Mom & Pop shops

• Protocols and normal values vary by clinic

• Reasons: many
  – Different cameras
  – Software
  – Expertise/Preferences
Demand for Standardization

- Referring physicians
- Specialty societies
- Insurers

They expect that the methods and results from different institutions should be similar.
Consensus Recommendations for the Use of $^{18}$F-FDG PET as an Indicator of Therapeutic Response in Patients in National Cancer Institute Trials

Lalitha K. Shankar¹, John M. Hoffman², Steve Bacharach³, Michael M. Graham⁴, Joel Karp⁵, Adriaan A. Lammertsma⁶, Steven Larson⁷, David A. Mankoff⁸, Barry A. Siegel⁹, Annick Van den Abbeele¹⁰, Jeffrey Yap¹⁰, and Daniel Sullivan¹

¹Cancer Imaging Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; ²Division of Nuclear Medicine, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, Utah; ³Department of Radiology, University of California, San Francisco, California; ⁴Division of Nuclear Medicine, Department of Radiology, University of Iowa, Iowa City, Iowa; ⁵Division of Nuclear Medicine, Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania; ⁶Department of Nuclear Medicine and PET Research, VU University Medical Centre, Amsterdam, The Netherlands; ⁷Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, New York; ⁸Division of Nuclear Medicine, University of Washington, Seattle, Washington; ⁹Mallinckrodt Institute of Radiology, St. Louis, Missouri; and ¹⁰Department of Radiology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

Many therapeutic clinical trials have proposed using a measure of metabolic change to assess therapeutic response rather than relying on conventional anatomic measurements of changes in tumor size on CT or MRI. PET assessment of changes in $^{18}$F-FDG uptake by tumors is gaining acceptance as such a measure.

At the same time, it has become equally clear that the potential of $^{18}$F-FDG PET as such a tool will not be achieved unless standard protocols are developed so that data can be accumulated and compared across multiple clinical sites. Today, the methods of obtaining $^{18}$F-FDG PET scans and assessing $^{18}$F-FDG metabolism and uptake vary.

To provide such guidance and to help standardize the...
Consensus Recommendations for Gastric Emptying Scintigraphy: A Joint Report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine

Thomas L. Abell, M.D.,1 Michael Camilleri, M.D.,2 Kevin Donohoe, M.D.,3 William L. Hasler, M.D.,4 Henry C. Lin, M.D.,5 Alan H. Maurer, M.D.,6 Richard W. McCallum, M.D.,7 Thomas Nowak, M.D.,8 Martin L. Nusynowitz, M.D.,9 Henry P. Parkman, M.D.,10 Paul Shreve, M.D.,11 Lawrence A. Szarka, M.D.,2 William J. Snape Jr., M.D.,12 and Harvey A. Ziessman, M.D.13

This consensus statement from the members of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine recommends a standardized method for measuring gastric emptying (GE) by scintigraphy. A low-fat, egg-white meal with imaging at 0, 1, 2, and 4 h after meal ingestion, as described by a published multicenter protocol, provides standardized information about normal and delayed GE. Adoption of this standardized protocol will resolve the lack of uniformity of testing, add reliability and credibility to the results, and improve the clinical utility of the GE test.

Am J Gastroenterol. 2008 Mar; 103(3):753-63

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CCK cholescintigraphy

Standardization

GBEF = 53%
Kinevac (sincalide) Injection, Powder, Lyophilized, For Solution

[Bracco Diagnostics Inc.]

DESCRIPTION

Kinevac (Sincalide for Injection) is a cholecystopancreatic-gastrointestinal hormone peptide for parenteral administration. The agent is a synthetically-prepared C-terminal octapeptide of cholecystokinin. Each vial of sincalide provides a sterile nonpyrogenic lyophilized white powder consisting of 5 mcg sincalide with 170 mg mannitol, 30 mg arginine hydrochloride, 15 mg lysine hydrochloride, 9 mg potassium phosphate dibasic, 4 mg methionine, 2 mg pentetic acid, 0.04 mg sodium metabisulfite, and 0.005 mcg polysorbate 20. The pH is adjusted to 6.0 - 8.0 with hydrochloric acid and/or sodium hydroxide prior to lyophilization. Sincalide is designated chemically as L-α-aspartyl-O-sulfo-L-tyrosyl-L-methionylglycyl-L-tryptophyl-L-methionyl-L-α-aspartyl-L-phenylalaninamide. Graphic formula:

$$\text{SO}_3\text{H}$$

Asp — Tyr — Met — Gly — Trp — Met — Asp — Phe — NH$_2$

1 2 3 4 5 6 7 8

C$_{49}$H$_{62}$N$_{10}$O$_{16}$S$_3$ MW 1143.27 CAS-25126-32-3

For prompt contraction of the gallbladder, a dose of 0.02 mcg sincalide per kg (1.4 mcg/70 kg) is injected intravenously over a 30- to 60-second interval; if satisfactory contraction of the gallbladder does not occur in 15 minutes, a second dose, 0.04 mcg sincalide per kg, may be administered. To reduce the intestinal side effects (see ADVERSE REACTIONS), an intravenous infusion may be prepared at a dose of 0.12 mcg/kg in 100 mL of Sodium Chloride Injection USP and given at a rate of 2 mL per minute; alternatively, an intramuscular dose of 0.1 mcg/kg may be given. When Kinevac
Sincalide infusion methodologies

• Published methods
  – Total dose administered
    • 0.01, 0.015, 0.02, 0.03, 0.04, 0.05 µg/kg
  – Length of infusion
    • Bolus, 1, 2, 3, 5, 15, 20, 45, 60 minutes
  – GBEF lower limits of normal
    • < 30%, < 35%, < 40%, < 50%, < 65%
CCK infusion length to calculate a GBEF

1-3 minutes
10-15 minutes
30 minutes
45-60 minutes
Chronic Calculous Cholecystitis

Recurrent biliary colic
Inflammatory/fibrotic changes of chronic cholecystitis
Chronic Acalculous Cholecystitis

- Chronic cholecysitis **without stones**
- 5-10% of pts with chronic cholecysitis
- Recent literature suggests - higher
Histopathology

Identical to chronic calculous cholecystitis, but no stones

Inflammatory/fibrotic changes of chronic cholecystitis
Chronic Acalculous Gallbladder Disease

- Chronic acalculous cholecystitis
- Cystic duct syndrome
- Gallbladder spasm
- Gallbladder dyskinesia
- Biliary dyskinesia

All have recurrent biliary colic, poor contraction, cured by cholecystectomy
## Diagnosis of chronic acalculous gallbladder disease

**CCK cholescintigraphy**

- **Pickelman** Arch Surg 1985; 120:693
- **Fink-Bennett** J Nucl Med 1985; 26:1121
- **Brugge** Dig Dis Sci 1986; 31:461
- **Yap** Gastroenterol 1991; 101:748
- **Fink-Bennett** J Nucl Med 1991; 32:1695
<table>
<thead>
<tr>
<th>Name</th>
<th>Journal</th>
<th>Year</th>
<th>Volume</th>
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<td>Misra</td>
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<td>172</td>
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<td>Halverson</td>
<td>Arch Int Med</td>
<td>1992</td>
<td>152</td>
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<td>166</td>
<td>672</td>
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<td>Reed</td>
<td>Am Surg</td>
<td>1993</td>
<td>59</td>
<td>272</td>
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<td>Watson</td>
<td>Australas Radiol</td>
<td>1994</td>
<td>38</td>
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<td>J Lap Surg</td>
<td>1995</td>
<td>5</td>
<td>357</td>
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<td>Jones</td>
<td>Surg lap Endo</td>
<td>1996</td>
<td>6</td>
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<td>Khosla</td>
<td>South Med J</td>
<td>1997</td>
<td>90</td>
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<td>Chen</td>
<td>Surgery</td>
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<td>130</td>
<td>578</td>
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<td>Poynter</td>
<td>Am Surg</td>
<td>2002</td>
<td>68</td>
<td>382</td>
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<td>Majeski</td>
<td>Int Surgery</td>
<td>2003</td>
<td>88</td>
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## CCK Cholescintigraphy

Nonconfirmatory publications - # 6

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<thead>
<tr>
<th>Author</th>
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<tbody>
<tr>
<td>Davis</td>
<td>Am J Roentgenology</td>
<td>1982</td>
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<td>Raptopoulos</td>
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<td>Westlake</td>
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<td>Mishkind</td>
<td>American Surgeon</td>
<td>1997</td>
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<tr>
<td>Adams</td>
<td>American Surgeon</td>
<td>1998</td>
</tr>
<tr>
<td>Goncaves</td>
<td>American Surgeon</td>
<td>1998</td>
</tr>
</tbody>
</table>
Sincalide Cholescintigraphy
Prospective & Randomized

- 108 symptomatic patients
- Sincalide .02 μg/kg/h x 45 min (60 min)
- 40 normals (abnormal <40%)
- Low GBEF (21)
  - Randomized: 11 surgery - 10 controls

Yap et al., Gastroenterology 1991; 101:786
Sincalide Cholescintigraphy
Prospective & randomized study

• Surgery – 10/11 (92%) - cured
• No surgery – all remained symptomatic
  – 2 had intolerable symptoms and demanded surgery - cured
• pathology – 12 of 13 had chronic inflammation

Yap et al., Gastroenterology 1991; 101:786
Sincalide Cholescintigraphy
Large retrospective study

- 374 patients referred - suspected CAC
- Sincalide 0.02 µg/kg x 3 min
- Abnormal defined as GBEF (< 35%)
- Surgery: 105/108 - asymptomatic
- Medical: - 69 persistent symptoms
  - 13 improved with therapy for non-GB disease

Sincalide Cholescintigraphy

Large retrospective study – cont.

- Study had 27 normal volunteers
  - 16/27 (59%) - GBEF less than 35%
  - Not used to establish normal values

Fink-Bennett, J Nucl Med 1991

- This methodology and these normal values came into common use
Sincalide Methodology

- Why do the clinical studies have discrepant results?
- What is the proper methodology for infusion?
- Does methodology matter?
- What are GBEF normal values?
Evidence-based Medicine

Does GBEF predict outcome after cholecystectomy for CAC?

Systematic reviews and meta-analyses


### Table 3. Summary of Results of Studies Evaluating the Utility of CCK-CS in Patients With Suspected Chronic Acalculous Gallbladder Dysfunction

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Journal Type</th>
<th>Study Design*</th>
<th>GBEF Cut-Off Value</th>
<th>CCK-CS Infusion Rate</th>
<th>Number of Patients †</th>
<th>% Female</th>
<th>Study Quality ‡</th>
<th>Study Outcome §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pickelman (8)</td>
<td>Surgery</td>
<td>3</td>
<td>50%</td>
<td>2 min</td>
<td>19</td>
<td>84</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Raptopoulos (9)</td>
<td>Radiology</td>
<td>3</td>
<td>40%</td>
<td>2 min</td>
<td>8</td>
<td>NS</td>
<td>Poor</td>
<td>(−)</td>
</tr>
<tr>
<td>Westlake (10)</td>
<td>Medicine</td>
<td>3</td>
<td>65%</td>
<td>30 min</td>
<td>26</td>
<td>77</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Yap (11)</td>
<td>Medicine</td>
<td>1</td>
<td>40%</td>
<td>45 min</td>
<td>95</td>
<td>83</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Mills (12)</td>
<td>Surgery</td>
<td>3</td>
<td>35%</td>
<td>3 min</td>
<td>142</td>
<td>79</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Zech (13)</td>
<td>Surgery</td>
<td>3</td>
<td>50%</td>
<td>2–3 min</td>
<td>83</td>
<td>84</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Fink-Bennett (14)</td>
<td>Radiology</td>
<td>3</td>
<td>35%</td>
<td>3 min</td>
<td>342</td>
<td>76</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Halverson (15)</td>
<td>Medicine</td>
<td>4</td>
<td>35%</td>
<td>3 min</td>
<td>12</td>
<td>92</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Sorenson (16)</td>
<td>Surgery</td>
<td>3</td>
<td>35%</td>
<td>3 min</td>
<td>18</td>
<td>67</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Reed (17)</td>
<td>Surgery</td>
<td>4</td>
<td>35%</td>
<td>4 min</td>
<td>30</td>
<td>90</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Watson (18)</td>
<td>Radiology</td>
<td>3</td>
<td>50%</td>
<td>45 min</td>
<td>51</td>
<td>88</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Barron (19)</td>
<td>Surgery</td>
<td>4</td>
<td>35%</td>
<td>3 min</td>
<td>38</td>
<td>79</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Smith (20)</td>
<td>Surgery</td>
<td>3</td>
<td>60%</td>
<td>3 min</td>
<td>55</td>
<td>NS</td>
<td>Poor</td>
<td>(−)</td>
</tr>
<tr>
<td>Jones (21)</td>
<td>Surgery</td>
<td>3</td>
<td>35%</td>
<td>3 min</td>
<td>32</td>
<td>91</td>
<td>Poor</td>
<td>(−)</td>
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<tr>
<td>Khosla (22)</td>
<td>Medicine</td>
<td>3</td>
<td>35%</td>
<td>3 min</td>
<td>49</td>
<td>88</td>
<td>Poor</td>
<td>(+)</td>
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<tr>
<td>Canfield (23)</td>
<td>Surgery</td>
<td>3</td>
<td>50%</td>
<td>NS</td>
<td>200</td>
<td>NS</td>
<td>Poor</td>
<td>(−)</td>
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<tr>
<td>Frassinelli (24)</td>
<td>Surgery</td>
<td>4</td>
<td>40%</td>
<td>NS</td>
<td>181</td>
<td>75</td>
<td>Poor</td>
<td>(+)</td>
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<tr>
<td>Adams (25)</td>
<td>Surgery</td>
<td>3</td>
<td>35%</td>
<td>3–5 min</td>
<td>50</td>
<td>84</td>
<td>Poor</td>
<td>(−)</td>
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<tr>
<td>Goncalves (26)</td>
<td>Surgery</td>
<td>3</td>
<td>35%</td>
<td>3 min</td>
<td>78</td>
<td>94</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Klieger (27)</td>
<td>Radiology</td>
<td>3</td>
<td>35%</td>
<td>3–5 min</td>
<td>52</td>
<td>71</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Yost (28)</td>
<td>Surgery</td>
<td>3</td>
<td>35%</td>
<td>NS</td>
<td>33</td>
<td>76</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Chen (29)</td>
<td>Surgery</td>
<td>4</td>
<td>35%</td>
<td>NS</td>
<td>176</td>
<td>NS</td>
<td>Poor</td>
<td>(+)</td>
</tr>
<tr>
<td>Poynter (30)</td>
<td>Surgery</td>
<td>4</td>
<td>35%</td>
<td>15 min</td>
<td>26</td>
<td>NS</td>
<td>Poor</td>
<td>(+)</td>
</tr>
</tbody>
</table>
Only one randomized/controlled study

“Comprehensive, rigorous trial, but it had fatal flaws”

–No sham group, thus bias possible
–Non-validated measures of outcome
–Absence of information on both groups regarding symptom severity

Does GBEF predict outcome after cholecystectomy for CAC?
A systematic review

- Meta-analysis is not possible
- Quality evidence is lacking, precluding definitive recommendation regarding its use”

• Problems and biases with literature
  – Outcome assessment unblinded
  – No justification of sample size
  – Patients and physicians were expecting a benefit from surgery

Recommendation

- Data do not support the use of GBEF in patient workup

“Well-powered prospective randomized controlled study is needed”

Standardization

• Quality data is still needed to confirm the utility of CCK cholescintigraphy to diagnose chronic acalculous disease.

• However, first the infusion method and normal values must be standardized.
Cholecystokinin (CCK)

- 33 amino acid polypeptide hormone
- C-terminal octapeptide is the physiologically active portion of CCK
- Sincalide (Kinevac®) is a C-terminal octapeptide analogue
Cholecystokinin binds to:

- Stimulatory receptors
- Inhibitory receptors
Cholecystokinin - sincalide

- Other physiologic effects in the gastrointestinal tract:
  - Increases intestinal peristalsis
  - Inhibits gastric emptying
  - Increases bile/pancreatic secretion
  - Suppresses appetite
Sincalide Cholescintigraphy

Three factors determine the amount of gallbladder contraction:

- Total dose (mg) administered
- Length of infusion (minutes)
- Dose rate (mg/kg/min)
Dose (total)
3-min infusions

0.005 to 0.04 µg/kg

0.01 µg/kg

0.02 µg/kg

Dose; ng/kg for 3 minutes

Krishnamurthy, 1982
**Dose (total)**

45-min infusions

0.01, 0.02, and 0.04 µg/kg

---

Sarva, 1985

---

Placebo

0.01 µg/kg

0.02 µg/kg

0.04 µg/kg

---

Sarva, 1985
Dose-rate

(µg/kg/min)

for same length of time (15 min)

Spellman, 1979
CCK Pharmacokinetics

- Pharmacokinetic studies suggest that methodology matters.
GBEF Normal Subjects - 1990

- 31 normal subjects (20M, 11F)
- Sincalide 1.5 µg x 1-2 min
  - GBEF ranged from 7% to 85%
  - No normal values established
  - 13/31 (42%) had a GBEF < 35%

Sincalide 1-min vs. 45-min

- 0.02 µg/kg x 1-min GBEF 11-92%
- 0.02 µg/kg x 45-min GBEF 65-96%

Limitations of study
- Not truly normals
- Different subject groups
- All were males
- Normal values not determined

Sincalide Normal Values

0.02 \( \mu g/kg \) - 3-min vs. 30-min

- 23 normal subjects (13 F, 10 M)
- Age (range 20 to 46, mean 27 ± 7)
- All subjects received both dose rates
- Normal GBEF values were determined

<table>
<thead>
<tr>
<th></th>
<th>3-min vs. 30-min</th>
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<tr>
<td><strong>Sincalide Normal Values</strong></td>
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<tr>
<td>Mean GBEF</td>
<td>52 ± 26%</td>
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<tr>
<td></td>
<td>70 ± 20%</td>
</tr>
<tr>
<td>Range</td>
<td>0-100%</td>
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<td>25-97%</td>
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<td>Normal values</td>
<td>&gt; 0%</td>
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<tr>
<td></td>
<td>&gt; 30%</td>
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<tr>
<td>GBEF &lt; 35%</td>
<td>8/23 (35%)</td>
</tr>
<tr>
<td></td>
<td>2/23(&lt;10%)</td>
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<tr>
<td>Adverse symptoms</td>
<td>48%</td>
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<td>0%</td>
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Sincalide Normal Values

0.01 μg/kg – 3-min vs. 60-min

- 20 healthy normal volunteers
- Age 21-52 (19 F, 2 M)
- All had both infusion methods
- Purpose: compare methodologies and establish normal values

Ziessman, et al., Radiology 2001; 221:404
## Sincalide Normal Values

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<tr>
<td><strong>#1</strong> 3-min</td>
<td>0.02 µg/kg</td>
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<tr>
<td><strong>#2</strong> 3-min</td>
<td>0.01 µg/kg</td>
</tr>
<tr>
<td><strong>#1</strong> 30-min</td>
<td>0.02 µg/kg</td>
</tr>
<tr>
<td><strong>#2</strong> 60-min</td>
<td>0.01 µg/kg</td>
</tr>
</tbody>
</table>

#1 Ziessman et al.. J Nucl Med 1992; 33:537
#2 Ziessman, et al.. Radiology 2001; 221:404
# 3-min vs. 30-60 min infusions

<table>
<thead>
<tr>
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<th>Sincalide Dose rate</th>
<th>GBEF (&lt; 35%)</th>
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</thead>
<tbody>
<tr>
<td>#1 3-min</td>
<td>0.02 µg/kg</td>
<td>8/23 (35%)</td>
</tr>
<tr>
<td>#2 3-min</td>
<td>0.01 µg/kg</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td>#1 30-min</td>
<td>0.02 µg/kg</td>
<td>2/23 (10%)</td>
</tr>
<tr>
<td>#2 60-min</td>
<td>0.01 µg/kg</td>
<td>1/20 (5%)</td>
</tr>
</tbody>
</table>

Fatty meal

Serum CCK

GB volume

Wiener, 1981
Sincalide $0.02 \, \mu g/kg$

Serum CCK

1 min infusion

60 min infusion

Minutes

Hopman, WPM. Br Med J 1986; 292:375
- CCK receptors
Sincalide Cholescintigraphy

What is the best infusion methodology?

- 1-3 minutes
- 10-15 minutes
- 30 minutes
- 45-60 minutes
Poor CCK infusion methodologies

- **Bolus infusion (< 30 sec)**
  - Spasm of gallbladder neck
  - Poor gallbladder contraction


- **1-3 minute infusion**
  - No normal values
  - High false positive rate – 30-35%
  - High incidence side effects – 49%
15-minute sincalide infusion

- 15 normal volunteers (5F, 10 M)
- 12 symptomatic pts. (8 F) (no GB dis.)
- 15-min sincalide infusion (0.02 µg/kg)
- Normal: ≥ 35% (mean 75 ± 20 SD)

30-minute sincalide infusion

- Ziessman, et al.
  - Sincalide 0.02 µg/kg over 30 minutes
  - Normal GBEF (#23) (>30%)

- Shaffer EA, et al.
  - Sincalide 20 ug/kg/h x 30 min
  - Karolinska CCK 0.02 U/kg/min x 30
  - Normal values (#23) (>65%)

45-60 minute sincalide infusions

- Yap, et al. - prospective, randomized
  - 40 normal controls (GBEF <40%)
  - 0.02 µg/kg/h x 45 min, EF @ 60 min

- Ziessman, et al.
  - 20 normals (GBEF <40%)
  - 0.01 µg/kg over 60 minutes
Sincalide Cholescintigraphy

What is the best infusion methodology?

– 3 minutes
– 15 minutes
– 30 minutes
– 45-60 minutes

Do we have to infuse for 60 minutes?!
Multi-center trial
GI council (Bracco funded)

- 60 normal subjects – 3 studies each
  - $0.02 \, \mu g/kg \times 15 \, \text{min}$
  - $0.02 \, \mu g/kg \times 30 \, \text{min}$
  - $0.02 \, \mu g/kg \times 60 \, \text{min}$
- Normal values (95% confidence)
- Lowest coefficient of variation
Conclusions

- CCK infusion methodology matters
- Standardization is necessary
- Normal values must be established for the methodology selected
Sincalide cholescintigraphy

- After the best infusion method established:
- Well-designed prospective multicenter randomized trial evaluating the utility of CCK cholescintigraphy
Nuc Med Clinics

Mom & Pop shops

• Protocols vary by clinic

• Reasons: different
  – Instrumentation
  – Software
  – Expertise/Preferences
  – No standard protocol
Future Nuclear Medicine Clinics

Standardization

• Same protocols
• Same normal values
• Satisfied customers