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COMMENTARY

Ketamine to the Rescue in Status Epilepticus?

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This transcript has been edited for clarity.

Robert D. Glatter, MD: Hello and welcome. I'm Dr Robert Glatter, advisor and editorial board member for Medscape Emergency Medicine.

Managing patients with refractory status epilepticus can be quite challenging for all clinicians. Traditional approaches have utilized benzodiazepines, such as lorazepam, midazolam, and diazepam, along with loading antiepileptic medications, including levetiracetam, valproic acid, and propofol. When such a process fails to control seizure activity, using ketamine may offer superior control for refractory status epilepticus.

Here to discuss this is Dr Peter Antevy, an EMS physician and medical director for Coral Springs–Parkland Fire Department, along with Dr Ken Scheppke, an EMS physician and chief medical officer for Palm Beach County Fire Rescue in Florida. Welcome, gentlemen.

Kenneth A. Scheppke, MD: Thank you.

Peter M. Antevy, MD: Thanks, Rob.

Glatter: This is such an important topic. All of us take care of seizure patients pretty commonly in the emergency department (ED). Ken, I want to start off by asking you how you manage typical status epilepticus patients in the ED. Also, can you talk about refractory status epilepticus and your approach to management?

Scheppke: Both Peter and I are subspecialty board-certified EMS, so our arena is actually the prehospital field. Status epilepticus is a real problem for us because unlike our hospital-based colleagues, we have a limited armamentarium of what we can use. We don't have a whole hospital pharmacy from which to draw on. For us, if midazolam does not work, traditionally the answer has been "diesel and step on it" to get to the hospital, where you can start the treatments you just mentioned in the ED setting.

Glatter: Is intramuscular Versed (midazolam) your go-to when you have a patient who's been seizing for more than 5 or 10 minutes and you come upon them in the field?

Scheppke: The RAMPART study, which came out a few years ago, set the standard of care for prehospital medicine in using 10 mg of intramuscular (IM), intravenous (IV), or intraosseous (IO) midazolam. We use all three routes in the prehospital field. It generally does a good job for us and it's very well tolerated by our patients. But we have the issue of, if that doesn't work, what other option is there in the prehospital environment?

Glatter: Peter, how do you manage this for pediatric patients?

Antevy: In the ED, we use benzodiazepines first and then we typically try Keppra (levetiracetam). Fosphenytoin has kind of taken a step back, but we try levetiracetam and then fosphenytoin. When I can, I also try phenobarbital, and that takes care of most of those kids.

I had a child a couple of years ago who had influenza A; it was H1N1. He was admitted to the hospital and they gave him the entire kitchen sink. Nothing ended up working until days later when they ended up giving him a ketamine infusion. We have those medications, but it's really the anesthetics that are the end game for us on the hospital side of things.

Using Ketamine for Benzodiazepine-Resistant Status Epilepticus

Glatter: Ken, can you tell us about the poster you presented recently at the National Association of EMS Physicians, and then subsequently at the Society for Critical Care Medicine? I'm quite interested.

Scheppke: I'd be happy to. The Palm Beach County Fire Rescue and Coral Springs–Parkland Fire Department combined forces. Together, we have 58 EMS fire rescue stations covering a population of approximately 1.3 million people. We get about 130,000 EMS calls per year, so we've had a fair number of patients who experience seizures.

The problem, as I mentioned before, is if our midazolam standard dose does not work, what can we do? We already carry

ketamine for multiple different protocols. Our paramedics are very comfortable with it because we've been using it for years for agitated patients, procedural sedation, intubation, and even for pain control. Adding it on for status epilepticus, specifically for benzodiazepine-resistant status epilepticus, made sense to us.



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Source: Kenneth A. Scheppke, MD and Peter M. Antevy, MD/Twitter

We started using ketamine as a protocol. We were giving <u>100 mg IV</u> or IO to adults (or the equivalent dose to children), or giving <u>3 mg/kg IM</u> to adults and children. We enrolled 22 patients, ranging in age from 5 to 86 years, over the course of three calendar years between the two agencies.

We had two outcomes. Our primary outcome was for the benzodiazepine-refractory status epilepticus to stop. What we found was that the seizure stopped in 21 out of the 22 cases (95.5%), which was remarkable.

The secondary outcome included the presence of oxygen desaturation. Because we're combining to CNS depressants in the same patient, were there any hypoxia events at any time (with hypoxia defined as less than or equal to $90\% O_2$ saturation)?

The hypoxia events occurred in five of the cases, but of those cases, two had hypoxia before we even got to ketamine. We really can't blame those two cases on ketamine. The remaining three cases occurred after administration of ketamine.

All five patients had normalization of their O_2 sat with really simple maneuvers. Four out of five came back with just supplemental oxygen. One required bag-valve mask for a minute or two. Of these five cases, we did have a patient who was intubated after arriving to the ED, but by then the end-tidal CO_2 was normal and the O_2 sat was normal. We believe that the emergency physician chose to do that simply for airway protection, because at that point the seizures had abolished but the patient was still sedated.

Glatter: Well, those are impressive data. For any practicing emergency physician or EMS physician, that's golden. Would you agree, Peter?

Resistance to Using Ketamine: Is It Safe?

Antevy: It really is a drug that's safe in the hands of many types of practitioners. As medical directors of large EMS

systems, we feel it is safe to provide it as an option to our EMS professionals.

Glatter: There have been many case series in the past 5-10 years that have looked at using ketamine in refractory status epilepticus. For some reason, it just hasn't caught on. Propofol is used more commonly, but using that in the field might be an issue. What do you think the resistance to using ketamine really revolves around?

Scheppke: I'm glad you brought that up because I think there's a lot of misunderstanding with ketamine. Ketamine has gotten a bad reputation based on some science that it didn't control end-tidal CO₂ and was blamed for raising intracranial pressure, which in fact is a myth. It's unfortunately one of the persistent myths in medicine that it raises intracranial pressure. It does not. There's similar evidence debunking the statement that it raises intraccular pressure.

There's a lack of comfort level among my emergency medicine colleagues. In contrast, paramedics are very comfortable with ketamine because we've been using it for many years. That's part of the issue.

When you look at status epilepticus, just about all of our main seizure medications work on the GABA receptor. As we know, the longer you have a seizure, the more the GABA receptor gets downregulated. At the same time, the NMDA receptor gets upregulated. That's where ketamine works. If you have a GABA drug that fails, it makes sense that an NMDA blocker would work. That's what we see in this study.

Glatter: Going to ketamine much sooner in the process, at least in my experience, would make sense. Having seen patients seizing for 25 minutes up to an hour would just be quite dangerous. Peter, I'm sure you would agree with this.

Antevy: Yes. I've been in pediatrics for 20 years now and we've been using ketamine for all of those years. For the pediatric population, ketamine is very safe. When I went into EMS in 2010 and we started introducing ketamine, everyone became a bit paranoid and freaked out about it. I think many people were fearful of using ketamine in adults, but we now understand that that's not so true. We have to get rid of that theory, like Ken said.

Glatter: Obviously, there's a wide margin of safety. <u>Airway reflexes aren't suppressed</u> and <u>ketamine is very safe</u>. At least in the times I've used it, I've never had any concerns—a rare case of maybe laryngospasm, but that's almost unheard of. With that said, I think that the drug really has validity and value in the ED, as well as in the prehospital setting.

Scheppke: This is used in an emergency. I think we have to look at this the same way we look at stroke alerts and STEMI alerts. Status epilepticus is life-threatening and even neurologically damaging for those who don't die from this problem. It's an emergency to get these seizures stopped. I think the failure to aggressively treat this up front is a problem for our patients. For us to go straight to ketamine after a failure of midazolam makes a lot of sense in the prehospital environment.

Glatter: Do you think you'll have any opportunity to conduct a randomized controlled trial looking head-to-head at ketamine versus propofol in recalcitrant cases?

Scheppke: Propofol is an interesting medication as well. I certainly think that it has a role in status epilepticus. When we look at what we carry in the prehospital side, we have limited options and limited space. We don't have necessary cooling capabilities (some medications require refrigeration).

We like medications that have multiple indications, such as ketamine, where we'd use it for pain, intubation, and sedation of violent patients, and now we can use it for status epilepticus. I'm not sure that we'll see the trial done in the prehospital environment, simply because propofol doesn't lend itself as well to the prehospital environment. I'd love to see a hospital study on that.

There's such a paucity of literature on ketamine use early on for refractory status epilepticus. It's really only been used as a last-ditch effort, which doesn't make a lot of sense to us. Again, I think it has to do with the comfort level that we have with this particular medication. It's a medication that's been poorly understood and it's quite a safe drug.

As you mentioned, it has a <u>ceiling effect on respiratory depression</u>, and the patients frequently maintain their airway reflexes. I'd like to see a randomized controlled study between propofol and ketamine, but early-on use is the key.

Glatter: Peter, would you agree?

Antevy: Yes. I would say that we'll never see a propofol study. We have a database of 1300 EMS agencies and all their medications. Zero carry propofol, whereas 547 of those carry ketamine. We're seeing the ketamine roll through those agencies and be adopted very quickly, whereas *en masse* propofol is not.

The only downside about ketamine is that it comes as three different concentrations. The agencies and ED personnel who do adopt this have to be proficient in how to give it. Giving it by IV, it has to be more dilute. Giving it IM, you can use a more concentrated version. As long as you have those safety precautions and side rails in place, this is a safe drug and has very few side effects.

Glatter: In hypotensive patients, ketamine has the advantage as well. There's also a role in patients that can't tolerate benzodiazepine and are hypotensive.

Proper Dilution and Administration

Scheppke: Absolutely. That's one of the reasons it lends itself to the EMS side, especially for the hemodynamically unstable patients.

Peter makes a point in terms of the downsides of the various medications, particularly with ketamine when giving it as IV rapid bolus. When we give it IV or IO to adult patients, we use humeral head intraosseous because of its much better flow rates. We dilute the medication in a 50 cc bag of normal saline and hook it up to a 60-drop set. If you run that wide open, it runs over 2 minutes.

You want to give ketamine as a very slow IV, diluted medication over the course of 2 minutes to prevent many of the side effects. When you give ketamine too fast, you can get laryngospasm. Even though it's not known for respiratory depression, when you give it really fast, you can get some transient respiratory depression. Diluting it and giving it in a little slower IV helps with that.

Glatter: I've even read a case report recently of a pregnant woman who received ketamine and actually did quite well. There were no adverse fetal effects up to 38 weeks after delivery. That's encouraging to hear, especially for pregnant women. That's a challenging situation.

Scheppke: It is. One of our contraindications to ketamine is pregnancy, simply because some risks are unknown. It's not that it wouldn't work, but we don't know what would happen to the fetus. I'm pleased to hear that case report.

Glatter: It would be interesting to talk about that with obstetricians and see what their viewpoint is in the setting of eclampsia/preeclampsia.

Any additional points you would like to add?

Final Words of Advice

Antevy: I would just say that people should seriously consider ketamine, but also don't just jump and add it to your protocol and think it's going to be a miracle medication. We've seen many agencies that tried it and don't get the mechanics right. It took us a little while, and Ken came up with these very simple, easy-to-give methods.

If you think about it, you end up having five different things you're going to give ketamine for, and you give it five different ways. It can get kind of complex and you can end up making an error. Tread cautiously and just do it in the appropriate way at your agency.

Scheppke: I would add the caution that when you give it <mark>IV or IO, it needs</mark> to be diluted in a similar mechanism to the way we just described. Another reason why it's a great EMS drug is that it can be given IM, and in our study, IM was just as effective as IV or IO.

Just like with the RAMPART study, we know that IM midazolam works really well, and IM ketamine is a good backup for those agencies that can't get IV or IO.

Antevy: I'll add one last thing: notifying the hospitals of what you're doing. Whether you are using ketamine in a hospital or in the EMS setting, notify the colleagues who are going to be inheriting those patients from you as to what you're doing.

Glatter: This has been quite informative. Thank you both for spending time here to discuss your protocol at each institution you work with. Again, I really appreciate it.

Scheppke: It's our pleasure. Thanks for having us on.

Antevy: Thanks, Rob. I appreciate it.

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