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# Prospective study of post-transfusion hepatitis after cardiac surgery in a British centre

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## Abstract

A series of 248 consecutive patients undergoing cardiac surgery were examined in a prospective study of post-transfusion hepatitis in a single British centre. Patients received a total of 1796 units of blood or blood products (mean blood transfusion 6.28 units per patient). During five to 30 days after operation 38 of the patients showed an increase in serum transaminase activities. There was no serological evidence for fresh infection by hepatitis A or B virus, cytomegalovirus, Epstein-Barr virus, or herpes virus in any of these patients. The increase in transaminase activities was unexplained and reached over 100 IU/l (normal < 40 IU/l) in six patients. The incidence of acute short incubation post-transfusion non-A, non-B hepatitis was therefore thought to be 2.4%.

These six patients had normal liver function six months after transfusion but a further two of the surviving 228 patients had raised serum transaminase activities at six months. In one of these, liver biopsy disclosed chronic persistent hepatitis; in the other, alcoholic liver disease was suspected. The incidence of significant chronic liver disease after blood transfusion possibly attributable to a non-A, non-B hepatitis agent was therefore only 0.4%.

## Introduction

No major British prospective study of post-transfusion hepatitis has been carried out in the era of sensitive serological tests to exclude infection with hepatitis A virus or hepatitis B virus; thus no clear indication of the recent incidence of post-transfusion non-A, non-B hepatitis in Britain is available. In the most recent major British study conducted between 1969 and 1971,<sup>1</sup> in which tests for hepatitis B surface antigen (HBsAg) and anti-HBs were carried out by immunodiffusion, the probable incidence of non-A, non-B post-transfusion hepatitis was 30 out of 768 patients (3.9%).

We decided to study non-A, non-B post-transfusion hepatitis in a single centre in Britain; in particular we wished to examine the frequency with which clinically significant chronic liver disease might arise.

## Patients and methods

We studied prospectively 248 consecutive patients over the age of 16 who were undergoing both routine and emergency cardiac surgery. A clinical history and results of examination were recorded for each patient, taking particular note of previous jaundice, hepatitis, blood transfusion, drug treatment, and the presence of liver disease.

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**Preoperative laboratory records**—Preoperative screen of full blood count, liver function values (bilirubin concentration and serum alkaline phosphatase, aspartate transaminase, and  $\gamma$ -glutamyltranspeptidase), and serum protein urea, creatinine, and electrolyte concentrations was made. HBsAg (enzyme linked immunosorbent assay (ELISA), Abbott Ltd) was measured and serum stored at  $-80^{\circ}\text{C}$  for virological examination.

**Postoperative laboratory records**—The number of units of blood, fresh frozen plasma, and platelets given to each patient during and after surgery was recorded. Measurement of liver function values was carried out on alternate postoperative days until death or discharge; serum was saved and stored at  $-80^{\circ}\text{C}$  at each sampling. In addition, serum alanine aminotransferase activity was measured on postoperative days 2, 4, and 6.

**Follow up after discharge**—All surviving patients were seen six months after operation. Liver function values (including alanine aminotransferase activity) were measured and serum stored for virological examination. In addition, 44 patients (selected only because they lived within 10 miles (16 km) of the hospital) were seen every two weeks for two months and at monthly intervals thereafter to six months; blood was drawn for liver function tests and serum storage on each occasion. All patients were instructed to report to their general practitioner and to contact one of us (JC) if any symptoms suggestive of hepatitis occurred (malaise, anorexia, rigors, joint pains, dark urine, jaundice).

**Virological studies**—Markers of hepatitis infection—HBsAg, anti-HBc, anti-HBs, and anti-hepatitis A virus IgM—were determined using ELISA methods. Epstein-Barr virus and cytomegalovirus were tested by fluorescent antiglobulin techniques with specific anti-IgG and anti-IgM immunoglobulins on 1/8 diluted patient sera. Testing for herpes simplex virus was by standard complement fixation test.

## Results

**Liver function tests**—All patients showed a rise in serum activities of aspartate transaminase and creatine phosphokinase with normal alanine transaminase activity within two days after operation. This reflected cardiac release of aspartate transaminase and creatine phosphokinase. Thirty eight patients had a second increase in activity of aspartate transaminase between postoperative days 5 and 30. The duration of the increase varied between two and 12 days. All had returned to normal by day 30. In six patients the activity exceeded 100 IU/l, which in one case was associated with reoperation. In none of the 38 patients was there any abnormality in liver function values when tested six months after operation. Of all 248 patients, 228 survived to six months; of these, only two had abnormal aspartate and alanine transaminase activities at that time. The first was a heavy drinker ( $>140$  g ethanol/day) with abnormal preoperative bilirubin and  $\gamma$ -glutamyltranspeptidase values who had continuing postoperative heart failure; this man declined liver biopsy. The second patient had a preoperative aspartate transaminase activity of 45 IU/l; he was discharged on postoperative day 8 with normal liver function values. He was readmitted with a sternal wound infection six days later, when the aspartate transaminase activity was 67 IU/l. Monthly checks of liver function values thereafter showed persistently raised aspartate and alanine transaminase activities to six months. Liver biopsy at six months showed mild chronic persistent hepatitis. None of the 44 "local" patients closely followed up to six months developed any abnormality of transaminase activities after discharge.

**Mortality**—There were 20 deaths; two occurred preoperatively. Of 14 patients who died postoperatively before discharge, three showed a pronounced rise of transaminase activities but liver biopsy showed no evidence of hepatitis. Four patients died after discharge of well documented cardiac dysfunction.

**Blood transfusion**—Altogether 1559 units of blood, 215 units of fresh frozen plasma, and 22 units of platelets were transfused. The mean transfusion requirement was 6.28 units. There was no relation between the volume of blood transfused and the rise of postoperative transaminase activities.

**Drugs**—No single drug or combination of drugs was found to be solely associated with the rise in transaminase activities in the 38 patients.

**Virological studies**—Acute and convalescent sera were tested from (a) the 38 patients with raised transaminase activities five to 30 days postoperatively, (b) the two patients with abnormal transaminase activities at six months, and (c) 49 patients who developed early (within two postoperative days) "postpump" jaundice not associated with raised transaminase values. The results were as follows. No

patients showed evidence of new infection with hepatitis A virus (anti-hepatitis A virus IgM), Epstein-Barr virus (anti-Epstein-Barr virus IgM), or cytomegalovirus (anti-cytomegalovirus IgM) either in the preoperative serum sample or postoperatively. No patient was positive for HBsAg preoperatively or postoperatively. Two patients were positive for anti-HBc and anti-HBs both preoperatively and postoperatively (indicating previous exposure to the hepatitis B virus). In three patients herpes simplex complement fixation test titres rose by two or more postoperatively compared with preoperative values.

## Discussion

We examined patients undergoing cardiac surgery both because of the high mean blood transfusion requirement and so that comparison could be made with other studies from the United States,<sup>1</sup> Italy,<sup>2</sup> Sweden,<sup>3</sup> and Japan.<sup>4</sup> Interpretation of raised serum transaminase activity after cardiac surgery is difficult since a minor increase may be seen in association with heart failure, cardiac muscle damage, haemolysis, and sepsis; furthermore, a reaction to a drug or anaesthetic agent cannot be excluded. The Medical Research Council study<sup>1</sup> suggested that post-transfusion hepatitis might be defined as having occurred when transaminase activity rose above 100 IU/l (normal  $<40$  IU/l) after transfusion in the absence of any other obvious cause. By this criterion we found six cases among 248 patients, an incidence of 2.4% in the period up to 30 days after transfusion. In the present instance serological testing excluded the possibility of infection or reinfection by hepatitis A or B virus, cytomegalovirus, Epstein-Barr virus, or herpes virus as the cause in these six patients. Our results may be compared with the 30 out of 768 cases (3.9%) found in the MRC study after exclusion of cases of type B hepatitis or cytomegalovirus infection, which may well have been non-A, non-B post-transfusion hepatitis, although infection with type A virus was not excluded and serological testing for type B hepatitis infection was insensitive.

The incubation period for short incubation non-A, non-B hepatitis is thought to be around two to five weeks,<sup>1</sup> but presumed non-A, non-B hepatitis occurring as early as five days after transfusion with factor VIII concentrate has been well documented.<sup>8,9</sup> By this criterion all 38 patients identified as having raised transaminase activities five to 30 days after transfusion in the present study fell within the short incubation period.

Since no regular blood samples were taken from the majority of patients between 30 days and six months after operation we cannot exclude periods of transaminitis or mild clinical hepatitis in that time possibly corresponding to a long incubation non-A, non-B virus. The following facts, however, suggest that such episodes, if they occurred, were probably rare and certainly mild: (a) none of the 44 "local" patients followed up developed transaminitis in the period; (b) no patients reported themselves, or were reported by their general practitioners, to have symptoms suggestive of clinically significant hepatitis when seen at the careful six month follow up; (c) only two out of 228 survivors had any abnormality of transaminase activity six months after operation when all were checked, in one of whom the abnormality was probably due to alcohol abuse and chronic heart failure. We suggest that the patient with chronic persistent hepatitis may represent the only case of chronic non-A, non-B liver disease after transfusion of over 1500 units of blood in this study.

The incidence of possible post-transfusion non-A, non-B hepatitis after cardiac surgery was low in our study (3.2%) as compared with other, similar studies from other countries, all of which used volunteer donor blood; the incidence was 14.6% in one study from the United States,<sup>1</sup> in Italy 17.8%<sup>2</sup> (13.8% in patients receiving blood only), in Sweden 18.9%,<sup>3</sup> and in Japan 30.4%.<sup>4</sup> Katchaki and colleagues from the Netherlands<sup>10</sup> found a low incidence of post-transfusion non-A, non-B hepatitis (3.4%) closely comparable to our results.

We conclude that non-A, non-B hepatitis after blood transfusion from a largely British blood donor group probably leads to clinically significant chronic liver disease very rarely indeed.

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## Chloramphenicol toxicity in neonates: its incidence and prevention

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#### Abstract

The incidence of dose related chloramphenicol toxicity was determined in 64 neonates from 12 hospitals. Ten of the 64 exhibited symptoms attributed clinically to chloramphenicol toxicity. Nine received the dose prescribed and one an overdose. Symptoms of the grey baby syndrome were observed in five of the 10 babies; four babies suffered reversible haematological reactions; and one baby was described as very grey. Peak serum chloramphenicol concentrations in these 10 babies ranged from 28 to 180 mg/l and trough concentrations from 19 to 47 mg/l. Serum chloramphenicol concentrations above the therapeutic range (15-25 mg/l) were observed in a further 27 neonates (two had received a 10-fold overdose), none of whom showed signs of toxicity.

Serious toxicity was associated with either prescription of dosages greater than that recommended or overdose of chloramphenicol. High concentrations in young neonates may be avoided by prescribing and giving the recommended dose and then careful monitoring; concentrations should be maintained between 15 and 25 mg/l. No babies with concentrations within this range showed clinical signs of toxicity.

#### Introduction

Despite concern about its toxicity chloramphenicol is widely used to treat neonatal meningitis.<sup>1</sup> Three types of toxicity

have been described—namely, the grey baby syndrome,<sup>2</sup> reversible dose related haemopoietic disturbances,<sup>3</sup> and idiopathic marrow aplasia unrelated to dosage.<sup>4</sup> Serum chloramphenicol concentrations between 40 and 200 mg/l have been reported in association with the grey syndrome,<sup>5</sup> and reversible bone marrow suppression related to dosage may occur when serum concentrations exceed 25 mg/l.<sup>6</sup> Irreversible marrow aplasia is a rare complication (incidence 1/20 000 to 1/80 000 patients treated) and has a high mortality. Its occurrence is unpredictable.

The incidence of dose related chloramphenicol toxicity in the newborn is unknown. There is no general agreement on the desirable therapeutic range of chloramphenicol concentrations, but serum concentrations of 10-20 mg/l<sup>7</sup> and 15-25 mg/l<sup>8</sup> are often quoted. As the minimum inhibitory concentration of chloramphenicol for some Gram negative rods may be as high as 6 mg/l and only 30-60% of the drug crosses the meninges it would seem more appropriate to maintain serum concentrations in the range 15-25 mg/l provided that such concentrations are not associated with toxic manifestations.

In this study, which was carried out between March 1978 and August 1981, we determined the incidence of dose related chloramphenicol toxicity in 64 neonates receiving chloramphenicol for life threatening infections. We assessed the value of measuring serum concentrations of the drug and the possibility of predicting toxic effects and establishing the therapeutic range of chloramphenicol concentrations.

#### Patients and methods

**Study population**—We studied 64 neonates (less than 28 days old) from 12 hospitals who formed part of a larger study on the penetration of antibiotics in neonatal meningitis.<sup>1</sup> Their gestational ages ranged from 26 to 40 weeks and their birth weights from 770 to 4420 g. All the babies were scrutinised during treatment for signs and symptoms of the grey baby syndrome—that is, vomiting, respiratory distress, abdominal distension, ashen grey cyanosis, flaccidity, and cardiovascular collapse. Adverse haematological reactions were also sought.

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