Q+A with Robert Rebhun, DVM, PhD

Compounded drugs—customized preparations of medications that are not commercially available in the desired formulation or strength—are becoming more and more routine in veterinary medicine. But there is increasing evidence that these drugs are not always as strong as their labels claim, putting veterinary patients at risk for unintended under-dosing or overdosing. Here, UC Davis assistant professor and assistant research scientist Dr. Robert Rebhun talks about a recent study, spearheaded by UC Davis veterinary researchers, that found major inaccuracies in the strength of the compounded version of a popular chemotherapy drug.

Q: What sparked this study?
A: Among the different chemotherapy drugs that we regularly give to our patients is one called CCNU. It’s one of the staples in several of our protocols. The drug is most commonly used to treat animals with histiocytic sarcoma, mast cell tumors, and lymphoma. Normally, we buy drugs like CCNU from the pharmaceutical companies, and they’re FDA approved formulations and regulated through the FDA. But when CCNU suddenly became unavailable, we turned to compounding pharmacies, which are special pharmacies able to create particular drugs to fit the unique needs of patients—in this case, a compounded version of CCNU. However, once we began using the compounded version of CCNU, we began to notice that we weren’t seeing the usual level of toxicity associated with the drug.

Q: What do you mean by toxicity?
A: Normally, when we give chemotherapy, we expect the patient’s white blood cell count to go down. But we were not seeing low white cell counts in the patients being treated with the compounded drug—or they weren’t as low as we would expect. So we went back in our records and started comparing the blood work of the animals being treated with the compounded version of CCNU with the blood work of past patients that had gotten the FDA-regulated drug. And that’s when we realized there was a significant difference in the toxicities we were seeing. And if there is a drug that we can’t really afford to have be “off,” it’s chemotherapy.

Q: How big was the difference?
A: Only 25 percent of the animals being treated with the compounded CCNU developed neutropenia, which is an abnormally low white cell count. But neutropenia occurred in 100 percent of the animals treated with the FDA approved form of CCNU. That is a significant difference. Also, for those animals treated with the compounded CCNU that did see a white blood cell decline, we looked the severity of that decline. Ultimately, we found that both the incidence and the severity of those counts were dramatically less than what we would expect to see.

Q: Have there been other studies in this space looking at this same issue?
A: Yes, in equine medicine. The accuracy of compounded formulations is something that has been identified as a problem with other types of drugs used to treat horses. Interestingly, one issue with any study of the efficacy of compounded drugs is that for most of them, you’re not expecting to see toxicity like we are with chemotherapy. So you may be trying these drugs and they may not be working but you don’t know it. In our case, we were able to make the clinical observation first and then test to confirm what we were seeing.

To do that testing, we turned to Scott Stanley and Heather Knych, both associate professors in
the UC Davis Kenneth L. Maddy Equine Analytical Chemistry Laboratory. They had published studies looking at the efficacy of several compounded drugs used to treat horses—so the expertise in investigating compounding drugs was already here, at UC Davis. When we showed them the clinical data, they were fascinated. Their expertise is not in chemotherapy, but what was so interesting to them is that our findings truly started from a clinical observation. So they were excited to team up with us.

**Q:** How common is compounding in veterinary medicine?
**A:** It is becoming more and more common. One of the potential benefits of compounding is that it allows you in some ways to be more accurate in your dosing—in theory, at least. For example, the FDA-regulated CCNU comes in 10mg or 40mg capsules. If a patient needs 45mg as their calculated dose, they would get rounded down to 40mg because 45mg capsules aren’t available. But if you go through a compounding pharmacy, you can get the drug in capsules of any size. With chemotherapy drugs, the margin of safety in very narrow, and the difference between the most effective dose and the toxic dose is very small—so some believe that using compounded chemotherapy drugs can maximize the effectiveness of the treatment. Also, there’s a cost issue. Sometimes compounded drugs can be much more affordable to our clients, and that’s not trivial. The compounded version of an FDA-approved drug that costs $600 or $700 a month might cost a third as much. So both dosing and cost are driving factors behind the increased popularity of compounding.

**Q:** What are the big-picture implications of your study?
**A:** There is no doubt that there needs to be better oversight in the production and sale of compounded drugs. But for now, raising awareness of the issues with compounded drugs is critical—and that is our primary goal. Veterinarians and owners need to weigh the pros and cons of compounding and be aware of the risks associated with opting for a compounded drug—namely, that you may not be getting what you want. In this case, we found that the compounded capsules were weaker than they should have been. But what if there were too much medicine in that pill? If that mistake is made—if all of a sudden it is more potent than expected—then the toxicity would be expected to go up. And in chemotherapy that would be just as bad.

**Q:** Was this study funded by the CCAH?
**A:** Scott Stanley’s group initially covered the costs associated with the testing. But very quickly we brought our findings to the CCAH, because there are four or five other drugs we think it is important to look at. That’s where the CCAH stepped in very quickly and said they’d cover the cost for the analysis of these other drugs. That’s ongoing now; we’re actively doing that as we speak.