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Case Report

A Rare Case of Propofol-Induced Acute Hepatitis in after a Brief Endoscopic Retrograde Cholangio-Pancreatography (ERCP)

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ARTICLE INFO

Article history:
Received: 8 February, 2020
Accepted: 26 February, 2020
Published: 28 February, 2020

Keywords:
Propofol
hepatitis
endoscopic retrograde cholangio-pancreatography

ABSTRACT

Background: Given its favourable pharmacokinetic parameters, propofol is commonly used for sedative procedures. The agent is extensively metabolized in the liver and there are sporadic reports of propofol induced acute hepatitis.

Case: A 73-year-old Chinese lady underwent a routine endoscopic retrograde cholangio-pancreatography with propofol sedation who developed deranged liver function tests 4 hours post procedure peaking on day 1. She improved with conservative management only and no other causes for the clinical picture was found. A review of the literature revealed several case reports where propofol have been implicated as a triggering factor.

Conclusion: Although propofol produces rapid recovery without major adverse effects in the vast majority of cases, it is worth bearing in mind the possibility of idiosyncratic reactions that are detrimental to the liver.

Introduction

Propofol is a commonly used intravenous hypnotic agent for sedation, induction and maintenance of anaesthesia. It usually produces a rapid recovery and without major adverse effects. The agent is extensively metabolized by the liver and eliminated by kidney. While it has been well documented that prolonged infusion of the drug of greater than 75 μg /kg/min for more than 24hrs could cause the propofol infusion syndrome that is characterized by lactic acidosis, the drug is generally considered safe for otherwise healthy patients, especially after brief exposure. There are, however, sporadic reports of propofol induced acute hepatitis in the literature and we present here a case involving an elderly Chinese lady who underwent a brief endoscopic retrograde cholangio-pancreatography under sedation with propofol.

Case Report

This case involved a 73-year-old Chinese lady with a two-year history of primary sclerosing cholangitis (PSC). She is otherwise of good past health and has no known drug allergies. She had a right hepatic duct stricture that was previously managed by balloon dilatation and pigtail catheter insertion. On this occasion she was scheduled to have an endoscopic retrograde cholangio-pancreatography (ERCP) for surveillance plus or minus intrahepatic duct (IHD) dilatation under monitored anaesthesia care.

On admission, her liver function tests, complete blood count, renal function tests and clotting profile were all within normal limits. Amoxicillin clavulanate (augmentin) was given as per local protocol for antibiotics prophylaxis. Propofol was administered via a target-controlled infusion with the Marsh model, titrating targeting effect site concentrations of 1.5 to 2.5 μg/ml. One dose of hyoscine butylbromide 20 mg was given prior to the common bile duct cannulation. The total dose of propofol given was approximately 250mg. The duration of the procedure was approximately half an hour and was uneventful and involved a balloon dilatation of the right hepatic duct. Post- dilatation cholangiogram showed a good result and no gross abnormalities were detected in the left hepatic duct. Blood pressure, pulse and pulse oximetry were stable and maintained well within 20% of baseline throughout the procedure. The recovery period was stable, and patient

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http://dx.doi.org/10.31487/j.SCR.2020.02.10

was discharged back to general surgical ward for observation. Intravenous augmentin was continued regularly every 8 hours as per ERCP protocol.

A blood sample taken at 4 hours post procedure showed elevation in the levels of the hepatic parenchymal enzymes alanine transaminase (ALT) and aspartate transaminase (AST), suggestive of hepatocellular damage. On post procedural day 1, the patient developed high fever and substantial LFT derangements. Most notably with a 14- and 27-fold increase in ALT and AST respectively (Table 1). While the bilirubin was also elevated, other liver enzymes including alkaline phosphatase, and serum amylase remained within normal limits. Viral hepatitis markers were negative. Patient did not reveal any history of herbal medicine use within 3 months before the event. She was a lifelong nondrinker and no other medications were given apart from those mentioned above. Subsequently paracetamol 500mg was given Q4H for fever, intravenous amoxicillin clavulanate was changed to tazocin 4.5g 8-hourly. A single dose of amikacin 500mg was given on day 2 due to persistent fever that subsided on day 3 accompanying a downward trend in liver enzymes. The patient was then discharged home on day 4 with oral augmentin. The patient was well and the liver enzymes normalised when tested on day 15. No organisms were grown from blood cultures.

Table 1: Liver function tests before and after ERCP.

	On admission	**Post-ERCP Day 0**	**Post-ERCP Day 1**	**Post-ERCP Day 2**	**Post-ERCP Day 3**	**15th day outpatient follow-up**	**Reference Interval**
Total Bilirubin	5	21	60 H*	61 H	25	10	4-23 umol/L
ALP	65	77	103	137 H	123	73	47-124 U/L
ALT	15	56 H	646 H	514 H	324 H	22	15-37 U/L
AST	22	125 H	1013 H	309 H	106 H	24	15-37 U/L
Amylase	88	110	70	58	N/A	N/A	25-124 U/L

ERCP: Endoscopic retrograde cholangio-pancreatography; ALP: Alanine phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; U/L: Unit/litre; *H: Higher than reference interval.

Table 2: Cases of acute liver toxicity after brief exposure to propofol reported in the literature.

	Patient and procedure	Total dose/duration of propofol	Liver enzymes evaluation	Investigations	Treatment and outcome
Anand et al[2]	17F, 56.8kg, unilateral femoral hernia repair	682mg	AST 1423 U/L (around 25-30 times normal) with an ALT of 1567 U/L (around 30 times of normal limits)	USG liver normal	Resolved spontaneously with supportive measures
Polo-Romerio et al[3]	66 M, ERCP	Brief sedation	AST and ALT 50 times greater than normal level	USG and CT abdomen normal	Resolved spontaneously with supportive measures
Nguyen et al[4]	62F, colonoscopy	250mg	AST 77 times greater than normal upper limit; ALT 44 times exceeds normal limits	Bx: hepatitis with severe activity and mild to focally moderate fibrosis, likely for toxin or drug reaction	Resolved spontaneously with supportive measures after liver biopsy
Kneiseler et al[5]	35F, unilateral stripping of varicose veins	540mg	Four- to sixfold elevated transaminases with impaired coagulation and jaundice	Bx: hepatocyte death and microvesicular fatty degeneration of 90% of the liver parenchyma	Daily IV prednisolone 250 mg, tapered to 40 mg while patient's condition improved rapidly. LFT normalized one year
Asai et al[6]	75F, 36kg, electroconvulsive therapy	Brief	AST 4684 U/L; ALT 3246 U/L; ALP 632 U/L,	Bx: mild lyphocytic infiltration of portal tracts, Positive drug lymphocyte-stimulation testing (DLST)	Glycyrrhizin 60ml/day, LFT normalized day 60 after treatment
O'Shea *et al*. [7]	33M with pontine haemorrhage, induction and post-intubation sedation	150mg for induction; 5 mcg/kg/min for 1 day	ALT 656 U/L; AST 240 U/L; ALP 174 U/L	USG unremarkable	LFT returned to normal levels after propofol infusion was stopped

U/L = international units per litre; ALT: Alanine transaminases; AST: Aspartate transaminases; ALP: Alanine phosphatase; USG: ultrasound; Bx: biopsy.

Discussion

In contrast to the well documented propofol infusion syndrome in which possible mechanisms have been proposed, propofol induced hepatic injury following low dose or brief exposure is rarely reported and appears to be a rare idiosyncratic reaction [1]. We identified only six case reports, the details of which are summarized in (Table 2). Most

patients recovered with supportive treatment, one case however developed acute liver failure and required long term steroid therapy.

In the case of the 17 years old girl, she received propofol as the sole anaesthetic agent and there was no apparent surgery complication from the femoral hernia repair. She presented with nausea and vomiting on post-operative day 1 and was treated with rehydration and supportive measures and the hepatitis was stabilized by day 3 and resolved within ten days. The pattern of acute liver injury seemed most likely to be caused by a severe ischaemic event or a drug-induced toxic injury. Since there was no evidence of a haemodynamic or hypoxic event, the author concluded that there was a casual relation between propofol and that episode of acute hepatitis.

The case involving the 66 years old male undergoing a brief ERCP for residual choledocholithiasis following recent biliary pancreatitis, received propofol as sedation. At 48 hours after the procedure, he was readmitted for acute abdominal pain, nausea, vomiting and elevated liver enzymes. Extensive investigations ruled out other causes of acute liver toxicity. The patient was treated with supportive measures and liver function normalized at his 2-month follow-up.

The lady who underwent a colonoscopy was diagnosed with acute hepatitis at 2 weeks after exposure. Liver biopsy was performed and suggested drug or toxin injury. Since the only new exposure was propofol for the lady, propofol-induced acute hepatitis was suspected. Similar to the previous cases, the liver enzymes were normalized rapidly with supportive measures. In the fourth case, a 35-year-old Caucasian woman developed acute liver failure one week after propofol for stripping of varicose veins. Contrary to other cases, this patient had severe liver failure, presented with increasing transaminases, bilirubin, INR and encephalopathy, which did not resolve spontaneously. She was treated with prednisolone and ursodeoxycholic acid. Six months later, the second biopsy revealed only minimal steatosis and minimal periportal hepatitis and patient still received long-dose corticosteroids to maintain normal transaminases levels.

The 75-year-old lady was a Japanese with refractory depression and received a course of electroconvulsive therapy consisting of 3 treatments each involving propofol. This elderly patient developed acute hepatitis on day 18 after the first treatment, which was 5 days after the exposure. Abdominal ultrasound and other blood tests were normal to rule out other causes of acute hepatitis. Drug-lymphocyte stimulation testing (DLST) for propofol was positive. The author also adopted a scoring system recommended by the 2004 Drug-Induced Liver Injury Workshop is commonly used as a diagnostic criterion for drug-induced liver injury, with a reported sensitivity of 98.7% and a specificity of 97%. The patient scored 10 on the diagnostic criteria and thus received a definitive diagnosis of propofol-induced hepatocellular liver injury. Patient was treated with glycyrrhizin at a dose of 60ml/day. After 60 days of glycyrrhizin, the liver enzymes normalized. In the final case deranged liver function tests was noted on second day of infusion at which time the propofol was stopped. He required supportive treatment and cessation of the infusion.

The above cases occurred in patients spanning a wide age range undergoing very different and predominantly non abdominal procedures. This support the notion that is likely to be an idiosyncratic reaction. While in this case report the patient has a background of primary sclerosing cholangitis, derragements in liver function tests is generally more cholestatic rather than a hepatitis picture with this condition [8]. What is noteworthy with this case is the rapidity with which the hepatitis developed, lending support to it being propofol induced in aetiology, given there were minimal periprocedural haemodynamic instability and no other known hepatic toxins given.

Propofol is frequently used for sedation in short surgical procedures Consequently it is important to recognize the rare complication of propofol-induced acute liver hepatitis. Although the prognosis of propofol-induced liver hepatitis is promising in most of the cases reported in the literature, there is the potential of it leading to liver failure that warrants longer term treatment. Therefore, it is important to monitor the patient closely once the diagnosis is suspected and provide supportive treatment until the condition resolves.

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