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FEATURED EXPERT

Antidrug Vaccines to Treat Substance Use and Addiction

An interview with Thomas Kosten, MD

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Interviewed by Mark Gold, MD

Congratulations on your career to date and most recent work. Can you explain the idea behind your anti-drug vaccines? Are there any of your papers you'd suggest the reader look at?

Abused drugs are far too small to produce antibody responses. The vaccines work by covalently attaching the abused drug to 20 to 30 exposed amino acids on a carrier protein such as tetanus toxoid and then injecting this vaccine into humans to produce antibodies to both the tetanus toxoid and to the abused drug, because the drug now "looks like" part of this toxoid. The resulting antibodies bind the abused drug when it is used by any route of administration and trap it in the blood stream.

When the antibody-drug complex passes through the kidney or liver, the drug is stripped off of the antibody and either excreted or metabolized to an inactive metabolite that does not bind to the antibodies (these metabolites do not "cross react" to the antibody because of their different chemical structure). The antibody also acts as a buffer to greatly slow any entry of the abused drug into the brain if a very large dose of the drug is used, which would overwhelm the binding capacity of the amount of antibody present. This slowed entry makes the drug non-reinforcing (e.g. oral cocaine is minimally reinforcing, while smoked or IV cocaine is highly reinforcing due to rate of entry into the brain).

We have a number of review papers over the past four years describing this mechanism of action. An important point is that it takes three to four vaccinations over a period of about three months to develop sufficient antibody levels for this treatment to be effective, and patients must come back for these repeated vaccinations. This complicates outpatient use, but contingency management has been most effective for completion of these initial vaccination protocols.

Is the idea to block the drug's reinforcing effects? What about overdose effects? Are each of the vaccines specific to a single drug or class of drugs?

Yes, the antibodies block reinforcing effects, but a slower process like overdose is still possible unless the drug is typically taken in very small quantities when abused – such drugs include PCP and fentanyl. These vaccines are highly specific to a class of drugs and have limited cross-reactivity. For example, opiates fall into at least five classes – morphine, methadone, buprenorphine, oxycodone, fentanyl – and a separate vaccine would be needed for each one.

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What happens if the drug abused is cocaine? Heroin? How would this be preferable to methadone or buprenorphine? Naltrexone?

For opiates, naltrexone is a better choice as a broad-spectrum blocker, but it does not effectively block the super-agonists related to fentanyl. However, these high potency agents are ideal targets for vaccine development, which is underway. Cocaine is an ideal drug for a vaccine because it is highly specific, has inactive metabolites and has an enzyme in the blood – cholinesterase – that breaks down cocaine so that keeping cocaine in the blood stream by the antibody can more efficiently inactivate it than is possible with any other abused drug.

The new high potency cholinesterase enzymes developed and tested by Teva in the last few years makes the ideal combination with the cocaine vaccine. In animal studies using both the enzyme and vaccine together, we simply could not give any dose of cocaine no matter how high to produce any effects on the animals. Thus, this would be a true overdose protection for cocaine.

How long would a single antidrug vaccine treatment last?

These antibodies persist at high levels for about three months and then require a booster vaccination about every three months.

Are there risks that would prevent vaccination of women? Other risks? Adverse effects?

There are no specific risks from these tetanus toxoid based vaccines for women, since tetanus vaccine is even given to pregnant women. The antibodies cross over the placenta so that the fetus would also be protected. So far, the several types of anti-addiction vaccines have been used in hundreds of patients over the past 15 years with no serious adverse events related to the vaccine, although overdoses are still possible.

Are any approved for use? Why?

None are approved for use by the FDA because they have not met the criteria set for efficacy with either cocaine or nicotine. There have been no safety concerns, and a cocaine vaccine, particularly combined with the enhanced cholinesterase, would be the most likely to meet FDA efficacy standards relatively easily. We are working with Teva to move this approach forward, but stigma and finances make this a very slow process.

Many experts think that the current opioid epidemic will be followed by a cocaine epidemic. What treatments exist for a cocaine-dependent patient or those presenting to an ED with a cocaine overdose? Are you developing for cocaine overdose? Cocaine addictions?

As suggested above, yes, we have a new and much more potent cocaine vaccine than we previously tested, but we need funds to move it forward. This vaccine combined with the Teva or other enhanced cholinesterases (Indivior also has one) would prevent overdoses. The enzyme would likely be too slow for reversing overdoses, but a monoclonal anti-cocaine antibody would acutely reverse an overdose the way naloxone works for opiates. So far the cost of monoclonals has made this approach unrealistic.

What about methamphetamine?

We have a methamphetamine vaccine and hope to have it in humans within a year or so, if our funding continues from NIDA.

What kinds of studies are you doing right now? Planning?

The studies are all in animals with methamphetamine, cocaine, nicotine and fentanyl vaccines using a highly effective new adjuvant that has been used in humans at 50 times the dose needed for raising our antibody levels up to sevenfold higher than our previous cocaine vaccine. That previous cocaine vaccine failed because about half of the patients did not attain therapeutic antibody levels. With a sevenfold increase in mean levels, very few and hopefully no patients will not attain full therapeutic blocking levels of the antibodies.

Anything else to add?

You covered it all, just send money. This is a difficult area for getting venture capital as well as NIDA funds to manufacture and get initial FDA approval to use these vaccines in humans. BUT the future looks very promising for biologicals as we reach the limits of pharma investment in small molecules for brain diseases like addictions.

Would you like to be interviewed by Dr. Mark Gold or submit questions for an expert to answer?

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