

attenuation factor probably underestimates the acoustic exposure in fluid-filled tissue.

A homogeneous tissue model with attenuation coefficient of 0.3 decibels/cm megahertz throughout the beam path is commonly used when estimating exposure levels. The model is conservative in that it overestimates the *in situ* acoustic exposure when the path between the transducer and site of interest is composed entirely of soft tissue. When the path contains significant amounts of fluid, as in many first- and second-trimester pregnancies scanned transabdominally, this mode may underestimate the *in situ* acoustic exposure. The amount of underestimate depends on each specific situation.¹³

So as, we gaze appreciatively at the "donut" surrounding the nerves, what is that increased exposure time doing on a cellular basis? We do not know. But the injection of fluid may alter tissue acoustic attenuation factors to more closely resemble *in vitro* conditions favorable to inertial cavitation, the effects of which increase with exposure time. The same product literature notes that we should structure the performance of studies to minimize exposure times.

In addition, bubbles represent an acoustical interface where energy release occurs. These bubbles may be iatrogenic or produced in the rarefaction phase of the acoustical wave.^{14,15} Are practitioners assiduous about avoiding bubbles in the injected local anesthetic? What happens to a room-temperature, nondegassed liquid injected into a body-temperature subject? What of bubbles in a local anesthetic to which sodium bicarbonate has been added? Data show that bubbles decrease the cavitation threshold from 1.9-2.4 MPa to less than 0.65 MPa (filtered water data).¹² Product information for the SonoSite L38X/10-5 probe (SonoSite, Inc., Bothell, WA) shows an acoustical pressure of 2.345 MPa in the PW/Doppler mode or 2.89 MPa in the CPD mode. We have no information on the effect(s) of these potential sources of ultrasound cytotoxicity/neurotoxicity enhancement.

Ongoing studies in which thousands of ultrasound-assisted regional anesthetics have been performed without notable adverse effects are reassuring.¹⁶ However, we remember other reports wherein the remarkable safety of spinals in tens of thousands of cases were discussed, and then a complication shows up; *i.e.*, transient neurologic symptoms. The flip side to those observations is that if effects do occur, such as those I have been discussing above, they are unusual events with high significance. Again, for those of us familiar with product development, one would want to specifically identify and mitigate just such occurrences through risk analysis. However, we have not performed or obtained that risk analysis for ultrasound-guided regional anesthesia.

In lieu of an outright moratorium on ultrasound-guided regional anesthesia, we must at least take reasonable precautions until additional research results are available: Limiting local anesthetic concentration to that necessary for achieving the desired result, limiting

ultrasound exposure times, eliminating bubbles in injection solutions, not carbonating local anesthetics, warming local anesthetic solutions before use (degassing), and not spending time admiring the "donut." Until safety questions have been definitively answered, ultrasound-guided regional anesthesia deserves a continued high level of scrutiny.

Philip C. Cory, M.D., St. James Healthcare, Butte, Montana.
pcory@littleappletech.com

References

- Lynch NM, Cofield RH, Silbert PI, Hermann RC: Neurologic complications after total shoulder arthroplasty. *J Shoulder Elbow Surg* 1996; 5:53-61
- Koff MD, Cohen JA, McIntyre JJ, Carr CF, Sites BD: Severe brachial plexopathy after an ultrasound-guided single-injection nerve block for total shoulder arthroplasty in a patient with multiple sclerosis. *ANESTHESIOLOGY* 2008; 108:325-8
- Hebl JR, Horlocker TT, Pritchard DJ: Diffuse brachial plexopathy after interscalene blockade in a patient receiving cisplatin therapy: The pharmacologic double crush syndrome. *Anesth Analg* 2001; 92:249-51
- Ang ES Jr, Gluncic V, Duque A, Schafer ME, Rakic P: Prenatal exposure to ultrasound waves impacts neuronal migration in mice. *Proc Natl Acad Sci U S A* 2006; 103:12903-10
- Davies P: Hazards of ultrasound (letter). *BMJ (Clin Res Ed)* 1984; 289:559
- Yoshida T, Kondo T, Ogawa R, Feril LB Jr, Zhao QL, Watanabe A, Tsukada K: Combination of doxorubicin and low-intensity ultrasound causes a synergistic enhancement in cell killing and an additive enhancement in apoptosis induction in human lymphoma U937 cells. *Cancer Chemother Pharmacol* 2008; 61:559-67
- Feril LB Jr, Kondo T: Biological effects of low intensity ultrasound: The mechanism involved, and its implication on therapy and on biosafety of ultrasound. *J Radiat Res* 2004; 45:479-89
- Jernberg A: Ultrasound, ions and combined modalities for increased local tumour cell death in radiation therapy [thesis]. Karolinska Institutet, Stockholm, Sweden: 2007; 1-35
- Miyoshi N, Tuziuti Z, Yasui K, Iida Y, Riesz P, Sostaric JZ: Ultrasound-induced cytotoxicity of cancer cells is enhanced in the presence of micron-sized alumina particles. *Ultrasound Sonochem* 2008; 15:881-90
- Milowska K, Gabryelak T: Reactive oxygen species and DNA damage after ultrasound exposure. *Biolmol Eng* 2007; 24:263-7
- Riesz P, Kondo T: Free radical formation induced by ultrasound and its biological implications. *Free Radic Biol Med* 1992; 13:247-70
- American Institute of Ultrasound in Medicine: Consensus Document Section 6. Mechanical bioeffects in the presence of gas-carrier ultrasound contrast agents. *J Ultrasound Med* 2000; 19:120-68
- M-Turbo Ultrasound System User Guide. SonoSite 2008
- Juffermans IJ, Dijkmans PA, Musters RJ, Visser CA, Kamp O: Transient permeabilization of cell membranes by ultrasound-exposed microbubbles is related to formation of hydrogen peroxide. *Am J Physiol Heart Circ Physiol* 2006; 291:595-601
- Skyba DM, Price RJ, Linka AZ, Skalak TC, Kaul S: Direct *in vivo* visualization of intravascular destruction of microbubbles by ultrasound and its local effect on tissue. *Circulation* 1998; 98:290-3
- Swenson JD, Davis JJ: Ultrasound-guided regional anesthesia: Why can't we all just stay away from the nerve? *ANESTHESIOLOGY* 2008; 109:748-9

(Accepted for publication July 23, 2009.)

Green Breast Milk after Propofol Administration

To the Editor:—We would like to report an unusual observation of green breast milk after propofol administration. A 33-yr old woman underwent emergency laparoscopic removal of an ectopic pregnancy under general anesthesia with 474 mg propofol as a target-controlled infusion, fentanyl, remifentanyl, mivacurium, and metamizole.

Preoperative medication included dimenhydrinate, metamizole, and piritramide, with additional metamizole, butylscopolamine, and metoclopramide postoperatively.

About 8 h after surgery, the patient reported that the first breast milk pumped showed a bluish green color, which changed to green during the course of the day, and which resolved 48 h postoperatively. Urine color was not monitored. Metabolites of phenoles like propofol (2, 6-diisopropylphenol) are a known cause of green urine.¹ The exact chromophoric compound responsible is not known. As propofol is also excreted into the breast milk,² it was suspected as a cause in this case.

A breast milk sample obtained 30 h after the initial color change was evaluated for possible propofol conjugated metabolite content. The sample was acid hydrolyzed, extracted with ethyl acetate, and analyzed by gas chromatography/mass spectroscopy, but there was no significant differ-

Support was provided solely from institutional and/or departmental sources.

ence in the free propofol concentration (24 ng/ml) as compared with an unhydrolyzed sample, and thus no evidence for conjugated propofol metabolites.³ Metoclopramide, which can cause green urine,⁴ could not be detected in the breast milk sample. Green breast milk is described after iron intake. Also, low casein and lactose content might cause green breast milk.⁵

In conclusion, a still unknown chromophoric substance, presumably derived from propofol, caused a green coloration of the breast milk in this patient. Risks to a nursed infant are unknown. The mechanism of propofol coloration of breast milk remains unknown.

Torsten Birkholz, M.D.,* Gerlinde Eckardt, Ph.D., Stefan Renner, M.D., Andrea Irouschek, M.D., Joachim Schmidt, M.D.

*University Hospital Erlangen, Erlangen, Germany. t.birkholz@gmx.de

References

1. Bodenham A, Culank LS, Park GR: Propofol infusion and green urine. *Lancet* 1987; 2:740
2. Nitsun M, Szokol JW, Saleh HJ, Murphy GS, Vender JS, Luong L, Raikoff K, Avram MJ: Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; 79:549-57
3. Guitton J, Desage M, Lepape A, Degoute CS, Manchon M, Brazier JL: Quantitation of propofol in whole blood by gas chromatography-mass spectrometry. *J Chromatogr B Biomed Appl* 1995; 669:358-65
4. Gillett MJ, Burnett JR: Medications and green urine. *Intern Med J* 2006; 36:64-6
5. Slivka H, Eisenfeld L, Worthley C: Green breast milk. *Conn Med* 1993; 57:763-4

(Accepted for publication July 29, 2009.)