

A Rare Case of Propofol-Induced Acute Liver Failure and Literature Review

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Key Words

Acute liver failure · Drug toxicity · β -Oxidation · Free fatty acids · Transient elastography · 2,6-diisopropylphenol (propofol)

Abstract

The incidence of drug-induced acute liver failure is increasing. A number of drugs can inhibit mitochondrial functions, alter β -oxidation and cause accumulation of free fatty acids within the hepatocytes. This may result in hepatic steatosis, cell death and liver injury. In our case, propofol, an anesthetic drug commonly used in adults and children, is suspected to have induced disturbance of the mitochondrial respiratory chain, which in consequence led to insufficient energy supply and finally liver failure. We report the case of a 35-year-old Caucasian woman with acute liver failure after anesthesia for stripping of varicose veins. Liver histology, imaging and laboratory data indicate drug-induced acute liver failure, presumably due to propofol. Hepatocyte death and microvesicular fatty degeneration of 90% of the liver parenchyma were observed before treatment with steroids. Six months later, a second biopsy was performed, which revealed only minimal steatosis and minimal periportal hepatitis. We suggest that propofol led to impaired fatty acid oxidation possibly due to a genetic susceptibility. This caused free fatty acid accumulation within hepatocytes, which presented as hepatocellular fatty degeneration and cell death. Large scale hepatocyte death was followed by impaired liver function and, consecutively, progressed to acute liver failure.

Introduction

As the incidence of acute and fulminant viral hepatitis in the industrialized world is constantly decreasing, drug-induced liver injury nowadays represents a major cause of acute liver failure (ALF). In developed countries, drug-induced liver injury accounts for nearly 2–5% of hospital admissions for jaundice, and for more than 50% of cases of ALF, with a significant number of patients undergoing a lethal course unless eligible for liver transplantation [1, 2]. In the pathogenesis of drug-induced hepatotoxicity, cell death is a crucial event leading to several clinical manifestations [2, 3]. A key feature of most drugs causing ALF is the production of toxic metabolites that either elicit an immune reaction or directly affect cell signaling in hepatocytes and cholangiocytes [3]. In humans, drug-induced liver injury can provoke almost all manifestations of acute and chronic liver disease. Most cases of drug-induced hepatotoxicity present histological features of hepatocellular damage, cholestasis and/or steatosis. Infrequently, a granulomatous reaction may be encountered [4].

In a minority of individuals receiving drugs, unpredictable adverse drug reactions occur which, in the absence of allergic symptoms (e.g. rash, eosinophilia, ANA or LKM) are presumed to be idiosyncratic events. Idiosyncratic reactions can even occur after an intermediate to protracted latency for more than 5–90 days and may exhibit a dose-related toxicity in rare susceptible individuals [5]. In addition, certain drugs inhibit mitochondrial functions, e.g. β -oxidation, which leads to free fatty acid (FFA) accumulation within the hepatocytes. Consequently, this results in steatosis and cell death with liver failure [6]. Indeed, it has recently been described that propofol (2,6-diisopropylphenol), an alkylphenol derivative which has sedative as well as hypnotic characteristics, can influence mitochondrial functions [7–9]. Pharmacokinetics of propofol follow a three compartment linear model: it presents with a fast distribution to tissues, a rapid metabolic clearance and a slow return to the circulation [8]. In this report we present the clinical course of a case of propofol-induced ALF, review the current literature and discuss its clinical relevance, underlying molecular and pharmacogenetic mechanisms and potential therapeutic options.

Case Report

A 35-year-old Caucasian woman, who underwent anesthesia with a total dose of 540 mg of propofol for the stripping of varicose veins of the right leg, was admitted to our hospital with the clinical diagnosis of ALF. One week after surgery, four- to sixfold elevated transaminases were documented for the first time. After hospital admission a liver biopsy was performed due to elevated liver enzymes, impaired coagulation and progradient jaundice (fig. 1). Histologic findings revealed florid and lobar accentuated as well as chronically persistent hepatitis with hepatocyte death, hepatocellular cholestasis and microvesicular fatty degeneration of 90% of the liver parenchyma (fig. 2a). These findings were consistent with the diagnosis of toxic liver damage, most likely caused by propofol. Because of the continuously elevated transaminases, bilirubin, INR and encephalopathy the patient was referred to the liver transplant centre of the University of Essen for transplant evaluation.

Medical history was uneventful and earlier laboratory tests had always been in within normal limits. She had undergone hepatitis A and B vaccination years before, and there was no history of any medications or herbal drugs during three months before the event. Alcohol consumption was denied. Family history was unremarkable and there was no history of recent traveling. The serology for hepatotropic viruses (HAV, HBV, HCV, HIV, EBV, HSV and CMV) was negative. Laboratory tests for autoimmune markers (ANA, ANCA, LKM, SMA) and other entities such as Wilson's disease or Budd-Chiari syndrome revealed no abnormalities. Compound heterozygosity was found while testing for hemochromatosis. Furthermore, initial liver biopsy did not show any pre-existing chronic liver cell damage.

Ultrasound revealed hepatomegaly and an inhomogeneous parenchyma without splenomegaly. The hepatic vasculature appeared regular. Perihepatic and hypogastric ascites was found. Upper endoscopy was performed to rule out esophageal varices. Transient elastography (FibroScan®, Echosens, Paris, France) revealed liver stiffness, consistent with characteristic alterations in liver stiffness in patients diagnosed with ALF (own unpublished data) (fig. 3). As her mental status was stable, we continued the basic transplant evaluation.

As combination therapy with corticosteroids and ursodeoxycholic acid has been shown to be a safe and efficient treatment for nonalcoholic toxic liver failure [10], therapy with 250 mg prednisolone per diem intravenously was started. The dose was subsequently tapered off to 40 mg per diem. During the course of treatment the patient's condition improved rapidly. AST, ALT and bilirubin decreased to slightly elevated levels and INR levels remained stable (fig. 1). Thirty days after admission the clinical situation was significantly improved, encephalopathy and icterus had resolved and the patient was discharged. Six months later, a second biopsy was performed, which revealed only minimal bridging fibrosis and less steatosis as well as minimal periportal hepatitis (fig. 2b).

To investigate the potential impact of genetic alterations in metabolizing enzymes on the clinical course we sequenced the genes of UDP-glycosyltransferase 1 family, polypeptide A9 (*UGT1A9*) and cytochrome P450, subfamily IIB, polypeptide 6 (*CYP2B6*), which catalyze the initial metabolizing step of propofol inactivation and excretion [11, 12]. Sequencing was performed as previously described [13–15]. Analysis revealed a heterozygous *1a/*1c genotype for *UGT1A9* (<http://www.ugtalleles.ulaval.ca>) as well as a heterozygous variant-genotype *1J/*5A for *CYP2B6* (<http://www.cypalleles.ki.se>).

One year after first admission the patient presented in good healthy condition, with liver enzymes, bilirubin and INR within normal ranges. Although ultrasound did not show any signs of portal hypertension, liver parenchyma was still inhomogeneous. Liver stiffness measured by transient elastography had decreased to 7.9 kPa. The patient still received a therapy with low-dose corticosteroids as an increase in transaminase levels was noted when corticosteroid administration was tapered off completely.

Discussion

Drug toxicity is often classified as intrinsic versus idiosyncratic. Intrinsic toxicity is dose-dependent, reproducible in animal models and occurs in every individual that is exposed to a sufficient dose of a certain drug. In contrast, idiosyncratic reactions are unpredictable and caused by the inability of single individuals to tolerate a given compound. They can manifest as hypersensitivity reactions accompanied by clinical symptoms such as fever, rash, and/or eosinophilia. Another type of idiosyncratic reaction is attributable to pharmacogenetic differences between individuals, i.e. genetic polymorphisms in the metabolism of certain substances [4].

Although 2,6-diisopropylphenol (propofol) is commonly used for sedation and introduction and/or maintenance of anesthesia, this is the first case report describing ALF due to propofol [9]. In the literature, there are three cases of acute hepatitis after brief sedation with propofol reported so far (table 1) [16–18].

As a matter of fact, histological findings in our case included extensive hepatocyte necrosis as well as fatty degeneration of 90% of the lobar parenchyma. However, there have been reports of hepatocellular injury related to sedation with propofol in intensive care units, particularly in children [7, 19, 20]. Parke et al. reported five cases of children who had been sedated with propofol and developed respiratory failure, metabolic acidosis and died in the end by refractory bradyarrhythmia in spite of critical care management. Postmortem examination of the liver performed in three of the five children revealed massive fatty degeneration [20]. Propofol infusion syndrome (PRIS), which is characterized by metabolic acidosis, lipemic plasma and myocardial failure, has been described in the literature [9]. In addition, hyperkalemia, hepatomegaly and rhabdomyolysis are key features of PRIS [21]. ALF, however, has not yet been described

in this context. Development of PRIS has mainly been reported in patients undergoing long-term sedation with propofol, but also during anesthesia of not more than five hours duration [9, 22, 23]. Although our patient does not match the criteria for PRIS, she developed a massive fatty liver. By excluding other known causes for this condition, it is to be suspected that there is an actual causality between the use of propofol and ALF [24].

As to the proposed mechanisms of propofol-induced liver injury, it has been assumed that propofol-induced disturbance of the mitochondrial respiratory chain, which in consequence leads to insufficient cellular energy supply and consecutive cell death, might be the cause of PRIS [25, 26]. Indeed, in animal models propofol causes relevant damage to the mitochondria [27]. Furthermore, it has been described that propofol affects the generation and/or the maintenance of the transmembrane electrical potential [27] and impairs the electron flow along the mitochondrial electron chain [28]. In humans, propofol is believed to affect fatty acid oxidation by inducing an increase in malonylcarnitine, which leads to an inhibition of carnitine palmitoyl transferase 1, a mitochondrial transport protein for long-chain fatty acids [29]. Wolf et al. described a secondary inhibition of the respiratory chain at complex II [29]. In summary, entrance and utilization of FFAs is impaired [25]. Moreover, reduced cytochrome C oxidase activity in the presence of propofol has also been reported [7, 22]. Recently, Ypsilantis et al. described serious liver damage with focal hepatocyte necrosis and cholangitis in addition to low-grade hepatitis and steatosis in propofol-sedated rabbits during prolonged mechanical ventilation [19]. In addition, it is well known that certain drugs inhibit mitochondrial functions and, by rendering the pathway of β -oxidation inefficient, cause an accumulation of FFAs within the hepatocytes which culminates in steatosis [6]. Intriguingly, recent studies suggest that such intracellular FFA accumulation promotes death receptor expression, which leads to a reactive increase in the hepatocytes' susceptibility to apoptosis and/or necrosis and, thereby, significantly promotes liver injury [30, 31].

Glucuronidation of propofol in the liver is the main pathway of its metabolism [32]. The glucuronidation of propofol is catalyzed by UGT1A9 [11]. Another important pathway is the oxidation of propofol to 4-hydroxy-propofol, by enzymes of the cytochrome P-450 family [33]. It has been shown that CYP2B6 is the predominant isoform involved in the oxidation of propofol in human liver microsomes [34, 35]. In addition to that CYP2B6 is believed to be the principal determinant of interindividual variability in the hydroxylation of propofol by human liver microsomes [12]. For both enzymes it is well known that genetic variations can lead to clinically relevant alterations of propofol metabolism [36, 37]. Therefore, we decided to perform further examinations concerning genetic polymorphisms in our patient with regard to the enzymes mentioned above. Sequencing of *UGT1A9* revealed a homozygous wild-type genotype of the coding region and two heterozygous single nucleotide polymorphisms in the regulatory promoter region, corresponding to a *1a/*1c diplotype. It has been shown that these promoter polymorphisms did not influence the amount of UGT1A9 on the protein level [38]. The patient carries the heterozygous CYP2B6 variant genotype *1J/*5A. Heterozygous CYP2B6 *5 allele carriers showed a significantly decreased expression and activity of CYP2B6 [15]. However, these results could not be confirmed for heterozygous *5 allele carriers in a second study, but this was possibly due to small sample size [14]. Therefore, an impact of this variant on the clinical course cannot be excluded, but it is very likely that the patient carries variants in other genes (e.g. in β -oxidation-related genes) contributing to the fulminant course of this adverse drug reaction (fig. 4).

With regard to our observations it might be reasonable to keep in mind that there are few cases of liver complications after administration of propofol. These are most probably due to idiosyncratic drug reactions. Patients treated with propofol should be monitored closely and if there are signs of hepatitis or ALF an idiosyncratic drug reaction should be considered as possible cause after other causes have been excluded.

Table 1. Cases of acute hepatitis after brief sedation with propofol reported in the literature

Paper	Patient's sex, age	Total dose of propofol	Laboratory analysis	Liver biopsy	Outcome
Anand et al. [18]	female 17	682 mg for femoral hernia repair	ALT 1,567 U/l, AST 423 U/l	not performed	AST 20 U/l, ALT 62 U/l 10 days later
Polo-Romero et al. [17]	male 66	brief sedation for therapeutic ERCP	AST and ALT ↑ 50 times the reference value, slight increase in GGT, AP, total bilirubin 8.9 mg/dl	not performed	2 months follow-up: patient was asymptomatic, liver enzymes were normal
Nguyen and Borum [16]	female 62	250 mg for colonoscopy	AST 2,309 U/l, ALT 1,313 U/l, AP 322 U/l, total bilirubin 4.8 mg/dl	hepatitis with severe activity and mild to focally moderate fibrosis	normalization of transaminases in outpatient laboratory testing

Fig. 1. a Course of ALT and AST. **b** Course of bilirubin.

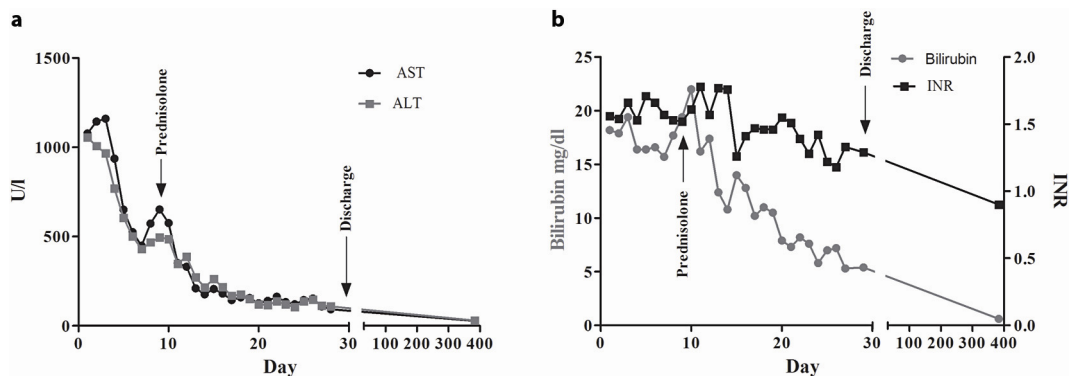


Fig. 2. Liver histology (HE staining). **a** Before therapy. **b** After therapy.

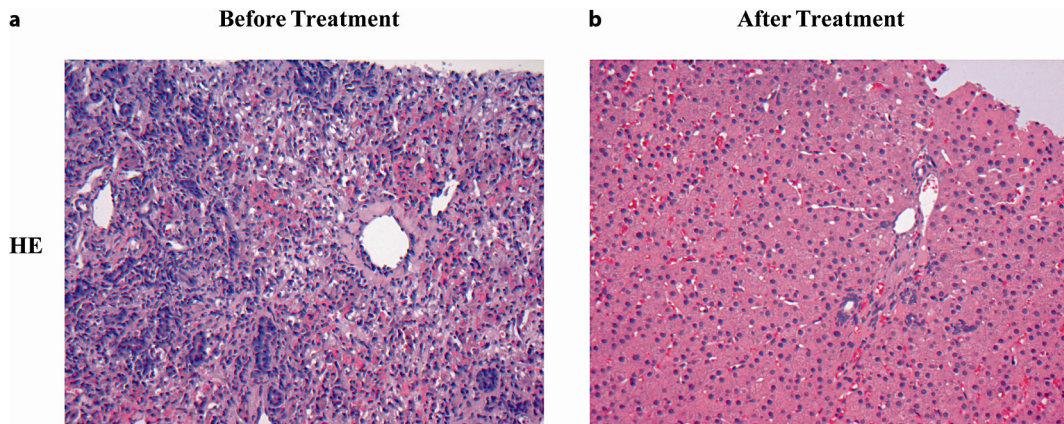


Fig. 3. Elastography of the liver (Fibroscan®).

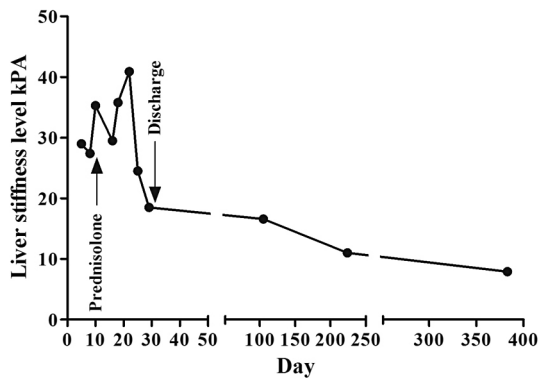
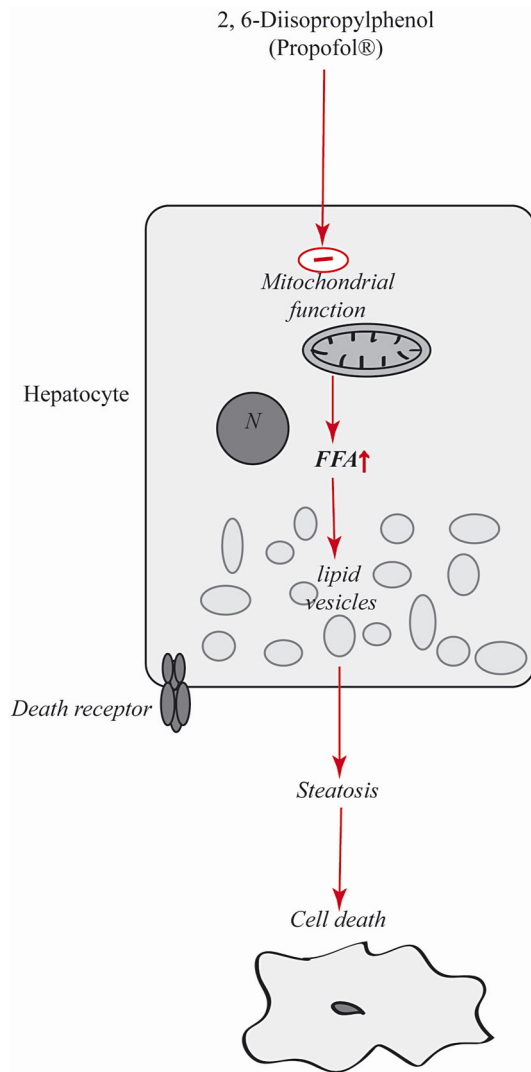


Fig. 4. Possible pathomechanism of Propofol®-induced liver failure. N = Nucleus; FFA = free fatty acids.



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