The Effect of Phenobarbital on the Accuracy of Technetium-99m Diisopropyl Iminodiacetic Acid Hepatobiliary Scintigraphy in Differentiating Biliary Atresia from Neonatal Hepatitis Syndrome

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Abstract

Biliary atresia (BA) and neonatal hepatitis syndrome (NHS) are major causes of cholestatic jaundice in infancy. Technetium-99m diisopropyl iminodiacetic acid hepatobiliary scintigraphy (^{99m}Tc-DISIDA scan) is widely used in the differentiation of these two entities. The objective of this study was to evaluate the effect of phenobarbital premedication on the accuracy of ^{99m}Tc-DISIDA scan. Ninety-five cholestatic infants (38 females and 57 males) with an age range of 2 weeks to 4 months (mean 2.1 mo) who underwent ^{99m}Tc-DISIDA scan testing were retrospectively reviewed. The patients were divided into 3 groups according to the history of phenobarbital administration prior to ^{99m}Tc-DISIDA scan examination. Group 1 (n = 48), group 2 (n = 29), and group 3 (n = 18) received phenobarbital at the dosage of 5 mg/kg/day for at least 5 days, less than 5 mg/kg/day or less than 5 days, and no premedication, respectively. The accuracy of ^{99m}Tc-DISIDA scan in differentiating BA from NHS in group 1, 2, and 3 was 72.92 per cent, 89.66 per cent, and 100 per cent, respectively. No significant difference was seen between the patients who received and did not receive phenobarbital in terms of age at presentation, age at onset of jaundice, and liver function tests. In conclusion, phenobarbital therapy may not be necessary prior to ^{99m}Tc-DISIDA scan examination in the evaluation of cholestatic infants and thus a delay in diagnosis and surgical therapy of BA can be avoided.

Key word : Scintigraphy, Phenobarbital, Biliary Atresia, Neonatal Hepatitis

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Biliary atresia (BA) and neonatal hepatitis syndrome (NHS) are frequent causes of cholestatic jaundice in infancy. BA is a progressive obliterative cholangiopathy affecting all or part of the extrahepatic biliary tree and, in many cases, the intrahepatic bile ducts which eventually leads to the loss of normal connection between the biliary system and the intestine[1]. NHS is caused by various etiologies leading to cholestatic jaundice without extrahepatic obstruction. These intrahepatic causes of cholestasis include intrahepatic bile duct paucity syndrome, infections, metabolic, and genetic diseases. No matter what the cause of cholestasis is, most patients develop cirrhosis, so called biliary cirrhosis. It is difficult to differentiate BA from NHS due to the similarity of clinical manifestations and the lack of a specific diagnostic test. The distinction is crucial because the treatment of BA is surgical, whereas NHS can be managed medically. The surgical therapy of BA is hepatic portoenterostomy which is an operation to resect the obliterated bile ducts and reestablish biliary drainage to the intestine. Early diagnosis of BA is essential because early surgical intervention is associated with a better outcome[2].

Hepatobiliary scintigraphy, such as technetium-99m diisopropyl iminodiacetic acid scintigraphy (^{99m}Tc-DISIDA scan) has been widely used to establish the patency of extrahepatic bile duct. Phenobarbital, in a dose of 5 mg/kg/day for at least 5 days, is routinely used prior to the examination. It accelerates biliary excretion of iminodiacetate (IDA) compounds in those with patent extrahepatic bile ducts, whereas it has no effect in those with BA. Therefore, phenobarbital theoretically increases the accuracy of ^{99m}Tc-DISIDA scan in differentiating BA from NHS. Scintigraphic visualization of tracer in the intestinal tract by 24 hours, with or without visualization of the gallbladder, indicates patency of the extrahepatic biliary ducts and thereby excludes BA.

Cholestatic infants usually seek medical advice at the age of more than 2 months and it is well recognized that the success rate of surgical repair for BA declines sharply after 2 months of age[3]. The 5 days required for phenobarbital administration in order to optimize diagnostic yield may ultimately affect the outcome by delaying surgical intervention. Therefore, the authors performed this study to evaluate the necessity of phenobarbital therapy prior to ^{99m}Tc-DISIDA scan in differentiating BA from NHS.

METHOD

Population study

Ninety-five cholestatic infants who underwent ^{99m}Tc-DISIDA scan examination from January 1997 to December 2001 were retrospectively reviewed. Since the standard recommended dose of phenobarbital prior to ^{99m}Tc-DISIDA scan examination is 5 mg/kg/day for at least 5 days[4], the patients were divided into 3 groups according to the history of phenobarbital administration prior to the test. Group 1 (n = 48), group 2 (n = 29), and group 3 (n = 18) received phenobarbital at the dosage of 5 mg/kg/day for at least 5 days, less than 5 mg/kg/day or less than 5 days, and no premedication, respectively.

The diagnosis of NHS was made by the presence of radioisotope in the intestine (Fig. 1) or intra-operative cholangiography (IOC) plus liver biopsy in case of non-visualized radiotracer in the intestine (Fig. 2). BA was diagnosed by the absence of radiotracer in the intestine and confirmed by exploratory laparotomy and/or IOC. Operative finding of BA was classified into 4 anatomic types according to the site of extrahepatic bile duct obstruction[5].

Scintigraphy technique

The scan was performed after intravenous injection of 1.85 MBq/kg of ^{99m}Tc-DISIDA. Acquisition was done using a single-head gamma camera (GE-Camstar) equipped with a low-energy general purpose collimator. Sequential static images 3 minutes per image in anterior and lateral views were acquired immediately after radiotracer injection and then every 15 minutes until 1 hour. Thereafter, acquisition was made half-hourly until 6 hours. If excretion into the intestinal tract was seen, the imaging was then terminated. A 24-hour delayed image was needed if there was no intestinal activity within 6 hours.

Statistical analysis

One-way analysis of variance was used to compare age at presentation, age at onset of jaundice, and liver function tests of the patients in the 3 groups. Statistical significance was taken at a p-value of 0.05. Statistic calculation was done by a commercial statistic software package (SPSS version 11; SPSS Inc., Chicago, IL, USA).

RESULTS

Of 95 cholestatic infants, 38 were female and 57 were male. The patients ranged in age from 2

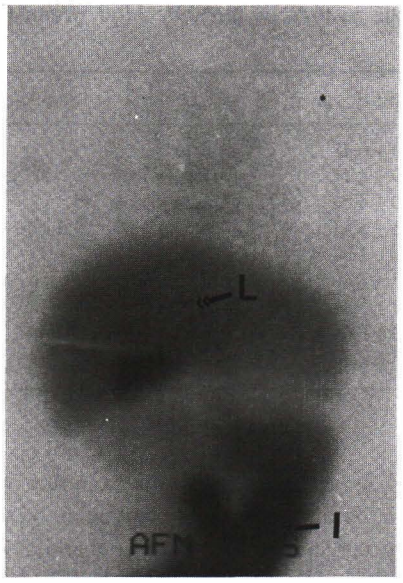

Fig. 1. **Normal hepatobiliary scan showing radiotracer in the intestine.**

L = Liver, I = Intestine

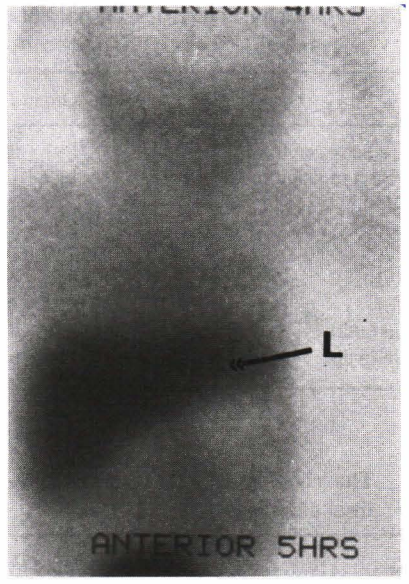

Fig. 2. **Abnormal hepatobiliary scan with no visualized radiotracer in the intestine.**

L = Liver

weeks to 4 months (mean 2.1 mo). Final diagnosis was BA and NHS in 41 and 54 infants, respectively. The diagnosis of NHS in 16 patients with absence of radiotracer in the intestine was confirmed by IOC and liver biopsy. No significant difference was seen between patients who received and did not receive phenobarbital in terms of age at presentation, age at onset of jaundice, and liver function tests as shown in Table 1. The accuracy of ^{99m}Tc-DISIDA scan in differentiating BA from NHS in group 1, 2, and 3 was 72.92 per cent, 89.66 per cent, and 100 per cent, respectively (Table 2).

DISCUSSION

The destruction of extrahepatic bile ducts and potential extension to involve the intrahepatic biliary tree in BA result in progressive neonatal cholestasis, which should be diagnosed by 60 days of age in order to institute appropriate surgical therapy. Kasai showed that 90 per cent, 50 per cent, and 17 per cent of infants operated on before 60 days, between 60 and 90 days, and after 90 days of age, respectively sustained bile drainage[3]. Prompt diagnosis of cholestatic infants may expedite surgery for BA and preclude unnecessary surgical exploration for NHS. Unfortunately, no single test is consistently reliable in differentiating BA from NHS.

Ultrasound is used to rule out choledochal cyst, stone, and to identify vascular and other anomalies sometimes associated with BA[6]. The absence of a gallbladder on a fasting study is suggestive but not diagnostic of BA[7,8]. Ultrasound is very operator-dependent, and provides less reliable data.

Liver biopsy is highly specific for the diagnosis of BA, but only in centers with expertise in interpretation[6]. It has been reported that percutaneous liver biopsy can provide an exact diagnosis of BA in 94 per cent to 97 per cent of all cases[9]. Bile ductular proliferation is the most diagnostic histopathologic sign of BA. The interpretation of a single liver biopsy is also limited by the dynamics of disease. In some cases, 2 biopsies separated in time by a week or two are required to arrive at the diagnosis of BA [6]. However, liver biopsies are often deferred until patients are 6 weeks of age, when the portal tract changes are best developed[1]. Giant cell transformation of hepatocytes is more diagnostic of NHS than of BA, but occasional cases of BA show striking giant cell changes. Considerable overlap histopathology prevents discrimination between BA and NHS.

Table 1. The characteristics of patients categorized by the history of phenobarbital premedication prior to ^{99m}Tc-DISIDA scan examination.

	Group 1	Group 2	Group 3	P-value
Age at presentation (mo)	1.97 ± 0.25	2.13 ± 0.28	2.46 ± 0.76	0.113
Age at onset of jaundice (mo)	1.59 ± 1.23	2.69 ± 3.17	1.89 ± 1.99	0.147
TB (mg/dl)	12.48 ± 9.14	10.30 ± 4.02	11.25 ± 3.58	0.607
DB (mg/dl)	2.43 ± 5.65	8.31 ± 3.57	8.55 ± 3.09	0.985
AST (U/L)	265.19 ± 192.07	244.14 ± 134.34	270.22 ± 232.19	0.259
ALT (U/L)	151.54 ± 121.61	162.17 ± 81.06	148.89 ± 68.30	0.226
AP (U/L)	1,258.28 ± 741.76	1,053.19 ± 560.61	813.35 ± 531.92	0.054
Albumin (g/dl)	4.17 ± 0.55	4.04 ± 0.66	4.03 ± 0.63	0.581
Globulin (g/dl)	2.00 ± 0.73	2.23 ± 0.90	2.32 ± 0.81	0.313

Table 2. The relation of ^{99m}Tc-DISIDA scan and final diagnosis.

	Diagnosis	^{99m}Tc-DISIDA scan	
		Excretion	Non excretion
Group 1	BA	0	16
	NHS	19	13
Group 2	BA	0	14
	NHS	12	3
Group 3	BA	0	11
	NHS	7	0

BA = Biliary atresia, NHS = Neonatal hepatitis syndrome.

Imaging with an IDA preparation labeled with technetium-99m, such as diisopropyl-IDA (DISIDA) or para-isopropyl-IDA (PIPIDA), is employed in the investigation of cholestatic infants. These radiotracers are concentrated within the bile, thereby providing an image of bile flow, even in the presence of severe cholestasis. However, the lack of tracer in the gut may not represent an obstructive defect, but rather a liver parenchymal disease process in which uptake or concentration of the tracer is poor. In severe NHS, there is poor hepatic extraction, and tracer accumulation in the liver is largely due to hepatic blood pool rather than hepatocyte extraction. To facilitate bile flow, patients often receive phenobarbital (5 mg/kg/day) for 3-5 days prior to undergoing the scan. Evidence has suggested that a hepatobiliary scan after three to seven days of phenobarbital therapy is a highly accurate test for differentiating BA from other causes of neonatal jaundice[4,10,11].

Phenobarbital is a potent inducer of hepatic microsomal enzymes and has been shown to increase bilirubin conjugation and excretion. In addition, phenobarbital enhances uptake and excretion of certain compounds and increases canalicular bile flow[12, 13]. The choleretic effect of phenobarbital is thought to be independent from enzyme induction[14,15]. This is mainly due to an increase in the bile salt-independent fraction of canalicular bile flow possibly through an increase in canalicular Na+-K+ ATPase activity[16]. There have been reports of 85-91 per cent accuracy, 97-100 per cent sensitivity, and 67-82 per cent specificity for scintigraphy without phenobarbital premedication in the diagnosis of BA[17,18]. It is unlikely to give the exact recommended dose of phenobarbital because of patients' small size. The duration of phenobarbital given to the patients depends on the waiting time for the ^{99m}Tc-DISIDA scan examination. However, the dosage and duration of phenobarbital premedication in this study were still around 5 mg/kg/day and 5 days, respectively as recommended. The patients who underwent the examination after the year 2000 did not receive phenobarbital because the authors were uncertain about the necessity of the premedication. The 100 per cent accuracy of the test without phenobarbital administration in the present study may be caused by selection bias. The clinical features including acholic stool, older age and higher direct bilirubin level of patients in group 3 might be strongly suspicious of BA, therefore, patients underwent the examination without premedication. However, age at presentation and liver function tests were not statistically different among those 3 groups. Prospective randomized controlled trials are needed to verify the necessity of phenobarbital prior to the scan.

The ^{99m}Tc-DISIDA scan itself is time-consuming and has at least 10 per cent false-positive and false-negative yields[9]. It is also not very effective when serum bilirubin levels are high. It has been

shown that hepatocyte uptake of DISIDA drops to 36 per cent at bilirubin of 10 mg per cent[19]. The authors also analyzed bilirubin levels for potential confounding effects in patients with NHS. The difference of bilirubin levels was not significant between those with and without visualized tracer in the intestinal tract. BA can be ruled out if a patent biliary tree is shown with passage of isotope activity into the bowel[11]. All patients with excretion of radiotracer in the present study were jaundice-free after following their clinical course for 12 months.

SUMMARY

Phenobarbital therapy may not be necessary prior to ^{99m}Tc-DISIDA scan examination in the evaluation of cholestatic infants. Further investigation is needed for the appropriate approach to avoid delayed diagnosis of BA and to eliminate the risk of subjecting an infant who has cholestasis due to intrahepatic causes to needless laparotomy.

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ผลของฟีโนบาร์บิทาลต่อความแม่นยำของการตรวจ 99mTc-DISIDA Scintigraphy ในการวินิจฉัยแยกโรคระหว่างโรคท่อน้ำดีตีบตันและตับอักเสบในทารก

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โรคท่อน้ำดีตีบตันและตับอักเสบเป็นสาเหตุหลักของอาการเหลืองชนิด cholestasis ในทารก การศึกษานี้ประเมินผลของฟีโนบาร์บิทาลต่อความแม่นยำของการตรวจ technetium-99m diisopropyl iminodiacetic acid hepatobiliary scintigraphy (^{99m}Tc-DISIDA scan) ในการวินิจฉัยแยกโรคระหว่างโรคท่อน้ำดีตีบตันและตับอักเสบในทารก ผู้ป่วยเด็กที่มีภาวะ cholestasis และได้รับการทำ ^{99m}Tc-DISIDA scan ที่โรงพยาบาลจุฬาลงกรณ์ ตั้งแต่ 1 มกราคม 2540 ถึง 31 ธันวาคม 2544 จำนวน 95 คน (เพศหญิง 38 คนและเพศชาย 57 คน) อายุระหว่าง 2 สัปดาห์ถึง 4 เดือน (อายุเฉลี่ย 2.1 เดือน) จำแนกผู้ป่วยเป็น 3 กลุ่มตามประวัติ การได้รับยาฟีโนบาร์บิทาลก่อนการตรวจ ^{99m}Tc-DISIDA scan กลุ่มที่ 1 (48 คน), กลุ่มที่ 2 (29 คน), และกลุ่มที่ 3 (18 คน) ได้รับยาฟีโนบาร์บิทาลขนาดมากกว่า 5 มก/กก/วัน อย่างน้อย 5 วัน, ได้รับยาน้อยกว่า 5 มก/กก/วัน หรือน้อยกว่า 5 วัน, และไม่ได้รับยา ตามลำดับ

ผลการศึกษาพบว่าความแม่นยำของการตรวจ ^{99m}Tc-DISIDA scan ในการวินิจฉัยแยกโรคระหว่างโรคท่อน้ำดีตีบตันและตับอักเสบในทารกของกลุ่มที่ 1, 2, และ 3 เป็นร้อยละ 72.92, 89.66, และ 100 ตามลำดับ เมื่อพิจารณาอายุที่ได้รับการตรวจ อายุที่เริ่มเหลืองและผลการทำงานของตับระหว่างผู้ป่วยทั้งสามกลุ่ม พบความแตกต่างอย่างไม่มีนัยสำคัญทางสถิติ โดยสรุปจากผลการศึกษาพบว่าผู้ป่วยทารกที่มีภาวะ cholestasis อาจไม่จำเป็นต้องได้รับฟีโนบาร์บิทาลก่อนการตรวจ ^{99m}Tc-DISIDA scan และสามารถทำการวินิจฉัยโรคท่อน้ำดีตีบตันรวมทั้งทำการผ่าตัดรักษาได้รวดเร็วขึ้นเนื่องจากไม่ต้องรอให้ผู้ป่วยได้รับยาก่อน

คำสำคัญ : เวชศาสตร์นิวเคลียร์, ฟีโนบาร์บิทาล, ท่อน้ำดีตีบตัน, ตับอักเสบ

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