

Sincalide – A Review of the Clinical Utility, Proper Infusion Methodology,
and Alternative Cholecystogogues

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Abstract

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 minutes. Production problems sometimes limit the availability of sincalide. In that case, non-FDA 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 hours prior to 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.

Introduction

Sincalide (Kinevac®) is an amino acid polypeptide hormone analogue of cholecystokinin (CCK). 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 FDA approved form of sincalide. Unfortunately, it has been commercially unavailable at various times due to 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 clinical situations. It is indicated prior to cholescintigraphy when the patient has not eaten for 24 hours 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 prior to the study does not mean that the gallbladder has indeed contracted. Sincalide is also used at some biliary referral centers prior to 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, e.g., recurrent right upper quadrant colicky pain, except the patients do not have stones, and thus it is more difficult to diagnose. Sincalide can assist in making this diagnosis. The disease has been called by various other names, including cystic duct syndrome, gallbladder spasm, and gallbladder dyskinesia. At pathology these patient's 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 CCK is produced in the proximal small bowel, then released systemically, thus producing its physiologic effects. However, if a patient has delayed gastric emptying (gastroparesis), the time required for food products to move from the stomach to the duodenum and release of CCK is delayed, sometimes markedly. Thus the gallbladder may not contract fully during the normal clinical observation time and a false positive study (abnormal study in a normal patient) may result. The patient may have his gallbladder removed inappropriately, which does not relieve his/her symptoms.

To produce gallbladder contraction, a meal with more than 10 grams of fat is required. Various fatty meals have been used (1), including but not exclusively EnsurePlus (2), milk (3) and corn oil (4). It is imperative to use a meal that has established normal values. With eight ounces of EnsurePlus, an abnormal gallbladder ejection fraction (GBEF) is less than 33% (2); for 250 cc of milk, less than 51% (3). However, overall data is somewhat limited. Normal values depend on the composition and size of the meal. For patients that can take nothing by mouth (NPO), there is really no intravenous alternative. Erythromycin may contract the gallbladder, but there is limited data regarding its use in this situation, appropriate intravenous dose, or normal values.

Proper Infusion Methodology for Sincalide

The package insert for Kinevac has not changed since its original FDA approval in the 1960s and it states that the drug should be infused over 30 to 60 seconds. 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 minutes. 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, a number of 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 JNM that compared a 3-min infusion with a 30 minute infusion in the same normal subjects (8). With the 3-min infusion of 0.02 µg/kg, there was wide variability in results, so much so that normal values could not be calculated. However, when the same patients on another day received a 30 minute infusion, it was possible to calculate normal values. A similar study was subsequently published in 2001 which compared a 3-min infusion to a 60 minute infusion (9). Again normal 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, normal values could be determined, although they were different than the results of the 30-minute infusion in the above study. Importantly in both studies 50% of normal subjects developed nausea or abdominal cramps with the 3-min infusion; however, no subjects had adverse symptoms with either the 30 or 60 minute infusions. This strongly suggests that a short infusion may result in a false positive clinical patient study, potentially resulting in cholecystectomy when really not indicated nor beneficial.

In 2010, a multicenter investigation of 60 normal subjects was initiated by the Gastrointestinal Council of the SNM (now the General Nuclear Medicine Council of the SNMMI) and published in the JNM (10). Each normal subject received 3 different infusions of 0.02 µg/kg sincalide on separate days, including a 15 min, 30 min, and 60 min infusion. Both the 15 min and 30 min infusions resulted in a wide variability of GBEF response and clinically useful normal values were not able to be determined. However, the 60 minute infusion showed much less variability in these same normal subjects and clinically useful normal values could be determined. Normal was found to be equal or greater than 38%.

With the 15 minute infusion, some of the subjects developed nausea and or abdominal cramping. This was not seen with either the 30 or 60 minute infusion.

In 2010 the SNM Practice Guideline for Hepatobiliary Scintigraphy stated that the 60 minute infusion was the method of choice for sincalide infusion (11). In 2011 Consensus Recommendations of an Interdisciplinary Panel, made up of gastroenterologists, surgeons, and nuclear medicine physicians, was published in both the gastrointestinal and nuclear medicine literature. It recommended the 60 minute infusion methodology (12).

There is only one 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 if they 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 compared to this prospective study, published by Yap, et al. in 1991. They infused 0.02 $\mu\text{g/kg/h}$ sincalide over 45 minutes but continued imaging through 60 minutes and quantifying at 60 minutes. This method of infusion is slightly different, but actually quite similar to the 60 min infusion method. These investigators also studied 40 normal 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 $\mu\text{g/kg}$ over 60 minutes.

Sincalide cholescintigraphy is best performed as an outpatient when the patient is asymptomatic and an outpatient. 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 study is interpreted as diagnostic that gallbladder disease is not the patient's problem, however, an abnormal study is read as indeterminate and recommended to be repeated at a later date as an outpatient.

Whatever, the clinical indication, sincalide should be infused using the same methodology, a 60 minute infusion of 0.02 µg/kg sincalide.

In spite of 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. Normal subjects and patients with infusions of 3 to 15 minute 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 minute infusions.

Various drugs may inhibit gallbladder contraction and should be withheld prior to the study for 48 hours. 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 contract and should be avoided prior to testing.

Conclusion

Sincalide is a valuable pharmacologic intervention with cholescintigraphy, when used appropriately. There a number of indications, e.g., to empty the gallbladder in a patient fasting > 24 hours prior to cholescintigraphy. A common indication is to evaluate a patient for suspected chronic acalculous gallbladder disease. This study should be preferably performed as an outpatient. The method of infusion is important. The recommended method is to infuse 0.02 µg/kg over 60 minutes. A GBEF of < 38% is abnormal. Fatty meals have limitations, particularly in patients with delayed gastric emptying. When used the specific meal should have well-established normal values.

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