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Fractionated Dose Cholecystography: A Comparison Between Iopanoic Acid and Sodium Ipodate

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Two randomised groups of 100 subjects each, undergoing oral cholecystography, were given either a 6 g fractionated dose of iopanoic acid (Telepaque) or sodium ipodate (Biloptin) to determine the relative merits of this dose schedule. Exclusions to the study were pregnancy and iodine sensitivity. Calculi or abnormal gallbladder opacification were present in 45% of subjects. Both agents were equally effective in demonstrating abnormalities, although bile duct visualisation was better using iopanoic acid ($P < 0.05$). Of 46 subjects with abnormal cholecystograms subsequently undergoing surgery, all had the diagnosis confirmed. Side effects occurred in 63% of all subjects, being twice as common in those taking iopanoic acid ($P < 0.01$). Sodium ipodate in a large fractionated dose is favoured because of the lower occurrence of side effects without loss of diagnostic accuracy.

The stimulus for this study arose from a report by Burhenne and Obata (1975) who showed optimal gallbladder opacification at a single visit using a 6 g fractionated dose of iopanoic acid (Telepaque). Similar studies have not been performed with sodium ipodate (Biloptin), a contrast claimed to have fewer side effects (White and Fischer, 1962).

To our knowledge there is no study of the relative merits of fractionated doses of sodium ipodate compared with iopanoic acid and this we have undertaken.

METHODS

Two hundred symptomatic patients referred for oral cholecystography were studied. The indications for oral cholecystography were abdominal pain (179), pancreatitis (12), jaundice or abnormal liver function tests (6) and as part of the work-up of patients requiring a jejuno-ileal bypass for obesity (3). Liver function tests were normal in all except one patient.

Patients were randomised into two groups of 100 each, one group receiving iopanoic acid and the other sodium ipodate. A plain X-ray of the gallbladder area was performed prior to the ingestion of contrast material. Patients were instructed to take all 12 tablets on the day before the examination in four equal divided doses. They were encouraged to adhere to a low-fat diet and drink at least 2 litres of milk-free fluid. Side effects were documented and these included nausea, vomiting, diarrhoea, pruritus, skin rash or dysuria. Radiographs were taken before and after fat (10 ml of corn oil) was ingested. Tomography was performed if no opacity of the gallbladder was seen on the initial film, or if otherwise indicated.

Two radiologists, unaware of the clinical history or of the contrast agent given, reported each cholecystogram independently. Their assessment of the efficacy of each contrast agent included: (1) radio-opacification graded 0–4 (0 – none, 1 – poor, 2 – moderate, 3 – normal, 4 – dense); (2) the presence, type and number of calculi and any other significant abnormality; (3) the ability to identify bile ducts for at least 4 cm in length and at least 4 mm in width. Radiographic features indicative of gallbladder disease were the presence of stones, grade 0 or 1 opacification, and the visualisation of bile ducts in the absence of gallbladder filling.

Statistical analysis was performed using the χ^2 test for independence in contingency tables. Follow-up surgical data was obtained in 48 patients.

RESULTS

The occurrence of abnormalities with the two contrast agents is shown in Table 1. Forty-three patients taking iopanoic acid demonstrated an abnormality. There was a similar incidence of abnormality in the sodium ipodate group, 48 patients having an abnormal cholecystogram.

The bile ducts were well visualised in 114 patients, of whom 65 had taken iopanoic acid and 49 had

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Table 1 – Cholecystographic findings in 100 patients given iopanoic acid and 100 patients given sodium ipodate

Radio-density	*Iopanoic acid*		*Sodium ipodate*	
	Number of patients	*Number with calculi*	*Number of patients*	*Number with calculi*
0	12	4	18	2
1	12	8	13	6
2	18	10	28	12
3	44	9	38	5
4	14	0	3	0
Total	100	31	100	25

Table 2 – Occurrence of side effects

	Iopanoic acid	*Sodium ipodate*
Diarrhoea	70	9
Nausea	30	32
Dysuria	11	9
Vomiting	9	7
Pruritis	2	3
Rash	1	2
Total	123	62

received sodium ipodate. This difference was significant ($P < 0.05$).

The occurrence of side effects, according to the contrast given is shown in Table 2. The occurrence of the different side effects was similar in both groups with one exception, namely diarrhoea, which was eight times more common in patients taking iopanoic acid. Of 48 patients undergoing subsequent surgery, 46 had been shown to have an abnormal cholecystogram (Table 3). The two patients with normal cholecystograms were found to have no calculi at surgery and histology revealed only mild chronic cholecystitis. One patient was reported as having grade 1 opacity and at operation no calculi were found. Histopathology showed only mild cholecystitis. At the time of cholecystography this patient had abnormal liver function tests.

DISCUSSION

A major disadvantage of a single 3 g dose of contrast medium is its failure to produce gallbladder opacification sufficient for diagnosis at the first examination in 25% of patients (Mujahed *et al.*, 1974). This has led to the use of larger, single doses and fractionated doses of cholecystographic agents. Burhenne and Obata (1975) demonstrated that when 6 g of iopanoic acid was given in a fractionated dose over a two-day interval no repeat studies were required. The advantage of this dose schedule can be

Table 3 – Correlation of cholecystogram result with operative findings and histopathology

Cholecystogram result	*Number of patients*	*Calculi found at operation*	*Histopathology*	
Grade 0	11	9	Empyema (2)	
Grade 0 and calcified stones	6	6	Chronic cholecystitis (8)	
			Acute on chronic cholecystitis (7)	17
Grade 1	1*	0	Mild chronic cholecystitis (1)	
Grade 1 and stones	7	7	Chronic cholecystitis (7)	8
Grade 2 and stones	14	14	Chronic cholecystitis (13)	14
			Lymphoid hyperplasia (1)	
Grade 3 and stones	7	7	Chronic cholecystitis (5)	
			Acute on chronic cholecystitis (1)	
			Cholesterolosis (1)	7
Grade 4 and no stones	2	0	Mild chronic cholecystitis (2)	2
Totals	48	43		48

* Cholecystogram performed when liver function tests were abnormal.

attributed to a greater entero-hepatic circulation, more complete absorption and subsequently better concentration of contrast within the gallbladder. Similar advantages of reinforced cholecystography were noted by Mandelstam and Rosenbaum (1975) and Koehler and Kyaw (1973), but in these studies evaluation of contrast toxicity was not undertaken.

In the present study, sodium ipodate and iopanoic acid were of equal diagnostic value and there was a high proportion of abnormal cholecystograms. This may be related partly to the selection procedure, but the efficacy of the dose of contrast given may also be a factor. Bile ducts were visualised more often with iopanoic acid whereas previous studies using a single 3 g dose had not shown any significant difference between the two contrast media (Juhl *et al.*, 1963; White and Fischer, 1962).

The high incidence of side effects suggests that the more common toxic effects are dose-related. Juhl *et al.* (1963) and White and Fischer (1962) in their similar studies with 3 g doses of sodium ipodate and iopanoic acid, showed a much lower overall incidence of side effects, but confirmed the greater frequency of bowel disturbance associated with iopanoic acid. In our study, side effects were never of major significance. It is unlikely that the degree of diarrhoea or vomiting in any patient contributed to poor gallbladder opacification. Iopanoic acid produced twice as many side effects but this was solely accounted for by an eight-fold increase in the incidence of diarrhoea. No patient developed renal failure.

A rationale to the correct performance of cholecystography is evolving. On the basis of this study, we favour sodium ipodate in a large fractionated dose since it has fewer side effects without loss of diagnostic accuracy. Administration of the contrast medium over 12 h with a further interval of 14 h prior to X-ray, allows adequate absorption, bile salt mobilisation and an active entero-hepatic circulation to ensure gallbladder concentration (Berk and Loeb, 1976).

Further studies are needed to clarify the optimal dose of contrast medium which would give maximum diagnostic information with minimum patient discomfort. We also recommend that fluid intake be high during the time of taking the contrast agent in an attempt to prevent renal complications.

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