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TWO APPROACHES TO KETAMINE MOVE FORWARD FOR COMPLEX REGIONAL PAIN

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Two approaches to using ketamine to treat the complex regional pain syndrome (CRPS) - one employing anesthetic doses, the other subanesthetic - both show promise despite the risks associated with prolonged administration of the drug, researchers say.

Neither technique has yet been validated in a randomized, or even an open prospective trial; indeed, the more extreme of the two approaches, using ketamine to induce a coma, has not been published in a peer-reviewed journal. What's more, the senior researchers involved in the two approaches are unwilling to vouch support for the others' techniques.

Yet both research teams have ardent supporters; both are reporting dramatic progress in treating the otherwise intractable condition; both believe their technique works by disrupting central sensitization of pain transmission neurons, which they see as key to the disorder; and both have followed fascinating paths to investigate new uses for an old drug.

This drug has a bad reputation, far in excess of truth, because of how it was initially used, where terrible hallucinations and emergence reactions were associated with it, said Rodney E. Willoughby, Jr., MD, Associate Professor of Pediatrics at the Medical College of Wisconsin in Milwaukee. I can attest to how leery people are of this drug, even for an infection that is otherwise one hundred percent fatal.

INDUCED COMA FOR RABIES

Dr. Willoughby gained international attention last year after he treated a 15-year-old girl who had unwittingly contracted rabies from the bite of an infected bat and had not been vaccinated. With no other known treatment, he and colleagues quickly opted to induce a coma with ketamine because the drug had shown neuroprotective and anti-viral effects against rabies in animal studies, and because much of the destructive effects of the infection are due to disordered brain function, rather than pathophysiologic destruction. The girl became the first known survivor of rabies without receiving a vaccine (*N Eng J Med* 2005;352:2508-2514).

In his view, Dr. Willoughby said in an interview, The ability of anesthesiologists and other experts to use this drug safely with good outcome cannot be disputed.

What is disputed, however, is the extent to which the two ketamine regimens being tested for the pain syndrome will prove most effective with the least side effects.

CRPS (type 1 was formerly known as reflex sympathetic dystrophy, or RSD) is a chronic pain condition, which typically occurs out of proportion to the severity of local traumatic injury, and worsens rather than improves with time. The pain usually affects one limb with dramatic changes in color and temperature of the skin, intense burning sensation, skin sensitivity, sweating and swelling.

The coma-induction regimen grew out of work by German researchers who had previously used ketamine to treat

phantom-limb pain syndrome, said Robert J. Schwartzman, MD, Chairman of Neurology at Drexel University School of Medicine in Philadelphia. He has co-authored two meeting abstracts on the approach and championed it in the lay press.

One of the German doctors had a relative with RSD that was not responding to [any other] treatment so he tried the [ketamine-induced coma] treatment and it worked, Dr. Schwartzman said.

(Dr. Willoughby said he understood that the German team's discovery was in fact a chance finding involving a patient with pre-existing CRPS who suffered severe trauma in a car accident. They had to induce a coma to protect the brain, Dr. Willoughby said. When they brought the patient out of the coma, the chronic pain was gone. It had nothing to do with theory. It was an incidental observation.)

In any case, once the German team became confident enough in the new approach to begin talking about it informally at international meetings, Dr. Schwartzman began referring patients who had tried and failed every other treatment.

KETAMINE TREATMENT REGIMEN

To date, he said, 30 patients have been treated by the German physicians, led by Ralph-Thomas Kiefer, MD, and Peter Rohr, MD, of Eberhard-Karls University in the city of Tuebingen. Treatment is initiated by bolus injections of ketamine (0.5 mg/kg) and midazolam (2.5-5 mg) until deep sedation is reached. Therapy is maintained with infusions of ketamine (3-7 mg/kg/h) and midazolam (0.15-0.3 mg/kg/h) over five days. On the fifth day infusions are slowly tapered.

So far, nine of the 30 patients have experienced complete and permanent remission from their previously intransigent symptoms, Dr. Schwartzman said. Of the remaining 21 patients, all of whom had at least a partial remission, seven were entirely pain-free for six to seven months, after which the pain slowly returned, he said. Ten of the patients are now being treated by Dr. Schwartzman with subanesthetic doses of ketamine in an attempt to boost the initial effect.



Figure. Dr. Robert Schwartzman: Subanesthetic doses help but do not cure patients. Only the anesthetic doses have cured patients. We have done subanesthetic doses in 100 patients without a cure.

Side effects, Dr. Schwartzman said, have been minimal. Patients do experience hallucinations, he said. We try to prevent this by giving the patient midazolam and clonidine when they are in a coma. Some patients have experienced weight loss, abnormal appetite, and abnormal sweating for up to a month. There have been no severe complications. Pneumonia developed in five of the 30 patients, and kidney infections in six, but all responded to treatment. Detailed psychological tests performed in 15 of the 30 patients before and after treatment have shown no change of mental function, he added.

A paper he has co-authored with the German researchers on their results has been rejected by one journal and submitted to another, Dr. Schwartzman said. We're going to have a hell of a time getting it published, he said. The journal editors want a double-blind controlled series. You can't do that with coma.

FIRST US STUDY APPROVED

Although he has not yet employed the procedure himself, Dr. Schwartzman will be collaborating on the first US study of the technique, which has just been approved by the institutional review board at Tampa General Hospital in Florida. The study will be led by Anthony F. Kirkpatrick, MD, Aitnat Professor of Anesthesiology and Director of the Pain Management Center at the University of South Florida in Tampa.

I see between 200 and 300 new patients with RSD each year, Dr. Kirkpatrick said. I probably see more than anybody else in the world now. I've referred so many patients for the treatment in Germany that it reached a point where I had to prove it to myself, using our standards of scientific proof.

The study will involve up to 10 patients with advanced disease that affects multiple limbs, and is progressing despite other treatments. Three patients will initially be treated with ketamine-induced coma, after which a safety monitoring board will review the results.

If the safety factors look acceptable, said Dr. Kirkpatrick, we'll do seven more. The cost to each patient will be \$25,000, slightly less than the estimated \$30,000 in total costs for patients traveling to Germany, he said.

CASE REPORTS: SUBANESTHETIC APPROACH

As for the alternative subanesthetic approach to using ketamine for CRPS, the first peer-reviewed report of a single case study was written by Ronald E. Harbut, MD, PhD, June 2002 in *Pain Medicine* (3:147-155) with a remarkable editor's introduction: This report of a single case study is presented in unusual detail because of the exceptional promise of the technique described, and the importance of further study.

The treatment was built on the pioneering work of Graeme E. Correll, MBBS, a Fellow of the Australian and New Zealand College of Anaesthetists [sic]. Having begun his career as an anesthesiologist in remote jungle villages of Papua-New Guinea, where medical resources were scarce, Dr. Correll relied on low-dose intravenous ketamine as an analgesic, and became well versed in carefully titrating it to avoid the hallucinations typically associated with higher doses. Upon moving to the more developed community of Mackay, Australia, he found the low-dose ketamine to be useful for patients with chronic pain that had been unresponsive to other treatments.



Figure. Dr. Anthony Kirkpatrick: I've referred so many patients for the treatment in Germany that it reached a point where I had to prove it to myself, using our standards of scientific proof.

Eventually, Dr. Correll's work came to the attention of Dr. Harbut while he was working in Mackay on an assignment as a visiting anesthesiologist from the United States. After returning to the US, Dr. Harbut developed a treatment protocol in 2002 while at the Mayo Clinic in Scottsdale, AZ. He is now Director of the Neuropathic Pain Treatment Center and Assistant Professor in Anesthesiology and Pain Medicine at the Milton S. Hershey Medical Center in Pennsylvania. Following Dr. Correll's method, Dr. Harbut treated a 44-year-old woman with a nine-year history of intolerable CRPS that left her all but home-bound and using a cane. Treatment began with 10 mg/hr of ketamine, increased by 10 mg/hr every two hours to a maximum of 30 mg/hr, and was maintained for six days, by which time the patient's pain had completely disappeared and she had tapered off her sustained-release oxycodone by 50 percent, which was completely discontinued at one month.

A second report, co-authored by Dr. Correll, Dr. Harbut, and others, followed 15 months later in *Pain Medicine* (2004;5:263-275) describing the case notes of 33 patients previously treated by Dr. Correll and colleagues in Australia. They initially achieved complete pain relief in 25 (76 percent) of the patients, partial relief in six (18 percent), and no relief in two (6 percent) patients. The relief lasted at least three months in 54 percent of the patients, and at least six months in 31 percent. Twelve of the patients received a second round of the ketamine after the initial treatment, and all 12 experienced complete relief of their CRPS pain initially, including four who remained pain free for over three years.

Dr. Harbut likened ketamine therapy to the healing of a broken bone. If someone breaks a bone and you simply put the two pieces back together, they won't immediately heal. However, if you add a splint and hold the bones juxtaposed and steady for a period of time, and take away the splint later, the bone is healed. I think that the ketamine treatment does something similar; it lends support and allows the abnormally sensitized nerve cells to heal themselves, so that when you finally take away the ketamine, the pain is reduced or gone.

This second report stood out with the addition of a black-box warning at the end, which noted that recent animal studies had found dose-dependent neurotoxic reactions in the cingulate or retrosplenial cortices of adult rats given the drugs phencyclidine and MK-801 which, like ketamine, are NMDA (N-methyl-D-aspartate) antagonists. Treatment with the drugs for 24 to 96 hours resulted in irreversible neuronal degeneration and death in the retrosplenial cortex and other certain regions of the adult rat brain, the warning noted. But this effect, as well as the previously known psychomimetic and cardiostimulatory side effects of NMDA antagonists, appeared preventable with alpha-2-adrenergic agonists, such as clonidine, guanabenz, or dexmedetomidine. As a result, the authors recommended that suitable neuroprotective agents be included whenever ketamine infusion therapy is undertaken for the purpose of treating CRPS.

Clonidine has become the agent of choice for preventing the potential complications of ketamine, according to Dr. Harbut. Drs. Harbut and Schwartzman agree on the need to treat CRPS by disrupting central sensitization through the blockade of NMDA receptors.

The original injury to a peripheral nerve causes central sensitization of pain transmission neurons, said Dr. Schwartzman. The bottom line is that the body's pain cells become hyper-activated.

But they part ways on how to use ketamine. Subanesthetic doses help but do not cure patients, Dr. Schwartzman said. Only the anesthetic doses have cured patients. We have done subanesthetic doses in 100 patients without a cure.

Dr. Harbut would not comment on the use of ketamine to induce coma, but said of his subanesthetic approach, I believe this area of work is going to become and stay extremely exciting for years to come, because of the relief it has and will bring to care for intractable CRPS. The difference between a cure versus remission is how long the relief lasts after treatment.

Clearly, not all patients with CRPS treated with subanesthetic ketamine respond with meaningful or lasting relief. On the other hand, some patients do respond well. The longest remission we have seen thus far has been about three years.

Perhaps surprisingly, Dr. Willoughby, who successfully used ketamine to induce a coma in the rabies case, expressed reservations about Dr. Schwartzman's approach. While complete remission in nine out of 30 patients would be a slam dunk if confirmed, he said, the published results with the subanesthetic approach look almost as impressive. The question then is why you have to push it that far, he said.

But two neuro-intensivists said they thought that ketamine-induced coma sounded like a reasonable approach worth further testing.

It could seem crazy to a neurologist who is not used to practicing in a critical care environment, who is not used to using ketamine as adjunctive pain medicine, said Claude Hemphill, MD, Associate Professor of Neurology at the University of California-San Francisco, and Director of Neuro-critical care at San Francisco General Hospital. In the neuro-intensive care unit (NICU), he said, Treating pain with large doses of sedative agents is an everyday thing. They might even end up on the ventilator for a week as they're deeply sedated to coma or near coma. So I don't think it's *a priori* unethical to put someone in a coma just because they're in severe pain and not critically ill. If they have disabling pain, that's fair to consider.

Neuro-intensivist Stephan A. Mayer, MD, Associate Professor of Clinical Neurology and Neurosurgery at Columbia University School of Medicine and Director of the medical center's NICU, supports the underlying theory of using a pain holiday to achieve long-term remission.

The more pain you're in, the more pain you're in, said Dr. Mayer. The pain-sensitive structures in your brain become irritated and hyper-sensitized. It becomes this vicious cycle. What Schwartzman may be doing is breaking a vicious self-propagating cycle of pain, through analgesic sedation. If in fact it really works, it's of interest because it provides insight into the very nature of chronic pain.

He drew a parallel between the experimental method for treating CRPS and an established treatment for status epilepticus. These are seizures that repeatedly hammer the brain and don't stop, Dr. Mayer said. You get stuck in this self-propagating nightmare. What we find in neuro-intensive care is the only thing that will work is a definitive seizure holiday. We put the patient under anesthetic-level sedation for a day or two days, or sometimes a week.

What no one disputes is the need for an effective remedy for CRPS. These patients get morphine, dorsal column stimulators - none of it works, said Dr. Schwartzman. As a result, I've got a three-year waiting list. That's bizarre. There are thousands and thousands of these patients.

Ultimately, we all want to find a way to improve the quality of life of those who suffer with intractable and intolerable CRPS, Dr. Harbut said. Although the early findings are optimistic, more work is needed to further establish the safety and efficacy of this novel approach.

ARTICLE IN BRIEF

□ Two teams of investigators are reporting dramatic progress in treating chronic regional pain syndrome - one group with anesthetic doses of ketamine, the other with subanesthetic doses of the agent.

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