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Evaluation of mebrofenin hepatoscintigraphy in neonatal-onset jaundice

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Abstract *Background*. The prognosis of infants with prolonged neonatal jaundice is dependent on early diagnosis because of the need for prompt surgical management of biliary atresia.
Objective. To evaluate the usefulness of $^{99m}Tc^{m}$-trimethylbromo-iminodiacetic acid (TBIDA, mebrofenin) in the investigation of infantile jaundice.
Materials and methods. A retrospective study was undertaken of 58 patients with unexplained prolonged neonatal jaundice. Sixty-eight scans were reviewed.
Results. Mebrofenin scintigraphy confirmed the presence of a choledochal cyst in three of the four cases with that diagnosis. There were no false negative results in the nine patients with extrahepatic biliary atresia (EHBA). Three further infants had an incorrect histological diagnosis of EHBA. A gall bladder was identified by US in each case and in one of these, scintigraphy showed gut excretion. In the 16 patients with no gut excretion by 24 h, the final diagnoses were intrahepatic cholestasis ($n = 7$), Alagille's syndrome ($n = 3$), neonatal hepatitis ($n = 3$), alpha-1-antitrypsin deficiency ($n = 2$) and juvenile xanthogranuloma ($n = 1$). Seven infants had repeat scintigraphy after the administration of ursodeoxycholic acid (URSO). This changed five non-excretors with hepatitis into excretors. Two infants with hepatitis continued to show non-excretion after URSO, but a gallbladder was identified by US in both.
Conclusions. Mebrofenin scintigraphy is accurate in confirming the presence of a choledochal cyst and in refuting the diagnosis of EHBA. While histology and scintigraphy are each 100 % sensitive for the diagnosis of EHBA, neither, individually, is accurate and the investigation of prolonged neonatal jaundice requires a multi-modality imaging strategy.

Introduction

In prolonged neonatal jaundice, with significant conjugated hyperbilirubinaemia more than 15 % of total bilirubin [1], it is important to obtain rapid diagnosis because early surgical intervention in extrahepatic biliary atresia (EHBA) considerably improves patient outcome [2, 3]. Hepatobiliary scintigraphy plays an important role in the diagnostic work-up of neonatal jaundice. The majority of previous studies in infants have used $^{99m}Tc^{m}$-labelled iminodiacetic acid (IDA) and its analogues [4–6]. The most recently available analogue, $^{99m}Tc^{m}$-trimethylbromo-iminodiacetic acid (TBIDA, mebrofenin) has been shown to have better hepatic uptake and excretion [7]. The clinical value of mebrofenin has previously been assessed in adults, but there have been very limited studies of its value in infants [8]. We have evaluated the role of $^{99m}Tc^{m}$-mebrofenin hepatoscintigraphy in infants with jaundice, in particular in cases of suspected EHBA, comparing the

Table 1 Summary of the diagnoses and investigative findings in 58 children with neonatal jaundice (*GB* gallbladder present on US, *No GB* absent gallbladder on US, *OTC* operative cholangiogram, *TPN* total parenteral nutrition, *CMV* cytomegalovirus, + liver biopsy obtained, – liver biopsy not obtained)

Final diagnosis	Case	U/S	TBIDA	Liver biopsy	Confirmation
Choledochal cyst	1	Cyst	Excretion	–	Laparotomy
	2	Cyst	Excretion	–	Laparotomy
	3	Cyst	Excretion	–	Laparotomy
	4	Cyst	Excretion	–	Laparotomy
EHBA	5	No GB	No excretion	EHBA	OTC/Laparotomy
	6	GB	No excretion	EHBA	OTC/Laparotomy
	7	No GB	No excretion	EHBA	OTC/Laparotomy
	8	No GB	No excretion	EHBA	OTC/Laparotomy
	9	GB	No excretion	EHBA	OTC/Laparotomy
	10	No GB	No excretion	EHBA	OTC/Laparotomy
	11	No GB	No excretion	EHBA	OTC/Laparotomy
	12	No GB	No excretion	EHBA	OTC/Laparotomy
	13	GB	No excretion	EHBA	OTC/Laparotomy
Neonatal Hepatitis	14	GB	Excretion	–	Clinical follow-up
	15	GB	Excretion	+	Histology
	16	GB	Excretion	–	Clinical follow-up
	17	GB	Excretion	+	Histology
	18	GB	Excretion	+	CMV Culture
	19	GB	Excretion	+	Histology
	20	GB	Excretion	–	Clinical follow-up
	21	GB	Excretion	–	Clinical follow-up
	22	GB	Excretion	+	Histology
	23	GB	Excretion	–	CMV Culture
	24	No GB	Excretion	+	Histology
	25	No GB	No excretion	+	Clinical follow-up
	26	GB	No excretion	+	Histology
	27	GB	Excretion	+	Histology
	28	GB	Excretion	+	Histology
	29	GB	Excretion	+	Histology
	30	GB	Excretion	+	Histology
	31	GB	Excretion	+	Histology
	32	GB	Excretion	+	Histology
	33	GB	Excretion	+	Clinical follow-up
	34	GB	No excretion	+	Clinical follow-up
	35	GB	Excretion	+	CMV Culture
	36	GB	Excretion	+	Histology
	37	GB	Excretion	+	Histology
	38	GB	Excretion	EHBA	Clinical follow-up
Non-specific aetiologies	39	GB	No excretion	+	OTC/histology
	40	GB	Excretion	+	Cholestasis on histology
	41	GB	No excretion	EHBA	Cholestasis/OTC
	42	GB	No excretion	+	Cholestasis on histology
	43	GB	Excretion	+	TPN Related
	44	No GB	No excretion	+	Cystic Fibrosis Related
	45	GB	No excretion	+	Related to ALF
	46	GB	No excretion	+	TPN Related
	47	GB	Excretion	+	Cholestasis on histology
	48	No GB	Excretion	+	TPN Related
	49	GB	Excretion	+	TPN Related
	50	No GB	No excretion	+	TPN Related
Alagille's Syndrome	51	GB	No excretion	+	Histology/radiology
	52	No GB	No excretion	+	Histology/radiology
	53	GB	Excretion	+	Histology/radiology
	54	GB	No excretion	+	Histology/radiology
Alpha-1-Antitrypsin Deficiency	55	GB	Excretion	+	Serum level
	56	GB	No excretion	EHBA	Serum level/OTC
	57	No GB	No excretion	+	Serum level
Juvenile Xanthogranuloma	58	No GB	No excretion	+	Laparotomy/OTC

sensitivity and specificity of the examination with both US and histology obtained from liver biopsy.

Materials and methods

All mebrofenin hepatobiliary scans performed on infants with hyperbilirubinaemia (conjugated more than 15% of total) from December 1994 to December 1996 at Birmingham Children's Hospital were retrospectively reviewed. Fifty-eight infants (35 boys, 23 girls,) had 68 mebrofenin hepatobiliary scans. Patients' ages at the time of initial investigation ranged from 2 weeks to 26 weeks (median 6 weeks). Seven patients had repeat scans following treatment with ursodeoxycholic acid (URSO); one patient had four scans. For each patient the result of the scan was compared with the US findings and histology obtained from liver biopsy, if the patient had one. Comparison was made of the sensitivity, specificity and accuracy of the three investigations in diagnosing EHBA. Any complication and difficulties with each procedure were recorded.

All patients received phenobarbitone (5 mg/kg) for at least 5 days prior to the radionuclide study. They then received an intravenous injection of 37 MBq $^{99m}Tc^{m}$-mebrofenin. Imaging was carried out using a low-energy multipurpose collimator with the patient in the supine position. Images were acquired for 3 min every 15 min for 1 h. Delayed images were obtained at 2 h and 3 h, and at 24 h if there had been no excretion at 3 h. The images were interpreted by two experienced paediatric radiologists (S.C. and H.M.A.). In patients with a history suggestive of neonatal hepatitis and US demonstration of either biliary tree dilatation or 'sludge' within the gallbladder, but with no gut excretion at 24 h, a repeat scan was performed following the administration of URSO 20 mg/kg b.i.d. for 48 or 72 h, in an effort to improve biliary clearance. These patients were classified as excretors if activity was then seen in the bowel on the repeat imaging up to 24 h.

Abdominal US was performed on all patients within 72 h of the mebrofenin scan. Patients were fasted for at least 6 h prior to the scan and images were initially obtained with a 5-MHz probe, and subsequently a 10-MHz probe if the gallbladder had not been identified. US was used to document the presence of a choledochal cyst, assess the appearance of the liver parenchyma, detect any evidence of bile duct dilatation, and identify the presence of a gallbladder or gallstones. Liver biopsies were performed on 49 patients, the biopsy site having been identified by US. Patients were also screened for underlying metabolic causes of jaundice and genetic causes such as Alagille's syndrome and alpha-1-antitrypsin deficiency. Blood and urine cultures were obtained for bacterial and viral pathogens.

Results

The results of the mebrofenin scans, US scans and liver histology are summarised in Table 1 along with the final diagnoses. Liver biopsies were undertaken, without complication, in 49 patients.

Choledochal cyst

There were four patients with a choledochal cyst, and all the cysts were identified by ultrasound. Three of these patients had a mebrofenin scan that demonstrated communication of the cyst with the biliary tree and in one patient, even though no communication was demonstrated, a filling defect in the liver compatible with a cyst was seen. The diagnoses were confirmed at laparotomy.

Table 2 Evaluation of imaging modalities in diagnosing EHBA

	Sensitivity	Specificity	Accuracy
Mebrofenin	(9/9) 100%	(33/49) 67%	(42/58) 72%
Ultrasound	(6/9) 67%	(44/49) 90%	(50/58) 86%
Histology	(9/9) 100%	(37/40) 92%	(46/49) 94%

Extrahepatic biliary atresia

There were nine patients with extrahepatic biliary atresia (EHBA), none of whom showed any bowel activity at 24 h on mebrofenin imaging. All had histological confirmation of the diagnosis. In six infants, no gallbladder was visible on US, but in the three remaining infants, US identified a gallbladder, which was small in two.

In three patients, liver histology was reported as consistent with EHBA. Although in two of these the mebrofenin scan showed no bowel excretion, operative cholangiography showed a patent biliary tree and gallbladder in all three. The final diagnoses in these cases were alpha-1-antitrypsin deficiency, hepatitis and intrahepatic cholestasis. The sensitivity, specificity and accuracy of the three investigations with respect to EHBA are recorded in Table 2.

Hepatitis

Mebrofenin scintigraphy showed no excretion in 3 of the 25 patients diagnosed as having neonatal hepatitis. All three were shown to have a gallbladder on US. Liver biopsy was performed in 20 patients and histology in 19 showed the typical findings of neonatal hepatitis. Subsequent follow-up to exclude other causes of jaundice, along with the results of biochemical and microbiological investigations, confirmed the diagnosis of hepatitis. One infant with a final diagnosis of hepatitis had a histological diagnosis of EHBA but had a gallbladder on US and showed gut excretion on mebrofenin scintigraphy.

Discussion

Mebrofenin is the best agent to use for hepatic scintigraphy because of its excellent hepatic extraction – 98% in normal subjects and greater than 70% with bilirubin levels up to 20 mg/dl, compared with $^{99m}Tc^{m}$-diisopropyl-iminodiacetic acid (DISIDA) which shows only

36 % hepatic extraction at a bilirubin level of 10 mg/dl [5]. With these improved levels of extraction, hepatic scintigraphy is of increasing value in the evaluation of prolonged neonatal jaundice.

US is still the primary investigation of choice for patients with hyperbilirubinaemia, due to its accessibility and ability to detect other intra-abdominal pathology. Unfortunately, liver US fails to positively identify hepatitis and the presence or absence of a gallbladder is not reliable in differentiating cases of biliary atresia. It is sensitive in the detection of choledochal cysts and is valuable in demonstrating asplenia and polysplenia, which have an association with biliary atresia. Therefore, in cases of suspected biliary atresia, patients should be commenced on phenobarbitone as soon as possible so as not to delay the radionuclide scan, and the US findings should not affect the indication for scintigraphy.

In many cases, liver biopsy is also performed to aid the diagnosis. The histological findings are important but are not 100 % specific. We recorded three cases in which there was a discrepancy between the initial histological diagnosis and the final diagnosis. In two cases, scintigraphy showed no excretion and liver histology was consistent with EHBA. Operative cholangiography, however, demonstrated a patent biliary tree. The final diagnoses in these patients were alpha-1-antitrypsin deficiency and intrahepatic cholestasis that had a slow clinical recovery. The third case in which there was an error in the histological diagnosis was a case of cholestasis related to chronic inflammatory disease in the liver. In this case, mebrofenin scintigraphy showed excretion into the bowel, which excluded EHBA. It is possible that biliary stasis might alter periductal histology causing diagnostic confusion. Diffuse alteration of intrahepatic ductules has been described in some patients with liver disease [9]. In five cases, there was improvement of excretion following treatment with URSO, suggesting that sludging of bile is a contributory factor.

Mebrofenin is the most important scintigraphic agent, especially for excluding EHBA. The presence of tracer within the small bowl excludes EHBA. Our results show 100 % sensitivity for its detection, but the reduced specificity of 67 % shows that other investigations are needed to confirm the diagnosis. False-negative results have only rarely been reported with other hepatoscintigraphy agents but never with mebrofenin [4, 10]. To help improve the false-positive rate some infants were given URSO, a bile-chelating agent that improves biliary excretion.

The role of phenobarbitone is controversial. Hepatoscintigraphy with other ^{99m}Tc^{m}-IDA agents performed after its administration has been reported to increase the diagnostic accuracy [11]. Other reports indicate that it may not be necessary [7]. There has not yet been a prospective study, which addresses the efficacy of phenobarbitone in mebrofenin scintigraphy. We did not encounter any problem with its administration.

The value of liver function tests in the evaluation of EHBA have been studied previously [12]. Only γ-glutamyltransferase (γGT) levels show a correlation with the diagnosis of biliary atresia, but there is still considerable overlap between positive and negative cases making them of limited usefulness. γGT levels were not evaluated in this study. Similarly, stool colour is not totally reliable. Complete and prolonged acholic stools favour biliary atresia, but this clinical sign was not consistently present in our study population.

Both US and hepatoscintigraphy are sensitive and specific for the detection of choledochal cysts, the imaging findings being confirmed at laparotomy. Our experience shows that negative US and mebrofenin scans exclude the diagnosis of choledochal cyst.

In summary, the prompt diagnosis of neonatal jaundice is important as surgically remedial disease shows much better prognosis the earlier it is instigated. The commonest disease amenable to surgical treatment is EHBA. The diagnosis of EHBA can be difficult and may need laparotomy and operative cholangiography. US plays an important role in the initial investigation of jaundice but is of limited value in the specific diagnosis of EHBA. Mebrofenin scintigraphy is valuable in excluding the diagnosis and along with liver biopsy helps reduce the number of cases requiring cholangiography. Liver histology is important in the investigative process but may occasionally be misleading. Both US and hepatoscintigraphy are valuable in the diagnosis of choledochal cysts.

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