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The Successful Anaesthetic Management of Crigler-Najjar Syndrome Type 2

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Abstract : *We describe the peri-operative management of a patient with Crigler-Najjar Syndrome type 2, who presents with acute cholecystitis and undergoes open cholecystectomy. We review the pathophysiology of this disease as well as the enzyme defect responsible; we highlight the important management principles during the pre- and postoperative period; and with the knowledge of the metabolic pathways involved and using applied drug pharmacokinetics we describe an anaesthetic technique that prevents further biochemical derangement in this condition.*

Keywords: *Crigler-Najjar Syndrome, Remifentanil, TAP Block, UDP-glucuronosyltransferase 1A1:*

I. Introduction

Crigler-Najjar Syndrome (CNS) type 2 is a rare autosomal recessive condition that results in impaired bilirubin metabolism. Unconjugated hyperbilirubinaemia in the peri-operative period has the potential to cause serious harm and may be precipitated by various anaesthetic agents [1]. A sound knowledge of the metabolic pathways involved is therefore essential to prevent any further metabolic derangement in these patients. To date there have only been a handful of case reports describing the anaesthetic management of this condition, however these span a number of decades and do not reflect newer anaesthetic techniques [2-4]. To our knowledge, this is the first description of the successful use of intra-operative remifentanil combined with a transversus abdominis plane (TAP) block for postoperative pain relief in a patient with CNS type 2.

II. Case History

A 37 year old male, weighing 75kg presented emergently complaining of a one day history of severe central abdominal pain in the absence of systemic upset. On clinical examination he was found to be apyrexial, icteric and had right upper quadrant pain with a positive Murphy's sign. He gave a history of biliary colic 8 years previously for which he had an ERCP. At that time he was noted to have a persistently elevated unconjugated bilirubin level, he underwent extensive haematological investigation and was diagnosed with Crigler-Najjar Syndrome type 2. He had no other significant medical problems and took no regular medications.

Laboratory investigations on presentation showed: haemoglobin 156 g/l; white cell count 13.7 $x10^9$/l, platelets 142 $x10^9$/l, total bilirubin 183 µmol/l, alkaline phosphatase (ALP) 73 IU/l, alanine aminotransferase (ALT) 15 IU/l, aspartate aminotransferase (AST) 20 IU/l, gamma glutamyl transferase (GGT) 10 U/l, albumin 51 $g.l^{-1}$, amylase 58 U/l and CRP 6.0 mg/l. Electrolytes and renal profile were normal.

A provisional diagnosis of cholecystitis was established, he was prescribed regular intravenous co-amoxiclav and admitted for observation.

Abdominal ultrasound on day 2 confirmed the diagnosis of acute cholecystitis and identified a gall stone in the neck of the gall bladder with associated mural thickening and peri-cholecystic fluid. The common bile duct was measured at 6mm. On day 3, total bilirubin peaked at 301 µmol/l and direct bilirubin 37 µmol/l (normal 0-5 µmol/l). Cholecystectomy was performed on day 7. Due to difficulty defining the biliary anatomy, attempts at a laparoscopic procedure were abandoned and the surgery converted to an open cholecystectomy.

For surgery, anaesthesia was induced with remifentanil 0.3 mcg/kg/min and propofol 180mg. Muscle relaxation was achieved with cis-atracurium 16mg and the trachea was intubated with a size 7.5 cuffed endotracheal tube. Anaesthesia was maintained using an oxygen, air and sevoflurane mix. Following induction, a bilateral TAP block was performed using a landmark technique using 20ml 0.375% levo-bupivacaine to each side. Intra-operatively the patient received co-amoxiclav 1.2g, morphine 10mg, paracetamol 1g and ondansetron 4mg. A morphine PCA was given for post operative pain control.

Reassuringly anaesthesia did not impact on bilirubin levels, indeed post operatively these continued their decline from the preoperative peak of 301 µmol/l (direct bilirubin 37 µmol/l). The patient made satisfactory progress, was able to resume oral diet quickly and was discharged on the fourth post operative day with a bilirubin of 82 µmol/l.

III. Discussion

This case report is one of only a handful reporting the anaesthetic management of patients with Crigler-Najjar Syndrome type 2 [2-4], and the first to successfully to describe the use of remifentanil.

CNS type 2, also known as Arias Disease, forms one of the five known inherited defects of bilirubin metabolism. It is a rare, autosomal recessive condition that results in a single base pair defect coding for the UDP-glucuronosyltransferase 1A1 enzyme (UGT1A1). This defect results in less than 10% enzymatic function compared to normal. In contrast, in CNS type 1 there is complete absence of this enzyme and the disease follows a more severe clinical course.

Normal function of this phase 2 enzymatic pathway is required for the conversion of insoluble unconjugated bilirubin into the more soluble glucuronidated form, which can subsequently be excreted from the body. Reduced UGT1A1 function results in high levels of unconjugated bilirubin. To a point, the increased levels of unconjugated bilirubin are buffered by binding to plasma proteins, mainly albumin. However as free plasma levels increase this lipid soluble entity may cross the blood brain barrier and lead to severe neurological sequelae. Neurological impairment has previously been described following anaesthesia [1].

The diagnosis of CNS type 2 is established by demonstrating a markedly elevated serum bilirubin with otherwise normal liver function tests. Exclusion of a haemolytic cause for the hyperbilirubinaemia and the presence normal liver architecture are also required. It is the extent of the rise in bilirubin that then determines the likely underlying enzymatic defect. In Gilberts syndrome the total serum bilirubin levels is from 1-6 mg/dL (17 -102 μmol/l); Crigler-Najjar syndrome type 2 6 - 20 mg/dL (102 – 342 μmol/l) and Crigler-Najjar syndrome type 1 20 - 45 mg/dL (342-770 μmol/l). CNS type 2 will respond with a drop in serum bilirubin in response to phenobarbital enzyme induction [5]. Definitive diagnosis is achieved with liver biopsy and UGT1A1 enzyme assay or genetic studies.

It can therefore be seen that minimising the free plasma fraction of unconjugated bilirubin and maintaining the synthetic capacity of the UGT1A1 enzyme form the management goals in these patients.

Stress, infection and the disease process itself can all lead to an increase in unconjugated bilirubin levels. Prolonged fasting and vomiting increase triglyceride metabolism, the resulting free fatty acids then displace bilirubin from albumin binding sites. It is important therefore to avoid prolonged fasting pre-operatively, maintain a baseline glucose infusion and to prevent postoperative vomiting. Drugs which have been shown to displace bilirubin from its albumin binding include sulphonamides, ceftriaxone, ampicillin, salicylates, and furosemide [6].

Many drugs used for anaesthesia have the potential to compete with bilirubin for the UGT1A1 and should be avoided. Remifentanil is a synthetic phenylpiperidine derivative with a short and predictable context sensitive half life. The metabolism of remifentanil is independent of the liver and occurs via non specific plasma and tissue esterases. In addition, as a co-agent it reduces the stress response to surgery and allows reduced concentrations of volatile anaesthetic agents to be used.

The most appropriate induction agent in CNS type 2 remains less clear. Although the safe use of thiopentone and propofol have both been described, theoretical concerns regarding both exist. Thiopentone has a high degree of protein binding and may cause bilirubin displacement from albumin binding sites, similarly the high fatty acid component of propofol may cause displacement. Propofol undergoes glucuronidation via UGT 1A9 and hydroxylation via the cytochrome system. Cis-atracurium is a benzylisoquinolinium that is only 15% protein bound and undergoes Hofmann elimination and to a lesser extent ester hydrolysis, it is independent of the bilirubin pathway. For maintenance of anaesthesia, concerns have been raised about possible hepatic impairment with the use of sevoflurane. Although a small proportion does undergo hepatic metabolism, this occurs via the cytochrome P450 (CYP2E1) system. Morphine and paracetamol both undergo glucuronidation however, these proceed via separate UGT isoenymes, namely UGT 2B7 [7] and UGT 1A9 respectively [8]. Similarly diclofenac is also metabolised via UGT 2B7 [9]. All these analgesics may therefore be used safely in the setting of UGT 1A1 dysfunction.

As part of a balanced technique, TAP blocks are effective at reducing postoperative pain and the associated stress response. Levo-bupivacaine has a high degree of protein binding, however it has much greater affinity for alpha 1 acid glycoprotein than for albumin and thus remains a safe choice. Furthermore undergoes hepatic metabolism but this proceeds via alkylation as opposed to glucuronidation.

IV. Conclusion

In summary, using knowledge of the enzymatic defect and drug metabolism we have presented the first documented use of intra-operative remifentanil and TAP blocks as part of a balanced anaesthetic technique for the management of a patient with Crigler-Najjar Syndrome type 2.

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