Morphine is metabolized by the liver (Stanski, Greenblatt and Lowenstein, 1978) and the metabolites excreted by the kidney. Recent advances in the estimation of morphine have, however, led to the emphasis being placed on the importance of its elimination by the kidney (McQuay and Moore, 1984a; Moore, Sear and Baldwin, 1984). Renal failure has long been known to prolong the action of morphine, and although this aspect has now been investigated further (Aitkenhead et al., 1984; Ball et al., 1985; Shelly and Park, 1985), the cause of the prolonged action remains obscure. In particular, the role of morphine metabolites has yet to be clarified. Morphine has a number of active metabolites, including morphine-6-glucuronide (Shimomura et al., 1971) and normorphine (Lasagna and De Kornfield, 1958; Johannesson and Milthers, 1962); the 3-glucuronide is thought to be inactive when administered parenterally (Sasajima, 1970; Shimomura et al., 1971). Initially, this was a pilot study to investigate the role of biliary excretion in the elimination of morphine, but we wish to report two patients who appear to illustrate the importance of the kidney in the elimination of morphine or its metabolites.

PATIENTS AND METHODS

Approval was obtained from the district Ethics Committee and informed consent was obtained from the parents of two children about to undergo orthotopic liver transplantation. Preoperative details are summarized in table I. Both children had end-stage liver failure unresponsive to other medical and surgical treatment. One had congenital biliary atresia, the other cholestatic jaundice following neonatal hepatitis; both had secondary biliary cirrhosis. Renal function in both patients was thought to be normal in the preoperative period although, in retrospect, patient 2 had unrecognized renal impairment at this time: her

| Table I. Details of two children before liver transplantation |
|------------------|------------------|------------------|
|                  | Patient 1        | Patient 2        |
| Age (yr)         | 3.5              | 2.5              |
| Sex              | M                | M                |
| Weight (kg)      | 14.0             | 7.5              |
| Diagnosis        | Congenital biliary atresia | Neonatal hepatitis + cholestatic jaundice |
| Bilirubin (mmol litre⁻¹) | 372             | 320              |
| Alkaline phosphatase (mmol litre⁻¹) | 1430            | 2390             |
| Urea (mmol litre⁻¹)    | 2.2              | 12.1             |
| Creatinine (μmol litre⁻¹) | < 100           | 60               |
plasma urea concentration was increased although her plasma creatinine concentration was within normal limits.

Anaesthesia was introduced with thiopentone; alcuronium was given to facilitate tracheal intubation and controlled ventilation. Anaesthesia was maintained with halothane and nitrous oxide in oxygen. Following the induction of anaesthesia, but before surgery, a blood sample (baseline) was taken and morphine 1 mg kg\(^{-1}\) was administered i.v. as part of the anaesthetic regimen. Further blood samples were taken at 5, 10, 15, 20, 30, 40,
50, 60 min after the administration of the morphine while venous access was secured and monitoring commenced—but before the start of major surgery. Blood removed for sampling was replaced by blood to maintain fluid balance. Further blood samples were taken from each child after surgery.

Plasma morphine, morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G) concentrations were measured by high pressure liquid chromatography (HPLC). The standards used were morphine (Evans Medical Ltd, Beaconsfield) and M-3-G (Sigma Chemical Corporation); M-6-G was synthesized using a modification of the technique described by Yoshimura, Oguri and Tsukamoto (1968) and obtained through Napp Research Centre, Cambridge. Samples were prepared in control plasma for calibration, quality control and validation. Calibration curves were constructed for all three compounds.

Solid phase Bond Elut C18 cartridges (Jones Chromatography, Llanbradach, Glamorgan) were used to extract morphine and the two metabolites from plasma. Subsequent quantification was by HPLC using ultraviolet absorption at 210 nm to estimate M-3-G concentrations and electrochemical detection at +0.9 V (v. silver–silver chloride) to measure morphine and M-6-G. The lower limit of detection for M-3-G by ultraviolet absorption was 10 ng ml\(^{-1}\) and for morphine and M-6-G by electrochemical detection was 1.5 ng ml\(^{-1}\). Recovery from plasma for all three compounds was greater than 90%.

Pharmacokinetic parameters were determined using ESTRIP (Brown and Manno, 1978) to estimate terminal slopes. Clearance was calculated as dose \((D)\) divided by the area under the curve (AUC) where AUC was estimated from the data points by the linear or logarithmic trapezoidal method and extrapolated to infinity. Volume of distribution at steady state was calculated as \(D.AUMC/AUC\) where AUMC is the area under the first moment curve, again extrapolated to infinity.

Clinical and biochemical indices of each patient's conscious level, and liver and renal function, as well as their opioid requirement, were recorded before and after surgery.

RESULTS

The plasma concentrations of morphine, M-3-G and M-6-G for both patients are shown in figure 1. During the first 1 h after the induction of anaesthesia, but before the start of major surgery, the plasma concentration of morphine increased initially to high values and then decreased rapidly in both patients. The pharmacokinetic parameters of morphine were: in patient 1, half-life 0.4 h, volume of distribution at steady state 4.4 litre kg\(^{-1}\) and clearance 93 ml min\(^{-1}\) kg\(^{-1}\); in patient 2, half-life 0.52 h, volume of distribution at steady state 3.4 litre kg\(^{-1}\) and clearance 68 ml min\(^{-1}\) kg\(^{-1}\).

The plasma concentration of M-3-G increased in both patients, but more steeply and to higher values in patient 2. The concentration of M-3-G then decreased in patient 1, whereas it was maintained in patient 2. Plasma M-6-G concentration increased to a peak at approximately 15 min in patient 1 and was maintained at this value subsequently. In patient 2, however, the concentration of M-6-G increased gradually for the first 15 min, but continued to increase thereafter such that at the end of the 1 h the value was higher than that of the morphine base.

Patient 1, 24 h after his original dose of morphine, had no detectable morphine, M-3-G or M-6-G present in his plasma. Patient 2, 24 h after her original dose of morphine, had no detectable morphine base, but the concentrations of M-3-G and M-6-G were unchanged from concentrations measured at 60 min.

Intraoperative details for both patients are shown in table II. The duration of surgery and the blood loss were similar in both patients and both received a large blood transfusion. Patient 2, however, was anuric throughout the operation, whereas patient 1 had an adequate urine output.

The patients' postoperative urine outputs, conscious levels and opioid requirements are shown in figure 2. Patient 1 maintained a urine output of approximately 1 ml kg\(^{-1}\) h\(^{-1}\). He required the regular administration of fentanyl, in spite of which he remained difficult to sedate and further morphine was required 26 h after the initial dose to allow satisfactory control of ventilation. Patient 2 continued to have an

<table>
<thead>
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<th>Table II. Operative details</th>
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<tr>
<td>Patient 1</td>
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<tr>
<td>Duration of surgery (h)</td>
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<tr>
<td>Blood loss (ml kg(^{-1}))</td>
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<tr>
<td>Transfusion requirement (ml kg(^{-1}))</td>
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<tr>
<td>Urine output (ml kg(^{-1}))</td>
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inadequate urine output. In addition, although she received no further opioid, she continued to be unresponsive to painful stimuli and had pin-point pupils throughout this period.

Both patients started to produce bile promptly after surgery and continued to do so, indicating reasonable recovery of liver function.

Patient 2 eventually responded to diuretic therapy and had a large diuresis. One hour after the start of her diuresis, she became responsive to
stimuli and her pupils enlarged slightly. Six hours later she required further opioid.

**DISCUSSION**

Although the liver has long been thought of as the site of morphine metabolism (Stanski et al., 1978), recently, patients with cirrhosis have been shown to eliminate morphine normally (Patwardhan et al., 1981). It has also been suggested that morphine is metabolized in patients with hepatic failure (Hug et al., 1979), but no details were provided of the assay method used to estimate the concentrations of morphine in that study. Extrahepatic sites of morphine metabolism, such as the kidney (McQuay and Moore, 1984b) and the gastrointestinal tract (Park, 1985) have been postulated.

Both the patients described had liver failure during the preoperative period, yet both metabolized morphine rapidly; morphine concentrations decreased and the concentrations of M-3-G and M-6-G increased. Although neither patient was capable of producing bile at this time, the concentrations of morphine decreased. This may refute the importance of the biliary excretion of morphine.

The clearance of morphine in these children was greater than that previously reported in children (Dahlstrom et al., 1979). This may reflect the different methods used to estimate the plasma morphine concentration, or it may result from the relatively short sampling period available in our study before surgery was undertaken with the consequent haemodynamic instability.

The main differences between the two children were their renal function, and their plasma M-3-G and M-6-G concentrations. Patient 1 had normal renal function and had eliminated all detectable morphine, M-3-G and M-6-G by 24 h after the administration of the initial dose. Patient 2 had impaired renal function and a poor urine output. Morphine base was no longer detectable at 24 h, but high concentrations of M-3-G and M-6-G were present in spite of a large intraoperative blood transfusion to replace an operative blood loss approximating to her circulating blood volume. This accumulation of morphine metabolites would appear to indicate that an adequate urine output is important for their elimination. The clinical evidence of recovery in patient 2 when her diuresis started adds support to this hypothesis.

M-3-G is thought to be inactive parenterally, but M-6-G is known to be a powerful analgesic (Shimomura et al., 1971); however, its other actions are unknown. Patient 2 was unresponsive to pain and had pin-point pupils in association with the increased concentrations of M-6-G and this may indicate other opioid-like properties, particularly sedation. This assay method used was calibrated for only M-3-G and M-6-G. Other metabolites which may be active (e.g. normorphine) were not measured.

**CONCLUSION**

The two patients described illustrate that morphine can be metabolized rapidly, even in the presence of severe liver failure. Impairment of renal function with a low urine output in one of the patients was associated with accumulation of morphine-3-glucuronide and morphine-6-glucuronide and with prolonged narcosis. Morphine has active metabolic products and it may be these that produce the clinically observed prolonged action of morphine in patients with renal failure.

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