Biochemical and Histopathological Effects of Iohexol and Iopromide Contrast Media on the Liver of Wistar Rats

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Abstract

Background: Certain chemical drugs like contrast media have the potential to cause liver injury even when administered within the range of diagnostic purpose.

Objectives: This study compared biochemical and histomophological liver changes of two (2) low osmolar contrasts media (LOCM) Iohexol and Iopromide on Wistar Rats.

Methods: The study was experimental, Iohexol (350mg I/mL) and Iopromide (300mg Iodine/mL) were administered at varying doses and blood sample collected and liver organs harvested at different time interval for biochemical and histopathological laboratory evaluation respectively.

Results: No significant difference is seen in mean value of aminotransferases, except alkaline phosphatase and albumin when LOCM Iohexol is compared with Iopromide regardless of the dose and time interval of administration. Histomorphological changes however showed moderate necrosis of the hepatocytes which appeared higher with Iohexol when compared with Iopromide at higher dose 1 week after administration.

Conclusion: The findings of the study showed Iohexol have the least toxicity to liver when compared with Iopromide especially when administered intravenously at higher doses and 1 week internal.

Keywords: Biochemical. Histopathological, Iohexol, Iopromide, Contrast agent

Introduction

The most successful and widely applied contrast media in use today are the iodinated contrast media because of their high-contrast density, firm binding to the benzene molecule, and low toxicity [1, 2]. They are commonly used in diagnostic and image guided interventional procedures such as angiography, computed tomography (CT), conventional radiography, magnetic resonance imaging, interventional cardiology and imaging of the hepatobiliary system. Liver injury from drug hepatotoxicity can results in hepatocyte cell death and inflammation. The cascade of events leading to Drug induced liver damage and the cell death subroutine of the cell depend largely on the drug. Leading to necrosis or apoptosis, while cell death in idiosyncratic is usually the result of engagement of the innate and adaptive immune system (likely apoptotic), involving death receptors (DR) [3].

Experimental studies of the tolerability of uroangiographic contrast media (CM) in wistar rats with cirrhosis of the liver showed that marked worsening of cirrhosis occurred after administration of both ionic and non-ionic CM. Even in patients with healthy livers, the use of ionic and nonionic substances for visceral angiography results in slight temporary increases in hepatic enzymes. The maximum increase in liver enzymes (alkaline phosphatase, glutamate pyruvate transaminase, glutamate oxaloacetate transaminase) is seen between 48 and 72 hours after contrast media administration [4]. This study compared biochemical and histomophological liver changes of two (2) low osmolar contrasts media (LOCM) Iohexol and Iopromide on Wistar Rats.

Materials and methods

Ethics

The experimental study was consistent with ethical principles of animal's experimentation and

guidelines as established by the National Institute of Veterinary Research Vom Jos Plateau State.

Animal Studies

A total of 80 Wistar rats randomly selected from the animal center of the research institute aged 3 - 4 months and weighing between 120 – 152 grams were randomly divided into 13 groups. Group 1: (Iohexol 350 mg I/mL), Group 2: (Iohexol 700 mg I/mL), Group 3: (Iohexol 1400 mg I/mL), Group 4: (Iopromide 300 mg I/mL), Group 5 (Iopromide 600 mg I/mL), Group 6: (Iopromide 1200 mg I/mL). The same contrast media doses of Iohexol and Iopromide were used for groups (7, 8, 9, 10, 11, 12) and a control group 13 (0.9% NaCl). Each group consists of at least six (6) rats housed in a cage and allowed to acclimatize for 3 weeks in the animal house before the commencement of study. During that period they were monitored to ensure a high level of hygiene and cleanliness of the housing system and also to ensure that they were in good condition. Pellet diets (vital feed) were regularly and sufficiently given to them as food. They also have access to fresh, portable, uncontaminated drinking water. After acclimatization, contrast media were administered via the tail vein. 72 hours later the animals in groups (1-6) including control were sacrificed under anesthesia. Blood samples were collected by direct puncture to the heart under anesthesia for biochemical analysis of liver function such as transaminase, alkaline phosphatase, albumin and bilirubin. The liver organ is then resected ***en bloc*** and fixed in 10% formalin solution. The same procedure was performed 1 week later for animals in groups (6 – 13). For microscopic examination, the liver tissues in all the groups were fixed in formalin and embedded in paraffin. Tissue sections from each block were stained with hematoxylin/eosin for histopathological evaluation. We performed histopathological examination of the liver to assess parenchyma necrosis, vascular and inflammatory changes.

Statistical analysis

Biochemical data were analyzed using analysis of variance (ANOVA). Statistical package for social sciences (SPSS) version 23.0 Chicago version. A value of $P < 0.05$ was accepted as the significance level.

Results

Biochemical evaluation

There were no significant differences ($P > 0.05$) between iohexol and iopromide after 72 hours of intravenous administration (Groups 1 – 6) for alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, alkaline phosphatase (ALK) was higher ($P > 0.05$) in the iopromide groups (4, 5, and 6) than in the iohexol groups (1, 2, and 3). Similar, there was no significant difference significant difference ($P > 0.05$) between iohexol and iopromide after 1 week of intravenous administration (Groups 1 – 6) for alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, alkaline phosphatase (ALK) was higher ($P > 0.05$) in the iopromide groups (4, 5, and 6) than in the iohexol groups (1, 2, and 3) (Table 1).

Histopathological alterations

Pathological findings for the liver are summarized in table (2). Normal liver tissues were seen in control group. Mild necroses were noted in iohexol group 3 and 7 when compared with iopromide group 4 and 12 which showed moderate – severe necrosis of the liver 72 hours and 1 week respectively after intravenous administration. Multifocal bridging inflammation was also noted in the iopromide groups at higher do Table 1: Comparison between Iohexol and Iopromide at Different Dose Levels after Intravenous Administration (IVA)

Animal Groups	ASAT (IU/L)	ALAT (IU/L)	ALB (g/L)	ALKP (IU/L)	T.BIL (IU/L)	C.BIL (Umol/L)
			72 hours after IVA			
Group 1 & 4 (Low Dose)	1.00	1.00	0.92	0.00*	0.22	1.00
Group 2 & 5 (Medium Dose)	0.19	1.00	0.08*	0.01*	1.00	0.15
Group 3 & 6 (High Dose)	1.00	0.27	1.00	0.00*	0.74	1.00

Animal Groups	ASAT (IU/L)	ALAT (IU/L)	ALB (g/L)	ALKP (IU/L)	T.BIL (IU/L)	C.BIL (Umol/L)
			1 week after IVA			
Group 7 & 10 (Low Dose)	0.09	1.00	0.72	0.00*	0.35	1.00
Group 8 & 11 (Medium Dose)	1.00	1.00	0.20	0.02*	0.00*	0.84
Group 9 & 12 (High Dose)	1.00	1.00	0.31	0.01*	0.23	0.01*

Table 2: Summary of Histological Findings of Liver between Iohexol and Iopromide at Different Dose Levels after Intravenous Administration (IVA).

Dose	Histological Presentations	
	Iohexol	Iopromide
	72 hours after IVA	
Low	Normal	Normal
Medium	Normal	Normal
High	Mild necrosis of the hepocytes	Moderate-severe necrosis of the hepocytes
	1 week after IVA	
Low	Normal	Normal
Medium	Normal	Normal
High	Mild necrosis of the hepocytes	Moderate-severe necrosis of the hepocytes

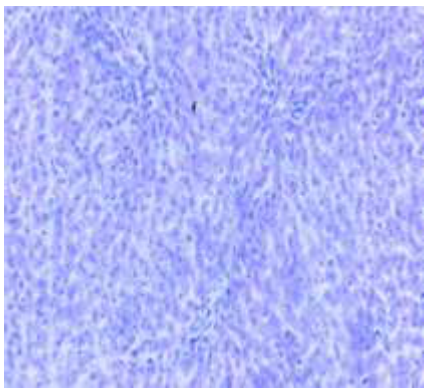

Fig 1(a)

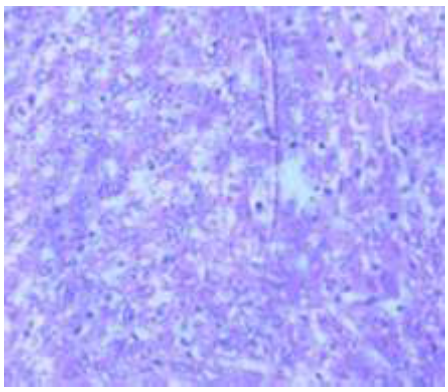

Fig 1 (b)

Fig 1: Mild necroses (a) in iohexol group and (b) Moderate-severe necrosis of the liver parenchyma in iopromide group after intravenous administration.

Discussion

The activities of liver enzymes may be influence by various chemical substances including contrast media [5]. These chemical substances can influenced the enzyme mechanism and can serve either as inhibitors or inducers [6]. Liver pathology is an important tool for identifying and characterizing liver injury whether or not biochemical changes are also identified. The types of liver injury from such biochemical reactions include steatosis (fatty liver), liver necrosis, cirrhosis, cholestasis, hepatitis etc. In this present study we assessed the biochemical changes of liver function after intravenous administration of iohexol and iopromide. Our findings showed no significant difference between groups for ALT and ASP after 72 hours and 1 week between iohexol and iopromide. Similar study by topcu *et al* had also compared changes in ALT and ASP to determine the effect of contrast media on the

hepato-pancreato-biliary system in rats [7]. Their results which showed no significant difference after 15 days of contrast medium administration which agrees with the findings of this present study but contrary to study done by O'Connor et al which showed difference after 17 hours, though their study compared high and low osmolar contrast media, the findings are similar with this present study after 1 week and beyond. This present study also compared the ALP levels between iohexol and iopromide, but contrary to other parameters of liver function test, there was a significant increase in ALP level in iopromide group at different doses compared with iohexol. These findings also agree with the findings of Topcu et al [7].

In studies of pigs, only slight statistically non-significant changes in the hepatic enzymes were observed after administration of both ionic and non-ionic substances (iohexol) in relatively high doses for selective coeliac angiography with a balloon occlusion of the coeliac trunk. Further experimental studies of the tolerability of uroangiographic contrast media (CM) in wistar rats with cirrhosis of the liver showed that marked worsening of cirrhosis occurred after administration of both ionic and non-ionic CM. Even in patients with healthy livers, the use of ionic and non-ionic substances for visceral angiography results in slight temporary increases in hepatic enzymes. The maximum increase in liver enzymes (alkaline phosphatase, glutamate pyruvate transaminase, glutamate oxaloacetate transaminase) is seen between 48 and 72 hours after contrast media administration [4].

Many chemicals are known to cause liver necrosis, an acute injury that involves the rupture of the plasma membrane and cell death. Among the common toxicants that manifest such effects are the halogenated hydrocarbons, such as carbon tetrachloride, chloroform etc. Other hepatotoxicants include acetaminophen, phosphorus, beryllium, tannic acid, and allyl alcohol. Most of these substances produce reactive metabolites that covalently bind with unsaturated lipids and proteins present at high concentrations in subcellular membranes, inducing lipid peroxidation. Other mechanisms and biochemical changes that may be manifested in liver necrosis include disturbance of Ca^{2+} homeostatis, depletion of glutathione, mitochondrial damage, inhibition of protein synthesis, and binding to macromolecules. Exogenous substances like paracetamol. [8], carbon tetrachloride [9], amatoxins, herbal plants like Atractylis gummifera and Callilepsis laureola [10], Larrea trdentata [11] and Teucrium polium [12] also causes necrosis. Such injury is largely confined to a particular zone of the liver lobule. It may also manifest as a very high level of alanine aminotransferase and severe disturbance of liver function leading to acute liver failure.

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