CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18467/S13

MEDICAL REVIEW(S)

DIV

Division of Medical Imaging, Surgical and Dental Drug Products

Medical Imaging Drug Group

Labeling Review

DEC 20 1993

NDA: 18-467/S-013 & 014

Sponsor: The DuPont Merck Pharmaceutical Co.

Drug: Hepatolite, Kit for the Preparation of Technetium Tc 99m Disofenin

Date of Submission: July 26,1991 for S-013
April 8, 1992 for S-014

Submissions provide for:

S-013 - the addition of a radiation dosimetry table to the package insert which would characterize the effect of the radiation dose to patients with jaundice.

S-014 - the addition of two new clinical indications

1. The diagnosis and evaluation of acute cholecystitis when performed with morphine sulfate augmentation.

2. The diagnosis and evaluation of

Background: Supplement 013 received an approvable letter dated April 2, 1993. This letter contained labeling changes and a request to submit draft labeling incorporating these changes. Supplement 014 received an approvable letter dated April 13, 1993. This letter approved only the morphine augmentation portion of the supplement and also contained labeling revision requests. The company has responded to both of these supplements with a draft package insert which incorporates all of the labeling changes requested in both approvable letters. In addition, while doing the labeling review of this draft label dated August 6, 1993, I noticed that the radiation dosimetry section had not been revised since the drug was originally approved and that new calculations were available and should be incorporated into this revised draft package insert. I requested the company to update that portion of the package insert also. The "final revised draft" package insert was then submitted dated November 23, 1993. On December 16, 1993, we requested the company to move several of the paragraphs into different sections of the package insert

On December 17, 1993, we received their "last final revised draft package insert" incorporating these changes.

Review: The revised draft label (dated December 16, 1993) has incorporated all of our labeling requests for both S-013 and 014. The draft package insert is acceptable as submitted.

Recommendation:

I recommend that an approval letter be sent for both S-013 and 014.

/S/

Susan Lange
Consumer Safety Officer
December 20, 1993

/S/

MD 12/20/93

Concur:
A. Eric Jones, M.D.
Group Leader, Medical Imaging Drug Group

MAR 1 [illegible] 1994

Division of Medical Imaging, Surgical and Dental Drug Products

Medical Imaging Drug Group

Labeling Review

NDA: 18-467/S-013 & 014

Sponsor: The DuPont Merck Pharmaceutical Co.

Drug: Hepatolite, Kit for the Preparation of Technetium Tc 99m Disofenin

Date of Submission: February 25, 1994

Submission provides for: final printed labeling (FPL) for the following approved supplements:

S-013 - the addition of a radiation dosimetry table to the package insert which would characterize the effect of the radiation dose to patients with jaundice.

S-014 - the addition of one new clinical indication

1. The diagnosis and evaluation of acute cholecystitis when performed with morphine sulfate augmentation.

Background: Supplements 013 and 014 received approval letters dated December 29, 1993, which requested FPL identical to the draft labeling on which the supplements were approved.

Review: The FPL dated February 25, 1994, is identical to the draft labeling for the approved supplements and is acceptable as submitted.

Recommendation:

I recommend that an acknowledge and retain letter be sent for the FPL for both S-013 and 014.

/S/

Susan Lange
Consumer Safety Officer
March 15, 1994

/S/ M.D - 3/18/94

Concur:
A. Eric Jones, M.D.
Group Leader, Medical Imaging
Drug Group

DW

MEDICAL OFFICER'S REVIEW/HFD-1[illegible]
NDA 18-467

OCT 19 1993

MOR DATE: October 8, 1993

SUBMISSION DATE: August 6, 1993
Amendment No. 1 to Supplements
S-013 and S-014

RECEIVED DATE: September 8, 1993

SPONSOR: DuPont Merck
No. Billerica, MA

AGENT: Hepatolite Kit
For the preparation of Technetium Dosofenin.

Clinical Evaluation

Applicant in responding to recommended changes in labelling as set out in FDA letter dated April 13, 1993, requests the substitution of word "may" for in the precautionary statement "In the cases where there has been no visualization of the gall bladder after 60 minutes of scanning, morphine may be carefully administered...." This word change makes the statement optional and not compulsory as the firm points out. In our opinion, this change is an improvement which should have been recommended initially. The revised package insert (#513060 dated June 1993) incorporated this change as well as all recommendations of the FDA letter dated 04-13-93.

Action Recommended

Send letter to firm approving word change.

/S/

E. H. Chacalos, M.D.

Group Leader Comments:

/S/ 10/19/93

I agree.

A.E. Jones, M.D.

cc:
HFD-160
HFD-161/CSO/Lange
HFD-160/MO/Chacalos
HFD-160/SMO/Jones
HFD-160/DDir/Love

Medical Officer's Review/HFD-160

MAR 23 1993

NDA# : # 18-467

MOR Date: 25 February 1993

Submission Date: 26 July 1991
S-013 special supplement for label revisions
(Radiation Dosimetry)

Received Date:

Sponsor: Dupont Merck Pharmaceutical Company
North Billemica, MA

Agent: Hepatolite Disofenin

Clinical Evaluation

Package insert # 511895 dated June 1989 has been revised to include radiation dosimetries to jaundiced patients with malignant obstructive disease as calculated by( ) Data is based on 5 human subjects and on kinetics for the liver "predicted" for various disease categories. It is not clear whether these numbers were actually determined in patients with the diseases in question in question. In any event the absorbed radiation dosages are not too different to matter very much.

However, adverse reaction section also needs to be revised to include deaths attributed to this class of drugs to this NDA and others dealing with hepatobiliary imaging agents.).

Action Recommended

1. The revised radiation dosimetry tables in insert are acceptable.

2. The adverse reaction section needs to be revised to include deaths as set out in MOR dated 12-5-91

E.H. Chacalos, M.D.

/S/

/S/ M.D. 3/23/93

April 11, 1989

Radiation Dose Estimates for Tc-99m DISIDA in Various Disease States*

Organ	Estimated Radiation Dose Category: (1) mGy/MBq	(1) rad/mCi	(2) mGy/MBq	(2) rad/mCi	(3) mGy/MBq	(3) rad/mCi	(4) mGy/MBq	(4) rad/mCi	(5) mGy/MBq	(5) rad/mCi
Gallbladder Wall	0.038	0.14	0.037	0.14	0.038	0.14	0.038	0.14	0.022	0.081
Lower Large Intestine Wall	0.066	0.25	0.060	0.22	0.064	0.24	0.064	0.24	0.0016	0.005
Small Intestine	0.048	0.18	0.044	0.16	0.047	0.17	0.046	0.17	0.0035	0.013
Upper Large Intestine Wall	0.094	0.35	0.086	0.32	0.092	0.34	0.091	0.34	0.0052	0.019
Liver	0.0079	0.029	0.016	0.061	0.0098	0.036	0.010	0.038	0.080	0.30
Ovaries	0.021	0.077	0.019	0.071	0.020	0.075	0.020	0.075	0.0021	0.007
Red Marrow	0.0041	0.015	0.0040	0.015	0.0041	0.015	0.0040	0.015	0.0024	0.009
Bone Surfaces	0.0039	0.014	0.0040	0.015	0.0039	0.014	0.0039	0.014	0.0036	0.013
Testes	0.0018	0.0068	0.0017	0.0064	0.0018	0.0067	0.0018	0.0066	0.00085	0.003
Urinary Bladder Wall	0.024	0.089	0.024	0.087	0.024	0.088	0.024	0.088	0.019	0.07
Total Body	0.0039	0.014	0.0040	0.015	0.0039	0.014	0.0039	0.014	0.0044	0.01

* Based on kinetic data gathered in 5 human subjects and on kinetics for the liver predicted for categories (1)-(4) in Coenegracht et al. Eur. J. Nucl. Med. 8(4): 140-144, 1983. Category definitions are: (1) Normal, (2) Jaundiced patients-malignant obstructive disease (3) Jaundiced patients-benign obstructive disease, (4) Jaundiced patients-heptocellular disease, (5) Complete retention in liver. Assumed distribution and retention:

Liver - 80% uptake. Kinetic model:

	Uptake Half-time (min)	Elimination Half-time (min)
(1)	5.0	22.0
(2)	3.2	63.0
(3)	4.0	33.0
(4)	4.9	36.5
(5)	-	360

Gallbladder: 10% of activity leaving liver is cleared to gallbladder. 75% of this is cleared after 3 hrs., remaining 25% cleared after 9 hours, to small intestine.

GI Tract: 90% of activity leaving liver plus clearance from gallbladder. Follows kinetics as in ICRP 30.

Remainder: 20% not taken up by the liver is cleared through the urinary bladder (15%, T_b=0.2 hours) or retained indefinitely (5%).

MEDICAL OFFICER'S REVIEW
NDA 18-467

DATE: Sept. 18, 1992

SEP 18 1992

SUBJECT: Hepatolite

SUBMISSION DATE: April 8, 1992, S-014; divisional comments by Dr. Chambers dated August 16, 1992; consultant's review (Dr. Fredd) dated Sept. 15, 1992; MOR dated July 9, 1992.

REVIEWER"S COMMENTS:

I do not agree with several points and the general thrust of Dr. Chamber's comments as set out in his memo dated

However I fully agree with comments and implications thereof by consultant (Dr. Fredd, HFD-180) as presented in his memo dated Sept. 15, 1992, namely (1) that the firm should have analysed the pivotal studies; (2) that the application is not approvable; and (3) that it should never have been filed in the first place.

RECOMMENDATIONS:

Since the disagreements appear irresolvable it would seem that only two options are feasible, namely;

1. Issue a non-approvable letter as recommended in my MOR dated July 9, 1992 requiring firm to do or provide two or more adequate and well-controlled studies using their own drug for each of the four indications with an analysis and format as set out in sections 314.50(5) and (6) of the regulations.

or

2. Reassign the NDA to a medical officer who agrees with Dr. Chamber's views.

/S/

E.H. Chacalos, M.D.

Noted. New studies or an adequate analysis of publications is needed.

/S/

A.E. Jones, M.D. 9/18/92

P 1

MEDICAL OFFICER'S REVIEW/HFD-160
NDA 18-467

OCT 28 1992

MOR DATE: July 9, 1992 OCT 28 1992

SUBMISSION DATE: April 8, 1992
Supp s-014 Addition of 3-4 new indications

RECEIVED DATE: May 14, 1992

SPONSOR: The Du Pont Merck Pharm. Co.
Radiopharmaceutical Division
331 Treble Cove Road
No. Billerica, MA 01862
(509) 667-9531

AGENT: Hepatolite, kit for the preparation of Technetium Tc99m Disofenin

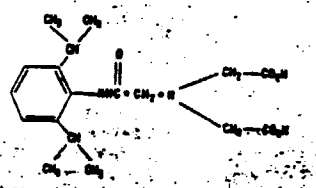
DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Disofenin - 20mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.24mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.8mg

Prior to lyophilization the pH is adjusted to between 4-5 with HCl and/or NaOH. The contents of the vial are lyophilized and stored under nitrogen.

The drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection.

The structure of disofenin is shown below:



The precise structure of stannous technetium-disofenin complex is unknown at this time.

OBJECTIVE OF SUPPLEMENT

To change indications to read (additions in bold type):

INDICATIONS AND USAGE: Technetium Tc99m Disofenin is indicated as a hepatobiliary imaging agent. Hepatolite is indicated in the diagnosis of acute cholecystitis as well as to rule out the occurrence of acute cholecystitis in suspected patients with right upper quadrant pain, fever, jaundice, right upper quadrant tenderness and mass or rebound tenderness, but not limited to these signs and symptoms.

In otherwise healthy individuals, non-visualization of the gallbladder *4 hours* after administration of Hepatolite following a 2-6 hour fast and in the presence of activity in the small intestine is indicative of a diagnosis of acute cholecystitis. Under the same conditions in an otherwise healthy person, visualization of the gallbladder during a *1 hour* scintigraphy is effective in excluding a diagnosis of acute cholecystitis. If the gallbladder is not visualized by 1 hour, scanning must continue for four hours or until the gallbladder is visualized.

Hepatolite® Kit for the preparation of Technetium Tc99m Disofenin is indicated in the diagnosis and evaluation of acute cholecystitis when performed with intravenous morphine sulfate augmentation. Morphine administration enhances sphincter of oddi tone increases intraluminal common bile duct pressure sufficient to overcome resistance and diverts radiotracer into the gallbladder if the cystic duct is patent. This permits the diagnosis or exclusion of acute cholecystitis within 60 minutes of the start of imaging. 0.04mg/kg morphine sulfate, diluted in 10ml saline is administered intravenously over three minutes if there is non-visualization of the gallbladder after 60 minutes provided there is a small bowel visualization. Acute cholecystitis is confirmed if there is persistent non-visualization of the gallbladder 30 minutes post morphine administration.

Cholescintigraphy is only partially effective in the diagnosis or excluding the diagnosis of acute cholecystitis in other conditions such as trauma, intercurrent disease, total parenteral nutrition (TPN) and nothing by mouth (NPO) status, all of which frequently result in false positive results (non-visualization). False negatives (visualization) are rarely seen in certain patients with cholelithiasis (myriad of small stones).

Hepatolite® Kit for the preparation of Technetium Tc99m Disofenin is indicated in the diagnosis and evaluation of chronic acalculous disorders of the biliary tree when performed with Cholecystokinin (CCK) augmentation. Cholecystokinin and its analogues cause the gallbladder to contract, the sphincter of oddi to relax, augment of pyloric sphincter contraction, enhance bowel motility, increase secretion of bile, pancreatic enzymes and enterokinase. CCK may be useful (1) as a pretreatment in patients fasted for longer than 24-48 hours or receiving total parenteral nutrition to reduce false-positive studies in suspected acute cholecystitis (2) to prevent false-negative studies in acalculous cholecystitis (3) to evaluate functional disturbances of the gallbladder or cystic duct by gallbladder ejection fraction response.

CLINICAL EVALUATION

The following new indication was approved in FDA letter dated Oct. 31, 1988 on basis of MOR dated 6-6-1988 (Zolman)(Supp s-009, for diagnosis of acute cholecystitis in suspected patients)

INDICATIONS AND USAGE: Technetium Tc99m Disofenin is indicated as a hepatobiliary imaging agent. Hepatolite is indicated in the diagnosis of acute cholecystitis as well as to rule out the occurrence of acute cholecystitis in suspected patients with right upper quadrant pain, fever, jaundice, right upper quadrant tenderness and mass or rebound tenderness, but not limited to these signs and symptoms.

In otherwise healthy individuals, non-visualization of the gallbladder *4 hours* after administration of Hepatolite following a 2-6 hour fast and in the presence of activity in the small intestine is indicative of a diagnosis of acute cholecystitis. Under the same conditions in an otherwise healthy person, visualization of the gallbladder during a *1 hour* scintigraphy is effective in excluding a diagnosis of acute cholecystitis. If the gallbladder is not visualized by 1 hour, scanning must continue for four hours or until the gallbladder is visualized.

Cholescintigraphy is only partially effective in the diagnosis or excluding the diagnosis of acute cholecystitis in other conditions such as trauma, intercurrent disease, total parenteral nutrition (TPN) and nothing by mouth (NPO) status, all of which frequently result in false positive results (non-visualization). False negatives (visualization) are rarely seen in certain patients with cholelithiasis (myriad of small stones).

According to this MOR dated 6-6-1981 sensitivities and specificities for diagnosing acute cholecystitis were usually above % and accuracies rarely below % which seems to reflect current clinical expectations. This was all based on published reports.

We quote from this MOR (6-6-88):

> "a sufficiently long period of time for scanning and surgical pathology as the method of final diagnosis yielded more than 97% sensitivity. Two retrospective trials in which the number of patients without disease was large enough produced similar results. For comparison, the trials with only the clinical diagnosis available had a slightly lower sensitivity, but still 95%, or more. In contrast, the trials which compiled cases with TPN, NPO, after trauma and with intercurrent diseases resulted in markedly decreased parameters.
>
> With the same qualifications, the lowest positive predictive value was 92% and negative predictive value 98%. The accuracy was rarely below 97% and in several instances it was the maximum, 100%.
>
> The specificity was determined in prospective experiments only on 14 patients with the overall result of 93%. A prospective trial to determine specificity of this procedure poses ethical questions and, therefore, one needs to consider the retrospective studies. In two large ones, the outcome was 100% and 97%.
>
> These highly satisfactory results were obtained in a fairly large population of patients (43), a total of 109 subjects being studied prospectively. The clinically diagnosed patients (733) seemed to likewise benefit from the procedure (Table 1). Thus, the evidence presented here appear both substantial and convincing.
>
> An average sensitivity and specificity over 95% when found in a well defined population of patients denote, by current standards, an excellent diagnostic tool. The reality that the results were obtained in several localities throughout the world negates somewhat the fact that prevalancies of the disease in various places are not available. Thus, while the predictive values cannot be assigned a broadly applicable number, the repeatability of the findings in the subpopulations may reasonably translate into an expected, acceptable reliability of the efficacy assessment."

From these overly optimistic appraisals of published studies it would seem that Hepatolite is almost perfect in diagnosing acute cholecystitis or ruling it out with accuracies approaching 100%, provided of course, that all diseases, conditions or precise methodologies which could reveal false results are excluded.

However firm is still not satisfied with these incredibly "accurate" results and wishes to shorten imaging times to 1 1/2 hours from 4 and to increase accuracies even further if this is indeed possible. We note that baseline sensitivities and specificities in studies used to demonstrate improvements with morphine and cholecystokinin are considerably lower than what the firm claimed and submitted in the supplement for the initial indication of acute cholecystitis. This is reflected in the analyses of the published studies in the MOR dated 6-6-88. Apparently one cannot make more perfect what is almost perfect to begin without first making it less perfect. Perfection has to be reduced to be reintroduced and this is precisely what was done in some of these published studies.

We should like to make a few points about the diagnosis of acute cholecystitis with hepatobiliary imaging agents to put the matter in perspective.

It has become the practice and usage to confirm acute cholecystitis by hepatobiliary scintigraphy or less effectively with ultrasound in suspected patients. If this is the basis of the clinical diagnosis it may not reflect the pathological diagnosis in many cases or to clearly differentiate from a chronic cholecystitis. We quote from one well known source (Anderson, Pathology 7th edition, vol. 2, pp1441) on pathological findings in acute cholecystitis:

> "In acute cholecystitis, the viscus is enlarged, firm, and discolored reddish brown, with an increase in thickness of its wall up to tenfold. This is caused by spreading of the tissue elements and filling of the spaces with edema fluid and extravasated blood. The lumen usually contains a mixture of bile, blood, and pus. Gallstones usually are not present.
>
> Microscopically, the epithelium may be preserved over extensive areas. Elsewhere it is either shed or missing. All the layers are spread apart and are densely infiltrated with erythrocytes and neutrophilic granulocytes in fibrin or in an amorphous pink substance. In the distended capillaries, margination of white blood cells is conspicuous. The changes are more pronounced about blood vessels and involve all the layers, including the perimuscular layer and the serosa.
>
> Commensurate with the intensity of the inflammatory process, the clinical signs and symptoms, too, are severe. There is intense pain in the right upper abdomen radiating toward the right shoulder, associated with abdominal rigidity, malaise, nausea, and other signs of beginning peritonitis. The acute process is usually progressive and may end in perforation of the gallbladder with focal abscess or diffuse peritonitis. In rare instances, the inflammation may subside.

Chronic cholecystitis with superimposed acute cholecystitis. Acute cholecystitis more frequently occurs in a gallbladder with chronic cholecystitis containing biliary calculi than in an intact gallbladder. Occurrence of chronic and acute cholecystitis in the same gallbladder often is referred to as acute exacerbation of the chronic process, although actually the acute inflammation is superimposed on the chronic inflammatory process.

Grossly, such a gallbladder differs little from one with acute cholecystitis except for the presence of calculi within the viscus. Red, brown, or creamy pus fills the lumen. The calculi may be of any variety, although mixed gallstones of the faceted type are most common. The mucosa is angry red, velvety, and ragged, with frequent erosions. The waterlogged wall is many times the usual thickness, and the serosa is discolored red and brown, with flakes of fibrin giving the peritoneal surface a ground-glass opacity.

Microscopically, the mucosal folds are coarse, low, or absent. The epithelium varies in height. Rokitansky-Aschoff sinuses are numerous. The muscular coat is greatly hypertrophied with an increase of the intermuscular connective tissue and thickening of the perimuscular layer. In all the layers there is a scattering of lymphocytes, plasma cells, and large mononuclear cells. In addition, a hemorrhagic fibrinopurulent exudate covers denuded areas of the mucosa. All the lawyers are greatly spread apart by inflammatory edema and infiltrated with freshly extravasated erythrocytes and neutrophilic granulocytes. The serosa; surface is covered by fibrin.

Chronic cholecystitis with superimposed acute cholecystitis is a well-known entity. This is the lesion that most commonly necessitates surgical intervention and removal of the gallbladder.[40] The clinical signs and symptoms are those of acute cholecystitis. Because of the presence of biliary calculi, obstruction of the common bile duct may occur, and jaundice may accompany the process. In acute cholecystitis without cholelithiasis, jaundice does not occur unless there is concomitant hepatitis or cholangitis. Perforation of the gallbladder, with subsequent focal or diffuse peritonitis, is a common sequel of acute cholecystitis superimposed on chronic cholecystitis with cholelithiasis."

Can one realistically accept a clinical diagnosis as decisive which is itself based on and confirmed by scan to evaluate the accuracy of the scan when used with morphine or cholecystokinin to diagnose acute cholecystitis? Ultimately one would be comparing the scan findings with themselves and obtaining excellent but meaningless accuracies.

Secondly, morphine may itself produce false positive results. It itself may produce spasms in the neck of the gallbladder

particularly when given as a bolus, a fact not mentioned in the proposed insert. Below is one list of factors which can produce false positives (Shaw in Pharmacy International, Dec 1985, p294).

TABLE VIII. Drugs and diseases that may affect hepatobiliary imaging studies with ^{99m}Tc-labeled iminodiacetic acid derivatives

False positive bile duct obstruction	
Acute pancreatitis	Morphine
Alcoholism	Parenteral alimentation
Butorphanol	Pethidine (meperidine)
Fasting	
Hepatic artery infusion chemotherapy	
Other effects	
Focal lung uptake: metastasis from hepatoma	
Breast uptake: exogenous hormonal stimulation	
Decreased liver uptake: nicotinic acid	

The false positives are themselves a subject of controversy. We quote from Kim & Podoloff's editorial (J.Nucl.Med. 32:1233, 1991):

> "The false-positive rate is controversial. Fink-Bennett et al. (5) and Flancbaum and Alden (8) reported that it is low, although Fig et al (9) have recently shown a rate as high as 60% in a group of seriously ill patients. Rapid biliary to bowel transit of the radiotracer or insufficient quantity of the radiotracer remaining in the hepatocytes seems to be responsible for the false-positive studies. Stasis of the gallbladder with water reabsorption from the bile may also cause the gallbladder to become filled with viscous bile. This may prevent entry of the radiocompounds into the gallbladder."

They also note some other potential causes of false positives and illustrate the difficulty of differentiating acute from chronic cholecystitis. Again we quote:

> "The persistent nonvisualization of the gallbladder in the presence of normal excretion into the small intestine is highly suggestive of acute cholecystitis in the symptomatic patient. Chronic cholecystitis is suggested when symptoms have abated and the gallbladder does not visualize. However, failure of the gallbladder to fill can be attributed not only to the obstruction of the cystic duct but also to prolonged fasting, total parenteral nutrition, pancreatitis, hepatocellular disease, alcoholism, and critical illness (4). False-positive cholescintigraphy has been reported in more than one-third of the critically ill patients with suspected acute cholecystitis (3). The mechanism for nonfilling of the gallbladder in these

patients is unclear, but it may be related to altered biliary dynamics and water resorption."

If surgical intervention is based principally on positive scan findings and more likely discouraged by negative scans than obviously pathological findings at surgery will not be able to detect most false negatives. This would increase or favor high sensitivities. And if a positive scan is associated with mild clinical symptoms surgical intervention would be less likely whilst severe symptoms and a positive scan would increase the likelihood of surgical intervention. This would have the effect of increasing the true positive incidence and practically eliminating the false p incidence. Thus indications for surgery have built-in biases favoring high accuracies, for the hepatobiliary imaging agent.

Admittedly it is difficult to establish accuracies in diagnosing acute cholecystitis. However the firm and many investigators have neatly circumvented these problems by excluding all known conditions or diseases and more precise experimental designs that could produce too many false positives or false negatives and by comparing clinical diagnoses based in large measure on the scan itself with the results of the scan to attain phenomenal accuracies and in many cases almost perfect results. It seems that initial results are only then less than perfect when they must be if they are to show improvements using morphine or cholecystokinin. This may be clinical practice and custom but surely not clinical science or reliable scientific evaluations of true efficacy.

DATA CLAIMING TO SUPPORT NEW INDICATIONS (according to firm)

To support those 3-4 additional indications applicant has submitted 87 reprints of diverse sorts. A scant overall summary claiming that many of these publications support additional claims was also submitted but no detailed analyses of studies they deemed pivotal or adequate and well-controlled. Indeed we could find no discussion as to the adequacy of the studies methodologies, reliabilities or potential flaws in any of the studies.

Applicant has also submitted package inserts for Kinevac (Sincalide for injection, c-terminal octapeptide of cholecystokinin) and Morphine sulphate.

To give a flavor as to what was presented we give a table purportedly to support the proposed new additions. We note often the applicant's product was not even used in several of the studies.

IV. LITERATURE REVIEW AND SUMMARY

(a) Summary Table of Morphine-Augmentation Clinical Studies

Ref#	Year	# subjects	tracer	morphine dose	SENS	SPEC
Vasquez (15) (meta analysis/review)	1988	180	Tc IDA (NOS)	0.04mg/kg	98.8%	88.9%
Choy (6)	1984	36	Tc PDG	0.04	96%	100%
Grund (12)	1986	21	Tc Disofenin	0.04	100%	89%
Kim (9)	1986	40	Tc Disofenin	0.04	100%	82%
Vasquez (42)	1987	40	Tc Disofenin	0.04	100%	85%
Olsen (38)	1987	12	Tc Disofenin	0.04	100%	88%
Mehta (39)	1987	31	Tc Disofenin	0.04	100%	100%
Flancbaum (40)	1989	18	Tc Disofenin	0.05-0.1		
Flancbaum (41)	1990	68	Tc Disofenin	0.05-0.1	97%	95%
Vasquez (11)	1988	40	Tc Disofenin	0.04	100%	85%
Fig (17)	1990	51	Tc Disofenin	0.04	94%	64%
Louridas (44)	1987	41	Tc Disofenin	0.04	83%	97%
Louridas (43)	1987	9	Tc Disofenin	0.04		
Fink (7)	1991	61	Tc Disofenin Tc Mebrofenin	0.04	95%	99%
Keslar (8)	1987	31	Tc Disofenin	0.04	100%	83%
Kistler (45)	1991	32	Tc Mebrofenin	2mg	93%	78%

(b) Summary Table of "CCK"-Augmentation Clinical Studies

Ref#	Year	# subjects	tracer	"CCK" dose
Fink (30)	1991	374	Tc Disofenin	0.02 mcg/kg sincalide
Swayne (28)	1986	87	Tc Disofenin	0.02 mcg/kg CCK
Brugge (27)	1986	36	Tc Disofenin	0.02 mcg/kg sincalide
Pickleman (24)	1985	36	Tc Disofenin	0.02 mcg/kg sincalide
Topper (22)	1980	34	Tc PIPIDA	0.2 mcg/kg sincalide
Newman (23)	1983	25	Tc HIDA	CCK
Davis (70)	1982	20	Tc PIPIDA	0.02 mcg/kg sincalide
Fink (26)	1986	374	Tc Disofenin	0.02 mcg/kg sincalide
Fink (2)	1991	REVIEW	Tc Disofenin	0.02 mcg/kg sincalide
Williams (67)	1989	99	Tc HIDA	CCK
Masclee (66)	1989	8	Tc HIDA	CCK
Raymond (65)	1988	101	Tc Disofenin	0.02 mcg/kg sincalide
Zech (29)	1991	83	Tc Disofenin	0.04 mcg/kg sincalide
Masclee (62)	1990	6	Tc HIDA	CCK-33
Masclee (61)	1989	18	Tc HIDA	CCK-33
Masclee (60)	1989	6	Tc HIDA	CCK-33
Masclee (59)	1989	40	Tc HIDA	CCK-33
Schaffer (58)	1982	11	Tc HIDA	0.02 U/kg CCK
Schaffer (57)	1984	25	Tc HIDA	0.02 U/kg CCK
Westlake (56)	1990	26	Tc Disofenin	0.02 mcg/kg sincalide
Clas (55)	1989	9	---	0.02 mcg/kg sincalide
Daignault (54)	1988	42	Tc Disofenin	0.02 U/kg CCK
Sylwestrowicz (53)	1988	83	Tc Disofenin	0.02 U/kg CCK
Spellman (52)	1979	19	Tc HIDA	CCK
Stone (51)	1988	50	Tc Disofenin	0.02 mcg/kg sincalide
Pomeranz (50)	1985	67	Tc Disofenin	CCK
Masclee (49)	1989	6	Tc HIDA	CCK
Kim (47)	1990	14	Tc Disofenin	0.03 mcg/kg sincalide
London(46)	1983	10	Tc Disofenin	0.02mcg/kg sincalide
Kistler (45)	1991	32	Tc Mebrofenin	0.02 mcg/kg sincalide
Fink (35)	1985	14	Tc Disofenin	0.02 mcg/kg sincalide
Krishnamurthy (48)	1984	5	Tc IDA (NOS)	CCK
Pellegrini (64)	1985	16	Tc PIPIDA	0.02 U/kgCCK-33
Annese (68)	1991	20	Tc Diethyl-IDA	CCK

We find this totally inadequate as definitive evidence for efficacy. Perhaps the medical officer (Dr. Zolman) who recently approved the acute cholecystitis indication might take a look at this supplement. However if adequate and well-controlled studies using the firm's product and with clear-cut safeguards against biases and preselections of data are to be demanded, firm will have to do their own prospective adequate and well controlled studies.

We list below other reasons for not accepting only published studies.

CONCLUSIONS AND RECOMMENDATIONS

1. Submission and the 87 reprints or references are inadequate to support the 3-4 new indications. Applicant has done no adequate and well-controlled studies at all.

2. Publications from the open literature as sole support for new indications are unacceptable for the following reasons:

   2a. There is a strong tendency for only positive studies to get published whilst negative studies seem rarely to get published if at all and are often times not ever submitted to journals.

   2b. It is difficult if not impossible to clearly establish that a published study is adequate and well-controled as required by law since often much pertinent information is left out.

   2c. It is impossible to determine whether there was a preselection of favorable data and a exclusion of much unfavorable data, or if mentioned at all whether the reasons for exclusion were filmsy and invalid. In brief the authenticity of statements cannot be checked and validated.

   2d. There is no way we could get a hold of <u>all</u> the individual patient report forms or the raw data. Would the investigator and his studies be available for an FDA inspection?

   2e. We would not be able to validate the studies with an FDA inspection or substantiate that protocols were actually followed and adequate safeguards imposed which rule out biases on unwarranted exclusions of data.

3. If the clinical diagnoses of acute cholecystitis is confirmed by the scan or largely based on the scan and used as the controls then the accuracies of the scan would ultimately amount to comparing scan findings with themselves and almost perfect results would be achieved which indeed has been the case in the past.

4. The selections of patients for surgical intervention and therefore confirmations by surgical pathology are themselves biased in the direction of few false positives and no false negatives. (see above)

5. Applicant has not identified and analysed two adequate and well-controlled studies amongst the many publications for each of the 3-4 indications.

ACTION RECOMMENDED

1. Reject in toto this submission clearly stating that these reprints alone suffice not to support the 3-4 indications,

2. Give submission to medical officer who originally approved the acute cholecystitis indication for a second opinion (Dr. Zolman).

3. If the firm wishes to pursue these indications they should be asked to do their own prospective adequate and well controlled studies and with their product. Two for each indication which should be randomized, double blinded and include a sufficient number of patients for the requisite statistical power. Each statement and each claim has to be supported by two or more adequate and well controlled studies.

   For example; (However firm should design their own reliable protocols in greater detail)

A. A double-blinded, randomized study comparing sensitivities and specificies after morphine at 1 1/2 hours and without morphine at 4 hours. This is to include an independent and valid confirmation of the diagnosis of acute cholecystitis for all patients.

   The final diagnosis is not to be based on the scan at all or solely on the biased selections of patients for surgical intervention and pathology. Long term follow up and other findings should be given equal or greater weight. This pertains to all studies.

B. Two adequate and well controlled studies in patients fasting longer than 24-48 hours with and without sincalide (an analogue of cholecystokinin).

C. Two adequate and well controlled studies in patients with cholecystitis with and without sincalide.

D. Two or more adequate and well controlled studies demonstrating the reliability, accuracy and reproducibility of gall bladder ejection fraction with sincalide and its variations in each specific disease. The procedure itself

should be validated. (i.e. Gallbladder ejection fractions) and potential sources of error identified.

Moreover they should be asked to identify which studies in the publications they deem as pivotal and adequate and well controlled for each of the four indications. These should be analysed and their adequacy and objectivity justified. However these studies will be used only as further support not as a definite demonstration of efficacy for which the applicant's own prospective adequate and well controlled studies will alone be deemed demonstrative.

In the meantime a non-approvable letter should issue forthwith. The applicant should be asked to do its own adequate and well-controled prospective studies as outlined above and full reports submitted.

/S/

E.H. Chacalos, M,D.

I agree with Dr. Chacalos. Studies to verify these claims are needed.

/S/

A.E. Jones, M.D.
7-23-92

We have received consultative replys from Dr. S. Fridd, Director HFD-180 who noted that the sponsor provided no analysis of the literature & He reviewed the references and did not recommend approval of (Sincalide).

Dr Curtis Wright reviewed the references from the applicant & recommended the use of morphine but with limited & not exclusive wording.

/S/ M.D 10/23/92

cc:
HFD-160/Div File
HFD-161/CSO/Lange
HFD-160/MO/Chacalos
HFD-160/SMO/Jones
HFD-160/DDIR/Chambers
Typed by: JO

Group Leader's Comments
Medical Imaging, HFD-160

NDA 18-467
Submitted: 4/8/92
M.O.R.: 7/9/92
Agent: Hepatolite Kit (Technetium Tc 99m Disofenin)
Sponsor: The Du Pont Merck Pharmaceutical Company.

OCT 12 1992
12

The applicant submitted eighty-seven references to support the following two supplemental claims: (quote)

1. "The diagnosis and evaluation of acute cholecystitis when performed with intravenous morphine sulfate augmentation.

2. The diagnosis and evaluation of

The sponsor further stated: (quote)

"In support of these new clinical indications we have reviewed and summarized the published results from the clinical literature."

The applicant's review consisted only of statements without any mention or direct reference to the submitted literature. Dr. Chacalos reviewed the submission and rejected it for invalid reasons.

The portion was consulted to HFD-180 and Dr. Steve Fredd reviewed the appropriate references and recommended disapproval of the associated claims.

The morphine related portion of the submission was consulted to HFD-007 and Dr. Curtis Wright reviewed the references and recommended approval with reservations on 9/22/92. Dr. Wright's recommendations are for wording to be placed in the indications section of the labeling however some of his comments are precautions rather than indications.

The following is a recommended revision of indications:

When the gall bladder fails to appear within the first 60 minutes of imaging after the administration of Hepatolite, a single 0.04 mg/kg dose of intravenous morphine, diluted in 10ml normal saline and administered over 3 minutes, has been reported to be effective in shortening the 4 hours usually required for observations, to 90 minutes. In patients who do not have acute cholecystitis, the use of morphine has been reported to result in visualization of the gallbladder within an additional 30 minutes.

False negative visualization of the gallbladder in cases of acute cholecystitis, and false positive failure of a normal gallbladder to visualize have been reported with both morphine augmentation and the standard 4 hours of observation.

The following should be included in the precautions section:

In cases where there has been no visualization of the gallbladder after 60 minutes of scanning, morphine should be carefully administered provided there is no contraindication to the use of narcotics. There should be clear evidence of patency of the common duct, such as observed entry of radiopharmaceutical into the small bowel, prior to the administration of morphine to such patients.

Morphine augmentation has not been associated with any serious adverse events in the reported cases, but the administration of morphine in biliary colic may increase patient discomfort, and the recommended dose of 0.04 mg/kg (2-4 mg) may be associated with significant respiratory depression and/or postural syncope in vulnerable patients. Facilities using morphine augmentation should be able to monitor patients for the adverse effects of narcotics and have the means at hand to manage them, including the ready availability of a specific narcotic antagonist such as naloxone.

Recommendations:

1. Disapprove the supplemental claim for the use of ( ) Dr. Fredd's review made this recommendation.

2. Approve the supplement claim for the use of morphine as advised by Dr. Wright. Amend the package insert for Hepatolite to include the indications and precautions statements as worded above.

/S/

A.E. Jones, M.D.
November 2, 1992

Concur
WAC 12/12/92

Medical Officer Review

NDA
~~IND~~ #: 18467 Hepatolite
Sponsor: DuPont-Merck
Type of Submission: Consultation
Date of Submission: August 27, 1992
Date Received: September 4, 1992
Date of Review: September 14, 1992
Date Cleared Peer Review: 9/22/92
Reviewer: Curtis Wright MD,MPH
Accounting Data: Review 8 hours, Consultation 1 Hour, Writing 2 Hours, Peer 2 hr, Revision 2.5 hours.

Abstract

This is consultation from HFD-160 about the use of a Tc-99 compound called Hepatolite for morphine-augmented scintillation scanning of the hepatobiliary tree in disorders of the gallbladder. There is substantial evidence that the technique works and is of acceptable risk, but there have been no adequate and well controlled trials to support the sponsor's desired labeling. Alternative labeling is presented which allows only more conservative claims.

Background

Technetium scanning is a recognized technique for the diagnosis of biliary disorders, including acute cholecystitis. Visualization requires that the isotope enter the bile, and the bile flow into the gall-bladder. Non-visualization of the gall-bladder (presumed to be due to disease) may occur either for metabolic (hepatocellular disease), pathologic (because the bile cannot enter the gall-bladder due to obstruction), or functional reasons (because the bile preferentially drains through the sphincter into the duodenum). Morphine causes an increase in the tonic contraction of the sphincter of Oddi, and may result in an increased likelihood of visualization of the gall-bladder. The net effect would be to increase the speed of visualization of the normal gall-bladder (the time required to confirm cystic duct patency) or to overcome functional blockage of the cystic duct.

The application is from the holders of an NDA for a TC-99 scanning compound, Tc99m Disofenin, (Hepatolite), and takes the form of an efficacy supplement for both morphine and augmented diagnostic testing.

Review Task

Agency precedent for such drug-drug diagnostic tests or procedures is that the use of the combination affects the labeling for both the original diagnostic agent (in this case Tc-99 Disofenin) and the agent to be added (in this case morphine). HFD-007 has been consulted since a determination must be made if the proposed use affects morphine labeling, and if the proposed labeling is adequate for the safe use of morphine. A final decision regarding the efficacy and/or safety of the scanning technique and/or isotope belongs to the parent division.

Material Reviewed

The material for consultation consisted of two jackets with the proposed labeling, copies of 15 peer reviewed literature articles covering morphine-augmented scanning in several hundred patients, and material on the safety of IV morphine administration from two current morphine NDA submissions under active review in HFD-007.

Proposed Efficacy Supplement

Hepatolite is currently approved for the diagnosis of acute cholecystitis, but a scanning period of up to 4 hours is recommended if the gallbladder is not visualized. The proposed efficacy supplement alters the labeling to include the following:

The intent is to claim that morphine augmentation allows shorter scanning times with no loss of accuracy. No controlled studies were performed by the sponsor to support this claim.

The specific review question is " **Does morphine administration at 60 minutes to patients whose gallbladders have not visualized provide results equivalent to imaging for an additional three hours, as currently recommended?"**

Literature Cited

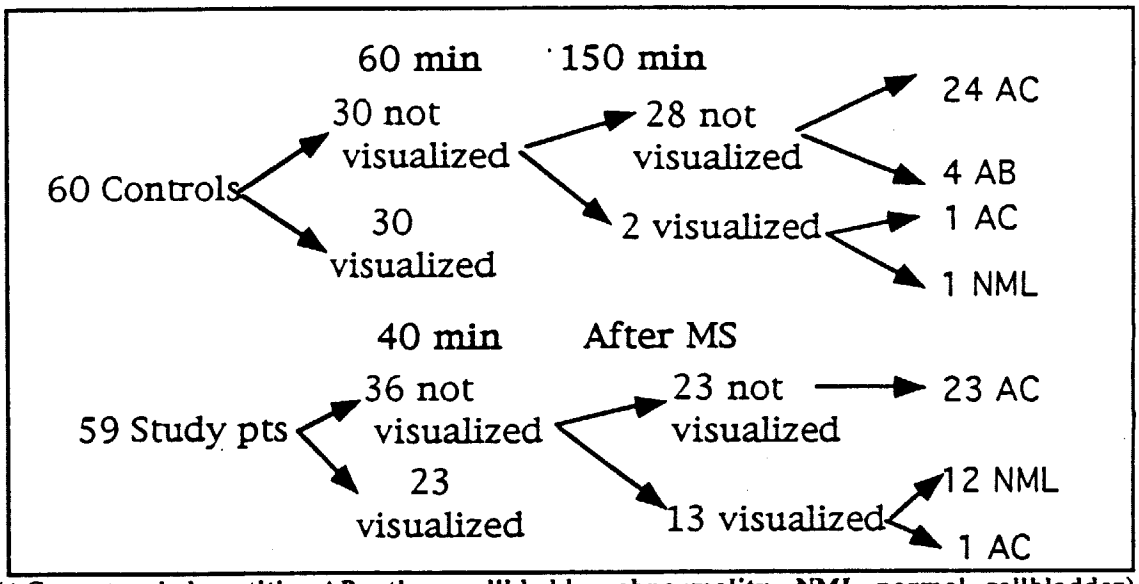
 # 4 CG Patch et al, "Naloxone Reverses Pattern of Obstruction of the Distal Common Bile Duct Induced by Analgesic Narcotics In Hepatobiliary Imaging."

This was a three patient case study in which obstruction of the distal biliary tree prevented visualization of entry of the radiopharmaceutical (Tc99 imidoacetic acid) into the small bowel. In two cases the administration of 0.8 mg naloxone resulted in radiological visualization of the distal bile duct and drainage into the small bowel within one minute after injection. In a third case, a patient who was found (at autopsy) to have obstruction of the common bile duct did not show any evidence of drainage into the small bowel after naloxone administration.

This case report provides confirmation of the opioid-antagonist effects of naloxone in reversing opioid-induced increases in tonus at the sphincter of Oddi. The effect is expected, plausible, and consistent with the current labeling for naloxone and morphine. This is not a controlled study but is enough evidence for a textual mention of the availability of naloxone in labeling.

#6 Choy et al, "Cholescintigraphy in Acute Cholecystitis: Use of Intravenous Morphine"

This was a case-control study in which 59 patients with a clinical presentation consistent with acute cholecystitis were scanned 40 minutes after receiving a Tc99 piridoxylideneglutamate preparation. Those who had no visualization of the gall bladder were given 0.4 mg morphine IV and rescanned after another 20 minutes. The experience of this group was then contrasted with 60 historical controls who had been scanned for up to 150 minutes. The results were as shown below:



(AC=acute cholecystitis, AB=other gallbladder abnormality, NML=normal gallbladder)

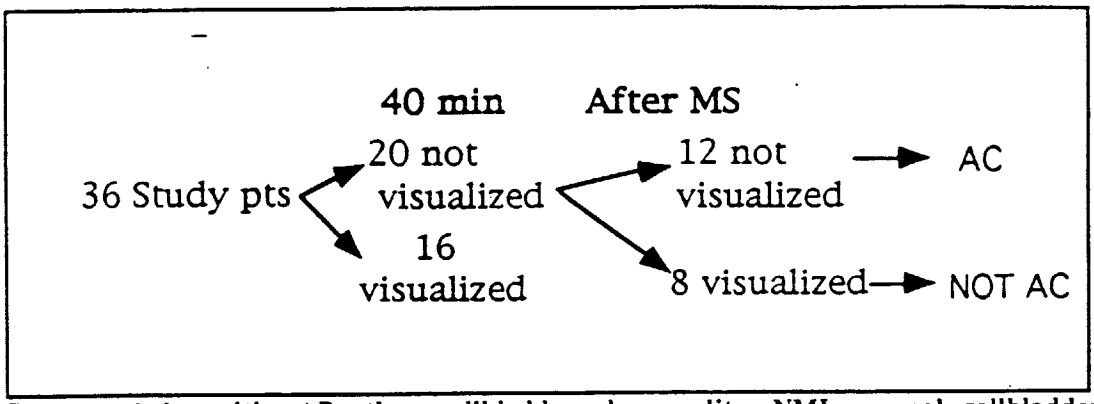
Of the 28 patients in the control group who did not visualize there were four false positive non-visualizations (1 small bowel obstruction, 1 carcinoma of the gall bladder, and two chronic cholecyctitis), and one false negative patient whose gall bladder did visualize who did have acute cholecystitis. In the morphine augmentation group there were no false positives and one false negative.

Owing to the relative rarity of the false positive diagnoses in the historical control group it was not possible to be confident in any sensitivity and specificity statistics generated from this study. It does provide strong evidence that the results of morphine augmented scans in this study were similar to longer scans in the historical control group.

 # 12 Grund et al "Hepatobiliary Imaging: The Diagnostic Use of Intravenous Morphine in Fasting Patients"

This was a study of morphine augmented Tc99 diisopropyl imidodiacetic acid scanning in 42 fasting patients. Fasting is associated with sludge and stone formation and/or hepatobiliary dysfunction, especially in patients receiving total parenteral nutrition. In this study (a case series), 42 fasting patients with fever, RUQ colic, and leukocytosis received a dose of isotope, and those who had non-visualization after 40 minutes received 0.04 mg/kg morphine and were scanned again after another 20 minutes.

Of the 42 patients studied, six had contraindications to that administration of morphine (not stated) leaving 36 patients studied. Of these 36, 16 visualized within one hour and 20 did not. Of those 20 who then received morphine, eight had prompt visualization and diagnoses other than acute cholecyctitis, 12 had persistent non-visualization. Of these 12, 4 were treated medically and eight had surgery and tissue-proven cholecystitis.



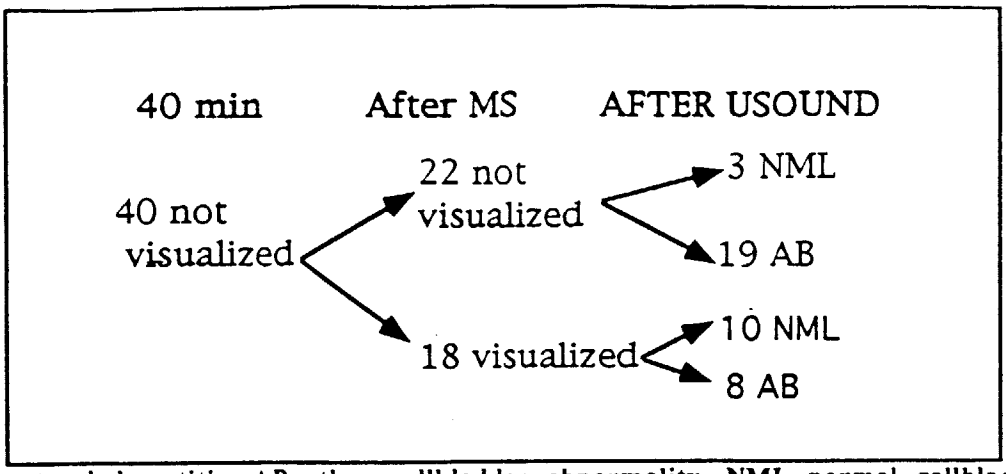
(AC=acute cholecystitis, AB=other gallbladder abnormality, NML=normal gallbladder)

This study had the weaknesses of a case series, but added safety data, and provided some evidence that a significant fraction of patients who did not visualize after 40 minutes did do so after a dose of morphine. The report is supportive of efficacy, and contributes some safety data.

 # 9 Kim et al. "Morphine augmented Cholescintigraphy in the Diagnosis of Acute Cholecyctitis"

This was a prospective, uncontrolled, case series of 40 patients undergoing Tc99 iminodiacetic acid scan for presumptive cholecystitis who did not visualize after 1 hour. Patients were selected for scan by the attending physician based on their usual criteria (unspecified) and referred to nuclear medicine for a scan to evaluate the visualization of the gall bladder to R/I or R/O cystic duct obstruction and/or non visualization. The study population consisted of patients whose gallbladders did not visualize after 1 hour.

Of the 40 patients who did not so visualize, all were given 0.04 mg/kg morphine, and rescanned for an additional 0-30 minutes. Of the 40, 18 patients visualized after morphine. These patients were sonogramed, and non-obstructing gallstones were found in 5 patients, sludge in 3 patients, and no pathology in 10 (no patient had to be taken to surgery in this group).



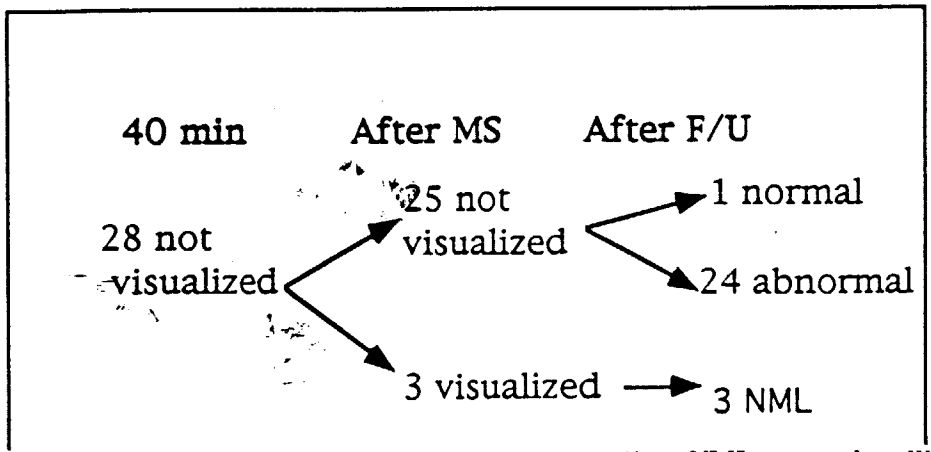
(AC=acute cholecystitis, AB=other gallbladder abnormality, NML=normal gallbladder)

Of the 22 patients who did not visualize after morphine administration and re-scanning, 6 had gallstones, 5 had sludge, 5 had acalculous cholecyctitis, 2 showed contraction, 1 showed distention, and 3 had normal sonograms. The text was ambiguous with respect to the patients who did visualize and a precise attribution could not be made.

This study did not really offer a comparison of 4 hour scanning v. 1 hour scanning, but it does provide strong evidence that a sizable fraction of patients not visualized by one hour will visualize after morphine. It also provides some evidence that morphine augmentation can result in the visualization of abnormal gallbladders (false negatives).

#42 Kim et al, "Use of Morphine in the Cholescintigraphic diagnosis of acute acalculous cholecystitis"

This was an abstract which may present some of the same patients presented in reference #9. (They may also be all new patients, it is simply not clear from the text). The patients consisted of 28 individuals with a clinical presentation consistent with acalculous cholecystitis. All who did not visualize received 0.04 mg/kg morphine. Three patients visualized after morphine, but only after an additional 4-8 hours of scanning. Twenty-five patients had persistent non-visualization. Sixteen patients went to surgery, and of these 15 had acute cholecystitis. Nine patients were managed medically with the diagnosis of acute cholecystitis, and all survived.

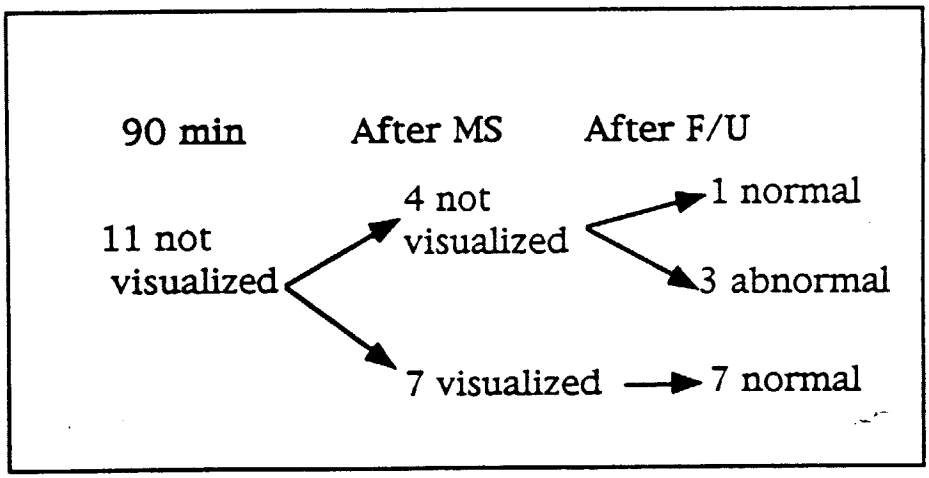


(AC=acute cholecystitis, AB=other gallbladder abnormality, NML=normal gallbladder)

This report provides some assurance that morphine augmentation does not greatly increase the false negative rate in acalculous cholecystitis. It is to be noted that since it took 4-8 hours for the 3 patients who visualized to do so, these patients would not have been found after the recommended additional 30 minutes of scanning. The contention of the authors that the specificity of the technique is improved in this condition is not supported.

#38 Olsen et al, "Clarification of the results of Cholescintigraphy via morphine administration."

This was a case series of 11 patients who had not visualized by 90 minutes after a standard Tc99 DISIDA scan. They were re-examined after a 4 mg dose of morphine. Seven of the 11 showed visualization, all seven were found either to have another infectious source of their fever & pain (4/7), or not to have a subsequent clinical course consistent with cholecyctitis (3/7). Of the four with persistent non-visualization, 3 had gall-bladder disease (2 obstructed cystic ducts & 1 extension of colon cancer) and one had a UTI.



 # 39 Vasquez et al, " Clinical Efficacy of IV Morphine Sulfate in Hepatobiliary Imaging for Acute Cholecystitis"

This was an abstract of a 40 patient case series of patients being scanned for symptoms and signs consistent with acute cholecyctitis who had not visualized after 60 minutes. It did not give enough data to determine what the actual clinical experience had been, but reported a specificity of 85% and a sensitivity of 100%.

 # 40 Flancbaum et al, "Use of Cholescintigraphy with morphine in critically ill patients with suspected cholecystitis"

This was an ICU study in which 18 patients being evaluated for a source of sepsis underwent morphine augmented scanning with Tc99 DISIDA or PIPIDA. The patients were selected from similar cases on the basis of not-visualizing after 60 minutes. Of these cases 17/18 visualized, and had a subsequent course consistent with diagnoses other than cholecystitis. The patient who did not visualize had acute gangrenous cholecystitis.

This case series provides substantial evidence that there are patients who do not visualize at 60 minutes who will do so after morphine augmentation. It suggests, but does not prove, that morphine augmentation may be of greatest use in patients on TPN or fasting, who have a high rate of false-positive scans due to physiologic block or sludge.

#41 Flancbaum et al, " Morphine Cholescintigraphy"

This was a case series (which may have included some of the patients from #40) of 68 patients evaluated for possible biliary tract sepsis during a two-year period at one institution who received morphine augmentation after initial non-visualization of the gall-bladder with Tc99 DISIDA or PIPIDA. The patients were split into three post-hoc groups; new cases of acute abdominal pain, sepsis evaluation in non-critically ill patients, and sepsis evaluation in critically ill patients.

Of 30 adults with acute abdominal pain who did not initially visualize, 24 failed to visualize after MS administration. Of these all were diagnosed as acute cholecystitis, 23 went to operation and one was treated with antibiotics. The six who visualized did not have a clinical course consistent with acute cholecystitis.

Of 13 sepsis workups in non-critically ill patients, 10 failed to visualize with MS and 3 did do so. Four of the patients went to operation and had acute infections (1 false negative).

Of the 25 sepsis workups in critically ill patients, 22 of 25 visualized with IV MS, and 3 did not do so. Of the three who did not visualize, one recovered without operation, one had acute cholecyctitis, and one was a false positive (normal GB).

One reasonable interpretation of this case series is that morphine augmentation is of some value in patients with acute abdominal pain (excluded 6 cases which visualized, denominator unknown), and of considerable value in patients on TPN or who are fasting (22 of 25 cases excluded). It is not, of course, in any sense a controlled clinical trial.

 # 11 Vasquez et al. "Clinical Efficacy of IV morphine administration in Hepatobiliary Imaging for Acute Cholecystitis".

This appears to be a re-publication of the data from #39.

 # 17 Fig et al, "Morphine Augmented Hepatobiliary Scintigraphy in the Severely Ill: Caution is in order"

This was a case series of 51 morphine augmented Tc99 scans in patients who underwent morphine augmented Scintigraphy. The study is unusual in that it clearly specifies the conditions for morphine augmentation (gallbladder not visualized, tracer seen in the small bowel, sufficient tracer in the liver to allow imaging). It was also useful in that it clearly showed that the means of establishing the final diagnosis is surgery or autopsy in positive scans (non visualization) (21/25 cases) and clinical course in negative ones (20/23).

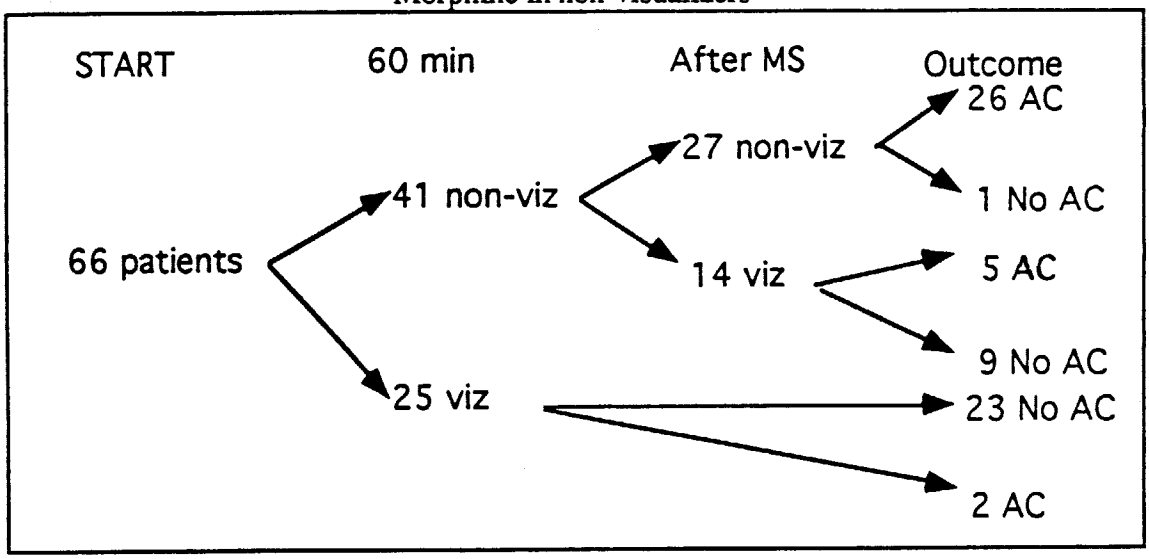
The case series reported the experience in three post-hoc groups; acute illness, patients with known hepatocellular disease, and severely ill patients (most on TPN). No false negatives were seen in the first two groups and a small number of false positives, but of 18 severely ill patients scanned there were six false positives (non-obstructed gall-bladders did not visualize) and one false negative (elderly patient with perforation).

This series acts to balance the report in #41, and suggests that a failure to visualize in a severely ill patient on TPN has a limited predictive value (PPV = 40%).

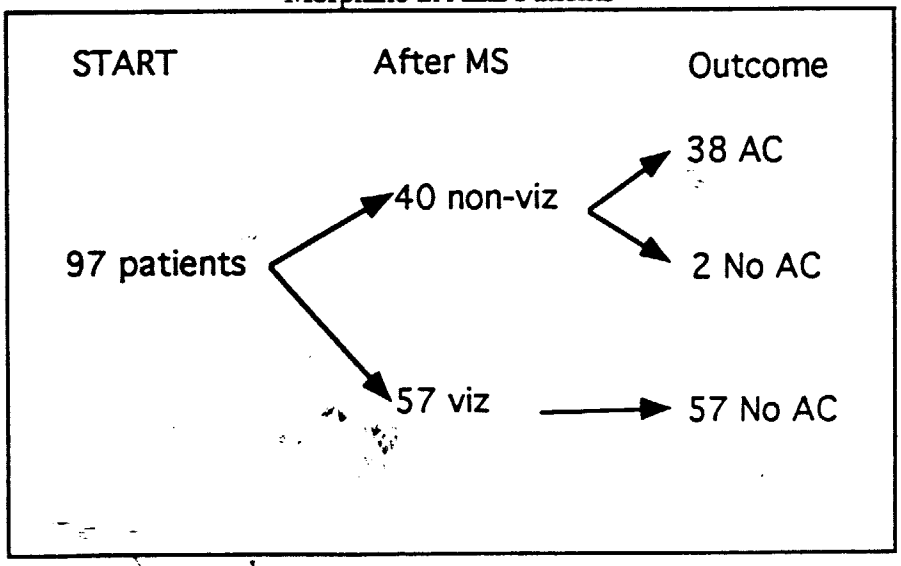
 # 44 Louridas et al, " Role of morphine administration with TC99 DISIDA in the diagnosis of acute cholecyctitis"

This was a report of two case series using morphine augmentation of scanning in acute RUQ pain & fever. In the first series 66 patients were scanned by a protocol that added MS augmentation in the case of all patients that did not visualize after 60 minutes. In protocol #2 morphine was given to all 97 patients at the start of the scan.

GROUP # 1
Morphine in non-visualizers



Group #2
Morphine in ALL Patients



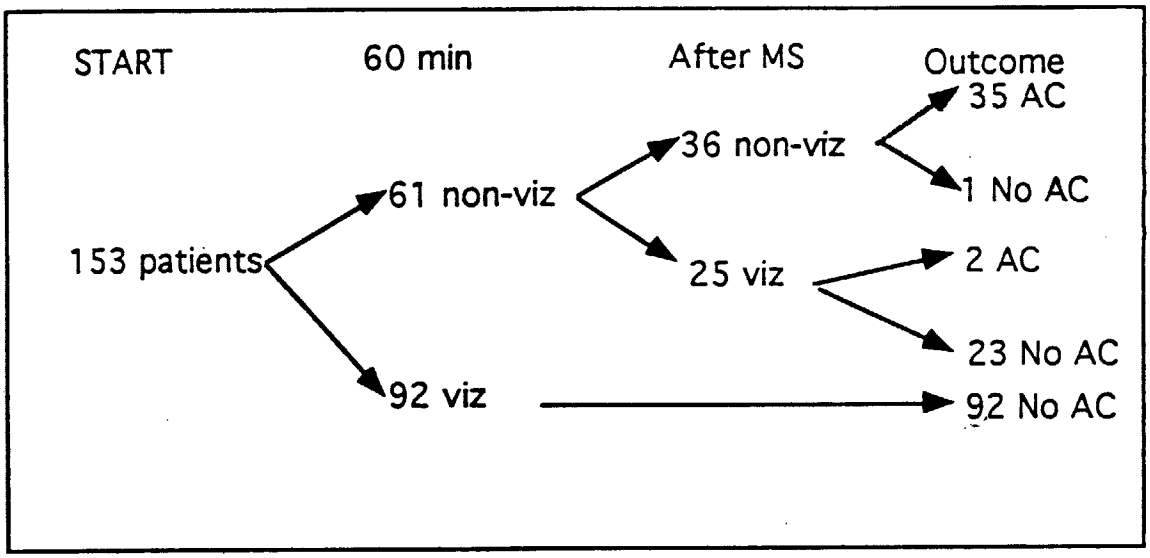
This is another uncontrolled study in which a direct comparison cannot be made, but there is some evidence that: 1) False negatives can occur with morphine augmentation and 2) immediate use of morphine made be made without either gross alteration of sensitivity and specificity or serious AE's.

 # 43 Louridas et al, " Morphine and Cholescintigraphic gallbladder filling"

This was a clinical pharmacology experiment in which nine patients with normal gallbladders underwent scanning on two consecutive days with and without morphine augmentation. Morphine was shown to markedly increase the speed of filling of the gallbladder from 60 minutes without morphine to 20 minutes after a single dose of 0.04 mg/kg IV. It presents substantial evidence that morphine speeds scanning in the NORMAL gallbladder, in a HEALTHY individual, scanning may be completed with 30 minutes.

 # 7 Fink-Bennet et al, " Morphine augmented Cholescintigraphy: its efficacy in detecting acute cholecystitis"

This was a case series of 158 patients scanned with TC 99 mebrofenin or disofenin in the evaluation of acute abdominal pain an fever possibly due to acute cholecystitis.



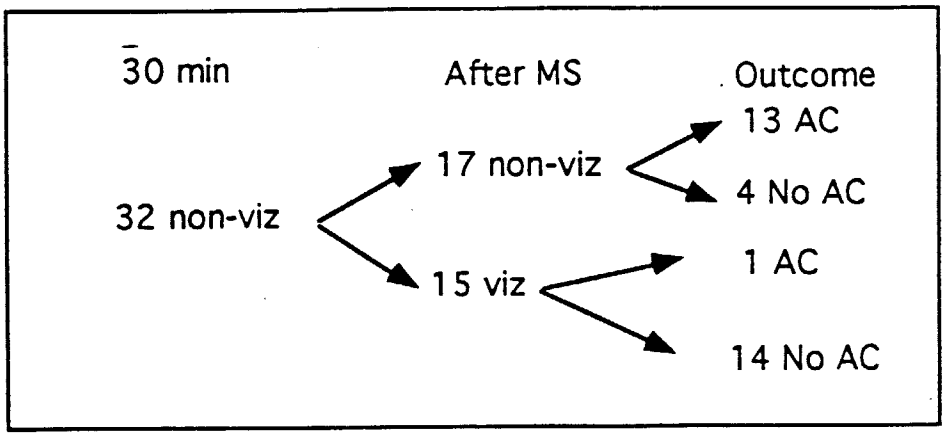
As may be seen, morphine augmentation assisted in the visualization of 23 additional normal gall-bladders, but may have been associated with 2 false positives. This study supports the utility of morphine augmentation (shorter scanning times) but does not provide a direct comparison.

 # 8 Keslar et al, " Hepatobiliary imaging and the use of Intravenous Morphine"

This was a 31 patient case series in which patients who were scanned (TC 99 DISIDA) for presumptive cholecystitis were given morphine as soon as it was clear that the isotope was draining into the small bowel (no obstruction was present). Of 31 patients there were 10 negative studies and two false positives (non-visualization) due to one case each of small bowel infarction and chronic cholecystitis.

 # 45 Kistler et al, " Morphine augmented Cholescintigraphy in acute cholecyctitis"

This was a 32 patient case series (TC 99 mebrofenin) in which patients who failed to visualize after 30 minutes were given IV morphine (2 mg) and scanned for an additional 30 minutes.



As may be seen, there were four false positives and one false negative by this technique.

Safety

All of these studies were conducted by the investigators as part of routine clinical work. All studies reported no serious adverse effects of morphine augmentation, although a number of reports described withholding morphine augmentation in cases where morphine administration was hazardous. All that can be said is that there were no reported deaths or severe adverse effects in the reported cases.

Discussion

Morphine is a pre-1938 drug which is usually supplied as a USP monograph item. It is an extensively genericized product that has roughly similar class labeling. Most of that labeling discusses the action of morphine on the sphincter of Oddi, and advises caution in giving the drug in cases of biliary colic. That precaution should stand, and the labeling for use of morphine in hepatobiliary scanning should be carried in the labeling of the scanning isotopes. The task is to decide on what should be in the labeling for Hepatolite. Although the use of morphine in this setting is technically a new indication for morphine, the effect of morphine on the GI tract is already in most labeling, and the data presented here is too weak for the imposition of a class-wide labelling change.There need be no changes in the class labeling for morphine for safety reasons, since the current precaution regarding increase in biliary tract tonus in the current labeling is accurate and should remain in effect.

None of the articles cited represent a direct test of 4-hour scanning against 90 minute scanning in acute cholecystitis, In that sense, there is no direct evidence from controlled clinical trials. On the other hand, there is experience in at least 300+ patients (it is impossible to be sure of the exact number due to overlap), and at least two clinical pharmacology studies showing direct evidence of the mechanism, specificity, and temporal course of the effect of morphine in augmenting the scanning process, as well as the specific reversal of the effect by the opioid antagonist naloxone.

The technique is based on a phenomenon that is known to occur (morphine's effect on the biliary tree), is biologically plausible, for which there is a large body of literature supporting its use, is obviously in wide use, and for which there are no reported adverse consequences. Unfortunately, the specific efficacy question "How does it compare to the approved 4 hour scan duration" has not been addressed in a controlled clinical trial.

How this supplement is handled will depend on the interpretation of policy by the parent division and lies beyond the province of this reviewer. The problem is similar to one we have faced in the area of drug-device combination with Patient Controlled Anesthesia (PCA), another technique that originated not with a commercial company but among the practice community. In that similar case we also had a wide body of literature, an absence of controlled trials of the product in question, and substantial evidence of adequate safety.

One possible solution is to allow the approval of the indication based on the literature, but to insist on language that reflects the weakness of the evidence, disallowing comparative claims unless supported by adequate and well-controlled clinical trials. In the case of morphine augmentation of HEPATOLITE, it is clearly a useful technique that gives results that are similar to 4 hour scanning, but claims it is "just as good" or "better" have not been proven.

Proposed Labeling (one alternative)

Current Labeling (INDICATIONS SECTION)

..... In otherwise healthy individuals, non-visualization of the gallbladder 4 hours after administration of HEPATOLITE following a 2-6 hour fast and in the presence of activity in the small intestine is indicative of a diagnosis of acute cholecystitis. Under the same conditions in an otherwise healthy person, visualization of the gallbladder during a 1 hour Scintigraphy is effective in excluding a diagnosis acute cholecystitis. If the gallbladder is not visualized by 1 hour, scanning must continue for four hours or until the gallbladder is visualized.

Morphine augmentation has not been associated with any serious adverse events in the reported cases, but the administration of morphine in biliary colic may increase patient discomfort, and the recommended dose of 0.04 mg/kg (2-4 mg) may be associated with significant respiratory depression and/or postural syncope in vulnerable patients. Facilities using morphine augmentation should be able to monitor patients for the adverse effects of narcotics and have the means at hand to manage them, including the ready availability of a specific narcotic antagonist such as naloxone.

The parent division should feel free to make any needed changes in this or any similar labeling for this product as long as the sense and balance of this text is preserved.

/S/ 9/22/92

Curtis Wright MD,MPH
Medical Review Officer

CC: Consult 18467 Hepatolite
HFD-007 Division file
HFD-007 E Emmet
HFD-007 C Wright
HFD- 340

D.J Spic 9/22/92

Division of Medical Imaging, Surgical and Dental Drug Products

Medical Imaging Drug Group

Labeling Review

DEC 20 1993

NDA: 18-467/S-013 & 014

Sponsor: The DuPont Merck Pharmaceutical Co.

Drug: Hepatolite, Kit for the Preparation of Technetium Tc 99m Disofenin

Date of Submission: July 26,1991 for S-013
April 8, 1992 for S-014

Submissions provide for:

S-013 - the addition of a radiation dosimetry table to the package insert which would characterize the effect of the radiation dose to patients with jaundice.

S-014 - the addition of two new clinical indications

1. The diagnosis and evaluation of acute cholecystitis when performed with morphine sulfate augmentation.

2. The diagnosis and evaluation of

Background: Supplement 013 received an approvable letter dated April 2, 1993. This letter contained labeling changes and a request to submit draft labeling incorporating these changes. Supplement 014 received an approvable letter dated April 13, 1993. This letter approved only the morphine augmentation portion of the supplement and also contained labeling revision requests. The company has responded to both of these supplements with a draft package insert which incorporates all of the labeling changes requested in both approvable letters. In addition, while doing the labeling review of this draft label dated August 6, 1993, I noticed that the radiation dosimetry section had not been revised since the drug was originally approved and that new Oak Ridge calculations were available and should be incorporated into this revised draft package insert. I requested the company to update that portion of the package insert also. The "final revised draft" package insert was then submitted dated November 23, 1993. On December 16, 1993, we requested the company to move several of the paragraphs into different sections of the package insert

On December 17, 1993, we received their "last final revised draft package insert" incorporating these changes.

Review: The revised draft label (dated December 16, 1993) has incorporated all of our labeling requests for both S-013 and 014. The draft package insert is acceptable as submitted.

Recommendation:

I recommend that an approval letter be sent for both S-013 and 014.

/S/

Susan Lange
Consumer Safety Officer
December 20, 1993

/S/ 12/20/93

Concur:
A. Eric Jones, M.D.
Group Leader, Medical Imaging Dru

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 15, 1992

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 18-467, S-014

TO: Dr. Jones, HFD-160

On August 27, 1992 you forwarded to us for review a supplement from Dupont for a new indication for Hepatolite i.e.

Hepatolite® Kit for the preparation of Technetium Tc99m Disofenin is indicated in the diagnosis and evaluation of chronic acalculous disorders of the biliary tree when performed with Cholecystokinin (CCK) augmentation. Cholecystokinin and its analogues cause the gallbladder to contract, the sphincter of oddi to relax, augment of pyloric sphincter contraction, enhance bowel motility, increase secretion of bile, pancreatic enzymes and enterokinase. CCK may be useful (1) as a pretreatment in patients fasted for longer than 24-48 hours or receiving total parenteral nutrition to reduce false-positive studies in suspected acute cholecystitis (2) to prevent false-negative studies in acalculous cholecystitis (3) to evaluate functional disturbances of the gallbladder or cystic duct by gallbladder ejection fraction response.

Cholecystokinin is marketed by Squibb, and does not contain these indications, nor have we received a supplement from Squibb. I assume that cholecystokinin would not be relabeled in an imaging agent label without relabeling the cholecystokinin products as well.

As to the basis for each claim proposed (1) TPN, 2) Prevent false negatives and 3) Evaluate functional disturbances , the sponsor has provided 87 references but no adequate analysis. The listing of pertinent clinical studies as provided by the sponsor is as follow:

Ref#	Year	# subjects	tracer	"CCK" dose
Fink (30)	1991	374	Tc Disofenin	0.02 mcg/kg sincalide
Swayne (28)	1986	87	Tc Disofenin	0.02 mcg/kg CCK
Brugge (27)	1986	36	Tc Disofenin	0.02 mcg/kg sincalide
Pickleman (24)	1985	36	Tc Disofenin	0.02 mcg/kg sincalide
Topper (22)	1980	34	Tc PIPIDA	0.2 mcg/kg sincalide
Newman (23)	1983	25	Tc HIDA	CCK
Davis (70)	1982	20	Tc PIPIDA	0.02 mcg/kg sincalide
Fink (26)	1986	374	Tc Disofenin	0.02 mcg/kg sincalide
Fink (2)	1991	REVIEW	Tc Disofenin	0.02 mcg/kg sincalide
Williams (67)	1989	99	Tc HIDA	CCK
Masclee (66)	1989	8	Tc HIDA	CCK
Raymond (65)	1988	101	Tc Disofenin	0.02 mcg/kg sincalide
Zech (29)	1991	83	Tc Disofenin	0.04 mcg/kg sincalide
Masclee (62)	1990	6	Tc HIDA	CCK-33
Masclee (61)	1989	18	Tc HIDA	CCK-33
Masclee (60)	1989	6	Tc HIDA	CCK-33
Masclee (59)	1989	40	Tc HIDA	CCK-33
Schaffer (58)	1982	11	Tc HIDA	0.02 U/kg CCK
Schaffer (57)	1984	25	Tc HIDA	0.02 U/kg CCK
Westlake (56)	1990	26	Tc Disofenin	0.02 mcg/kg sincalide
Clas (55)	1989	9	--	0.02 mcg/kg sincalide
Daignault (54)	1988	42	Tc Disofenin	0.02 U/kg CCK
Sylwestrowicz (53)	1988	83	Tc Disofenin	0.02 U/kg CCK
Spellman (52)	1979	19	Tc HIDA	CCK
Stone (51)	1988	50	Tc Disofenin	0.02 mcg/kg sincalide
Pomeranz (50)	1985	67	Tc Disofenin	CCK
Masclee (49)	1989	6	Tc HIDA	CCK
Kim (47)	1990	14	Tc Disofenin	0.03 mcg/kg sincalide
London(46)	1983	10	Tc Disofenin	0.02mcg/kg sincalide
Kistler (45)	1991	32	Tc Mebrofenin	0.02 mcg/kg sincalide
Fink (35)	1985	14	Tc Disofenin	0.02 mcg/kg sincalide
Krishnamurthy (48)	1984	5	Tc IDA (NOS)	CCK
Pellegrini (64)	1985	16	Tc PIPIDA	0.02 U/kgCCK-33
Annese (68)	1991	20	Tc Diethyl-IDA	CCK

Many of these studies do not use Hepatolite, and the sponsor makes some case that the indication, if granted, should only be for Hepatolite in the statement:

"A final point should be made that Tc IDA analogues other than

Technetium Tc99m Disofenin (Hepatolite®) have had infrequent review in the medical literature. Some clinicians have expressed concern with the use of cholescintigraphic agents having more rapid hepatobiliary clearance kinetics than Technetium Tc99m Disofenin (Hepatolite®) and the potential for this causing false positive results (2,7)."

In considering this I have looked at the larger studies (n=30 or larger) involving CCK augmented Hepatolite cholescintigraphy. These are references 24, [25, 26 and 30] (same study provided three times), 27, 28 and 65. Please note that the sponsor has not summarized each of these studies individually and has not provided adequate scientific evaluation of each.

There is no consideration of population studied, dose regimens, evaluation criteria, results including verification by some gold standard, sensitivity, specificity and predictive value. Nor has the sponsor discussed the different results found by the various investigators. Perhaps the following will give some indication of the patchwork nature of the database.

Reference 24 - Pickleman et al, Arch. Surg, Vol 120, June 1985. 36 patients with biliary colic and normal oral cholecystograms, upper GI series and gallbladder US had CCK augmented disofenin study. The protocol was different from other investigator's studies in that 2 doses of CCK might be given. Note: the sponsor's proposed labeling does not specify a dose regimen for CCK or an evaluation method or a standard for interpretation.

The purpose of this study was to predict symptom relief from cholecystectomy, not one of the proposed indications. Using an ejection fraction of < 50% the results for the entire cohort and those 19 patients having cholecystectomy were quite variable with the results provided as follows:

Clinical and EF Data*

Patient No.	EF, %	Pain Reproduction	Histologic Characteristics
1	0	Yes	Normal
2	0	No	Normal
3	17	Yes	CC and stones
4	20	No	CC
5	24	Yes	CC
6	30	No	CC
7	30	No	Normal
8	33	No	Normal
9	35	Yes	CC
10	35	No	Normal
11	38	Yes	Normal
12	40	No	CC
13	42	No	CC
14	48	Yes	Normal
15	50	Yes	CC
16	50	No	CC
17	71	No	Normal
18	84	Yes	CC
19	86	Yes	CC

*EF indicates ejection fraction; CC, chronic cholecystitis. All patients except patient 9 were symptom-free.

I do not see how these data support the sponsor's case.

Reference 25 (also the same article was submitted as 26 and 30) - Fink-Bennet et al, J. Nucl. Med. 1991; 32: 1695-1699

This is a retrospective study of CCK disofenin scintigrams in 374 patients with recurrent RUQ pain, biliary colic and a normal GB ultrasound or cholecystogram. Also 27 normal subjects, were studied. The dose of CCK was 0.2 ug/kg administered over 3 minutes. The criterion for an abnormal CCK study was an ejection fraction of less than 35%. The results for each patient are not given. Therefore we do not know whether results were clustered just below 35 or in the very low range.

The results are presented in subgroups:

1) 124 patients with clinically suspected chronic biliary disease. These patients had cholecystectomies. By my construct, 108 were true positives (T.P.) 7 were false negatives (F.N.), 5 were false positives (T.P.) and 4 were true negatives (T.N.)

With sensitivity defined as

$$\frac{\text{T.P.}}{\text{T.P. \& F.N.,}}$$

the sensitivity in this cohort is 94%

With specificity defined as

$$\frac{\text{T.N.}}{\text{T.N. \& F.P.,}}$$

the specificity for this cohort is 36%.

Even without considering prior probabilities and predictive value, the results of this cohort are not reassuring re specificity.

2) Of 221 medically treated patients clinically suspected of chronic biliary disease with symptom outcome as the gold standard, the sensitivity by my calculation was $\frac{69}{69 \text{ \& } 9}$ or 89%

and specificity was $\frac{130}{130 \text{ \& } 13}$ or 91%.

3) Of 27 individuals without a history of RUQ pain or biliary colic, 9 were negative, 16 were positive and two could not be

evaluated.

Of the 16 positives, 3 were true positives and an additional 5 were possibly true positives. We cannot based on the information given provide sensitivity or specificity estimates, but it is important to note that for a diagnostic test to be useful it must have acceptable predictive value over a wide range of patients with varying prior probabilities of disease. This has not been demonstrated in this study. It is not reassuring that of 25 patients with no biliary symptoms, 16 or 64% were positive. On the basis of no symptoms, these would all have to be considered false positives clinically. This would make for a specificity of $\frac{9}{9 \text{ \& } 16}$ or 36%.

Even if one considers 4 of the 16 as having some evidence of biliary disease (albeit not clinical and not treatable), the specificity would still be low - $\frac{13}{13 \text{ \& } 16}$ or 45%. The sponsor does not address this question, and must.

Overall this study provides some reason to further evaluate the test, but not substantial evidence for approval.

Reference 27 - Brugge et al, DDS, Vol 31, No. 5 (May 1986).

This was a study of 39 consecutive patients with "biliary symptoms" i.e. postprandial upper abdominal pain with nausea and a normal oral cholecystogram or US. 36 completed a bile analysis and CCK DISIDA scan. The purpose of the study was to characterize an early stage of cholesterol gallstone formation with physiologic data.

The CCK was given as a 20 minute infusion at a dose of 1 Ng/Kg/Min. Two ejection fraction cutoffs were used: 30% and 40%.

The results correlate crystal formation with ejection fraction and gallbladder pathology in the 15 cases where a cholecystectomy was performed.

TABLE 5. SENSITIVITY AND SPECIFICITY OF EJECTION FRACTION, CRYSTALS IN BILE

Condition predicted	*Test analyzed*	*Cutoff point (%)*		*Sensitivity*	*Specificity*
		Normal	*Abnormal*		
Acalculous cholecystitis	Ejection fraction	≥30	<30	8/11 = 73%	$\frac{1}{1}$ = 100%
	Ejection fraction	≥40	<40	9/11 = 82%	$\frac{1}{1}$ = 100%
	Crystals in bile	Absent	Present	9/11 = 82%	$\frac{1}{1}$ = 100%
Presence of crystals in bile	Ejection fraction	≥30	<30	11/14 = 79%	$\frac{18}{19}$ = 95%
	Ejection fraction	≥40	<40	12/14 = 86%	$\frac{16}{19}$ = 84%

The author notes that the specificity information is inadequate since only 1 patient had a normal gallbladder. The sponsor in noting a specificity of 100% for the test may be referring to this study. The sensitivity and specificity for the 21 patients who did not undergo cholecystectomy are not given. The sponsor has not fully presented or analyzed this study, and it is hard to say how it supports the sponsor's contentions.

Reference 28 - Swayne et al, J. Nucl. Medicine, Vol. 27, #6, June 1986.

This is an abstract without sufficient data for analysis. The author claims that the study gives a sensitivity of 89%, a specificity of 100% and an accuracy of 89%. Of the 89 patients studied, the abstract accounts for perhaps 50 patients. Since the abstract notes that 8 patients with negative studies had gallbladder polyps, it is not clear how the specificity was 100%. If the correlation was clinical, it is hard to understand how 3 false positives were put into the specificity ratio.

Reference 29 - Zech et al, SG & O, Jan. 1991, Vol 172

This retrospective study of 83 patients was done to evaluate the value of CCK disofenin scan to predict the symptomatic response to cholecystectomy. Here 0.04 mcg/kg were given and an ejection fraction less than 50% was used to separate positives and negatives.

Of the 83 patients, 71 were offered surgery and 60 had surgery. Of the 60, 57 were followed for symptom relief. 56 of these with positive scans had symptom relief while 1 with a negative scan also had symptom relief. The scan values are not given, so it is not possible to compare these results with other series. The authors do not give information on symptom relief in the 11 who did not have surgery, or on the 12 patients not offered surgery.

No information on specificity can be deduced from this incompletely reported series.

The foregoing were references cited by the sponsor as supporting the diagnostic efficacy of the procedure. They also list clinical study 65 done with disofenin. Reference 65, Raymond et al Eur. J. Nucl. Med, 1988, 14: 378-381, deserves comment.

This was a prospective study of 101 patients admitted for cholecystectomy. There was also a 27 patient control group of whom 12 had vague GI complaints (group A) and 15 had no complaints (group B) Octapeptide-CCK, 20 mg/kg in a 15 minute infusion used, and there was no a priori definition of a positive

or negative ejection fraction percentage. Rather the range of ejection fractions correlated with condition was presented in the following chart.

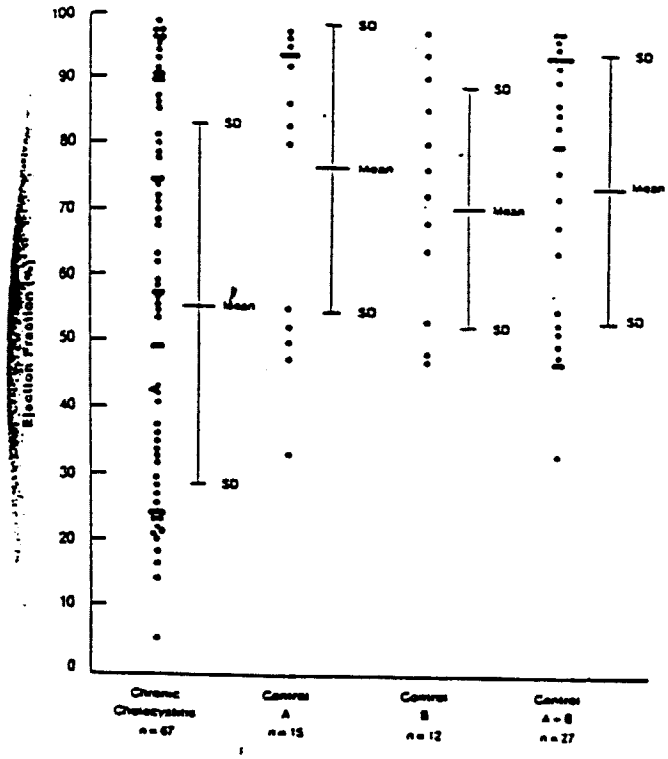


Fig. 2. Distribution of gallbladder ejection fractions in patients and controls. (SD, one standard deviation)

The considerable overlap in ejection fraction between normals and abnormals leads the authors to conclude the majority of patients with chronic cholecystitis cannot be distinguished from normals.

Summary

The sponsor has not provided substantial evidence to establish CCK augmented Hepatolite cholescintigraphy as an effective diagnostic test. The sponsor has provided only cursory evaluations of the literature provided. My review points up numerous questions about dose, range of patients population studied (particularly negative patients), ejection fraction percentage chosen to distinguish normal and abnormal, sensitivity and specificity problems, and missing data. A submission like this would not be filed in this division, and as it is, I cannot recommend that it be approved.

/S/

Stephen Fredd, M.D.

cc:
NDA 18-467
HFD-160/WChambers
HFD-180/Consult file
HFD-180/SFredd:9/15/92
f/t deg: 9/15/92/9/16/92
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