negative scans with diabetes and end-stage renal disease in three patients that may warrant further investigation. These three patients had acute acalculous cholecystitis with patent cystic ducts. We postulate that acute acalculous cholecystitis in these patients may be related to the small vessel disease of diabetes, producing focal ischemia and necrosis in distended gallbladders. The fourth patient with a false-negative scan was immunosuppressed and immunosuppression may have prevented the cystic duct obstruction that is usually associated with acute cholecystitis. If we had confined our analysis to patients who underwent surgery and did not have end-stage renal disease or immunosuppressive therapy, the sensitivity for detecting acute cholecystitis would have increased from 69% to 100% using strict criteria, and 71% to 85% using liberal criteria.

CONCLUSION

Pretreatment with 0.02 μg/kg CCK injected over 3–5 min followed by only 90 min of imaging was insufficient to identify all patent cystic ducts. The additional use of morphine augmentation increased significantly the detection of patent cystic ducts. This increased the positive predictive value and specificity of cholescintigraphy.

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EDITORIAL

Pharmacologic Intervention for the Diagnosis of Acute Cholecystitis: Cholecystokinin Pretreatment or Morphine, or Both?

Cholecystokinin (CCK) preadministration in conjunction with cholescintigraphy (using ^{131}I-rose bengal or ^{99m}Tc-dihydrothioctic acid) for the diagnosis of acute cholecystitis was first reported in 1975 by Eikman et al. (*1*). The authors attributed the improved efficacy of cholescintigraphy in their series in part to CCK pretreatment.

After introduction of ^{99m}Tc-iminodiacetic acid agent for cholescintigraphy (*2*), Weissmann et al. demonstrated that delayed imaging up to 4 hr increases the efficacy of the study compared to 1 hr imaging (*3*). Previous reviews indicated that CCK pretreatment can be used to shorten the imaging time from 4 hr to 60–90 min (*4–6*). On this basis, Chen et al. (*7*) present their evaluation, in this issue of the *Journal of Nuclear Medicine*, of whether 90 min of imaging after CCK pretreatment is sufficient to identify all patent cystic ducts, and whether addition of morphine augmentation improves the efficacy of cholescintigraphy. The article by Eikman et al. (*1*) was cited as a reference in one of the reviews and by Chen et al. Otherwise, no data seem to be available in the literature to support the above claim.

This issue deserves further clarification. Eikman et al. (*1*) did not imply that delayed imaging was unnecessary by stating, "Simple visual inspection of the images at 90 min was sufficient." Instead, their point was that *early images or quantitative analysis (from 110 min continuous acquisition) were unnecessary.* Also, they did not imply that delayed imaging was unnecessary by stating, "The improved reliability of the test is attributed to CCK pretreatment." The point was that *compared to detection of acute cholecystitis with conventional contrast radiologic technique*, improved detection is attributed to the use of CCK and, possibly, to the great sensitivity of the gamma camera. Delayed imaging was not even a routine part of the cholescintigraphy in 1975.

CCK pretreatment has been shown to be useful in certain conditions, although whether or not it obviates the need for delayed imaging cannot be answered at this time. In a series by Rosenthall et al., preadministration of CCK reduced false-positive results in patients with chronic cholecystitis (*8*). CCK pretreatment can be helpful in conditions in which functional resistance to tracer inflow may result from distention of gallbladder with viscous contents, such as during a prolonged fasting state, alcoholism and total parenteral nutrition (*9,10*). Kim et al. previously showed that approximately 50% of volunteers who had paired studies (without and with CCK pretreatment) showed more vigorous gallbladder filling after CCK pretreatment (*11*). Therefore, it can be stated that CCK will improve the efficacy of cholescintigraphy to some degree as compared to no pretreatment. Nevertheless, CCK pretreatment of all patients does not appear to have gained wide acceptance. At least fasting for 24 hr or longer appears to have become a routine indication to preadminister CCK in many laboratories.

MORPHINE AUGMENTATION

Following the introduction of morphine-augmented cholescintigraphy as an alternative to delayed imaging in 1984 by Choy et al. (*12*), several reports have been published on this subject (*13–17*). In most reports, morphine augmentation has been recommended primarily because of its logistic advantage but not necessarily because of its superior diagnostic accuracy. The general

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conclusion in the literature, in terms of efficacy, is that the two tests are diagnostically equivalent (*13–17*). By comparing the efficacy of the two approaches in comparable patient populations and through a reanalysis of published data, Kim et al. recently demonstrated that delayed imaging has a significantly lower specificity and positive-predictive value for acute cholecystitis than morphine augmentation (*18,19*).

Several potential shortcomings associated with morphine augmentation have been reported (*16*), including false-positive studies occurring in patients with chronic cholecystitis or hepatocellular disease, or in other severely ill patients (*13,19,20*). However, this problem is not unique to morphine augmentation. It can be even more serious with delayed imaging (*21,22*). Whereas Fink-Bennet and Balon (*16*) have suggested more delayed imaging in addition to the 30 min after morphine administration to reduce false-positive examinations, Kistler et al. (*13*) found no additional benefit in imaging up to 1 hr instead of 30 min. No definitive data are available in this regard. Second, in patients with acute acalculous cholecystitis, or with the "dilated cystic duct sign," increased intraluminal pressure after morphine administration potentially may result in more false-negative studies than delayed imaging (*14*). Fortunately, the occurrence of false-negative studies associated with dilated cystic duct sign and acute acalculous cholecystitis is rare enough to result in no significant difference in the sensitivity and negative predictive value between the two techniques, as discussed earlier. The negative predictive value in the series by Chen et al. also is not significantly different between two groups (CCK only versus CCK with morphine).

SINCALIDE PRETREATMENT VERSUS MORPHINE AUGMENTATION

The most widely used cholecystokinetic agent is sincalide (Kinevac, Bracco Diagnostics, Princeton, NJ), a synthetic C-terminal octapeptide of CCK. Chen et al. reported that imaging for 90 min after sincalide pretreatment (0.02 μg/kg over 3–5 min) was insufficient to identify all patent cystic ducts, and morphine augmentation increased the frequency of gallbladder visualization in these patients. This dosage protocol, despite its popularity, has been demonstrated to be nonphysiologic. Krishnamurthy et al. (*23*) have compared various sincalide doses, for a 3-min infusion technique, and demonstrated that 10 ng/kg (the rate of 3.3 ng/kg/min) produces maximal gallbladder emptying. Ziessman et al. (*24*) also have shown that 20 ng/kg of sincalide infused over 3 min produces brief and incomplete gallbladder emptying compared to the same dose infused over 30 min. An extreme example has been described (*25*), in which 20 ng/kg of sincalide infused over 3 min produced gallbladder emptying of only 10% immediately followed by 70% emptying with the same dose of sincalide infused over 10 min. Sarva et al. (*26*) reported that the infusion rate producing maximal gallbladder emptying was 20 ng/kg over 60 min. Although the optimal dose and duration of infusion is the subject of controversy, in general, longer infusion seems to produce more complete gallbladder emptying, probably due to the 2.5-min plasma half-life of sincalide.

It should be noted that a meticulous sincalide infusion technique is important to ensure good gallbladder emptying not only for the gallbladder ejection fraction measurement but also for the pretreatment. For the latter, it appears that less attention has been paid to the administration technique, perhaps because imaging is not performed during gallbladder emptying. A 30–45-min infusion is logistically inconvenient for pretreatment, unlike that for the measurement of gallbladder ejection fraction. A 3-min infusion at the physiologic rate of 3.3 ng/kg/min, as recommended by Krishnamurthy et al. (*23*), or an infusion over up to 10 min at the same or slightly lower rate would probably be adequate for this application. We have been using an infusion of 0.02–0.03 ng/kg over 10 min (*25*). This protocol is likely to produce a greater degree of gallbladder emptying than the protocol used by Chen et al. However, even with this protocol, 9 of 28 patients (32%) with gallbladder nonvisualization at 1 hr despite sincalide pretreatment had gallbladder visualization after morphine administration (*27*), which also suggests that sincalide pretreatment alone is not sufficient to visualize all patent cystic ducts. The two reports (*7,27*) essentially agree with each other with the exception of sincalide infusion protocol.

VARIANTS ASSOCIATED WITH MORPHINE AND CCK PRETREATMENT

Significantly delayed tracer excretion into the bowel, associated with prompt and progressive gallbladder filling, can be a normal variant seen in the fasting state (*28*). Morphine administered to the patient before the study can produce the same finding. This finding is well known and now is used in a positive way to enhance gallbladder visualization during cholescintigraphy.

In a series by Kim et al. (*11*), approximately 40% to 50% of subjects with prompt gallbladder filling showed a markedly delayed biliary-to-bowel transit after sincalide pretreatment, compared to only 4% of patients who did not receive CCK. Delayed biliary-to-bowel transit, when present, should not necessarily be read as abnormal. However, hyperacute or partial CBD obstruction may not be totally excluded in certain clinical settings, although this pattern, with intact gallbladder visualization, is not typical of CBD obstruction. In such a situation, CCK administration can help exclude CBD obstruction by contracting the gallbladder and demonstrating bowel activity (*11,29*). Our group (*30*) assessed the frequency of the need for sincalide administration in this situation to exclude CBD obstruction. Delayed or no excretion into the bowel after sincalide administration was seen only in patients with delayed clearance of liver parenchymal activity but never in patients with prompt clearance of liver parenchymal activity. It appears that if both gallbladder filling and clearance of liver parenchymal activity are prompt, then the study can be terminated without giving CCK despite the absence of bowel activity.

Kim et al. (*31*) have recently reported variable bile retention on cholescintigraphy after morphine administration. After morphine injection, the time-activity curve of the common bile duct slowly increased for a variable duration in nine patients, while it continued to decrease in eight patients. Common bile duct activity showed a continuously decreasing pattern between 1 hr and 2 hr in another group of 20 patients who did not receive morphine despite gallbladder nonvisualization at 1 hr. In summary, no significant effect of 2 mg of intravenous morphine on biliary kinetics was detected scintigraphically in a considerable proportion of patients. Also, there was considerable variation in the duration of the morphine's effect, when present. The impact of this variable or no visible effect of morphine on the efficacy of morphine-augmented cholescintigraphy is unclear, and further study is necessary.

NONBILIARY DISORDERS OR MEDICATIONS THAT MAY AFFECT GALLBLADDER FUNCTION

Conditions that may affect gallbladder contractility should be considered when using CCK. Atropine significantly reduces the gallbladder ejection period and ejection fraction (*32*). Gallbladder contractility can be decreased after or during octreotide therapy (*33*). A 50% reduction in ejection fraction has been reported in 7 of 10 patients with achalasia, compared to controls (*34*). The mechanism and clinical significance of this finding is uncertain. Other reported causes associated with reduced

gallbladder emptying include antiulcer gastric surgery (*35*).

SUMMARY

Recent data and reanalysis of the literature suggest that nonvisualization of the gallbladder on the delayed images of cholescintigraphy is a nonspecific finding. Morphine augmentation has a reasonably good, though imperfect, specificity and positive predictive value, that are significantly better than for delayed imaging, in addition to its logistical advantage (shortening the imaging time). The technique is recommended, therefore, for routine clinical use in patients with nonvisualization of the gallbladder at 1 hr. Further study seems to be necessary to assess the effect of variable or no visible effect of low-dose morphine among patients on the efficacy of morphine-augmented cholescintigraphy.

Sincalide pretreatment, when administered at the physiologic rate, is helpful in conditions in which functional resistance to tracer flow into the gallbladder are present. The results from the series by Chen et al. and by Kim et al. suggest that morphine augmentation can further improve the efficacy of the test even after CCK pretreatment. A comparison between the efficacy of delayed imaging and that of imaging for 60–90 min after CCK pretreatment is not available. Therefore, the latter does not obviate the need for delayed imaging when the morphine augmentation technique is not used.

Finally, the nuclear medicine physician should use the most optimal technique for the pharmacologic intervention, in other words, the dose and the rate of administration. Certain conditions and medications may affect gallbladder contraction. It is also important to be aware of the various physiologic and pharmacologic effects on imaging findings, not only those findings that are normal but also the undesirable variants. Failure to recognize such effects can lead to incorrect interpretations.

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