Three-dimensional Drip Infusion CT Cholangiography in patients with suspected obstructive biliary disease: A retrospective analysis on adverse reaction to contrast material and feasibility.

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Running head: 3D DIC-CT retrospective analysis of adverse reaction and feasibility
Abstract

The purpose of this study was to retrospectively evaluate prolonged drip infusion CT cholangiography (DIC-CT) regarding feasibility and frequency of adverse reactions to contrast material after administration of biliary contrast material (Biliscopin®). The medical records on patients who had undergone upper abdominal spiral CT with subsequent three-dimensional rendering of the biliary tract by means of DIC-CT during seven years were retrospectively reviewed regarding serum bilirubin concentration, adverse reaction and presence of visible contrast media in the bile ducts at CT examination. In total 153 consecutive examinations in 142 patients were reviewed. Contrast media was observed in the bile ducts at 144 examinations. In 110 examinations, the infusion time had been recorded in the medical records. Among these, 42 examinations had an elevated bilirubin value (>19 µmol/L). There were nine patients without contrast excretion, 3 of these had a normal bilirubin value and 6 had an elevated value (25-133 µmol/L). Two of the 153 examinations were inconclusive. One subject (0.7%) experienced a minor adverse reaction– a pricking sensation in the face. No other adverse effects were noticed.

We conclude that DIC-CT with an infusion rate of the biliary contrast agent iotroxate governed by the serum bilirubin value is a feasible and safe alternative to MRC in patients with and without impaired biliary excretion.

Key Words: Adverse reaction, meglumine iotroxate, CT cholangiography, volume rendering
INTRODUCTION

There are several noninvasive techniques to visualize the bile ducts: intravenous cholangiography, ultrasound, conventional CT and MR cholangiography (MRC). All of these methods have drawbacks. Intravenous cholangiography (IVC) has largely been abandoned due to poor contrast and poor spatial resolution. When ultrasound imaging of the lower biliary tree is carried out, approximately 50-70% of bile duct stones are not visualized due to reflection from overlying bowel gas [1-3]. Conventional CT without contrast administration often fails to resolve the non-dilated bile duct from the surrounding tissue. Bile duct stones are also often isodense with bile (up to 80% of the cases) [4]. MRC does not require any contrast agent to visualize the bile ducts, and dilatation and gallstones in the common bile duct are easily detected [5-8]. Unfortunately, MRC cannot be performed in all patients and hospitals due to limited availability of MRI or due to contraindications. An alternative method to MRC is therefore required. Drip infusion CT cholangiography (DIC-CT) could be such an alternative technique. The technique is sparsely used and relatively unknown.

At DIC-CT meglumine-iotroxate is used as contrast agent. It is excreted actively by hepatocytes into the bile ducts. When the bile ducts are obstructed, the excretion of bile and contrast media is decreased. It has therefore been assumed that DIC-CT cannot be performed in patients with elevated bilirubin values (>51 µmol/L) [9, 10]. There have also been reports on an unacceptable high number of adverse events after injection of meglumine iotroxate [11]. In all those studies the contrast media has been injected. It may be assumed that the excretion might be improved by infusing the contrast media at an infusion rate governed by the bilirubin levels. The contrast media concentration will thereby not exceed the excretion capacity of the hepatocytes. The infusion technique might also have influence on the number of adverse events.
The aim of this retrospective study was to evaluate prolonged drip infusion CT
cholangiography (DIC-CT) in patients with suspected obstructive biliary disease with respect
to feasibility and rate of adverse reactions after administration of the biliary contrast agent
(iotroxate).

MATERIAL AND METHODS: This is a retrospective study in 142 consecutive patients (68
men and 74 women, mean age 69 years, range 24 - 95 years) referred for investigation of
biliary disease during the period from January 1996 to January 2003. After approval by the
ethics committee for the region, the medical records of all patients were retrospectively
reviewed regarding bilirubin level, infusion time and adverse events. Adverse events were
defined as any signs of reaction to contrast media that occurred after the injection, such as
anaphylaxis, urticaria and respiratory distress.

Administration of contrast media
The serum bilirubin concentration was measured before CT examination using standard
clinical laboratory methods used at the hospital. 100 ml of meglumine iotroxate (Biliscopin®,
Schering AG, Berlin, Germany) 50 mg I/ml was administered by intravenous drip infusion.
To allow longer infusion times, the solution volume was increased by dilution with isotonic
sodium chloride. The infusion time was determined by the measured bilirubin level according
to a schematic protocol (Table 1). Following the guidelines from the manufacturer, the drip
infusion was started at a low infusion rate (0.5 ml/min) and increased to the desired infusion
rate during the following 3 to 5 minutes. The CT scan was started immediately after the
infusion was completed. For distension of the distal duodenum, the patients ingested two
glasses of drinking water immediately before the CT examination. To evaluate compliance to
the protocol, the medical records were reviewed regarding the given infusion time at the ward.

Scanning Parameters
Patients were scanned in the right oblique position by means of thin-section single-breath-hold helical CT in the cranio-caudal direction. Specific scan protocols varied depending on the CT scanner available at the time of examination (Table 2). Between December 1995 and November 1999, 102 patients were scanned with a single-slice CT scanner (Somatom A; Siemens Medical Systems, Forcheim, Germany). From December 1999 to November 2002, a 4-slice multi-detector CT scanner (Somatom Volume Zoom; Siemens Medical Systems, Forcheim, Germany) was used in 44 exams. Between December 2002 and January 2003, a 16-slice multi-detector CT scanner (Somatom Sensation16; Siemens Medical Systems, Forcheim, Germany) was used in 6 exams.

**Evaluation of contrast media excretion**

The attenuation in choledochus and liver was obtained retrospectively by measurement on the restored digital images in all examinations with bilirubin >19 µmol/L (n=42), as well as in 67 individuals also described in another study [12], 19 of the latter with bilirubin >19 µmol/L. In total, attenuation values from 90 (= 42 + 67 – 19) patients were obtained.

**Review of literature**

A MEDLINE search was performed for all clinical studies in English published during the period 1975-2004 concerning iotroxate using the words “Biliscopin” or “iotroxate”. All articles were reviewed for reports regarding adverse events. The pooled frequency of adverse events was calculated for all articles with a number of patients >100 where the contrast had been infused for 30 minutes or more.

**Statistical methods**

Data are given as mean (± standard deviation). Frequencies are given with their 95% confidence interval, computed with normal approximation. Statistical signficance was determined by simple linear regression analysis using SPSS v.12.0.1 (SPSS inc. Chicago, IL, USA).
RESULTS

Out of 153 examinations performed in 142 patients, one subject experienced a minor reaction (pricking sensation in the face) following the administration of 70 ml of contrast. In this patient, the pre-exam bilirubin value was normal (11 µmol/L) and the planned infusion time was 60 minutes. Four weeks later, the same patient successfully underwent a repeated CT cholangiography by means of the same infusion rate without any adverse reactions. In the other 141 patients (151 examinations), no adverse reaction was noted in the medical records. Thus, the observed frequency of adverse reactions in this material was 1/153 (0.65%).

The mean bilirubin value was 20 (±25) µmol/L. 42 patients had an elevated bilirubin value (defined as >19 µmol/L). Information regarding which infusion time that had been used at the ward had been noted in the medical records in 110 out of 153 examinations. The mean infusion time was 82 (±42) minutes. Disregarding potential measurement errors of at most 2 µmol/L, seven infusions (5%) had not been performed according to the protocol. Five of these received the infusion too fast and 2 too slow (Fig. 1).

Excretion of contrast media was observed in 93% (143/153) of all exams (one examination aborted due to potential contrast reaction). No visible secretion of contrast was reported in 9 patients (Table 3). In three of these, the infusion protocol had not been followed, with too fast infusion (bilirubin 73-133 µmol/L). The final diagnoses in the patients with no visible secretion are also shown in Table 3. Three of these had occlusive intraductal stones, all of which had been reported at the DIC-CT. Two patients had a malignancy affecting the bile ducts. One of these was reported at DIC-CT and the other showed signs of dilated bile ducts. The remaining 4 patients had hepatitis, pancreatitis, cholangitis or cholecystitis.

The observed attenuation in choledochus and liver at different bilirubin values is shown in Fig. 2.

Review of literature
In total, 42 original publications in English were found. Those with more than 100 patients and with an infusion time of 30 minutes or more are listed in Table 4 as well as the pooled number of adverse events (2.27%).

DISCUSSION

By adjusting the infusion rate of the contrast media to the bilirubin level (Table 1), contrast excretion into the bile ducts was observed in 93% of all exams. Excretion of contrast media was noted even when the bilirubin was as high as 159 µmol/L (Fig. 3-4).

In three of the nine cases without contrast media excretion, the infusion protocol had not been followed. The absence of contrast media in the bile ducts could also be explained by the final diagnosis in all patients without contrast medium excretion, e.g., by total or partial occlusion of the bile duct from stones, malignancy or inflammation, or by reduced excretion by hepatocytes due to inflammation, infection or malignancy. However, only two of the nine examinations without contrast excretion were inconclusive. In the other seven cases, DIC-CT findings could guide the referring physician to other examinations and the final diagnosis (Table 3).

Compliance to the drip infusion scheme

The compliance to the infusion scheme was good (94%) in the 110 examinations where information on which infusion time that had been used at the wards could be found in the medical records. Unfortunately all three patients with a bilirubin >100 µmol/L were among the seven patients that did not receive the correct infusion rate. The intended infusion rate (5 hours) could therefore not be evaluated. In 43 examinations (28%), the medical records did not contain information on the given infusion time. The compliance to the protocol might have been lower in that group.

Safety
The protein-binding characteristics essential for biliary contrast media increase the risk of adverse reactions [13, 14]. In a previously published review of the literature on the frequency of adverse reactions in examinations with short injection time (<10 min), the pooled number of adverse events was three times higher (16% vs. 5%) than after infusion (>30 min) of the same amount of contrast media [11]. The frequency of adverse events of iotroxate (Biliscopin®) at infusion has been reported to be as high as 3.4%, with a pooled frequency of 2.3% (Table 4). It has been proposed that the tolerance of intravenous biliary contrast media is improved when a slow infusion technique is used (up to one hour of infusion) [15]. Our study supports this proposal since there was only one adverse reaction, which was mild, in 142 patients and 153 examinations (0.65%). Of the 153 examinations 10 were performed in out-patients. These patients normally stay one hour at the x-ray department after the contrast injection has been completed. Due to the retrospective nature of this study, late mild adverse advents may not have been recorded in these 10 patients. More severe adverse reactions such as a skin rash, itches, etc. are however usually reported to the hospital by the patients and according to the routines of the hospital, adverse reactions are always noted in the medical records after an X-ray examination The hospital is also the only one in the district and no notes could be found about adverse advents in the patients’ files (files from departments of radiology, surgery and internal medicine were reviewed).

CONCLUSION

This study indicates that DIC-CT with an infusion rate of iotroxate governed by the bilirubin value is a feasible and safe tool in patients with and without impaired biliary excretion. The technique may be of use as an alternative to MRC in cases where MRC is contraindicated or not available.
References


Table. 1. Protocol for determining the infusion rate of iotroxate (Biliscopin®) based on the bilirubin level prior to the investigation. The same total amount of Iodine (5g) was given to all patients.

<table>
<thead>
<tr>
<th>Serum bilirubin (µmol/l)</th>
<th>Infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>40–60 min</td>
</tr>
<tr>
<td>21–40</td>
<td>1–3 hours</td>
</tr>
<tr>
<td>41–99</td>
<td>4 hours</td>
</tr>
<tr>
<td>&gt;100</td>
<td>5 hours</td>
</tr>
</tbody>
</table>

Table. 2 CT scanner parameters

<table>
<thead>
<tr>
<th>Type of scanner</th>
<th>Collimation</th>
<th>Pitch</th>
<th>Increment</th>
<th>mAs</th>
<th>kV</th>
<th>Number of examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Slice</td>
<td>1 x 5.0 mm</td>
<td>1.5</td>
<td>1 mm</td>
<td>200</td>
<td>120</td>
<td>103</td>
</tr>
<tr>
<td>Multi-slice</td>
<td>4 x 2.5 mm</td>
<td>1.5</td>
<td>1 mm</td>
<td>130</td>
<td>120</td>
<td>46</td>
</tr>
<tr>
<td>Multi-slice</td>
<td>16 x 0.75 mm</td>
<td>varying</td>
<td>0.5 mm</td>
<td>130</td>
<td>120</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 3. The bilirubin value, infusion time and final diagnosis in the nine cases where no secretion of contrast media was observed at DIC-CT.

<table>
<thead>
<tr>
<th>Bilirubin value, umol/L</th>
<th>Infusion time, minutes</th>
<th>Reported findings in medical records, final diagnosis</th>
<th>Reported findings at DIC-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>133</td>
<td>120*</td>
<td>Hepatitis Type B (^1)</td>
<td>wide bile duct</td>
</tr>
<tr>
<td>120</td>
<td>240*</td>
<td>Pancreatitis (^1, 2)</td>
<td>inconclusive</td>
</tr>
<tr>
<td>79</td>
<td>180</td>
<td>Intra ductal stone in choledochus and pancreatitis (^7, 2, 6)</td>
<td>Intra ductal stone</td>
</tr>
<tr>
<td>73</td>
<td>120*</td>
<td>Cholecystitis (^1, 2)</td>
<td>wide bile duct</td>
</tr>
<tr>
<td>30</td>
<td>unknown</td>
<td>Concrement in choledochus (^1, 2, 3, 6,)</td>
<td>Intra ductal stone</td>
</tr>
<tr>
<td>25</td>
<td>unknown</td>
<td>Concrement in choledochus, Total occlusion and Klatskin tumour (^5, 7)</td>
<td>Intra ductal stone, tumour</td>
</tr>
<tr>
<td>16</td>
<td>60</td>
<td>Distal stenosis in choledochus and pancreatitis (^4, 5, 7)</td>
<td>inconclusive</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>Total occlusion in choledochus, pancreas tumour (^2, 3)</td>
<td>wide bile duct</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>Post operative cholangitis/cholecystitis with bile fistula and leakage (^1, 6, 7)</td>
<td>fluid filled cavity</td>
</tr>
</tbody>
</table>

Infusion time not complying with the protocol indicated by * (all these received a too fast infusion). The method by which the final diagnosis was made is indicated by superscript numbers where 1 = laboratory findings, 2 = ultrasound, 3 = ultrasound with fine needle biopsy, 4 = MRCP, 5 = operation, 6 = ERCP and 7 = PTC.
### Table 4.

Published studies on the frequency of adverse reactions at infusion of iotroxate at intravenous cholangiography. Included are all studies with at least 100 patients using an infusion time of at least 30 min. The severity of the reactions is graded as reported. The numbers in superscript refer to the reference list.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Total</th>
<th>Minor</th>
<th>Intermediate</th>
<th>Severe</th>
<th>Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilsson et al. 1987(^{10,11})</td>
<td>1422</td>
<td>49 (3.4%)</td>
<td>41 (2.9%)</td>
<td>5 (0.35%)</td>
<td>3 (0.21%)</td>
<td>0</td>
</tr>
<tr>
<td>Daly et al. 1987(^{16,17})</td>
<td>286</td>
<td>4 (1.4%)</td>
<td>4 (1.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Joyce et al. 1991(^17)</td>
<td>100</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wigmore et al. 1993(^18)</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patel et al. 1993(^19)</td>
<td>113</td>
<td>3 (2.65%)</td>
<td>3 (2.65%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grunshaw et al. 1993(^20)</td>
<td>137</td>
<td>4 (2.92%)</td>
<td>3 (2.19%)</td>
<td>1 (0.73%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sacharias 1995(^21)</td>
<td>1,061</td>
<td>11 (1.04%)</td>
<td>11 minor + inter</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3,219</strong></td>
<td><strong>73</strong></td>
<td><strong>53</strong></td>
<td><strong>17</strong></td>
<td><strong>3</strong></td>
<td><strong>0</strong></td>
</tr>
</tbody>
</table>

**Frequency (95% confidence limits)**

|                |                |                |                |                |
|----------------|----------------|----------------|----------------|
|                | 2.27%          | 1.65%          | 0.53%          | 0.09%          |
|                | (1.75%-       | (1.21%-       | (0.28%-       |
|                | 2.78%)         | 2.09%)         | 0.78%)         |
|                |                |                |                |

\(^{10}\) Biliscopin® (iotroxate) (5-8.0 g iodine) infused over 30-120 minutes

\(^{17}\) approximately half of the studies with Biliscopin® (iotroxate) and half with Endomirabil® (iodoxamate)
Fig. 1. The infusion time of iotroxate (Biliscopin®) in relation to bilirubin level prior to the investigation. The recommended infusion times were followed in 103 out of the 110 cases (94%) where information on infusion time was found in the medical records. Cases in which the recommendations were not followed are encircled (n=7). Unfortunately, all of the three (3/110) examinations with a bilirubin value >100 µmol/L received a too fast infusion compared to the infusion scheme. The patient with the highest bilirubin value (159 µmol/L) had good diagnostic excretion of contrast in the bile ducts, the other two had no excretion.
Fig. 2. Attenuation in the common bile duct and liver at DIC-CT as a function of serum bilirubin before the examination.

Fig. 3. In spite of an elevated bilirubin value, a good contrast excretion can be observed when a prolonged infusion time is used. In this case, the bilirubin value was 78 µmol/L and the infusion time was 3 hours. Final diagnosis was status post choledochoduodenostomy.
Fig. 4. A vast number of biliary stones visualized in the common bile duct. Pre exam bilirubin was 29 µmol/L (infusion time not noted in the medical record). ERCP verified the bile duct stones.
Figure 2: Attenuation value (HU) distribution by Bilirubin levels (µmol/ml) for Choledochus and Liver.

- Choledochus:
  - <20 µmol/ml: n=53
  - 21 - 40 µmol/ml: n=29
  - 41 - 99 µmol/ml: n=5
  - >100 µmol/ml: n=3

- Liver:
  - <20 µmol/ml
  - 21 - 40 µmol/ml
  - 41 - 99 µmol/ml
  - >100 µmol/ml