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Don't Mix Off-label Use With Off-the-rack Pills

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A pregnant woman in Wisconsin received prenatal care from a family practitioner. The patient had hypertension, so at about 38 weeks' gestation, the decision was made to induce labor.

On May 15, 2012, the family practitioner used misoprostol to induce labor. The patient received 100 mcg vaginally at 12:24 PM. The recommended dosage for this indication is 25 mcg.

At 1:28 PM, fetal monitoring was stopped and did not resume until 5 PM. At that time, tachysystole (excessive uterine contractions) was noted, along with fetal heart decelerations. Terbutaline was administered to counteract the contractions, but the uterine activity remained excessive.

Variable late decelerations occurred at 11:36 PM. Prolonged decelerations were noted at 12:08 AM on May 16. The cervix was noted to be only 7 cm dilated. At 12:39 AM, fetal heart decelerations recurred and bradycardia developed.

Although the family practitioner was present at the bedside at 12:40 AM, a fetal scalp monitor was not applied until 1 AM. The family practitioner did not have privileges to perform a C-section without supervision, and it was 1:13 AM before a physician who could perform a C-section was summoned.

The on-call physician accomplished a vacuum delivery at 1:30 AM. Unfortunately, the baby was born with Apgar scores of 1 and 3 and a cord pH of 6.7, indicating severe metabolic acidosis. He was transferred to another hospital for neonatal care, including hypothermia treatments.

The child now has severe cerebral palsy, with gross motor involvement in the arms and legs. He can communicate through augmentative communication devices but cannot actually speak. He will require full-time care for the rest of his life.

The defense took the position that while the dosage of misoprostol was excessive, the drug was no longer active in the mother's body, based on its half-life, when the fetal distress occurred.

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VERDICT

Four days before trial, the case was settled for $9 million.

COMMENTARY

I suspect many of you have made a pot roast—and at least some of you have used the simple, tried-and-true method of putting the meat into the slow cooker with a packet of onion soup mix. It makes a tasty dinner with minimal effort. But onion soup packets are for making onion soup—not seasoning pot roast. Guess what? You just used that soup mix off-label!

As clinicians, we all use medications for clinical indications that haven't been specifically authorized by the FDA—and we shouldn't stop. Off-label prescribing is legal, common, and often supported by the standard of care.

But there is a risk: The pill or tablet prepared by the manufacturer is generally aimed at the intended on-label use, not off-label uses. In this case, misoprostol (brand name, Cytotec) is approved by the FDA for prevention and treatment of gastrointestinal ulcers and peptic ulcer disease. The package insert describes dosing as follows:

> The recommended adult oral dose of Cytotec for reducing the risk of NSAID-induced gastric ulcers is 200 mcg four times daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used.[1]

We should not be shocked, then, that Cytotec is supplied as 100- and 200-mcg round white tablets. However, it is frequently used off label for cervical ripening during labor at a dose of "25 mcg inserted into the posterior vaginal fornix."[2]

This brings us to the malpractice trap. While off-label use may be appropriate, off-label uses may not neatly "fit" with the substance prepared by the manufacturer. To be properly administered for cervical

ripening, the available tablet of misoprostol must be cut with a pill cutter or razor prior to administration.[3] Furthermore, dosage is more accurate if the tablet fragments are individually weighed after cutting.[3]

In this case, the discrepancy between the pill prepared by the manufacturer (100 mcg) and the dosage needed (25 mcg) appears to have caught the defendant family practitioner off guard. So the take-home message is: Use medications as supported by the standard of care—but when using a drug off label, do not assume the product supplied by the manufacturer is appropriate for use as is.

Another interesting aspect of this case is the defense strategy. Most clinicians are aware that the tort of negligence involves (1) duty, (2) breach, (3) causation, and (4) harm. However, it is more logically consistent to think of the elements in this way: (1) duty, (2) breach, (3) harm, and if harm has occurred, (4) examine causation (ie, the logical connection between breach and harm).

In malpractice cases, attorneys frequently focus on one of these specific elements. In this case, the physician's duty of care and the harm stemming from cerebral palsy are clearly established. Thus, breach and causation take center stage.

The defense lawyers acknowledged there was a breach, noting the dosage was "excessive." However, they argued that this error didn't matter because the drug was no longer active in the patient's body. In other words, there was no causal connection between the inappropriately high dose and the resultant uterine tachysystole and fetal distress. This is a difficult road for several reasons.

First, the chief danger of using misoprostol is uterine hyperstimulation and fetal distress. The defense would have to argue the hyperstimulation and fetal distress were coincidental and unrelated to the misoprostol—which carries a black box warning for these very adverse effects. The plaintiff's attorney is sure to make a big deal out of the black box warning in front of the jury—noting any reasonable clinician practicing obstetrics should be aware of the risks that come with misoprostol's use. You can almost hear the argument in summation: "It is so important, they drew a warning box around it."

Furthermore, making the argument that the misoprostol was not in the mother's system at the time the fetal distress started would entail dueling expert testimony about pharmacokinetics and bioavailability—concepts that are difficult for lay jurors to understand. Misoprostol has a half-life of about 20 to 40 min when administered orally and about 60 min when administered vaginally.[4] We know the mother received the overdose of misoprostol at 12:24 PM and a little over an hour later, fetal monitoring was discontinued, leaving the patient unmonitored for 3.5 hours. The agent would have been active or at least *potentially* active when the monitoring was discontinued—but, the defense argued, was the misoprostol biologically active at 5 PM when uterine tachysystole and late decelerations were noted?

The plaintiff's team might counter with an expert's explanation that misoprostol's bioavailability is increased 2- to 3-fold with vaginal versus oral administration. It would also be observed that compared with oral administration, vaginal administration of misoprostol is associated with a slower increase in plasma concentrations but longer elevations (peaking about 1-2 hours after vaginal administration).[5]

At best, the defense expert would be able to argue that the serum level likely peaked 1 to 2 hours after administration (1:24-2:24 PM) and was on its way down when the uterine tachysystole and late decelerations started. During cross-examination, plaintiff's counsel would secure key expert witness admissions that vaginal absorption is less studied and less certain than oral administration and that "there was no way to be sure" what the patient's blood level was when the fetal distress was finally detected. The expert would have to acknowledge the black box warning—a concept that is quite easy for a jury to grasp.

Most jurors would take a skeptical view of the defendant's argument that the negative outcome in this case was coincidental. Some might even be angered by it. This realization likely prompted the defense to settle this case for $9 million.

IN SUMMARY

Onion soup mix makes great soup, but it's an even better seasoning for pot roast. Similarly, there are pharmacologic agents that are effective for conditions for which they are not formally indicated. Do not withhold judicious off-label use of medications when appropriate. However, be aware that off-label uses may require extra attention, and dosing and administration may not be consistent with the product you have on hand. Don't hesitate to seek guidance from pharmacy colleagues when you have questions—they are

an underutilized resource and are generally happy to share their expertise. **CR**

REFERENCES

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