Anaesthetic considerations in progressive familial intrahepatic cholestasis (Byler's disease)

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Progressive familial intrahepatic cholestasis (PFIC) or Byler's disease is one of the most common forms of intrahepatic cholestasis of metabolic and genetic origin. Affected children progress to terminal cirrhosis before adulthood and at present the only curative treatment of PFIC is orthotopic liver transplantation (OLT). We present a retrospective review of 40 general anaesthetics administered in our hospital to 22 patients with PFIC undergoing various procedures. The clinical features of PFIC and the anaesthetic implications of chronic cholestasis in children (malnutrition, cirrhosis, portal hypertension, chronic hypoxaemia) are reviewed.

La cholestase intrahépatique progressive familiale (PFIC) ou maladie de Byler est une des formes les plus courantes de cholestase intrahépatique de cause métabolique et génétique. Les enfants qui en sont atteints évoluent vers la cirrhose terminale avant l'âge adulte. Jusqu'à présent, le seul traitement curatif de la PFIC est la transplantation hépatique. Nous avons revu de manière rétrospective 40 anesthésies générales administrées dans notre hôpital à 22 enfants souffrant de PFIC. Les différentes présentations cliniques de la PFIC et les implications anesthésiques de la cholestase chronique de l'enfant (malnutrition, cirrhose, hypertension portale, hypoxémie chronique) sont présentées.

Key words
ANAESTHESIA: paediatric, inhalation, intravenous;
LIVER: cholestasis, cirrhosis, hypoxaemia;
SYNDROMES: Byler's disease, progressive familial intrahepatic cholestasis.

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Although rare, Progressive Familial Intrahepatic Cholestasis (PFIC) or Byler's disease is one of the most common forms of intrahepatic cholestasis of metabolic and genetic origin.[1,2] Patients suffer from cholestasis and marked pruritus within the first months of life, and progress to end-stage cirrhosis before adulthood.[3] The precise metabolic defect responsible for this autosomal recessive disorder is still unknown.[2] Because of their liver disease, these children are submitted to several investigational and/or therapeutic procedures performed under general anaesthesia such as endoscopies, liver biopsies, biliary surgery and eventually liver transplantation.[4,5] We carried out a retrospective review of the anaesthetic records of 22 children with PFIC who underwent such procedures in our institution. The anaesthetic implications of the various clinical presentations of this disease will be discussed.

Review of the cases

We reviewed the anaesthetic and medical records of all the children with PFIC admitted to our hospital from 1985 to September 1994 to undergo a procedure requiring an anaesthetic. A total of 40 general anaesthetics were administered to 22 children. The following procedures were performed: six liver biopsies, six liver biopsies combined with an oesogastroscopy, 11 oesogastroscopies, three laparotomies, two bile duct diversion procedures (see below), two radiological explorations and 16 orthotopic liver transplantations (OLT). No other surgical procedures were performed on children with PFIC in our hospital during that period.

There were 13 boys and nine girls. Their ages and weights at the time of first anaesthetic in our hospital varied from 2 to 168 months (mean 48.5 ± 44.5 SD) and from 4.3 to 27 kg (mean 13.4 ± 6.6), respectively. A family history of cholestasis was recorded in one-third of the cases. All were subicteric or icteric (range of plasma total bilirubin concentration: from subnormal to 45 $mg \cdot dl^{-1}$ (=769 $\mu mol \cdot L^{-1}$)), 85% of them complained of pruritus and six had skin excoriations. None had chole-

lithiasis. A history of frequent spontaneous epistaxis in the absence of biological coagulopathy was present in five cases. Of these, one presented with complete synechiae of one nostril and another had a history of bleeding requiring blood transfusion after tonsillectomy at another hospital. Prothrombin times varied from 15 to 100% of control; plasma total cholesterol concentration was normal (150–250 $mg \cdot dl^{-1}$) in all patients and plasma gamma glutamyl transferase (GGT) concentration was normal (<45 $mg \cdot dL^{-1}$) in all but three. Of the 16 patients who had a radiological examination of long bones, ten presented diffuse osteopenia (<P5 for age), two had discrete signs of osteomalacia and only one had evidence of rickets. All patients undergoing pretransplant evaluation were systemically screened for hypoxaemia while breathing room air, either with blood gas analysis or with pulse oximetry: only one (age 60 months) was found to be hypoxaemic (PaO_2: 54 mmHg at FiO_2 21%) but this was not investigated further; none of the patients in whom intraoperative arterial blood gases were analyzed presented an abnormal alveoloarterial PO_2 gradient. These same patients also had an echocardiographic examination: the most common finding was an enlarged left atrium, which was interpreted as a sign of increased cardiac output; a small atrial septal defect was found in one child. Neurological examination was normal in all cases but two children had a history of seizures. Two patients were admitted with acute liver failure and underwent urgent OLT.

Most patients did not receive premedication; otherwise, only atropine *im* was administered. An inhalational induction technique was used 16 times (12 halothane, four isoflurane) while intravenous drugs were used 24 times (thiopentone two, etomidate seven, and propofol 15 times, respectively). Cricoïd pressure was applied until tracheal intubation was achieved in emergency cases or if ascites was present. Isoflurane was given for maintenance of anaesthesia if the procedure lasted more than a few minutes. Succinylcholine, pancuronium or atracurium were used when paralysis was necessary. Fentanyl was used 13 times, alfentanil 14 and sufentanil four times (Table I). One child was sedated for percutaneous liver biopsy with the combination of droperidol and diazepam administered by the radiologist. No untoward reaction (prolonged duration of action or postanaesthetic clinical deterioration of liver function) to any agent was observed. Although most of these children were small for their age, when an uncuffed endotracheal tube was inserted, the size which allowed an air leak between 20 and 25 cm H_2O did not differ from the rule (ID = [16 + age in years] $\cdot 4^{-1}$).

A thoracic epidural catheter was inserted in one patient and was used successfully per- and postoperatively. In another, a continuous *iv* infusion of morphine (15 to 20 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) was administered during the first 48 hr after surgery in the paediatric surgical ward. Most patients who underwent OLT received a continuous infusion of fentanyl *iv* during their early postoperative stay in the Paediatric Intensive Care Unit. Percutaneous liver biopsies were performed with ultrasound control in the paediatric radiology suite: deep sedation was achieved with alfentanil and propofol administered by an anaesthetist in addition to a local anaesthetic infiltration performed by the radiologist or paediatrician.

TABLE I Distribution of the anaesthetic agents used

Name	*Induction*	*Maintenance*
Halothane	12	0
Isoflurane	4	32
Thiopentone	2	0
Etomidate	7	0
Propofol	15	0
Succinylcholine	8	0
Atracurium	6	2
Pancuronium	0	16
Alfentanil	13	1
Fentanyl	6	13
Sufentanil	1	4

Sixteen patients underwent OLT: their haemodynamic tolerance and metabolic responses to the different stages of surgery were similar to those we observed in children with end-stage biliary cirrhosis caused by biliary atresia.[6] However, six of the first ten patients with PFIC undergoing OLT presented with major deficiencies in vitamin K-dependent clotting factors and fibrinolysis and were massively transfused peroperatively with factor IX cryoprecipitate, fresh frozen plasma, blood and platelets. They received a mean ± SD of 319 ± 158 $ml \cdot kg^{-1}$ of blood + plasma and 0.4 ± 0.3 units of platelets $\cdot kg^{-1}$ vs 150 ± 72 $ml \cdot kg^{-1}$ and no platelets for the others. Fortunately, this clinical condition has progressively disappeared due to the combination of better pretransplant nutritional support, earlier indication for transplantation and an improved surgical technique.

One boy (22 mo, 9.9 kg) died with multiple organ failure two months after undergoing a partial cutaneous biliary diversion procedure. His early postoperative period was complicated by high fever (39°C) of unknown origin and the massive production of ascites (>2 L per day) which could not be controlled despite medical treatment with diuretics, salt-poor albumin and paracentesis. Numerous investigations (among which two laparotomies

and the angiographic exploration of the supra hepatic vessels) failed to reveal any extrahepatic cause of this acute postoperative decompensation of apparently stable PFIC (prothrombin time 100% of control and total bilirubin 284 $\mu mol \cdot L^{-1}$ on admission).

Discussion

The disease

First described by Clayton *et al.*[7] in 1965 in a family of six Amish children, PFIC or Byler's disease is an autosomal recessive condition characterized by intrahepatic cholestasis and progressive changes to fibrosis and finally cirrhosis that leads to death during childhood. The exact mechanism of the disease is still unknown. Extremely low amounts of bile acids are detected in the bile of patients with PFIC despite their considerable accumulation in the serum, suggesting an inborn error of the biliary secretion of primary bile acids.[8] Clinically, the first symptoms of PFIC are episodes of cholestasis (pale stools, dark urine and pruritus) starting during the first year of life.[1-3,9] Persistent cholestatic jaundice usually develops during the following two to three years leading to other clinical manifestations such as pruritus, the severity of which is often out of proportion to the degree of hyperbilirubinaemia,[9] failure to thrive, gallstones, acute or chronic pancreatitis, digital clubbing. ...[1,7] Moreover, Whitington *et al.* report a high incidence of wheezing and of recurrent epistaxis in the absence of coagulopathy in their series.[9] The disease usually progresses by successive episodes of acute cholestasis which can be triggered by an intercurrent infection.[3] Signs related to malabsorption and malnutrition such as rickets, osteomalacia, a vitamin E deficiency-associated neurological syndrome (areflexia, ataxia)[1] and developmental delay appear if parenteral vitamins and a special diet are not provided.[10] The early introduction of parenteral fat-soluble vitamins (A, D, E, K) explains the absence of gross neurological abnormalities and the low incidence of rickets and osteomalacia in our series, although osteopenia was common. Chronic hepatic dysfunction progressively results in portal hypertension and consequently produces a state of hyperdynamic circulation, splenomegaly with hypersplenism, low plasma albumin and ascites. Hypoxaemia is likely to occur once portal hypertension is present[11] and may then be caused by abdominal distension, ventilation-perfusion imbalance, pulmonary infection or pulmonary arteriovenous shunting. To date, hypoxaemia has not been documented in children with PFIC but the presence of digital clubbing in the initial descriptions of the disease[1,2,7] gives support to the possible occurrence of hypoxaemia in these patients ... Bleeding oesophageal varices, ascites refractory to medical treatment and/or acute liver failure are the usual signs of the terminal stage of the disease.

Early in the disease, liver biopsy generally shows an aspecific pattern of cholestasis with normal biliary ducts; later, it shows various degrees of fibrosis and, finally, cirrhosis. The extrahepatic bile ducts are normal as demonstrated by ultrasound, retrograde cholangiography or laparotomy (some neonates or infants with PFIC unfortunately undergo a laparotomy with a presumptive diagnosis of biliary atresia).

The diagnosis of PFIC is based on the exclusion of the other familial causes of intrahepatic cholestasis (see below) and on the presence of normal plasma GGT and cholesterol concentrations.[2,9] Children with Arterio-Hepatic Dysplasia (Alagille's syndrome) present in infancy or early childhood with cholestasis caused by paucity of intrahepatic bile ducts. They also present with a particular facies (triangular face with broad forehead, moderate hypertelorism and flattened nose), cardiac disease (stenosis of the peripheral pulmonary arteries, either isolated or associated with other complex abnormalities), bone abnormalities ("butterfly"-like vertebral arch defect) and an asymptomatic embryological remnant in the anterior chamber of the eye (called posterior embryotoxon).[2] Their plasma GGT and cholesterol concentrations are very high and they often demonstrate multiple xanthomas. Benign recurrent intrahepatic cholestasis usually presents as recurrent episodes of cholestasis: plasma cholesterol concentrations are elevated during these attacks of cholestasis, but GGT levels may remain normal.[2,12] Despite years of repeated episodes of cholestasis, this disorder does not cause cirrhosis. Primary bile acid synthesis defects, such as the recently described deficiency in 3 beta-hydroxy-C27-steroid dehydrogenase/isomerase,[13] present in children with clinical features similar to PFIC but with no pruritus and normal serum bile acid concentration. Establishing the correct diagnosis is important because bile acid therapy can normalize liver function in these children.

At present, the only curative treatment of PFIC is OLT.[4,5] Medical treatment is symptomatic: cholestyramine[1,7,14] has some favourable effects on pruritus but does not improve clinical status; phenobarbitone is sometimes prescribed to reduce bilirubin concentration.[1] High-dose ursodeoxycholic acid gives good results in some patients.[9] Different surgical techniques have been proposed: internal biliary drainage is not effective but partial cutaneous biliary diversion[15] seems to relieve pruritus while normalizing serum bilirubin concentration and, in patients with no fibrosis at the time of operation, to reverse histological signs of cholestasis. Cholecystectomy should be avoided

in patients with PFIC because partial cutaneous biliary diversion involves anastomosing the dome of the gallbladder to the skin via a short jejunal conduit.[15]

Preoperative evaluation

Children with PFIC may present to the anaesthetist with a wide spectrum of clinical conditions ranging from mild cholestatic jaundice with normal liver function to terminal liver failure, or in emergency with bleeding oesophageal varices. In addition to the usual paediatric clinical examination, the hepatic function and nutritional status of the child should be carefully evaluated (Table II). As hypoxaemia is likely to occur and cyanosis is not easily detected in severely jaundiced children, we suggest that all patients should be screened systematically for hypoxaemia. The measurement of arterial haemoglobin oxygen saturation (SpO_2) with a pulse oximeter is not affected by hyperbilirubinaemia[16] and direct blood gas analysis is thus not necessary if SpO_2 is >90%. If hypoxaemia is present, contrast-enhanced echocardiography and/or pulmonary scintiscan will allow differentiation of pulmonary arteriovenous shunting from hypoventilation caused by ascites or a pulmonary disease.[11] Moreover, echocardiography will allow the early diagnosis of pulmonary hypertension, another possible complication of portal hypertension.[17] Hypoxaemia caused by pulmonary arteriovenous shunting is usually poorly improved by increasing FiO_2 but is reversible after successful OLT and is thus nowadays an indication for it.[5,11]

Regarding anaesthetic management, the use of invasive monitoring (arterial and central venous lines) in addition to pulse oximetry, capnography, NIBP, ECG, and temperature, should be adapted to the child's clinical condition and to the importance of the procedure. During controlled ventilation, care should be taken to avoid high airway pressures and hypocarbia because both reduce hepatic (arterial and portal) blood flow.[18] Anaesthetic agents with no or minimal hepatotoxicity should be used to avoid deterioration of liver function.

TABLE II Suggested preoperative evaluation in PFIC

History
- Recurrent epistaxis
  - Nasotracheal or nasogastric intubation to be performed gently.
- Chronic cough or wheezing
  - Elective procedure best postponed if intercurrent upper respiratory tract infection.
- Dyspnoea
  - Check for anaemia, ascites, hypervolaemia, infection and/or hypoxaemia.

Examination
- Splenomegaly
  - Is a sign of portal hypertension!
- Ascites
  - Consider as full stomach situation (risk of regurgitation, delayed gastric emptying)
- Digital clubbing
  - Evaluate for hypoxaemia
- Skin lichenification
  - Caused by pruritus: venous access possibly difficult, effectiveness of EMLA cream?
- Bruising, haematomas
  - Check coagulation
- Pulse oximetry
  - While breathing room air

Drugs
- Diuretics, propranolol and/or histamine-2 receptor antagonists?

Laboratory
- To be adapted to the findings of history and examination and to the date of the last results. We suggest: haemoglobin, platelets, PT, plasma total protein and albumin concentrations, hepatic enzymes, blood electrolytes ($hypoNa^+$ and $hypoK^+$ not usual if on diuretics) and arterial blood gas analysis if SpO_2 while breathing room air <90%.

Investigations
- Contrast-enhanced echocardiography and pulmonary scintiscan if hypoxaemia; right heart catheterization if pulmonary hypertension disclosed by echocardiography.

Anaesthetics: inhalational

Up to now, isoflurane has been the inhalational agent of choice in case of liver disease. It decreases total hepatic blood flow only slightly because it increases arterial hepatic blood flow.[18,19] Although halothane decreases total hepatic blood flow the most, this does not appear during short-lasting (<30 min) administration.[20] Moreover, halothane has been used in a series of children with cholestatic jaundice without liver function deterioration.[21] Therefore, we do not hesitate to use halothane for induction of anaesthesia in infants and small children in whom venous access is not easy to establish, thus avoiding the possible respiratory problems encountered during induction with isoflurane.[22] Sevoflurane for induction and maintenance of anaesthesia or desflurane for maintenance may be the inhalational agents of choice in the near future because they do not appear to have any hepatic toxicity and their effects on hepatic blood flow are similar to those of isoflurane.[23,24]

Anaesthetics: intravenous

In patients with liver disease, the metabolism and elimination of intravenous agents are influenced by various factors such as reduced hepatic blood flow, porto-systemic shunting, decreased hepatic enzymatic activity, alteration

of plasma protein binding and concurrent medical treatment (e.g., diuretics). The relative importance of each factor depends upon the hepatic extraction ratio of the drug considered: high extraction drugs (e.g., lidocaine, morphine, ketamine) depend on hepatic blood flow, while low extraction drugs (e.g., diazepam) depend on enzymatic activity.[25] Moreover, alterations in drug disposition and elimination may be, in part, dependent on the cause of liver dysfunction: e.g., primary biliary cirrhosis affects mainly the periportal regions and thus has little effect on drug metabolism, whereas alcoholic cirrhosis affects the perilobular regions and may therefore be associated with reduced oxidative metabolism.[26] On the other hand, although the liver plays the major role in drug metabolism, drug metabolizing enzymes (e.g., glucuronyl transferases) are also present in other tissues (kidney, lung, gut wall ...) and may be responsible for some extrahepatic metabolism.[27,28] Moreover, *in vitro* studies with normal hepatic microsomes have shown that an anaesthetic agent may interfere with the hepatic elimination of another concomittantly used agent.[29] Last, most human studies concerning the pharmacokinetic consequences of liver disease consider adult patients with compensated alcoholic cirrhosis and receiving a single bolus dose of the drug studied. It is difficult to draw clinically valid conclusions from these studies because the classic pharmacokinetic variables reported (half-lives, clearance, etc. ...) neither predict the rate of clinical recovery following drug administration nor consider pharmacodynamic factors which may modify the patient's response.[30]

The main effects of cirrhosis on the pharmacokinetic behaviour of *iv* induction agents and the effects of these agents on liver blood flow are summarized in Table III. Fortunately, the duration of action of a single dose of these agents is determined by redistribution from the brain to poorly vascularized tissues rather than by metabolism. However, hypoalbuminaemia decreases their protein binding[35] and may thus increase their pharmacodynamic effects.

The opioid chosen for peroperative analgesia depends upon the anticipated duration of surgery. For short procedures, our first choice is alfentanil which has similar pharmacokinetic behaviour in children with cholestasis as in normal age-matched patients.[38] For long procedures, we used repeated boluses of fentanyl for the first patients of the series while the last ones received a continuous infusion of sufentanil. In adults with uncomplicated alcoholic cirrhosis, the elimination half-life of a single bolus dose of fentanyl[39] or sufentanil[40] is similar to controls. Remifentanil, either in bolus doses (short procedures) or by continuous infusion, might soon become a good choice as it is metabolized by non-specific blood and tissue esterases.[41] The use of morphine, either in repeated bolus doses or by continuous infusion, to provide postoperative analgesia in children with severe liver disease requires careful assessment of its clinical effects by trained nurses using appropriate pain and sedation scores: although a single bolus dose of morphine undergoes rapid glucuronidation even in the presence of severe liver disease,[27,42] the elimination half-life of its unchanged form is prolonged[43] and an associated impaired renal function may lead to the accumulation of its active metabolites.[42]

TABLE III Induction agents

Drug	*Effect of cirrhosis*	*Effect on liver blood flow*
Thiopentone	/Volume of distribution and elimination half-life; if low albumin[35]	Transient /in portal flow[18]
Propofol	None if single dose[31,32]; considerable extra-hepatic metabolism[28]	None[33]
Etomidate	Prolonged elimination half-life if infusion[37]	?
Ketamine	?	Controversial[18]

TABLE IV Muscle relaxants

Drug	*Effect of cirrhosis*	*Clinical implication*
Succinylcholine	\Plasma cholinesterase activity[45]	/Duration of action
Atracurium	None[44]	None
Pancuronium	/Vd and \Cl[46]	Increase 1st dose /duration of action
Vecuronium	\CL[47]	/Duration of action if large dose
Mivacurium	\Cl by \plasma cholinesterase activity[48]	/Duration of action
Rocuronium	/VD and /mean residence time[49]	/Duration of action

VD = volume of distribution, Cl = clearance.

Muscle relaxants

Neuromuscular function should be monitored with a nerve stimulator in all patients with liver dysfunction due to the pharmacologic problems (Table IV) and the often-associated muscle wasting. For curarization of short duration, atracurium is currently our choice because its metabolism, owing to spontaneous Hoffman's reaction and non-specific plasma esterases, is independent of the liver.[44] Muscle relaxants do not affect hepatic blood flow.[18]

Local anaesthetics

Severe liver disease reduces both the metabolism of the

amide class of local anaesthetics and the plasma concentration of alpha$_1$-glycoprotein and albumin, thus exposing the patient to increased total and free plasma local anaesthetic agent concentrations.[50] This should be borne in mind when repeated injections or continuous infusions of local anaesthetics are used.

Mild analgesics

Paracetamol (acetaminophen) has been shown to accumulate in healthy children with fever after repeated doses over two to three days.[51] However, this accumulation did not result in increased transaminase levels or hepatotoxicity. It thus appears that usual doses of paracetamol (60–80 mg · kg^{-1} · d^{-1}) may be used for a short time in children with stable liver disease. On the contrary, non-steroidal anti-inflammatory drugs (NSAIDs) which are eliminated by hepatic bio-transformation, should be used very cautiously because pre-existing liver disease may alter their metabolism and protein binding thus exposing the patient to an increased fraction of free drug. Moreover, NSAIDs inhibit platelet function, may cause gastrointestinal bleeding and a few cases of hepatotoxicity have been reported. Last, their risk of renal toxicity is enhanced in the presence of hypovolaemia, cirrhosis, nephrotoxic antibiotics or concurrent diuretic therapy.[52] Known risk factors and drug side effects should thus be carefully evaluated before administering NSAIDs to children with stable PFIC.

To conclude, in our series of 22 children with PFIC, different anaesthetic agents were used without overt problems. When selecting the drugs to be administered to a child with PFIC, one should first consider the clinical stage of the disease: in addition to the usual preoperative paediatric examination, hepatic function and nutritional status should be carefully evaluated. Moreover, children presenting signs of portal hypertension should undergo systematic screening for hypoxaemia which could be due to pulmonary arteriovenous shunting. In all cases, anaesthetic agents with no or minimal hepatotoxicity should be used to avoid further deterioration of liver function. In the presence of decompensated liver disease (hypoalbuminaemia, prolonged prothrombin time, ascites and/or encephalopathy), the dose of these agents should be titrated to the patient's response, bearing in mind that hypoalbuminaemia reduces the protein binding of most intravenous agents. The choice of anaesthetic agent should then be tailored to the type and duration of the planned procedure.

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