serum isotype immunoglobulin G (IgG) would bind to the compound, sequester it in the periphery, and keep it away from the brain.

For our study, we aimed to achieve high levels of antibodies in mice, but we also focused on comparing adjuvants and routes of delivery. The right adjuvant and delivery route can mean the difference between protection and non-protection in mechanisms that are not always anticipated.

"The right adjuvant and delivery route can mean the difference between protection and non-protection in mechanisms that are not always anticipated."

Q:

Why did you choose the dmLT and LTA1 adjuvants?

EN:

I have been working on versions of these adjuvants for about 20 years now. They are unique since they can be used mucosally as well as parenterally. They have been really interesting molecules to study and my and others' research into how they can be applied to different vaccines has led to many unexpected findings [2,3].

dmLT is a double mutant of the heat-labile enterotoxin or LT, and it is a safer but still effective form of the native LT protein. You can use it orally, sublingually, or by injection. About 10 years into my research, I decided to design a better form of dmLT that does not contain its binding subunit, so it could be used nasally. This new form is LTA1, which is composed of the A1 enzymatic active domain of dmLT and its parent molecule, LT. However, unlike dmLT and LT, LTA1 does not bind to GM1 ganglioside on neuronal tissue and has no evidence of causing cranial nerve damage.

dmLT has successfully been tested in a series of clinical trials alongside a number of antigens, including for enterotoxigenic Escherichia coli and polio virus. LTA1 has not yet been tested in a clinical trial, but we are using it to develop a Klebsiella pneumonia vaccine, in collaboration with Jay Kolls here at Tulane University, which is scheduled for a first-in-human study in 1–2 years.

One thing that we were interested in when we first started our fentanyl study is the fact that a lot of opioid-use therapies involve buprenorphine films that are taken buccally or sublingually. There are also potential mucosal drug exposures including powder inhalations. We thought it would be highly relevant for this patient population if we could develop a mucosal approach that could be combined with the delivery of buprenorphine to help control and manage cravings, and a periodic mucosal vaccine dose to maintain high levels of antibodies.

Q:

What did you find regarding the effectiveness of different adjuvants and delivery routes?

EN:

As I said, similar to previous studies, we wanted both high levels of antibodies and to show that we are blocking the effect of the drugs. However, because we were testing dmLT and LTA1, which can be given orally, sublingually, or intranasally, we also wanted to explore different routes.

In our study, we compared the effects of the gold standard adjuvant for achieving high levels of antibodies (intramuscular alum) to intramuscular dmLT, sublingual dmLT, and intranasal LTA1. The mucosal routes all started as an intramuscular prime with subsequent mucosal

boosters, since we reasoned that the prime vaccination would cause a high level of systemic IgG and the mucosal boosters would work to maintain that response over time.

Interestingly, we identified high levels of anti-fentanyl antibodies in all of our vaccine test groups. However, when it came to blocking the drug from entering the brain, the best levels of protection from vaccination were observed with the mucosal booster groups—sublingual dmLT or intranasal LTA1. However, dmLT given parenterally can also protect animals from fentanyl [4].

Q:

What surprised you about your results?

EN:

We were curious why the mucosal groups showed a better immune response, since all the groups had high levels of antibodies of the main serum isotype IgG to fentanyl. An older study had observed that protection from opioids (e.g., oxycodone) and antibody isotypes generated in response to vaccination could be manipulated immunologically during immunization, much like altered adjuvant danger signals to the immune response [5]. Thus, we investigated further, looking for antibody affinity and antibody isotypes IgG1, IgG2, and IgA. To our surprise, the best correlation of protection was found in animals with the highest levels of IgA against fentanyl. This is surprising since IgA is expressed highly at mucosal surfaces whereas IgG is highest in circulating blood.

Upon some additional literature review, we discovered that gut-educated IgA plasma cells have been found to defend the meningeal venous sinuses [6]. Essentially, oral or mucosal exposure to pathogens induces plasma cells that travel to the brain. These tissue-resident plasma cells express high levels of antibodies so that when a mucosally-introduced antigen enters the bloodstream, it becomes trapped in the meninges and does not cross into the brain.

In our study, I think we may have tapped into this sophisticated mechanism for protecting the brain. I like to think of mucosal vaccination in the settings of substance abuse drugs as the means to create an antibody helmet. We are ensuring high levels of antibody around the brain, which is not necessarily reflective of the antibody levels in the bloodstream. However, further research is needed to confirm that this is indeed occurring with our vaccination approach.

When we discovered the importance of IgA, with the help of my collaborators Tom Kosten at Baylor College of Medicine and Colin Haile at the University of Houston, we re-examined data from Tom Kosten's previous clinical trial on a vaccine to stop cocaine addiction [7]. Though his study ultimately did not achieve its clinical endpoints, there were a small number of people who had significantly less cocaine use after they were vaccinated. Upon further investigation, we observed that IgA and not IgG levels were correlated to people who stopped or reduced their use of cocaine after vaccination versus the people who had not [8].

I believe that in order to protect the brain from substance abuse drugs we need a vaccination approach that is more sophisticated than just a generation of the highest level of circulating IgG. Tissue-resident antibody-secreting cells and antibody isotypes are likely critically important.

> "...in order to protect the brain from substance abuse drugs we need a vaccination approach that is more sophisticated than just a generation of the highest level of circulating IgG."

Q:

What are the potential challenges in implementing a fentanyl vaccine on a larger scale?

EN:

When you go from research to commercialization, one of the challenges is always manufacturing. You must manufacture large amounts of vaccine in a way that is not too costly. Another challenge is that fentanyl hapten is classified as a Schedule 1 drug, which affects how we can manufacture our vaccine. Manufacturers need a Schedule 1 license to work with fentanyl hapten and will have to implement careful safety procedures during conjugation reactions.

Another challenge has to do with delivery. There are still important questions that we must answer, likely during clinical trials, such as: will we end up using the injected form of the vaccine in humans? Will that mucosal booster be a critical step or can parenteral immunization with the right adjuvant also work? If mucosal delivery, will a delivery device also be necessary?

Furthermore, we must consider the duration of vaccine-mediated protection. This is an important point because of the practical concerns that come with multiple vaccinations, but also because some users may end up not wanting that protection. If you have someone who really wants to use fentanyl, will the vaccine block them permanently? Someone may intentionally try to use more fentanyl to overcome the vaccine's effects, could this put them at a higher risk of overdose and death if vaccine-mediated immunity decays overtime? We need to know the limits of the vaccine, and how those limits might affect its users.

Q:

How might your findings contribute to the broader understanding of immunotherapies for substance use disorders?

EN:

If we are able to show that IgG or IgA tissue-resident antibody secretion is the most important target, it could radically change how vaccine studies are being designed. Right now, for any vaccine to treat drugs of addiction, researchers look to drive the highest level of serum IgG. If we appropriately change the narrative to the key mechanisms of protection (e.g., driving the highest level of meningeal plasma cells to protect the brain), then we could design better vaccines for anything related to protecting the brain.

Q:

Looking to the future, what are your key goals or priorities in terms of your research?

EN:

It would be wonderful to be part of the team that gets a commercial product on the market to prevent fentanyl or other causes of death, pain, and suffering. Regardless, I am lucky to be able to participate and contribute to the knowledge that changes how vaccines are designed or how we approach what drives protective immunity.

We are all standing on the shoulders of giants, and I have so much appreciation for the scientists who have come before me. It would be great to add another block in the pyramid that is human knowledge and mentor the next generation of scientists along the way.

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BIOGRAPHY

ELIZABETH NORTON is an immunologist with 20 years of experience in evaluating immunity, vaccines, and microbial infections. Dr Norton began her training at the Centers for Disease Control (CDC) prior to completing a master's degree in Public Health and PhD in Biomedical Sciences at Tulane University, New Orleans, USA. She is currently an Associate Professor in the Department of Microbiology and Immunology at Tulane University with a research lab supported primarily through NIH grants and contracts. Her research focus includes immunity in special populations and the design of novel vaccines to generate systemic and mucosal protection from disease with the use of adjuvants.

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