Regarding Pharmacology, Part 3A

TO THE EDITOR: I read "Pharmacology, Part 3A" in the December 2018 issue of the *Journal of Nuclear Medicine Technology* by Geoffrey M. Currie (*1*). I am concerned about one aspect of the discussion, specifically that of cholecystokinin, or its analog, sincalide (Kinevac; Bracco Diagnostics, Inc.), and its proper clinical use. The article states that the recommended dose is 0.02 μg and should be infused over 3–5 min. This method of infusion has been discredited, dating back to 1992 (*2*). Three-min infusions have been shown to have a very wide range in gallbladder ejection fraction response in healthy subjects and because of this, normal values could not be determined 2001 (*3*). In addition, 50% of these healthy subjects develop nausea and abdominal cramping. When the same healthy subjects received slower rates of infusions of 30–60 min, there was much less variability in response and normal values could be determined, although they were different for the 2 different infusion rates. Furthermore, no subjects had adverse symptoms.

These findings led to a multicenter investigation sponsored by the Gastrointestinal Council of the Society of Nuclear Medicine (now the General Nuclear Medicine Council of the Society of Nuclear Medicine and Molecular Imaging [SNMMI]) to determine the optimal method of cholecystokinin-cholescintigraphy infusion by comparing 15-, 30-, and 60-min infusions of sincalide in 60 healthy subjects at 4 institutions (*4*). The 15-min infusion showed the widest range of response, and similarly clinically useful normal values could not be determined. Some of these healthy subjects had nausea and or abdominal cramping. The 30-min infusion showed less variability; however, normal values could still not be calculated. The 60-min infusion showed the least variability in these healthy subjects, and normal values could be determined (≥38% gallbladder ejection fraction). No patients had adverse symptoms with the 30- or 60-min infusion methods.

These published data strongly suggest that patients given short infusions may have false-positive studies (low gallbladder ejection fractions but without disease) and end up erroneously going to surgery to have their gallbladder removed. The data also suggest that the adverse symptoms are caused by the method of infusion and unrelated to the presence or absence of disease.

The SNMMI Practice Guideline for Hepatobiliary Scintigraphy 4.0, published in 2010, recommends a slow infusion of sincalide (*5*). Subsequently an interdisciplinary panel consisting of 12 gastroenterologists, surgeons, and nuclear medicine physicians met and then published recommendations in 2011 to standardize sincalide infusion methodology at all centers and specifically recommended the slow infusion method of 0.02 μg over 60 min (*6*).

REFERENCES

1. Currie GM. Pharmacology, Part 3A: interventional medications in renal and biliary imaging. *J Nucl Med Technol.* 2018;46:326–334.
2. Ziessman HA, Fahey FH, Hixson DJ. Calculation of a gallbladder ejection fraction: advantage of continuous sincalide infusion over the three-minute infusion method. *J Nucl Med.* 1992;33:537–541.
3. Ziessman HA, Muenz LR, Agarwal AK, Zaza AAM. Normal values for sincalide cholescintigraphy: comparison of two methods. *Radiology.* 2001;221:404–410.
4. Ziessman HA, Tulchinsky M, Lavely WC, et al. Sincalide-stimulated cholescintigraphy: a multicenter investigation to determine optimal infusion methodology and gallbladder ejection fraction normal values. *J Nucl Med.* 2010;51:277–281.
5. Tulchinsky M, Ciak BW, Delbeke D, et al. SNM practice guideline for hepatobiliary scintigraphy 4.0. *J Nucl Med Technol.* 2010;38:210–218.
6. DiBaise JK, Richmond BK, Ziessman HA, et al. Cholecystokinin-cholescintigraphy in adults: consensus recommendations of an interdisciplinary panel. *Clin Gastroenterol Hepatol.* 2011;9:376–384.

Harvey A. Ziessman
Johns Hopkins Medical Institute
601 North Caroline St., Suite 3231
Baltimore, MD 21278
E-mail: hziessm1@jhmi.edu

Published online Apr. 24, 2019.
DOI: 10.2967/jnmt.119.225706

Reply: Regarding Pharmacology, Part 3A

REPLY: Thank you, Harvey, for drawing this to our attention,

The discussion around sincalide (Kinevac; Bracco) dose rates is not lost on me, and I wrestled with this for some time with the original paper (*1*). I have provided a correction (*2*) to the section, recognizing the widespread use of the traditional 3- to 5-min infusion method and highlighting the more physiologic response the longer 60-min infusion provides.

I recognize the great work your team has done in validating longer infusion times and the recommendations of the consensus committee. Nonetheless, the *Journal of Nuclear Medicine Technology* has an international readership and some consideration needs to be given to global practices. Although I agree that the 60-min infusion method is a more physiologic response, I have some reservations about some of the other conclusions drawn in the literature and as such, aimed to uncomplicate that aspect of the paper (*1*).

The bulk of the literature, including yours, is built on the premise that there is variability in the normal value among healthy subjects (35%) and as a result, potential for false-positives. The issue I see with the gallbladder ejection fraction (GBEF) quantitation is the interpretation. For me, 35% is the value above which we can be reasonably certain (95%) represents absence of gallbladder dysfunction (even if other biliary disease is present). It does not and should not suggest that a value under 35% equates to abnormality or the notion of false-positives. Similar to the multiple ranges for post-Lasix renal imaging (<10 min is normal, >20 min is obstructed, and 10–20 min is dilated but not obstructed), biliary imaging needs a lower range, a second value representing the boundary below which we are 95% certain gallbladder dysfunction is present. The literature discrediting the 3- to

5-min infusion protocol does so on the basis of a single value capturing all, false-positives being a poor outcome, overlooking false-negatives, and absence of a genuine gold standard. So while the general philosophy is one I agree with, the evidence in my belief is insufficient to universally alter protocol. Indeed, there would be resistance to such a universal change due to the increased demands (time and supervision) of the 60-min infusion. Although the longer protocol may be easily accommodated in large teaching hospitals, private clinics running a tight budget will need stronger evidence for change that will commandeer staff and equipment time. The ongoing widespread use of the 3- to 5-min infusion globally is why I tried to simplify the dose parameters, especially given that this issue is not the actual learning foci of the paper.

The assertion that your 1992 paper (*3*) discredited the 3- to 5-min infusion method is perhaps a little strong, and it should be noted that the comparison was with the 30-min not 60-min infusion method. The various infusion methods should not be dismissed without evaluation of both false-positive and false-negative rates, which the cited work does not do. Your 2001 paper (*4*) highlights this and the inappropriate nature of using 35% as an arbitrary cutoff. The reference range needs determination and will be unique for each method of infusion. The subsequent research and recommendations based on comparison of 15, 30 and 60 min infusions is, therefore, flawed (although perhaps logical) in concluding that the 3- to 5-min infusion was omitted from evaluation because it had been previously discredited. The paper (*1*) made no assertions about 15- or 30 min infusions, and so this paragraph/discussion (*5*) is redundant. The paragraph (*5*) indicating the published data "strongly suggest" shorter infusions may have false-positives is overstated. It needs a robust gold standard and balance with false-negative outcomes in patients with disease. It also needs accommodation of the actual protocol I provided (*1*) for situations in which a GBEF was lower than 35% (second infusion or delayed imaging). Although I agree that adverse effects increase with a 3- to 5-min infusion, more robust investigation is required of false-positives and false-negatives using a definitive gold standard with various cutoffs and receiver operating characteristic analysis in order to establish a range above and below which we can be 95% certain of the outcome.

The current Society of Nuclear Medicine and Molecular Imaging guideline (albeit for sphincter of Oddi dysfunction only) and the bulk of literature are consistent with the 3- to 5-min infusion method. Moreover, both Food and Drug Administration (*6*) and manufacturer (Bracco) documentation (*7*) on appropriate use describe a rapid injection protocol. Furthermore, the recent literature on which international departments and professional bodies draw insight to inform protocols is quite variable. Although key recent literature universally suggests the longer infusion is most appropriate to reduce false-positives and unwanted symptoms, there is some debate about whether 30 or 60 min should be used, or indeed multiple 10-min infusions.

The great work done by Harvey's team does dominate the recent literature, and this was not ignored, just omitted on the basis of trying to get some consistency with practice. Although the 60-min infusion, in my mind, is the best approach, this is not new knowledge. Back in the 1980s here in Australia and globally, we used 60-min infusions for the same reason. But the trade-off between time and the perceived small benefit in reduced variability in the normal GBEF saw the shorter 3- to 5-min infusion almost universally adopted. The article (*1*) aimed to remove that debate and simplify, since it was off the central learning outcomes of the paper. I went with simple because it is still the most widely used approach (even if current evidence and historical evidence suggests otherwise), and it remains a more consistent approach than some of the less well standardized alternative meals being used. It is also worth noting that the risk of false-positive with the rapid infusion method is not simply a comparison of 3- to 5-min infusion versus 60-min infusion (or 30 min) as undertaken in the cited studies. As outlined in my original article (*1*), if the GBEF is below normal, this does not establish abnormality. It requires a second higher dose infusion or delayed imaging (just 2 alternative protocols). The short protocol is designed for convenience and shorter scanning time and is consistent with Food and Drug Administration and manufacturer recommendations, with a safety net of further investigation for those GBEFs below the normal value. This approach, as outlined in my paper (*1*), has not been evaluated by the recent literature against the longer infusion methods in terms of false-positive rates.

I recognize the value of the 60-min infusion but also recognize that if that was a MUST, many departments simply would not comply, and the universal benefits of the simplified protocol of 3- to 5-min infusion outweigh the local benefits of the 60-min infusion at the expense of alternative simple approaches. I know you would prefer me to simply say that 3–5 min is wrong and we must do 60 min, but in the context of my thinking and clinical practice, I do not think that is the best approach to this.

I appreciate your insight and comment.

Regards.

REFERENCES

1. Currie GM. Pharmacology part 3A: interventional medications in renal and biliary imaging. *J Nucl Med Technol.* 2018;46:326–334.
2. Currie G. Pharmacology part 3A: interventional medications in renal and biliary imaging [erratum]. *J Nucl Med Technol.* 2019;47:89.
3. Ziessman HA, Fahey FH, Hixson DJ. Calculation of a gallbladder ejection fraction: advantage of continuous sincalide infusion over the three-minute infusion method. *J Nucl Med.* 1992;33:537–541.
4. Ziessman HA, Muenz LR, Agarwal AK, Zaza AAM. Normal values for sincalide cholescintigraphy: comparison of two methods. *Radiology.* 2001;221:404–410.
5. Ziessman HA. Letter to the editor. *J Nucl Med Technol.* 2019;47:263.
6. Food and Drug Administration (FDA). Kinevac technical data. Access Data FDA website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/017697s032lbl.pdf. Accessed July 15, 2019.
7. Bracco. Kinevac technical Data. https://imaging.bracco.com/sites/braccoimaging.com/files/technica_sheet_pdf/us-en-2018-08-30-spc-kinevac.pdf. Accessed July 15, 2019.

Geoffrey M. Currie
Charles Sturt University
P.O. Box U102, CSU
Wagga Wagga, NS 2650, Australia
E-mail: gcurrie@csu.edu.au

Published online Apr. 24, 2019.
DOI: 10.2967/jnmt.119.225797