PROLONGATION OF MORPHINE ANAESTHESIA IN A PATIENT WITH GILBERT'S DISEASE: REPORT OF A CASE

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INTRODUCTION

THE USE OF MORPHINE (1–3 mg/kg body weight) as the predominant agent is now a well accepted anaesthetic technique, especially for patients with severe cardiopulmonary disease.[1–3] The advantages attributed to this type of anaesthetic management include: (1) cardiovascular stability, (2) abiltiy to utilize 100 per cent oxygen, and (3) facilitation of early postoperative respiratory care. The use of a large dose of morphine, however, may result in the development of a prolonged or intensified morphine effect in a patient who is unable to metabolize morphine in the usual fashion. This prolonged morphine effect might be anticipated in a patient who metabolizes bilirubin abnormally because these compounds are probably both detoxified through a common metabolic pathway.[4–6] A patient with Gilbert's Syndrome is presented as a case in point.

Case History

A 56-year-old, 75 kg white male with mitral stenosis and a five-year history of progressive congestive heart failure was admitted for operation. During the previous seven years, intermittent episodes of jaundice had occurred in times of stress such as exacerbated congestive heart failure, pneumonia and/or upper respiratory infection. Liver function studies during these periods of jaundice revealed a mild to moderate elevation in serum bilirubin to levels of 2–5 mg%. Bilirubin fractionation showed that the conjugated bilirubin was normal and that the unconjugated bilirubin was elevated. Other routine liver function studies were normal. There was no evidence for haemolysis. These findings were compatible with a diagnosis of Gilbert's Sydrome.[7–8] Regular medication included digoxin 0.25 mg/d, furosemide 40 mg/d, KCl 10 mg/t.i.d. and coumadin 5 mg/d.

Pertinent abnormal findings on this admission included atrial fibrillation with a ventricular rate of 80 beats per minute, jugular venous pressure of 12 cm with hepatojugular reflux, biventricular enlargement and bibasilar inspiratory rales. Cardiac catheterization and left ventricular angiograms confirmed the clinical impression of moderately severe mitral stenosis and mild mitral regurgitation. The chest roentgenogram was consistent with this diagnosis. Routine preoperative laboratory studies were normal. The serum albumen was 4.2 gm%, serum globulin 3.4 per cent and serum enzymes (alkaline phosphatase, LDH and SGOT) were within normal limits. The conjugated bilirubin was 0.4 mg% and the total bilirubin, 1.8 mg%.

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Hospital Course

Forty-eight hours prior to operation, all medication was discontinued and cephaloridine (LORIDINE) 500 mg intramuscularly twice a day was instituted. Premedication included 500 mg cephaloridine, 10 mg morphine sulfate, 10 mg diazepam and 0.5 mg atropine sulfate all administered intramuscularly. One hour after premedication the patient arrived at the operating suite adequately sedated. Induction of anaesthesia by the intravenous administration of 80 mg morphine sulfate was uncomplicated. Decamethonium 10 mg was utilized to facilitate intubation of the trachea. Halothane at 0.5–1.0 per cent inspired concentration was administered with balance oxygen in a semi-closed circle absorber system until the patient was placed on cardiopulmonary bypass. Before commencing extracorporeal circulation morphine sulfate 20 mg, sodium cephalothin 2 gm and d-tubocurarine 24 mg were administered.

A severely scarred and calcified mitral valve was replaced with a mitral prosthesis. After cardiopulmonary bypass the patient received only 100 per cent oxygen. The total time of anaesthesia was four hours. Postoperatively the vital signs remained stable and the patient was placed on controlled ventilation through a nasotracheal tube. Pulmonary gas exchange was within the normal range for a postoperative mitral valve patient. He received an additional 10 mg of morphine sulfate in 2 to 3 mg increments during the first 17 postoperative hours on controlled ventilation. Upon review of the nursing notes, it appeared that this administration of morphine was routine postoperative nursing care rather than for indication for analgesia or respiratory management.

Weaning from the ventilator was attempted twenty-two hours postoperatively, but the patient was excessively drowsy and obtunded and had a spontaneous respiratory rate of three per minute. At this time serum electrolytes and the body temperature were normal. The postoperative urine output averaged 75 ml/hr. Total serum bilirubin was 3.0 mg% with 2.6 mg% being in the unconjugated form and mild scleral icterus was evident. Serum enzymes associated with liver function were minimally elevated. The pupils were bilaterally pin-point in size. Arterial blood gas values were normal during controlled ventilation but respiratory acidosis (pH 7.32, P_{CO_2} 53, HCO_3^- 26, P_{O_2} 150) developed after several minutes of spontaneous respirations on a T-piece with 8 liters oxygen inflow (FI_{O_2} 50 per cent). Frequent ventricular premature contractions were also noted with attempted weaning.

Administration of intravenous naloxone in divided doses to a total of 0.4 mg resulted in immediate improvement in mental function and respiratory status without complete antagonism of morphine analgesia. One hour later, when the patient was able to generate 40 cm of water negative airway pressure and 1000 cc in vital capacity he was extubated. After extubation he had no recurrence of excessive drowsiness or obtundation, and respiratory function and arterial blood gases remained adequate. He did not require further administration of a potent narcotic or a narcotic antagonist. Only after the administration of naloxone did the patient realize that his operation was completed. He was discharged from I.C.U. on the third postoperative day in good condition.

Discussion

We believe that it is unusual for an otherwise healthy cardiac surgical patient who receives 1.0 to 1.5 mg/kg of morphine during anaesthesia to be significantly obtunded and depressed beyond the eighteenth postoperative hour. Provided that such patients do not receive supplemental morphine for several hours prior to attempted weaning, they are awake, co-operative, and easy to extubate.

Gilbert's Syndrome[7–9] is characterized by the presence of unconjugated hyperbilirubinaemia with a normal serum concentration of conjugated bilirubin and normal liver function. The total bilirubin rarely exceeds 5 mg% and the only abnormal physical finding may be scleral icterus. Clinically these patients are not affected by their disease, although in periods of stress, such as surgery or intercurrent illness, they may become transiently jaundiced. Examination of the liver by light microscopy is normal, but electron microscopy reveals thickening of the liver cells facing the sinusoidal lumen and widening of the Space of Disse as a result of increased collagen deposition.[7,10] It is possible that a defect in the hepatic uptake of bilirubin may be of significance, but recent evidence has suggested that the conjugating enzyme for bilirubin is qualitatively or quantitatively abnormal.[11,14] Since the biochemical mechanism(s) underlying Gilbert's Syndrome is unknown, this condition has also been referred to as idiopathic low grade unconjugated hyperbilirubinaemia.

The biodegradation of morphine in man includes N-demethylation to normorphine and possibly 0-methylation to codeine. However, the most important metabolic pathway for morphine metabolism is the formation of morphine 3-monoglucuronide by conjugation in the liver.[6,16] Ninety per cent of a parentally administered dose of morphine can be detected in the urine as conjugated morphine within 24 hours.[17] The conjugating system requires the synthesis of uridine diphosphoglucuronic acid (UDPGA) which, in turn, combines with morphine in the presence of glucuronyl transferase to form morphine glucuronide. Morphine glucuronide is water soluble and is excreted largely in the urine and to a lesser extent in the bile. The systems for the conjugation of morphine and bilirubin appear to be similar.[4–6] It is possible that morphine and bilirubin share the same conjugation process, which includes both hepatic uptake and the actual conjugation with glucuronide. Therefore, morphine and bilirubin may be competitors at the uptake or conjugating sites. We believe that impaired morphine detoxification can lead to clinically significant consequences, particularly when large doses of morphine are administered. Therefore, we suggest that patients with Gilbert's Syndrome, may not metabolize morphine in the normal manner and that these patients may exhibit a prolonged morphine effect.

Summary

The case is presented of a patient with Gilbert's Disease who received a predominantly morphine anaesthetic for cardiac surgery. He was excessively obtunded in the post-operative period. It is postulated that the defect responsible for the inadequate bilirubin conjugation which is characteristic of Gilbert's Disease may also

be responsible for a prolonged morphine effect since both compounds are probably metabolized in similar fashion by conjugation in the liver.

RÉSUMÉ

Nous présentons le cas d'un malade souffrant de la maladie de Gilbert qui a reçu, pour de la chirurgie cardiaque, une forte dose de morphine comme anaesthésique. Au cours des suites opératoires, il a été grandement obnubilé. L'on présume que la pathologie responsable pour la conjugaison inadéquate de la bilirubin qui caractérise la maladie de Gilbert peut bien également être responsable de l'effet prolongé de la morphine puisque les deux substances sont probablement métabolisées de la même façon par conjugaison dans le foie.

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