A Clinical and Radiological Trial of Meglumine Ioglycamate, a New Intravenous Cholangiographic Contrast Medium

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SUMMARY

The efficacy of meglumine ioglycamate was assessed in 100 unselected patients who underwent cholangiography for various reasons. Good to excellent opacification was achieved in 69% of all patients. A total of 17% of all patients showed side-effects, the majority of which were transient and of a minor nature. Blood pressure and liver function were apparently not affected, but SGOT levels increased transiently within 24 hours in 21% of patients. Renal excretion of the contrast medium occurred in 48% of patients, but in only 2 did it interfere with visualisation of the duct.


In this article we describe a clinical trial of meglumine ioglycamate (Biligram; Schering AG, Berlin), a new intravenous cholangiographic contrast medium which is to be introduced in South Africa in 1976. Meglumine ioglycamate has a molecular weight of 1518 with a molecular iodine content of 50%. Like Biligrafin (iodipamide) it is an acetrizoate dimer. Both substances contain 6 atoms of iodine in their molecules. Structurally they differ in the link between the two monomers. In meglumine ioglycamate the monomers are linked by oxygen and in meglumine iodipamide the monomers are linked by an ethyl group.

Meglumine ioglycamate is rapidly eliminated from human blood where approximately 95% of the administered dose is bound to the plasma proteins. The mean plasma half-life is 30 minutes. Hardly any Biligram is absorbed from the digestive tract and thus, once it has been excreted, very little enters the enterohepatic circulation. The compound is not metabolised to any great extent but most is eliminated as unchanged molecules with the faeces. A small quantity, 10 - 25%, is excreted with the urine.

The Biligram curve for biliary excretion after the injection is in the form of a plateau, while the curve for Biligrafin is peaked. The same applies to the concentration in the bile (Fig. 1).

Experimental studies in the rat have also indicated a significant difference in the hypotensive effect of these two media. The hypotensive threshold dose of Biligram was significantly higher than that of Biligrafin.

The LD50 of Biligram in rats is 9.4 g/kg, whereas the corresponding figure for Biligrafin is 5 g/kg body weight.

PATIENTS AND METHODS

Patients

There were 100 consecutive unselected patients on whom cholangiography was requested at Addington and King Edward VIII Hospitals, Durban. There were 62 Whites, 21 Blacks, 10 Coloureds and 7 Indians. Sixty-six were females and 34 were males. The age range was 21 - 91 years with a mean age of 47 year. Four children were under 10 years old. The mean weight for the entire group was 63 kg. Mean age and weight for the different racial groups are summarised in Table I.

TABLE I. MEAN AGE AND WEIGHT FOR DIFFERENT RACIAL GROUPS

<table>
<thead>
<tr>
<th>Race</th>
<th>Mean age (yrs)</th>
<th>Mean weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>68</td>
<td>77</td>
</tr>
<tr>
<td>Blacks</td>
<td>49</td>
<td>63</td>
</tr>
<tr>
<td>Indians</td>
<td>37</td>
<td>53</td>
</tr>
<tr>
<td>Coloureds</td>
<td>34</td>
<td>59</td>
</tr>
</tbody>
</table>

The clinical diagnoses of the patients were as follows: common bile duct calculus (59); gall-bladder disease (22); pancreatitis (9); roundworm obstruction (4); carcinoma of the pancreas (3); congenital spherocytosis (1); biliary bowel fistula (1); duodenal stricture (1). Twenty patients were cholecystectomised.

Administration, Dosage and Patient Monitoring

Fifty patients received a standard drip infusion of ioglycamate 17 g/100 ml infused at a constant rate over 30 minutes (iodine content 8.5 g). The remaining 50 patients, treated alternately, received a direct intravenous injection of ioglycamate 10.5 g/30 ml (5.3 g of iodine) slowly over an average period of 8 minutes.

Children received 0.6 ml/kg (injection), and 1.2 ml/kg (infusion), as recommended by the manufacturers.

A blood sample was taken from each patient before
Cholangiography. Serum bilirubin, alkaline phosphatase, serum albumin and serum lactate dehydrogenase (LDH) and SGOT were determined.

Blood investigations were repeated on the day after the cholangiogram and, when possible, on the third day after the cholangiogram.

Fig. 2. A — normal bile ducts with normal gall-bladder; B — dilated common bile duct containing calculi; C — dilated common bile duct in a cholecystectomy patient; D — normal common bile duct in a cholecystectomy patient.
Blood pressure readings were taken before and at the termination of the infusion. Side-effects were recorded according to the nature of the reaction, the duration, the time of onset from the start of the infusion and the severity. All examinations were supervised by a radiologist.

**Radiographic Technique**

Radiography was conducted in the 70-80 kV range with careful positioning and coning. Tomography was performed on all patients, at the stage of maximum opacification of the common bile duct.

Films were taken at the end of each direct injection and halfway through the drip infusions. Thereafter films were taken at 20-minute intervals up to 60 minutes, then again at 90 minutes and 120 minutes.

**Criteria for Radiodiagnostic Quality Assessment**

The X-ray films were assessed for diagnostic quality and were categorised as: (i) excellent visualisation of the common bile duct (Fig. 2A, B, C, D); (ii) good visualisation of the common bile duct; (iii) poor visualisation of the common bile duct; and (iv) non-visualisation of the common bile duct.

Gall-bladder opacification was noted. Renal excretion (pyelography) was assessed and when it interfered with duct visualisation this fact was noted.

**RADIOLOGICAL ASSESSMENT**

**Radiodiagnostic Quality**

The results of radiodiagnostic quality assessment are summarised in Tables II - IV. As would be expected, diagnostic quality diminished with abnormal liver function.

In general, the patients in whom an excellent or good result was recorded had normal or slightly depressed liver function tests, with bilirubin levels of 1,3 mg/100 ml or less.

The level of serum bilirubin is not always a reliable indicator of liver damage. One patient in whom good opacification was obtained, had a bilirubin of 2.7 mg/100 ml. The maximum bilirubin level at which cholangiography was attempted was 6.8 mg/100 ml. Cholangiography in this patient failed. There was no significant difference in diagnostic quality when either the 30-ml direct injection or the 100-ml drip infusion was used.

**TABLE IV. DEGREE OF OPAICATION WITH ABNORMAL LIVER FUNCTION TESTS**

<table>
<thead>
<tr>
<th></th>
<th>30-ml injection</th>
<th>100-ml infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Good</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Poor</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Failed</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

**Time of Maximum Opacification of Common Bile Duct**

The time of maximum opacification is summarised in Table V. Visualisation of the common bile duct is influenced by many factors. The most noteworthy are: (a) the rate and concentration at which the liver excretes the contrast medium; (b) rate of emptying of the duct; (c) diameter of the duct; (d) duct patency; (e) the standard of radiographic technique.

**TABLE V. TIME OF MAXIMUM OPAICATION**

<table>
<thead>
<tr>
<th>Minutes after beginning of procedure</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-ml injection</td>
<td>100-ml infusion</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>8</td>
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<td>50</td>
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<tr>
<td>60</td>
<td>11</td>
</tr>
<tr>
<td>60-90</td>
<td>8</td>
</tr>
<tr>
<td>90</td>
<td>0</td>
</tr>
</tbody>
</table>

The times of maximum opacification after direct injection of 30 ml of Biligram and after 100 ml drip infusion of Biligram are represented in Figs 3 - 4.

Peak incidence of maximum opacification occurred at 40 minutes after the start of the injection and at 60 minutes after the start of the infusion. Similar findings were recorded by Scholz et al. and by Nolan and Gibson.

The distribution of time of opacification for the post-cholecystectomy patients was similar to that of the whole series.

**Renal Excretion**

There was no evidence of renal excretion in 54 of the patients. Twenty-eight had direct injections and 26 had drip infusions.

Two patients had a pyelographic effect which interfered with duct visualisation. The remaining patients showed...
Observations in Children

One child was 2½ years old, one was 6 years old and two were 8-year-olds. The pre-examination clinical diagnosis in all patients was ascariasis with possible duct obstruction and 3 of the patients had markedly deranged liver function tests. In 2 of these patients opacification was not achieved while the 3rd showed poor duct visualisation. The 4th child showed excellent duct and gall-bladder opacification. No side-effects were recorded in any of the children.

Gall-bladder Opacification

Of the 80 patients who were not cholecystectomised gall-bladder opacification was achieved in 43. In all patients in whom opacification occurred there was some contrast medium detectable in the gall-bladder on the 60-minute film. In 37 patients the gall-bladder was not opacified. These included 14 patients in whom cholangiography failed totally. In 23 patients the ducts opacified but not the gall-bladder. These were assumed to have cystic duct obstruction or gall-bladder disease.

CLINICAL ASSESSMENT

Side-Effects

A total of 17 patients, of whom 12 had received a direct injection and 5 a drip infusion, showed reactions to the contrast medium. The majority of reactions were transient and of a minor nature. There were 6 patients with nausea, 2 with vomiting, 1 with flushing, 1 with arm pain, 1 with nasal stuffiness, 1 with salivation, 1 with bitter taste, 1 with urticarial rash and 2 with pruritus. None of these 16 patients required any treatment.

One patient experienced flushing, vomiting, urticaria and angioneurotic oedema of the face, which responded rapidly to 10 mg intravenous chlorpromazine. This patient had no history of allergy.

Included in the series were 2 asthmatics, 7 patients with a history of penicillin sensitivity and 1 patient who reacted to a previous urographic examination. None of these patients exhibited any reactions to Biligram. One patient with a history of hayfever developed nasal stuffiness during the procedure.

Such a low incidence of mild side-effects is worthy of note. The higher incidence of side-effects with the direct injection compared to the drip infusion corresponds with the findings of other workers.

Blood Pressure

There were no significant blood pressure fluctuations and no cases of hypotension. In 5 patients a fall in diastolic blood pressure of less than 10 mmHg was recorded. Immediately after the injection 1 patient exhibited a transient rise in diastolic blood pressure of 10 mmHg which returned to the pre-injection level within 15 minutes.

Liver Function

Serum albumin, bilirubin, alkaline phosphatase and LDH were not significantly affected by the procedure.
In 1 patient the SGOT levels showed a rise from a normal level of 10 units to 360 units in 24 hours (normal range 0 - 12 units).

A further 8 patients showed significant elevations within 24 hours from initial abnormal levels of between 15 and 20 units to levels of between 60 and 546 units.

Minor, transient fluctuations of less than 20 units were noted in 12 patients. Elevation of the SGOT level after cholangiography has been noted by various authors. SGOT is bound to mitochondria and also occurs free in the cytoplasm. An increase in serum levels of this enzyme might indicate minor cell damage.

**CONCLUSIONS**

The authors consider meglumine ioglycamate to be an important advance in the radiological investigation of the biliary tree. Excellent or good visualisation was achieved in 69% of the patients. A low incidence (17%) of minor side-effects was encountered. A slightly higher incidence of side-effects occurred with the direct injection. Renal excretion was noted in 48% of the patients but in only 2 patients did the pyelogram interfere with duct visualisation. Impairment of liver function resulted in a decrease in diagnostic quality of duct visualisation. There were no significant alterations in blood pressure in the series. Twenty-one per cent of the patients showed transient elevations of SGOT levels. In 4 children no adverse reactions were encountered. The injection technique employed was more time-consuming for the radiologist than the infusion. When taken in conjunction with the decrease in side-effects we feel that the drip infusion may have a significant advantage over the direct injection.

From the point of view of contrast quality, Biligram and Biligrafin are roughly equivalent. However, Biligram is better tolerated and has less effect on blood pressure. An important advantage of Biligram for injection is its favourable characteristic excretion curve which provides for protracted visualisation of the bile ducts. Also, Biligram is easier to inject than Biligrafin because of its lower viscosity.

We wish to thank Schering AG, Berlin, who supplied the Biligram used in this trial. We are also grateful to Dr Stanley Miller who controlled the examinations performed on the patients at King Edward VIII Hospital.

**REFERENCES**


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**MORTALITY AND MORBIDITY PATTERN IN MEASLES IN TANGA DISTRICT, TANZANIA**

The authors report a series of 250 children aged under 5 years who were admitted with measles to Bombo Hospital, Tanzania. The results confirmed, features of measles in tropical countries described elsewhere: the relatively young age group affected (40% aged under 1 year), and the association of measles with protein energy malnutrition. Pneumonia and laryngotracheobronchitis were the commonest complications, but gastro-enteritis was also important and carried the highest mortality rate (27%, with diarrhoea died).

A simple standard treatment regimen is proposed for use at health centres. It is suggested that measles immunisation should be given at 6 months and repeated at 9 months of age (a proposal that would be very expensive, logistically difficult and immunologically open to dispute).


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**THE POISONS INFORMATION CENTRE — ITS ROLE AND SCOPE**

Poisoning still remains one of the common paediatric emergencies of our times. Owing to the current manner of reporting, accurate statistics of deaths due to poisoning accidents are difficult to obtain. A survey of NSW hospitals, conducted by the Sydney Poisons Information Centre in 1973, showed that 9 children under the age of 5 years had died from accidental poisoning in the year 1972. Although serious morbidity and mortality are low, many thousands of children are seen in casualty departments and doctors' surgeries each year for a wide variety of accidental ingestions. Some have serious consequences; however, a large percentage of the substances accidentally ingested are non-toxic, yet children frequently suffer physical and psychological trauma from errors in overtreatment, and parents must endure financial loss and great anxiety.

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