Clinical Comparison of Two Contrast Agents for Oral Cholecystography: Radiologic Efficacy and Drug Safety of Iopanoic Acid and Iopronic Acid

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Oral doses of either iopronic acid (4.5 g Oravue, Squibb) or iopanoic acid (3 g Telepaque, Winthrop) were given to 98 patients requiring cholecystography. Radiographs were taken 13 to 16 hours after treatment showed good to excellent gallbladder opacification in 44 percent of patients after the first dose of iopronic acid and in an additional 29 percent after a second dose. Similar opacification occurred in 42 percent of patients after the first dose of iopanoic acid and in 34 percent after a second dose. Drug-related abnormalities in blood and urine tests occurred about equally in both groups and one patient in each group exhibited a clinically adverse reaction (diarrhea). Thus, the performance (radiographic efficacy and drug safety) of the new contrast agent, iopronic acid, was similar to a widely used drug, iopanoic acid.

An important problem associated with the use of iopanoic acid for oral cholecystography is the frequent failure to produce diagnostically suitable gallbladder opacification with the initial dose [1]. This failure necessitates repeating the examination to avoid false-positive diagnoses since many of these patients subsequently are shown not to have cholecystopathology or hepatic disorders [2]. Iopanoic acid also suffers from the disadvantage of producing an appreciable incidence of side-effects such as diarrhea, nausea, and transitory impairment of hepatic and renal function [3-8]. Although manipulation of diet [4,8] and drug regimen [9,10] can increase the incidence of adequate opacification, developing a new drug that produces fewer side-effects and more consistent gallbladder opacification would be a major improvement in oral cholecystography.

In the early seventies, Bracco Chemical Industries of Milan, Italy, synthesized and tested a new compound, iopronic acid (3-acetylamino-2,4,6-triiodophenoxy-ethoxy-methyl butanoic acid), which showed promise as an agent for oral cholecystography [11]. Iopronic acid was similar to other oral cholecystographic agents in being a triiodinated derivative of benzene but was different in the composition of the alkanoic side-chain, the moiety responsible for the molecule's lipophilic and hydrophilic properties. Iopronic acid was found to be superior to iopanoic acid not only in terms of intestinal absorption and biliary excretion but also in having a higher oral and intravenous LD 50 [11,12]. These early animal studies also showed that iopronic
acid gave better gallbladder opacification than iopanoic acid [11]. Furthermore, toxicity to kidneys, liver, and cardiovascular system was found to be lower for iopronic acid than for iopanoic acid in studies on rats, dogs, and rabbits [13,14].

Although not yet approved for clinical use in the United States, iopronic acid (Bilimiro, Bracco) was tested in Italy on over 1,100 patients with suspected liver, gallbladder, and intestinal disorders [14]. Oral doses of 3 to 9 g iopronic acid were reported to produce satisfactory gallbladder opacification in about 90 percent of these patients. Adverse side-effects to this drug occurred in less than 5 percent and these included transitory nausea, vomiting, and diarrhea.

Limited clinical trials have been conducted at several U.S. institutions but very little information has yet been published. What is available indicates that a single dose of 4.5 g iopronic acid (Oravue, Squibb) is effective in producing satisfactory opacification in normal subjects [15]. In another study, the same dosage of Oravue yielded good or excellent opacification in 88 percent of 180 patients; two patients experienced clinically adverse reactions that were limited to erythema and pruritic rash [16]. Side-effects from iopronic acid treatment were observed as abnormalities of laboratory test results, and these indicated transitory impairment of hepato-biliary or renal function in 38 of 90 patients (42 percent).

In order to examine further the usefulness of iopronic acid for oral cholecystography, we compared the efficacy and safety of iopronic acid to iopanoic acid in a double-blind study on patients requiring cholecystography.

SUBJECTS AND METHODS

Patients requiring oral cholecystography, usually because of suspected cholecystopathy, non-specific abdominal pain, or as part of a general radiological examination, were randomly assigned to receive either iopronic acid or iopanoic acid. The iopronic acid group consisted of 17 men and 31 women averaging 49 years of age (range, 17 to 84) and weighing 63.9 kg (range, 47.7 to 117). The iopanoic acid group consisted of 17 men and 33 women averaging 47.9 years of age (range, 19 to 75) and weighing 62.7 kg (range, 46.4 to 91.8 kg). None of these patients had received cholecystographic agents within one week of the start of the study, nor had any received intravenous pyelographic or angiographic contrast agents within 48 hours. Excluded from the study were pregnant women and patients with severe gastrointestinal disorders, ischemic heart disease, hyperthyroidism, homozygous sickle cell disease, phenochromocytoma, multiple myeloma, or moribund patients.

Shortly after consuming a fat-free evening meal, the patients received, by blind assignment, an oral dose of either 4.5 g iopronic acid (nine 500 mg capsules Oravue, Squibb) or 3 g iopanoic acid (six 500 mg tablets Telepaque, Winthrop). The amount of iodine in each dose was 2.55 g for iopronic acid and 2 g for iopanoic acid. After taking the drug, patients were permitted to ingest only water until the radiological examination was completed. Posterior-anterior films were made before drug administration and again 13, 14, 15, and 16 hours later. The radiographs were evaluated by a radiologist, other than the principal investigator, without knowing the patient's identity, the drug used, or the sequence of films. These films were rated on a scale of 0 to 3, based on the degree of opacification of the gallbladder and on the suitability for diagnosis: 0—no opacification; 1—fair opacification but not adequate for diagnosis; 2—good opacification and adequate for diagnosis; 3—excellent opacification and optimal for diagnosis. Patients whose films were scored 0 or 1 were given a second dose of the same drug 24 hours after the first dose and another series of radiographs
was made 13, 14, 15, and 16 hours after the second dose. These patients followed the same regimen used with the first dose.

Samples of blood and urine were collected from each patient before drug treatment and again 16 to 64 hours later, and in some cases, seven days later. Urine samples were examined for protein and glucose, red and white blood cells, microscopic casts and crystals; and the pH and specific gravity were measured. Blood samples were used for standard hemograms and for determining serum uric acid, BUN, serum transferases (SGOT and SGPT), alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, hepatitis B antigen, cholesterol, calcium, phosphorus, serum protein, albumin, glucose, creatinine, and creatinine clearance. Additionally, each patient was given a physical examination before drug administration and 16 hours afterwards; vital signs were monitored before and 0.5, 1, and 16 hours after the initial dose of contrast agent. On 48 patients, a physical examination was also performed at 64 hours. Thirteen patients received electrocardiographic examinations before and at least one time after drug treatment; all these studies were found to be normal before and after drug treatment.

Analysis of pretreatment tests indicated that renal function was normal in 93 percent of patients in the iopronic acid group and in 88 percent of the iopanoic acid group. On the basis of abnormally high BUN (24 mg/100 ml or more) and serum creatinine levels (1.6 mg/100 ml or more) renal function was moderately to severely impaired in 6 percent of patients in the iopanoic acid group and in 8 percent of the iopronic acid group. Pretreatment concentrations of serum bilirubin (normal range .1–1.3 mg/100 ml) were less than 1 mg/100 ml in 85 percent of the iopronic acid group and 88 percent of the iopanoic acid group. In 13 percent of both groups, bilirubin levels were 1 to 2 mg/100 ml. Of the remaining two patients, both in the iopronic acid group, one had a bilirubin level of 2.1 to 3.0 mg/100 ml, and the other was not determined.

RESULTS

Maximum gallbladder opacification yielding good or excellent visualization of the gallbladder was achieved in 21 patients (44 percent) after the first dose of iopronic acid and in 14 patients (29 percent) after a second dose. In 32 of these 35 patients, maximum opacification was first observed 13 hours after either the first or second dose. Of the 35 patients whose gallbladders were sufficiently opacified for diagnostic purposes, 26 were diagnosed as being normal, 8 had cholelithiasis, and 1 had adenomyomatosis. The radiographs of the remaining 13 patients were scored 0 or 1; and of these, four showed maximum opacity (rated 1) after the first dose while seven failed to show any opacification (rated 0 after both doses). These 13 patients with inadequate opacification did not seem to have any symptoms in common that could account for the failure of the drug to opacify the gallbladder, although before drug treatment, two of these patients had slightly elevated serum bilirubin levels (1–2 mg/100 ml) and one had levels between 2.1 and 3 mg/100 ml.

With iopanoic acid, maximum opacification producing good or excellent visualization of the gallbladder was achieved in 21 patients (42 percent) with the first dose and in 17 (34 percent) after a second dose. In a manner similar to iopronic acid, maximum opacification was first seen with iopanoic acid 13 hours after either the first or second dose in 35 of these 38 patients. Of the 38 patients who achieved diagnostically suitable opacification, 28 had normal cholecystograms, and nine had cholelithiasis. The remaining 12 patients (24 percent) had films rated 0 or 1; of these, only two showed
maximum gallbladder opacification with the first dose, and six failed to show any detectable opacification. As with the iopronic acid group, these patients did not appear to have any clinical symptoms or characteristics in common that could account for the failure of iopanoic acid to opacify the gallbladder, although two patients had slightly elevated bilirubin levels (1-2 mg/100 ml) prior to drug administration. Although good to excellent opacification was achieved in a slightly higher percentage of patients given iopanoic acid (76 percent) than was observed with iopronic acid (73 percent) (refer to Table 1), this difference was not statistically significant by chi-square test ($p > .05$).

Clinically adverse reactions occurred in one patient in each drug group. In one case, a moderately severe diarrhea occurred three hours after the first dose of iopanoic acid and lasted for 48 hours; and in the second case, mild diarrhea lasted for about seven hours after taking iopronic acid.

In each group there were a number of drug-related changes in blood and urine chemistry that suggested transitory impairment of hepato-biliary or renal function or both. Of the 22 patients in the iopronic acid group that showed abnormalities of test results, 11 exhibited changes of hepato-biliary function parameters. In these patients at least one of the following parameters was elevated beyond the normal laboratory range 16 hours after drug treatment: LDH, SGOT, or serum bilirubin. As indicated by elevated serum urinary nitrogen, urinary protein, serum creatinine, or creatinine clearance, five patients given iopronic acid had impaired renal function. Also, two patients given iopronic acid had changes in function parameters that indicated impairment of both hepato-biliary and renal function.

Of the 50 patients given iopanoic acid, 21 had abnormal laboratory test results. In six patients, the changes suggested impairment of hepato-biliary function; and in seven others renal function parameters were abnormal. Two of these 20 patients appeared to have impairment of both renal and hepato-biliary function.

Abnormalities of blood cell counts occurred in six patients given iopronic acid and in five patients given iopanoic acid. The most frequent changes were increases in neutrophils and decreases in lymphocytes after iopronic acid, and an increase in eosinophils with iopanoic acid.

**DISCUSSION**

Our study of 98 patients, who were representative of patients usually requiring oral cholecystography, indicated that there was little difference between iopronic acid and iopanoic acid in terms of both radiographic efficacy and drug safety. In fact, these two drugs appeared to be essentially equal in terms of degree and rapidity of

| TABLE 1 | The Degree of Gallbladder Opacification Achieved in Patients Receiving Either Iopronic Acid or Iopanoic Acid |
|---------|----------------------------------------------------------------------------------------------------------------|
| Degree of Gallbladder Opacification | Iopronic Acid | No. of patients | Iopanoic Acid | No. of patients |
| Good to Excellent (rated 2 or 3) | 35 (72.9%) | 38 (76.0%) |
| Fair (rated 1) | 7 (14.6%) | 6 (12.0%) |
| None (rated 0) | 6 (12.5%) | 6 (12.0%) |
| TOTAL | 48 | 50 |
gallbladder opacification, quality of radiographic image for visualizing cholelithiasis, and in the incidence of drug-associated laboratory test abnormalities and adverse reactions. Our clinical results are similar to those reported by Pizzolato and colleagues [16]. They found that iopronic and iopanoic acids given to patients requiring oral cholecystography resulted in diagnostically suitable gallbladder opacification in about 88 percent of the patients, and associated with both drugs was a similar frequency of adverse reactions and abnormalities in laboratory test results.

The conclusions regarding the similarities in diagnostic efficacy of the two drugs must be tempered with the realization that pathological correlation data are not available for non-opacification findings with iopronic acid. Data for iopanoic acid, on the other hand, suggest that examinations with this drug are highly accurate in predicting the presence of gallbladder pathology. Mujahed and colleagues retrospectively studied 5,000 cases involving oral cholecystography with iopanoic acid [17]. All 152 patients having surgery after exhibiting two non-opacification studies and not showing any evidence of extrinsic causes for non-opacification were found to have cholecystopathy. Similar types of data are needed for iopronic acid before a comprehensive judgment can be made about its diagnostic efficacy.

The finding that iopronic acid is neither better nor worse than iopanoic acid for opacifying the gallbladder is somewhat surprising since early laboratory tests suggested iopronic acid was a superior drug in terms of intestinal absorption, biliary excretion, and gallbladder opacification [11]. Iopronic acid is highly soluble in water, 2.1 g/100 ml at 37°C, pH 6.5 [18], and this property should enhance its absorption. On the other hand, the low water solubility of iopanoic acid is an important deterrent to intestinal absorption and contributes to the frequent failure of first dose opacification [19,20]. Estimates suggest that from 20 to 53 percent of patients with apparently normal liver, biliary, and gallbladder function do not develop diagnostically adequate gallbladder opacification with the initial dose of iopanoic acid [8,10]. However, our observations suggest that the higher water solubility of iopronic acid was not sufficient to alter the final outcome of the test as the degree of gallbladder opacification was about the same for the two drugs. This suggests that the failure of the two drugs to produce opacification in patients with normal hepatobiliary function is either not significantly limited by the water solubility of the drug or that the potential increase in efficacy of iopronic acid from its higher water solubility is counter-balanced by other factors different from those influencing the efficacy of iopanoic acid. Although our data are not sufficient to provide additional insight into why these two different drugs seem to behave similarly under clinical conditions, it is possible that the higher aqueous solubility of iopronic acid merely favors a more rapid uptake of the drug from the small bowel. This could then result in an earlier opacification. Such a difference, however, would only be apparent on radiographs taken at times earlier than those used in the present study. Furthermore, administering iopanoic acid with a fat-free meal may have reduced its radiographic efficacy. Stanley and coworkers [4] found that a higher percentage of patients achieved satisfactory gallbladder opacification when iopanoic acid was given with a fatty meal than when given with a fat-free meal (70 percent vs. 47 percent).

Finally, it is possible that significant improvements in oral cholecystography may not be forthcoming from new molecular designs; what is now available may be nearly chemically and pharmacologically optimal. Rather, additional improvement in radiographic efficacy may have to depend upon better methods for administration. Different regimens of drug administration have been tested, and some have been found to enhance the effectiveness of the contrast agent to yield diagnostically
suitable gallbladder opacification. Divided drug doses [9,10] and timing of administration with respect to fatty and non-fatty meals [4,8] have led to some improvements in the past. Of the many factors influencing drug efficacy, bile salts and alkalinity in the intestinal tract significantly enhance uptake of iopanoic acid [17,18]. It is possible that additional studies on the factors influencing intestinal uptake, blood transport, and metabolism of contrast agents may further illuminate these processes and provide the basis for additional improvements in drug efficacy.

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