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# Sincalide: A Review of Clinical Utility, Proper Infusion Methodology, and Alternative Cholescystogues

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Sincalide (Kinevac) is widely used in conjunction with cholescintigraphy for a variety of clinical indications. Over the years, numerous publications have verified the optimal infusion methodology. Published data and consensus recommendations emphasize that sincalide, 0.02 µg/kg, should be infused over 60 min. Production problems sometimes limit the availability of sincalide. In that case, non-Food and Drug Administration pharmacy-compounded sincalide may serve as an alternative. Fatty meals have also been used. Various illnesses and drugs may inhibit gallbladder contraction. Thus, these drugs should be withheld for 48 h before the study. Sincalide cholescintigraphy is most commonly used to diagnose or exclude chronic acalculous gallbladder disease. The study should preferably be performed as an outpatient procedure.

**Key Words:** sincalide; cholescintigraphy; chronic acalculous gallbladder disease; gallbladder; gastrointestinal

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**S**incalide (Kinevac; Bracco) is an amino acid polypeptide hormone analog of cholecystokinin. Its hepatobiliary physiologic effect is to increase bile secretion, cause the gallbladder to contract, and relax the sphincter of Oddi, resulting in bile drainage into the duodenum. There are very few reported side effects, mainly nausea and abdominal cramping when infused too rapidly. The only contraindications are a known allergic reaction to the drug, pregnancy, and intestinal obstruction.

Kinevac is presently the only Food and Drug Administration (FDA)–approved form of sincalide. Unfortunately, it has been commercially unavailable at various times because

of production problems. Non-FDA-approved sincalide is available from compounding pharmaceutical companies. These drugs have not been scientifically investigated to confirm equivalence to Kinevac, nor is quality control monitored by the FDA; however, they are commonly used out of necessity when Kinevac is not available. Some hospitals will not permit use of pharmacy-compounded drugs. An alternative formulation of sincalide by another company has been presented to the FDA for approval. If approved, availability should be much improved. Fatty meals are also used as an alternative to sincalide and will be discussed.

## CLINICAL INDICATIONS FOR SINCALIDE CHOLESCINTIGRAPHY

Sincalide cholescintigraphy has been demonstrated to be valuable in a number of clinical situations. It is indicated before cholescintigraphy when the patient has not eaten for 24 h or is receiving hyperalimentation, to empty the gallbladder of viscous bile that may prevent entry of the hepatobiliary radiopharmaceutical. However, it should be remembered that just because sincalide is given to a patient before the study does not mean that the gallbladder has indeed contracted. Sincalide is also used at some biliary referral centers before cholescintigraphy to diagnose sphincter-of-Oddi dysfunction. The rationale for its use is that it increases bile flow, stressing the sphincter of Oddi. Sincalide is also used after routine cholescintigraphy, either to differentiate a partial biliary obstruction from physiologic delayed clearance from the common duct or, most commonly, to diagnose or exclude chronic acalculous gallbladder disease (chronic acalculous cholecystitis). A diseased gallbladder does not contract normally.

Patients with chronic acalculous gallbladder disease typically have symptoms similar to the more common chronic calculous cholecystitis form of the disease, such as recurrent colicky pain in the right upper quadrant, except the patients do not have stones, and thus the disease is more difficult to diagnose. Sincalide can assist in making this diagnosis. The

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disease has been called by various other names, including cystic duct syndrome, gallbladder spasm, and gallbladder dyskinesia. At pathology these patients' gallbladders have evidence of chronic inflammation identical to patients with the calculous form of the disease.

#### FATTY-MEAL ALTERNATIVES TO SINCALIDE

When sincalide is not available, an alternative is needed. It has been suggested that a fatty meal is preferable to sincalide for evaluating gallbladder contraction because it is more physiologic and less expensive; however, there is a potential problem with this approach. Normally, when a healthy person eats a fatty meal, endogenous cholecystokinin is produced in the proximal small bowel and then released systemically, thus producing its physiologic effects. However, if a patient has delayed gastric emptying (gastroparesis), the time required for food to move from the stomach to the duodenum and for cholecystokinin to be released is delayed, sometimes markedly. Thus, the gallbladder may not contract fully during the normal clinical observation time, and a false-positive study (abnormal findings in a healthy patient) may result. The patient's gallbladder may be removed inappropriately, which does not relieve the symptoms.

To produce gallbladder contraction, a meal with more than 10 g of fat is required. Various fatty meals have been used (1), including but not exclusively Ensure Plus (Abbott Laboratories) (2), milk (3), and corn oil (4). It is imperative to use a meal that has established reference values. With 237 mL (8 oz) of Ensure Plus, an abnormal gallbladder ejection fraction (GBEF) is less than 33% (2); for 250 mL of milk, less than 51% (3). However, overall data are somewhat limited. Reference values depend on the composition and size of the meal. For patients who can take nothing by mouth, there is really no intravenous alternative. Erythromycin may contract the gallbladder, but there are limited data regarding its use in this situation, appropriate intravenous doses, and reference values.

#### PROPER INFUSION METHODOLOGY FOR SINCALIDE

The package insert for Kinevac has not changed since its original FDA approval in the 1960s and states that the drug should be infused over 30–60 s. The rationale was that a bolus infusion was known to potentially cause spasm of the cystic duct, preventing gallbladder contraction. Thus, in the 1980s and early 1990s, numerous nuclear medicine clinics began to infuse sincalide over 3–5 min. A large retrospective study published in 1991 claimed good clinical results with a 3-min infusion (5). Other smaller retrospective studies also claimed good results. Thus, this became a common method of infusion in the United States. However, several other published studies did not find this a useful method for confirming or excluding chronic acalculous gallbladder disease (6,7).

In 1992, a study was published in *The Journal of Nuclear Medicine* that compared a 3-min infusion with a 30-min

infusion in the same healthy subjects (8). With the 3-min infusion of 0.02  $\mu\text{g}/\text{kg}$ , there was wide variability in results, so much so that reference values could not be calculated. However, when the same patients on another day received a 30-min infusion, it was possible to calculate reference values. A similar study, which was subsequently published in 2001, compared a 3-min infusion with a 60-min infusion (9). Again, reference values were not able to be established with the 3-min infusion because of the wide variability of response in these subjects. However, with the 60-min infusion, reference values could be determined, although they were different from the results of the 30-min infusion in the above study. Importantly, in both studies 50% of healthy subjects developed nausea or abdominal cramps with the 3-min infusion; however, no subjects had adverse symptoms with either the 30-min or the 60-min infusion. This result strongly suggests that a short infusion may result in a false-positive clinical patient study, potentially resulting in cholecystectomy when really not indicated or beneficial.

In 2010, a multicenter investigation of 60 healthy subjects was initiated by the Gastrointestinal Council of the SNM (now the General Nuclear Medicine Council of the SNMMI) and published in *The Journal of Nuclear Medicine* (10). Each healthy subject received 3 different infusions of sincalide, 0.02  $\mu\text{g}/\text{kg}$ , on separate days, including 15-, 30-, and 60-min infusions. Both the 15-min and the 30-min infusions resulted in a wide variability in GBEF response, and clinically useful reference values were not able to be determined. However, the 60-min infusion showed much less variability in these same healthy subjects, and clinically useful reference values could be determined. Normal was found to be equal or greater than 38%. With the 15-min infusion, some of the subjects developed nausea or abdominal cramping. This effect was not seen with either the 30-min or the 60-min infusion.

In 2010, the SNM Practice Guideline for Hepatobiliary Scintigraphy stated that the 60-min infusion was the method of choice for sincalide (11). In 2011, the consensus recommendations of an interdisciplinary panel made up of gastroenterologists, surgeons, and nuclear medicine physicians were published in both the gastrointestinal and the nuclear medicine literature. The consensus recommendation was for the 60-min infusion methodology (12).

There is only a single randomized and prospective study in the medical literature that investigated the clinical utility of sincalide cholescintigraphy to predict whether a patient had chronic acalculous gallbladder disease and would have a good response to cholecystectomy (13). The study confirmed its utility. All other studies in the literature are retrospective and considered to be of lesser scientific quality than this prospective study, published by Yap et al. in 1991. They infused sincalide, 0.02  $\mu\text{g}/\text{kg}/\text{h}$ , over 45 min but continued imaging through 60 min and quantifying at 60 min. This method of infusion is slightly different from but actually quite similar to the 60-min infusion method. These investigators also studied 40 healthy subjects and found a

normal GBEF to be greater than 40%, again very similar to the 38% found in the multicenter study described above infusing 0.02  $\mu\text{g}/\text{kg}$  over 60 min.

Sincalide cholescintigraphy is best performed as an outpatient procedure when the patient is asymptomatic. Patients in the hospital may have reduced GBEFs due to various reasons other than gallbladder disease, including their acute illness or various medications. Morphine may inhibit gallbladder contraction. When clinicians insist we do a GBEF on inpatients, a normal result is interpreted as diagnostic that gallbladder disease is not the patient's problem; however, an abnormal result is read as indeterminate, and a recommendation is made to repeat the study at a later date as an outpatient procedure. Whatever the clinical indication, sincalide should be infused using the same methodology: a 60-min infusion of 0.02  $\mu\text{g}/\text{kg}$ .

Despite substantial literature to the contrary, some referring physicians still regard pain and nausea during sincalide infusion to be diagnostic of chronic acalculous gallbladder disease. However, pain during the study is almost always the result of the rate of infusion and not disease per se. Healthy subjects and patients with infusions of 3–15 min may have abdominal discomfort and nausea due to the rate of infusion, but this does not signify disease. And patients who do have chronic acalculous cholecystitis do not have pain during 30- or 60-min infusions.

Various drugs may inhibit gallbladder contraction and should be withheld for 48 h before the study. The known drugs include opiates and anticholinergic drugs, as well as nifedipine, indomethacin, octreotide, theophylline, benzodiazepines, phentolamine, isoproterenol, and progesterone. Nicotine and alcohol may also inhibit gallbladder contraction and should be avoided before testing.

## CONCLUSION

Sincalide is a valuable pharmacologic intervention with cholescintigraphy, when used appropriately. There are several indications, such as to empty the gallbladder in a patient fasting for more than 24 h before cholescintigraphy. A common indication is to evaluate a patient for suspected

chronic acalculous gallbladder disease. This study should be preferably performed as an outpatient procedure. The method of infusion is important. The recommended method is to infuse 0.02  $\mu\text{g}/\text{kg}$  over 60 min. A GBEF of less than 38% is abnormal. Fatty meals have limitations, particularly in patients with delayed gastric emptying. When used, the specific meal should have well-established reference values.

## DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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