Nano vaccine for hepatitis B shows promise for third world

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Chronic hepatitis B infects 400 million people worldwide, many of them children. Even with three effective vaccines available, hepatitis B remains a stubborn, unrelenting health problem, especially in Africa and other developing areas. The disease and its complications cause an estimated 1 million deaths globally each year.

In many poor countries, refrigerated conditions required for the current vaccines are costly and hard to come by. It's often difficult in the field to keep needles and syringes sterile. The need to have people return for the three shots currently required also limits success.

Now, a new vaccine that avoids these drawbacks has moved a step closer to human trials. Health researchers hope it will make it possible to immunize large numbers of children and adults in Africa, Asia and South America efficiently and safely.

Scientists at the Michigan Nanotechnology Institute for Medicine and Biological Sciences at the University of Michigan report that a novel, needle-less method for getting an immunity-stimulating agent into the body has proved non-toxic and able to produce strong, sustained immune responses in animal studies. The vaccine is based on a super-fine emulsion of oil, water and surfactants placed in the nose.

The research was supported by the Grand Challenges in Global Health initiative, which is funded by the Bill & Melinda Gates Foundation, the Foundation for the National Institutes of Health, the Wellcome Trust and

the Canadian Institutes of Health Research. The findings appear online in the journal *PLoS ONE*.

The nanoemulsion represents a new delivery method for an antigen already used in existing hepatitis B vaccines to activate the body's immune defenses.

"Our results indicate that needle-free nasal immunization, using a combination of nanoemulsion and hepatitis B antigen, could be a safe and effective hepatitis B vaccine, and also provide an alternative booster method for existing vaccines," says James R. Baker, Jr., M.D., the study's senior author and director of the institute. He also is Ruth Dow Doan Professor and allergy division chief in the U-M Department of Internal Medicine.

The nanoemulsion is made up of soybean oil, alcohol, water and detergents emulsified into droplets less than 400 nanometers in diameter.

The study suggests that the new type of hepatitis B vaccine will not have rigid cold storage requirements and could require fewer administrations than current vaccines, which require three shots given over a period of six months. Protective immunity with the new vaccine required only two immunizations in animals. The vaccine also avoids the risk of spreading needle-borne infections.

The nanoemulsion vaccine also avoids the temporary pain and redness that results after people get shots with the current vaccines, in which an irritating compound, alum, is used as an adjuvant, or enhancer of a vaccine's effect. There was no local inflammation at the nasal site of administration with the new vaccine.

This finding may be significant, because one of the major concerns for nasal administration of vaccines is that they can find their way to the

olfactory bulb in the brain and cause side effects, says Paul E. Makidon, D.V.M., co-first author of the study and a U-M research fellow. "Our studies, however, indicate no inflammation and no evidence of the vaccine in the olfactory bulb," he says.

Baker's team has published earlier studies affirming the promise of nasal nanoemulsions as a strategy for smallpox, influenza, anthrax and HIV vaccines. The nanoemulsion technology is patented by U-M and licensed to Ann Arbor-based NanoBio Corporation. Baker is a founder and equity holder of NanoBio.

Research details:

The research team determined effective doses of the antigen and nanoemulsion. In results obtained in mice, rats and guinea pigs, the nanoemulsion vaccine proved effective at producing three types of immunity: systemic, mucosal and cellular. Further toxicity studies in rodents and dogs showed the vaccine was safe and well-tolerated.

The vaccine was as effective as current hepatitis B vaccines in eliciting systemic protective antibodies in the blood of animals. The nanoemulsion acted as an effective adjuvant, without the need for a traditional adjuvant or inflammatory compound as in the current hepatitis B vaccines.

In addition, the nanoemulsion vaccine produced sustained cellular immunity in Th1 cells, which could make the vaccine useful in treating people with chronic hepatitis B whose own cellular immune responses are inadequate.

The animals given the nasal nanoemulsion in the study also activated a third type of immunity, mucosal immunity, which is gaining recognition among immunologists as a key first-line response to infectious agents in

diseases such as hepatitis B where mucosal tissues are involved in transmission. Baker and his team found the same effect of activating mucosal immunity that was seen in their previous studies of other nanoemulsion-based vaccines.

The researchers tested whether the vaccine could remain stable and effective even if not refrigerated. They found the nanoemulsion vaccine retained its effectiveness for six months when kept at 25 degrees Celsius (77 degrees Fahrenheit), and even was stable and effective for six weeks at 40 degrees C (104 degrees F). This suggests that refrigeration will not be needed for the final distribution of the vaccine in developing countries, making it easier to vaccinate underserved people.

Current studies are focused on developing the preclinical data required to enter human trials, Baker says. The researchers hope that the first human trial can begin within a year.

Source: University of Michigan