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

A Persson, MD\textsuperscript{1}, N Dahlström MD\textsuperscript{2}, Ö Smedby, MD, PhD\textsuperscript{1} and TB Brismar, MD, PhD\textsuperscript{3}.

\textsuperscript{1}Center for Medical Image Science and Visualization (CMIV), Linköping University Hospital, Sweden. \textsuperscript{2}Department of Radiology, Hudiksvall Hospital, Sweden, \textsuperscript{3}Department of Radiology, Karolinska University Hospital Huddinge, Sweden.

\textit{Correspondence:} Anders Persson, Center for Medical Image Science and Visualization (CMIV), Linköping University Hospital, Sweden. Department of Radiology, Linköping University Hospital, SE- 581 85 Linköping, Sweden. FAX: +46 13 222779

E-mail: anders.persson@cmiv.liu.se
**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(R)). 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

When diagnosing hepatobiliary disease ultrasound and MR cholangiography (MRC) are most frequently used. Endoscopic Retrograde Cholangiography (ERC) is often regarded as the gold standard when visualising biliary disease. The modality is invasive, user-dependent and may induce pancreatitis. It should therefore not be performed in patients where intervention is less certain. Ultrasound is easily tolerated by the patients and relatively cheap to perform. The modality is however user dependent and the image captions are not easily understood by the clinicians. MRC is superior in visualising the biliary system and the images are appreciated by the surgeons at surgical planning. It does not require any contrast agent to visualize the bile ducts, and dilatation and gallstones in the common bile duct are easily detected [1-3]. Unfortunately, MRC cannot be performed in all patients and hospitals due to limited availability of MRI or due to contraindications. MRC is also often inconclusive in patients with air in the biliary system such as after papillotomy or liver surgery with entero-hepatic anastomoses (e.g. Whipple’s operation and Billroth 2). Surgical clips after cholecystectomy may also give artefacts mimicking a ductal cancer or a stone [4, 5]. An alternative non-invasive method to ultrasound and MRC is therefore required.

Computed Tomography Cholangiography (CTC) is a fast and widely available technique to visualise hepatobiliary disease. Without contrast administration multi detector CT has been reported to have a sensitivity of 65% to 88% and a specificity of 84%-97% to detect gall stones [6, 7]. Techniques to improve the sensitivity and specificity by administering biliary contrast media orally [8] or intravenously [9, 10] have been developed, but are not so widely spread. Possible explanations for infrequent use of CTC might be the low resolution of single detector helical CT and reports on an unacceptable high number of adverse events after injection of meglumine iotroxate [11]. With the development of multiple detector CT the
resolution of CTC now exceeds that of MR. The number of adverse reactions with biliary contrast media is probably also improved by infusing the contrast media instead of injection.

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 (500 ml). 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.

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%). Of the 153 examinations 10 were performed in out-patients. These patients normally stay one hour at the radiology 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, itchies, 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 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).

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). All three patients with a bilirubin >100 µmol/L were among the seven patients who did not receive the correct infusion rate. The intended infusion rate (5 hours) could therefore not be evaluated.

Excretion of contrast media was observed in 93% (143/153) of all exams (one examination aborted due to potential contrast reaction). In patients with elevated bilirubin (>19 µmol/L) contrast media in the bile was observed in 36 out of 42 patients (86%). 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

When the bile ducts are obstructed, excretion of bile and contrast media is decreased. It has therefore been assumed that CT cholangiography cannot be performed in patients with elevated bilirubin values [9, 10]. In this study, the infusion rate of the contrast media was
adjusted to the bilirubin value (Table 1). The aim was to keep the concentration within the excretion capacity of the hepatocytes in order to optimise the concentrations in bile. By using this scheme a contrast excretion into the bile ducts was observed in 93% of all exams. In patients with elevated bilirubin (>19 µmol/L) contrast media in the bile was observed in 86%. Excretion of contrast media was noted even when the bilirubin was as high as 159 µmol/L (Fig. 3-4). It has previously been recommended not to perform CTC in patients with bilirubin >50 µmol/L (3 mg/dL) [14]. In this study, excretion was observed in four out of eight patients with bilirubin >50 µmol/L. In three of those without contrast excretion the infusion protocol had however not been followed (too fast infusion). Although absence of contrast media in the bile ducts is more likely in patients with greatly elevated bilirubin CTC is not useless in these patients - 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). The lack of excretion is also valuable information. Patients without excretion are likely to have either a total occlusion of the main bile duct/choledochus or a severely impaired hepatocyte function. The bilirubin value, if not already considerably elevated, is probable to escalate in these patients. In this study the lack of excretion could be explained by the final diagnosis in all patients (Table 3).

Safety

The protein-binding characteristics essential for biliary contrast media increase the risk of adverse reactions [11, 15]. 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 1.9% (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) [16, 17]. Our study supports this proposal since there was only one adverse reaction, which was mild, in 142 patients and 153 examinations (0.65%).

Clinical application

When ultrasound has been inconclusive at diagnosing choledocholithiasis MRC has the advantage of not exposing the patient to radiation and contrast media. On the other hand, in clinical practise the possibility to obtain an MR exam with short notice is limited. When comparing the sensitivity and specificity of contrast enhanced CTC to detect choledocholithiasis they are highly comparable to that of MRC (sensitivity 86-93% and 80-95% respectively and specificity 94-100% and 88-96% respectively) [3, 8, 18, 19]. CTC is also faster than MRC, which is of importance in patients with difficulties in lying in the supine horizontal position for a prolonged time or when evaluating severely ill patients.

CTC has been used to preoperatively evaluate aberrant bile ducts before laparoscopic cholecystectomy. The frequency of anatomic variants observed at CTC that may affect the outcome of laparoscopic cholecystectomy was estimated to 15% [16, 20, 21]. In clinical practise, the frequency of bile duct injuries is about 0.5-1.5% [22, 23]. The potential value of pre-operative mapping of the biliary system by using CTC must therefore be weighed against the cost and radiation.

By injection of contrast media via biliary drainage CTC has also successfully been used to visualize the extent of ductal invasion by hilar carcinoma [24]. Whether administration of contrast media orally or intravenously can obtain similar results in patients without drainage has not been shown.

In clinical practise CT Cholangiography has been reported to be the preferred modality to evaluate living donors prior to liver transplantation [25]. The main reported advantage to MRI and MRC was the superior mapping of the biliary tree [26] - otherwise the two modalities
were regarded as equal for the planning [25]. After introduction of CTC the use of intraoperative cholangiogram has been reported to be significantly reduced at living donor liver transplantation [27]. After liver surgery there is a risk of biliary leaks. In these patients and in patients with traumatic rupture of the biliary tree CTC may be useful to demonstrate the leak (fig 5) [28]. Cholescintigraphy can also demonstrate biliary leaks [29], but the resolution is low compared to CT. To our knowledge there is no other non-invasive technique to both prove and localize a leakage from the biliary tree (unless a functioning external biliary drainage is present, enabling a secondary cholangiography).

CTC has also been shown to provide kinetic and functional information [30]. This is however also possible in contrast enhanced MRC when hepatocyte specific contrast media is used (Gd-BOPTA and Gd-EOB-BOPTA). Further studies are required to evaluate which of contrast enhanced MRC and CTC should be chosen to evaluate kinetics.

The main disadvantages of CTC compared to MRC are the use of radiation and contrast media. In our study, including our review of the literature, the frequency and severity of adverse reactions was low when infusing the contrast media. The disadvantage of infusion is the need of supervision, which is impractical at a radiology department. In this study this problem was solved by admitting the patients to a ward for infusion prior to CTC.

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. In addition to those with inconclusive MRC or contraindications, CTC is a diagnostic alternative in patients that already are admitted to the hospital and in whom a reliable diagnosis or mapping of the biliary tree is required within a limited time. In younger patients non-ionising methods (i.e. MRC or a repeated ultrasound) should be pursued.
References


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Figure 2

The bar chart shows the attenuation value (HU) for different bilirubin levels (µmol/ml) in the Choledochus and Liver. The vertical axis represents the attenuation value, and the horizontal axis represents the bilirubin levels. The chart indicates the number of samples (n) for each category.

- **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: n=53
  - 21 - 40 µmol/ml: n=29
  - 41 - 99 µmol/ml: n=5
  - >100 µmol/ml: n=3
Additional files provided with this submission:

Additional file 1: Table and figures_TB.doc : 487KB
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Additional file 2: Main document Galla 1 BMC_final coloured changes.doc : 72KB
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