Sincalide-Stimulated Cholescintigraphy: What Is the Standard?

TO THE EDITOR: The article by Ziessman et al. adds to the further understanding of gallbladder physiology and the effect of cholecystokinin (CCK) stimulation (*1*). They suggest considering a 38% gallbladder ejection fraction (GBEF) as the lower limit of normal for a 0.02 μg/kg infusion of CCK-8 over 60 min and that their method of study should become the standard for routine clinical use. We would like to comment on some limitations inherent in the design, execution, and conclusions of their study that one should take into consideration in determining whether their method should become the standard.

Ziessman et al. chose a Food and Drug Administration–approved CCK-8 dose (0.02 μg/kg to be given over 0.5–1 min) but decided to infuse over 15, 30, or 60 min, thus changing the dose rate at each level. The gallbladder continues to empty during and for 8–12 min after CCK-8 infusion. An accurate measurement of GBEF, therefore, requires that the downward slope of the curve be included in the calculation of GBEF. Drug dose–response studies require that either the dose rate or the duration of infusion be kept constant to test the complete effect of the drug. Because the GBEF does not follow a Gaussian distribution, one cannot use the mean and SD to set the lower limit of the reference range. The mean and wide SD of GBEF values shown in their Table 1 confirm the variability of GBEF seen in healthy subjects. Therefore, one needs to establish the frequency or distribution data to set the lower limit for a normal response. For the gallbladder phase of the study, we collect data at 1 frame/min for 30 min; and beginning at 3 min, CCK-8 is infused at a rate of 3 ng/kg/min for 10 min. A GBEF value below 50% is considered abnormal. Approximately 50% of the patients with chronic acalculous or chronic calculous cholecystitis experience low- to moderate-intensity abdominal pain during or after CCK-8 infusion. The total duration of 90-min data collection allows diagnosis of various types of hepatobiliary and gastrointestinal diseases associated with bile formation and flow (*2*).

The study designed by Ziessman et al. is much longer (120 min) than our method (90 min), and abrupt termination of CCK-8 data collection at 120 min results in missing the downward slope of the curve in the calculation of an accurate GBEF (*2*). Paradoxic gallbladder filling seen in sphincter-of-Oddi spasm occurs immediately after termination of the CCK-8 infusion and will be missed if data collection is not continued for an additional 10–15 min. In addition, 60 min of continuous CCK-8 infusion induces bile transit throughout the small intestine, often reaching the colon. This prevents detection of CCK-8–induced intestinal hyperperistalsis indicative of irritable bowel syndrome seen with a shorter CCK-8 infusion. Radiolabeled bile is an excellent tracer not only for measurement of GBEF but also for detection of various other hepatobiliary and gastrointestinal diseases (*2*). Most patients who experience abdominal pain and discomfort with CCK-8 are likely to prefer a 30-min infusion over 60 min. The suggestion that their method of study should become the standard for routine clinical use may not be very appealing from the patient's point of view.

REFERENCES

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REPLY: The purpose of our investigation was to determine a sincalide infusion methodology that has the least variability (lowest coefficient of variation) by comparing 3 methods (15-, 30-, and 60-min infusions of 0.02 μg/kg) and to establish reference values (*1*). The 3-min infusion method was not investigated because it has previously been shown to have variable and unpredictable results (*2,3*). This sincalide investigation has the largest number of healthy subjects ever studied and is the first published multicenter study that established sincalide-stimulated gallbladder ejection fraction (GBEF) reference values, and no prior study has compared 3 different infusion methods in the same subjects. The statistical analysis is strong and confirms the significance of our results.

In their letter to the editor the writers state that they use a 10-min cholecystokinin-8 infusion with imaging for 27 min, allowing them to capture gallbladder emptying that occurs after the infusion stops, which they consider important. That may be true for methods with short infusion times. Our 15-min infusion showed minor additional emptying after infusion cessation (Table 1). However, the 30-min infusion showed no additional emptying after the infusion ends. A similar lack of additional emptying after the end of infusion was reported by others for a 45-min infusion method in healthy subjects and patients (*4*). Therefore, imaging after the end of cholecystokinin-8 infusion may capture additional emptying when short infusion methods are used, but it adds nothing to the longer (≥30 min) infusion methods.

The writers further state that they consider a GBEF value below 50% as abnormal. However, there are no published data to substantiate that claim. It is unclear, then, why these investigators continue to promote short infusions. Although they have published numerous papers claiming that less than 35% is abnormal for a 3-min infusion and less than 50% for a 10-min infusion, they have published no healthy-subject data to substantiate that statement (*5–8*). The closest they come is in a 2002 publication about a study in which they initially studied 21 healthy subjects (*6*). However, 8 subjects were excluded because their