EXTRAHEPATIC MORPHINE METABOLISM IN MAN DURING THE ANHEPATIC PHASE OF ORTHOTOPIC LIVER TRANSPLANTATION

A. BODENHAM, K. QUINN AND G. R. PARK

The primary site of morphine metabolism has been the subject of speculation [1, 2]. Historically it was assumed that the liver was the predominant organ involved in the metabolism of morphine, but the apparent sensitivity to morphine of patients in renal failure [3] suggested that the kidney might be a major alternative site. This study has examined the role of the liver in the metabolism of morphine in patients during the anhepatic phase of liver transplantation.

The operation of liver transplantation has been classified into several phases including dissection, anhepatic and reperfusion phases. During the dissection phase the diseased liver is “skeletonized” onto its vascular pedicles, namely the suprahepatic vena cava, the infrahepatic vena cava, the hepatic artery and portal vein, before removal. The anhepatic phase starts after clamping these vessels, following which the diseased liver is removed entirely. During this period, vessels of the donor liver are anastomosed to those of the recipient. When the anastomoses of the portal vein and inferior and superior venae cavae are completed the clamps are removed and the liver is reperfused with portal blood. Finally, the hepatic artery and biliary anastomoses are completed [4].

The altered physiology of the anhepatic period has been described previously [5]. The venous drainage of the lower half of the body and abdominal contents relies on the presence of collateral vessels which are present in the healthy human and increase markedly in the presence of portal hypertension. These venous collaterals provide a compromised venous return when the inferior vena cava is cross clamped. Although the perfusion of the kidneys and intestines is compromised, these patients usually produce 50–100 ml of urine during the anhepatic period. On reperfusion of the donor liver there is a large increase in venous return and improved circulation to the lower half of the body.

PATIENTS AND METHODS

We studied adult patients who were likely to have an uncomplicated intraoperative course. The study was approved by the Hospital Ethics Committee and written informed consent was obtained in all patients before operation.

With the exception of patients with small
EXTRAHEPATIC MORPHINE METABOLISM

intrahepatic tumours, most patients undergoing liver transplantation have advanced liver disease with associated porto-systemic shunts and coagulation problems. Surgery may be technically difficult, with large blood loss. The patients in this series were chosen to have a low risk of this complication: those with good coagulation, lack of concurrent medical problems and no previous intra-abdominal surgery.

Anaesthesia was conducted as described previously [6]. Patients were premedicated with an oral benzodiazepine and anaesthesia was induced with thiopentone and maintained with nitrous oxide and isoflurane in oxygen. Neuromuscular block was provided with suxamethonium followed by an infusion of atracurium. Analgesia was provided by intermittent bolus injections of fentanyl. Dopamine 2 μg kg⁻¹ min⁻¹ and mannitol 10 g h⁻¹ were infused to maintain urine output. Central and peripheral venous cannulae, a radial arterial cannula and urinary catheter were inserted as routine.

Baseline blood and urine samples were taken immediately before the anhepatic phase. Three minutes after the anhepatic phase had started, morphine 10 mg diluted in saline 10 ml was administered into a central vein; the delay was to allow acute haemodynamic changes to resolve. Blood samples were taken at 2, 5, 10, 15, 20, 30 and 40 min after injection and immediately before reperfusion. Urine samples were taken at 5 and 30 min and immediately before reperfusion.

On reperfusion the sampling was repeated, with blood and urine samples taken at the same times as during the anhepatic phase. Blood loss, blood replacement, urine output and body temperature were recorded for each stage. Blood samples were placed in lithium-heparin tubes, centrifuged at 3000 g for 5 min, and then separated into plain siliconized tubes with screw caps to minimize adsorption. Urine and plasma samples were stored at −20 °C for later analysis of morphine, morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G) and normorphine, using a method described previously [7, 8].

RESULTS

The details of the seven patients studied are shown in table I. All patients had significant hepatic dysfunction with the exception of patient No. 2 who had a solitary hepatoma. Table II lists some of the operative details of these patients.

Table I. Demographic data and presenting diagnosis of the seven patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex (M/F)</th>
<th>Weight (kg)</th>
<th>Presenting diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>M</td>
<td>56</td>
<td>Primary biliary cirrhosis + hepatoma</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>M</td>
<td>70</td>
<td>Carcinoma of liver</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>M</td>
<td>77</td>
<td>Sclerosing cholangitis + cholangiocarcinoma</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>F</td>
<td>60</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>F</td>
<td>60</td>
<td>Alcoholic cirrhosis</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>F</td>
<td>54</td>
<td>Chronic active hepatitis</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>M</td>
<td>60</td>
<td>Alcoholic cirrhosis + hepatoma</td>
</tr>
</tbody>
</table>

Although large by general surgical standards, blood loss was not excessive for this operation. All patients produced urine during the anhepatic period. The mean cold ischaemic time, defined as the period of cold storage of the livers before transplantation, was 406 (SEM 138) min. Liver survival is anticipated for a cold ischaemic time of up to 12 h using modern preservation fluids (more recently this has been extended to 24 h [9]).

Results of the assays for morphine and its metabolites in plasma are shown in figure 1, and for urine in table III. Plasma concentrations of morphine during the anhepatic period decreased rapidly, consistent with the distribution phase after i.v. injection, followed thereafter by little change. During the anhepatic phase, M3G was detectable in low concentrations in plasma (less than 7 ng ml⁻¹), but urinary concentrations increased to a maximum of 137 ng ml⁻¹. M6G was detected at a maximum of 1.4 ng ml⁻¹ in plasma and 22.3 ng ml⁻¹ in urine during this phase. Normorphine was undetectable in both plasma and urine throughout both the anhepatic and
**FIG. 1.** Mean (SEM) plasma concentrations of morphine (●), M3G (□) and M6G (○) during the anhepatic and reperfusion phases of orthotopic liver transplantation.

**TABLE III.** Urinary concentrations (mean (SEM)) of morphine, morphine-3-glucuronide and morphine-6-glucuronide during the anhepatic and reperfusion phases of liver transplantation in seven patients

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Morphine (ng ml⁻¹)</th>
<th>M-3-G (ng ml⁻¹)</th>
<th>M-6-G (ng ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anhepatic phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>0</td>
<td>4.1 (2.1)</td>
<td>8.8 (4)</td>
</tr>
<tr>
<td>30 min</td>
<td>315 (105)</td>
<td>31 (15)</td>
<td>5.8 (3.2)</td>
</tr>
<tr>
<td>60 min</td>
<td>2167 (424)</td>
<td>137 (39)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Reperfusion phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>1402 (305)</td>
<td>66 (24)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>60 min</td>
<td>812 (307)</td>
<td>132 (44)</td>
<td>11 (6)</td>
</tr>
</tbody>
</table>

reperfusion phases of the study. Mean concentrations of both plasma and urinary M3G increased rapidly on reperfusion of the transplanted liver, to a maximum of 236 ng ml⁻¹ and 132 ng ml⁻¹, respectively. Mean M6G concentrations increased in plasma to a maximum of 7.1 ng ml⁻¹ and decreased slightly in urine, to 11.4 ng ml⁻¹, during this period of the study.

**DISCUSSION**

The primary site of metabolism of morphine after therapeutic doses has been debated; so also has the clinical importance of the glucuronide metabolites [10–12] which have been shown to be active in animals [13] and man [14]. Clinical and laboratory studies have suggested two significant sites for morphine metabolism: the liver and kidneys. *In vitro* studies of isolated kidney and liver have shown the presence of uridine di-phosphoglucuronyl transferase (UDP glucuronyl transferase) [15, 16], although these do not relate necessarily to function *in vivo* (unpublished observations).

The historical conception of the liver as the major organ of morphine metabolism was contested by the studies in patients with renal failure discussed above and by studies suggesting normal pharmacokinetics in patients with cirrhosis [17]. However, a more recent study in such patients has shown a decrease in the clearance of morphine [18]. The differences between these studies may be related to the severity of the liver disease in the patients studied, but comparisons between patients are difficult, as conventional tests of liver function are poor predictors of changes in pharmacokinetics of drugs [19]. The metabolism of other drugs which undergo glucuronidation suggests that glucuronidation [20] may be relatively spared compared with other metabolic functions, such as oxidation, in severe liver disease. The alternative explanation is that the enzyme system UDP glucuronyl transferase is found in other extrahepatic sites such as the gut or kidney and these may be significant sites for metabolism in man.

Hug and colleagues [21] measured morphine metabolism during the anhepatic phase of liver
transplantation in man, but could not measure the metabolites directly. They found insignificant metabolism during this period. In contrast, studies in the functionally anhepatic dog showed that morphine was glucuronidated in approximately equal degrees by hepatic and extrahepatic tissues [22].

The lack of significant metabolism of morphine in our patients during the anhepatic period of liver transplantation suggests that, in the group of patients studied, the liver is the predominant organ of morphine metabolism. It is clear also that the transplanted liver begins to metabolize morphine rapidly, shortly after reperfusion. A previous study in this centre, using an identical technique measuring the metabolism of midazolam, demonstrated the presence of both major metabolites of midazolam (alpha-hydroxy midazolam and 4-hydroxy midazolam) during the anhepatic period [23]. The difference between the metabolism of midazolam and of morphine during the anhepatic period may be explained by the different metabolic pathways: midazolam undergoes phase I metabolism to its metabolites, whilst morphine metabolism is principally phase II. It is possible, therefore, that phase II metabolism is limited primarily to the liver.

Blood loss and subsequent replacement during the study would have a small dilution effect on measured morphine and metabolite concentrations. However, the loss was continuous rather than sudden in the patients studied. Bolus i.v. administration of drugs results in a rapid increase in plasma concentration and (with morphine) rapid distribution outside the vascular compartment. During this time the amount of blood lost and transfused was small. Similarly, during the elimination period studied, the contribution of blood loss and replacement, even of this magnitude, was small. Thus small changes in plasma concentrations of morphine and its metabolites resulting from blood losses and replacement may have occurred, but significant changes in pharmacokinetic parameters are unlikely.

The lung is known to metabolize and take up selectively certain endogenous and exogenous substances [24]. Studies in anaesthetized and postoperative patients showed significant uptake, but no metabolism of morphine [25, 26]. Although not metabolically active, the lung is thought to act as a reservoir for morphine and other basic drugs.

Increased clinical effects after morphine therapy in patients with renal failure suggested that the kidney may be important in morphine metabolism [2, 3]. This appeared to be supported by pharmacokinetic studies using non-specific assays which did not differentiate between unchanged morphine and its metabolites [1]. More recent work using HPLC [27] and a specific radioimmunoassay [28] has shown increased volumes of distribution and cumulation of metabolites, but no decrease in clearance of unchanged morphine in patients with end-stage renal disease. Thus it is thought that the cumulation of these metabolites (which are pharmacologically active) is the cause for the apparent sensitivity to morphine in patients with renal failure.

The appearance of morphine metabolites in urine during the anhepatic period, despite the plasma concentrations being undetectable, may be explained in two ways. The kidney may be concentrating the small quantities of morphine metabolites in the plasma which are undetectable by HPLC. Alternatively, the kidney could be an extrahepatic site for morphine metabolism (although, if it were, significantly larger concentrations of metabolites would be expected in urine).

Within the constraints of this model, we conclude that the liver is the major site of morphine metabolism in man.

ACKNOWLEDGEMENT

Mr K. Quinn was in receipt of a grant from Addenbrookes Hospital Trust Funds.

REFERENCES