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Plant-made drug reverses breathing paralysis

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Paralytic drugs like succinylcholine (SC) are often used during surgery or when critically ill patients require endotracheal intubation. But if the drug is not swiftly cleared from the patient's system, the results can be deadly.

In a new study, Tsafrir Mor, a researcher at Arizona State University's Biodesign Institute and assistant professor in the School of Life Sciencesshows that a plant-produced recombinant human enzyme butyrylcholinesterase (BChE) can rapidly reverse paralysis of the airways (or apnea) caused by succinylcholine.

The results, recently reported in the journal *PLOS ONE*, suggest an expanded role for trauma techniques like rapid sequence intubation (RSI) as well as other methods involving the use of succinylcholine, particularly in the pre-hospital arena, where a speedy intervention can mean the difference between life and death. Given the variety and frequency of conditions involving failed airways, a means of reversing SC-induced apnea may have profound implications.

"BChE is a promiscuous enzyme that can function as an effective, safe and versatile bioscavenger, but its use has been hampered by its availability," Mor says. "Plants expressing recombinant human BChE may provide the answer for this limitation."

The new findings build on earlier work by Mor's group, which demonstrated the potential for plant-made BChE to reverse the effects of organophosphate poisons, including pesticides and weaponized nerve

agents. Possibilities also exist for reversing the effects of acute cocaine overdose or using plant-derived BChE as a cocaine prophylactic, dampening the drug's euphoric effects and thereby discouraging use.

Succinylcholine is a neuromuscular blocking agent, commonly used in conjunction with a sedative during anesthesia, or to allow intubation to be carried out on an emergency basis. Succinylcholine is the drug of choice for such procedures due to the rapid onset and short duration of its effects, as it is rapidly cleared by the patient's serum BChE.

In certain patients however, clearance can be dangerously prolonged, leading to succinylcholine-induced apnea that can last several hours . The phenomenon has been recognized since the 1950s and may occur as a result of genetic factors or as an acquired condition. In either case, it is generally the result of a deficiency in the serum enzyme BChE.

Because of concerns regarding patient sensitivity to SC, use of the drug as an anesthetic in pre-hospital situations has been controversial. Lacking hospital resources to deal with patients exhibiting butyrylcholinesterase deficiency, first responders are often reluctant to undertake the risks involved in emergency endotracheal intubation. Currently, cases of post-SC apnea are typically managed in hospital settings through supportive care, due to a lack of safe, effective and plentiful reversing agents.

About 1 in 1800 administrations of succinylcholine result in prolonged apnea. Around 65 percent of these cases result from decreased hydrolysis of SC by BChE and its variants. Inability to hydrolyze succinylcholine can have a hereditary basis, with some patients carrying an abnormal variant of one or more genes responsible for succinylcholine hydrolysis. Depending on the particular mutation, these individuals can experience periods of apnea ranging from around two hours for those carrying one copy of the non-functional allele to 3-4 hours or more for those carrying two copies.

Additionally, BChE deficiency can be acquired as a result of conditions including cirrhosis, burns, liver cancer or malnutrition or as a side effect of some commonly prescribed drugs, including oral contraceptives. The authors of the current study note that the ability to reverse hereditary or acquired apnea could significantly improve the safety margin for succinylcholine, rapidly restoring normal breathing to an affected patient.

Rapidly and safely reversing succinylcholine-induced apnea may open new possibilities for respiratory management, including new devices or medications for acute trauma situations. Such strategies could be particularly useful in cases of upper airway obstruction, where neuromuscular blockage carries a risk of airway collapse and suffocation.

Although missing or nonfunctional serum BChE could potentially be replaced using blood products including stabilized serum, fresh frozen plasma or purified enzyme, such treatment carries the risk of blood-borne pathogens and prions as well as more common complications associated with transfusion. Mor notes that purification of the enzyme for various applications would necessitate dedicating the entire annual US blood supply to produce a sufficient number of doses.

The solution underlined in the new study involves producing recombinant butyrylcholinesterase in transgenic tobacco plants. The plants are modified to synthesize the BChE enzyme in their leaves. In a series of experiments involving both mice and guinea pigs, Mor demonstrates the ability of plant-derived BChE to reverse post-SC apnea. The method can be rapidly scaled up to provide a significant stockpile of the apnea-reversing agent, without the costs and attendant risks associated with purifying butyrylcholinesterase from blood products.

Further work by Mor and his colleagues will explore issues of pharmacokinetics, safety and efficacy.

More information: www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0059159

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