Sincalide-stimulated Gallbladder Ejection Fraction. Dr. Mark Tulchinsky

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Sincalide Cholescintigraphy: The Essentials

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Disclosure: Investigator, Consultant and Lecturer for Bracco Diagnostic, Inc.

Fasting

Postprandial or Post-CCK

Sincalide-stimulated Gallbladder
Ejection Fraction. Dr. Mark Tulchinsky

Radiopharmaceuticals

Proposed bis structure of $^{99m}$Tc-IDAs

Lidofenin

[(2,6-Xylylcarbamoyl) methyl]-iminodiacetic acid

Disofenin (DISIDA)

[(2,6-Diisopropylphenyl)carbamoyl]-imino]diacetic acid

Mebrofenin (BromIDA)

[(3-Bromomesityl)carbamoyl] Methyl]-imino]diacetic acid


Uptake of IDA is facilitated by carrier-mediated, non-sodium dependent, organic anionic pathway – similar to bilirubin

Radiopharmaceutical extracted by hepatocytes and transported without modification

Illustration by M. Tulchinsky
**Preparation for the GB Examination**

1. Select patients who are in their usual state of health (or illness) – NOT AN INPATIENT
2. Exclude the use of opioids (four half lives of a drug)
3. A fatty snack at 8-9 PM (empty out the GB)
4. Fasting after the snack (filling phase in AM)
5. Pre-treat with CCK, if NPO longer than 24 hours (should not be an issue, if #1 is true)
6. Schedule for early AM imaging, if possible (minimize inconvenience of long fasting)

Tulchinsky M. Hepatobiliary Scintigraphy. In: Diagnostic Nuclear Medicine, 2nd revised edition. Published 2005 Springer.

**Hepatobiliary Scintigraphy: Imaging Sequence**

- Baseline one-hour dynamic imaging depicts parenchymal uptake, bile excretion, and passage – can be replaced by anterior, right lateral and left anterior oblique spot static imaging at 1 hr post-injection
- Post sinalide dynamic imaging, carried out for 60 minutes (optimum protocol), depicts response to a stimulant (sinalide is recommended)
HBS: Digital Set-Up

- **Pre-sincalide Imaging**
  - 60 minute dynamic acquisition, 60 sec/frame, anterior (posterior is optional) projection(s), 128x128x16 matrix
    - Display in 15 frames (4 min/frame)
    - 2 or 3 static images to determine GB filling
      - Anterior, Right Lateral, Left Anterior Oblique (in order of preference) for 2 min each, 256x256x16 matrix

- **Post-sincalide Imaging**
  - Acquire dynamically for 60 min, 60 sec/frame, in left anterior oblique projection
  - Display in 15 frames (4 min/frame)
  - Calculate gallbladder ejection fraction (GBEF)

In anterior view the activity in the duodenum often contributes to (interferes with) activity in the gallbladder region!
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Anterior View

Left Anterior Oblique view separates GB from duodenal activity – makes good anatomical sense!
40° LAO – Separates GB from Duodenal Activity

Gallbladder Ejection Fraction Determination

- Stimuli:
  - Cholecystokinin-8 (sincalide) IV
  - Fatty meal
- GBEF calculation:
  \[
  \text{Net GB counts max} - \text{Net GB counts min} \times 100\%
  \]

Clinical Presentation

- Chronic disease (including functional) – often atypical clinical presentation:
  - Patients often referred for numerous expensive anatomical imaging procedures, often negative, over a long period of time
  - Stones in the GB may or may not be present – GB dysfunction is the key diagnostic finding
  - Surgery, cholecystectomy, is the only treatment option (except in SOD)

SOD = Sphincter of Oddi Dysfunction

Chronic Gallbladder or Biliary Disease: Spectrum of Conditions

- Acalculous
  - Biliary dyskinesia
  - Gallbladder dyskinesia
  - Chronic acalculous cholecystitis
  - Chronic acalculous biliary disease
  - Acalculous biliary disease
  - Cystic duct syndrome
  - Gallbladder spasm
  - Functional Gallbladder Disorder

- Calculous
  - Chronic calculous cholecystitis
### Historical Normal Values

<table>
<thead>
<tr>
<th>Min/µg per kg (Ref.)</th>
<th>GBEF (M±S.D.)</th>
<th>Range</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/0.02 (3)</td>
<td>52±42%</td>
<td>12-92%</td>
<td>22†</td>
</tr>
<tr>
<td>3/0.04 (1)</td>
<td>43±26%</td>
<td>15-88%</td>
<td>12</td>
</tr>
<tr>
<td>3/0.02 (1)</td>
<td>35±17%</td>
<td>17-59%</td>
<td>6</td>
</tr>
<tr>
<td>3/0.02 (5)</td>
<td>56±27%</td>
<td>0-100%</td>
<td>23</td>
</tr>
<tr>
<td>3/0.01 (4)</td>
<td>46±20%</td>
<td>12-74%</td>
<td>20</td>
</tr>
<tr>
<td>10/0.01 (6)</td>
<td>76±16%</td>
<td>37-96%</td>
<td>13</td>
</tr>
<tr>
<td>15/0.02 (2)</td>
<td>76±22%</td>
<td>32-98%</td>
<td>15</td>
</tr>
<tr>
<td>30/0.01 (5)</td>
<td>64±20%</td>
<td>26-95%</td>
<td>14</td>
</tr>
<tr>
<td>30/0.02 (5)</td>
<td>70±22%</td>
<td>17-97%</td>
<td>23</td>
</tr>
<tr>
<td>45/0.015 (3)</td>
<td>77±23%</td>
<td>65-96%</td>
<td>22†</td>
</tr>
<tr>
<td>45/0.015 (7)</td>
<td>75±12%</td>
<td>&gt;40%‡</td>
<td>40</td>
</tr>
<tr>
<td>60/0.01 (4)</td>
<td>68±16%</td>
<td>15-88%</td>
<td>20</td>
</tr>
</tbody>
</table>


† patients rather than normal volunteers
‡ 99% confidence limits

### The Pivotal Study of Normal Values for CCK-HBS

- Establish which infusion protocol has the least variability in GBEF:
  - 0.02 µg/kg over 15 min
  - 0.02 µg/kg over 30 min
  - 0.02 µg/kg over 60 min
- Evaluate the methods in healthy individuals – 60 volunteers
- The next step would be to take the best infusion method and test it in a randomized controlled clinical trial
Normal Values – Multicenter Study of 60 Volunteers

<table>
<thead>
<tr>
<th>Min/µg per kg</th>
<th>GBEF (M±S.D.)</th>
<th>GBEF Range</th>
<th>GBEF&lt;35%</th>
<th>CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15/0.02</td>
<td>56.9±29.4%*</td>
<td>-2 to 98%</td>
<td>16/60 (27%)</td>
<td>52%</td>
</tr>
<tr>
<td>30/0.02</td>
<td>70.9±24.5%*</td>
<td>8 to 99%</td>
<td>6/60 (10%)</td>
<td>35%</td>
</tr>
<tr>
<td>60/0.02</td>
<td>84.3±15.5%*</td>
<td>38 to 100%</td>
<td>0/60</td>
<td>19%</td>
</tr>
</tbody>
</table>

* Significantly different from other 2 infusion rates, p < 0.0001

Sincalide-Stimulated Cholescintigraphy: A Multicenter Investigation to Determine Optimal Infusion Methodology and Gallbladder Ejection Fraction Normal Values

Current Recommendation: 0.02 mcg/kg of Sincalide over 60 min

SNM Practice Guideline for Hepatobiliary Scintigraphy 4.0*

Cholecystokinin-Cholescintigraphy in Adults: Consensus Recommendations of an Interdisciplinary Panel
Interpretation of GBEF Results

- GBEF ≥ 38% - normal GB function
- GBEF < 38% - Abnormal GB function. In the proper clinical setting is consistent with functional gallbladder disorder:
  - Clinically, suffering from chronic episodes of biliary pain
  - No gallstones on US
- With gallstones the combination would suggest chronic calculous cholecystitis

Fatty Meal vs. CCK?

- CCK1 = 75.8 ± 16.3%
- CCK2 = 71.3 ± 17.4%
- MEAL = 53.6 ± 20.2%

Excluded were 8/21 prescreened because GBEF <35% after 3 minute injection
CCK vs. Fatty Meal Stimulation

- CCK infusion has a more predictable rate of GB contraction
  - Maximum GB emptying occurs shortly (within few minutes) after infusion ends
  - Independent of gastric emptying
- Fatty meal has a less predictable rate of GB contraction
  - It takes longer (variable) time to reach maximum contraction
  - Normal gastric emptying is required


Which statement is true about administration of sincalide or fatty meal for the study of gallbladder ejection fraction in stable patients with chronic abdominal pain and multiple gallstones?

A. It is relatively contraindicated
B. Should be avoided because of high frequency of abdominal pain during gallbladder stimulation
C. Results in abnormal ejection fraction in more than 85% of such patients
D. The ejection fraction is normal in over 50% of such patients
There are many practitioners who are concerned about giving sincalide or fatty meal to patients with gallstones. There is no evidence in the literature to support this concern. Cholelithiasis is not listed among the contraindications in sincalide package insert (A is wrong). It makes intuitive sense to expect higher rate of abdominal pain in those patients during sincalide or fatty meal stimulation. However, this concern was not substantiated in clinical trials. In fact, abdominal pain was experienced by only one out of 67 patients with gallstones during sincalide infusion in one study (1), hence answer B is wrong. In another study of such patients 77.4% had normal ejection fraction (2); therefore, answer D is correct and C is incorrect. Most unselected patients with gallstones who are referred for gallbladder ejection fraction would be expected to have a normal ejection fraction.

References:
Multiple GB stones: Is it safe to give sincalide (CCK)?

If you do proceed with hepatobiliary study, would the GB fill?
If it does fill, what is your prediction on resulting GBEF?

Case 3
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Case 3

GBEF: 88 %
Which statement is true about gallbladder nonvisualization during 60 minutes after radiopharmaceutical injection to a properly prepared patient with suspected functional gallbladder disorder and no symptoms during or within past 3 days prior to hepatobiliary scintigraphy?

A. The patient likely having acute cholecystitis
B. The finding indicates abnormal gallbladder and no further imaging is needed during this test
C. Morphine augmentation is indicated to make sure the gallbladder fills during this study
D. The patient should have delayed images until the gallbladder activity is demonstrated

Not seeing the gallbladder during 60 minutes of cholescintigraphy is an abnormal finding and can be seen in chronic or acute cholecystitis. However, acute cholecystitis is associated with symptoms and signs of this illness, therefore, it is unlikely in the described patient (answer A is incorrect). Normal individuals who are properly prepared for the hepatobiliary scintigraphy invariably show gallbladder activity during the first 60 minutes of observation. It was found to be true in 60 normal volunteers who were imaged three separate times in one study (1), which amounts to gallbladder visualization by 60 minutes in every one of 180 tests of patients with normal gallbladder function. Therefore, not seeing the gallbladder during 60 minutes is definitely abnormal (answer B is correct). There is no further information to be obtained in the described patient by manipulations aimed at filling the gallbladder (options C and D are incorrect) later, either by morphine or delayed imaging. The most that such manipulation can offer is differentiation of acute from chronic cholecystitis. This would be a senseless exercise in someone who is having no symptoms or signs of acute cholecystitis.

29 Y/O FEMALE WITH CHRONIC, INTERMITENT ABD/P, ASYMPTOMATIC IN THE PAST 5 DAYS

Abdominal CT 5 days ago was normal, patient is asymptomatic around time of imaging

Activity in the duodenum - no GB visualization at 1 hour = abnormal study = gallbladder dysfunction
No GB visualization after morphine

Doesn’t mean acute cholecystitis in asymptomatic pt!

Further imaging after the 1st hour contributes nothing except possible confusion.

Post Morphine
2 min/frame