Comparative Investigation of Iohexol and Iopromide Contrast Media: Effect on Renal Function and Histomorphology of Wistar Rats.

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Abstract

Background: Contrast induced nephropathy is one of the major cause of hospital mortality and morbidity and their effect is known to reduce by decrease in their osmolality.

Objective: The purpose of this study is to compare the effect of intravenous administration of Iohexol and Iopromide on renal function and histomorphology of wistar rats.

Methodology: 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: There is a significant increase in mean value creatinine, when Iohexol was compared with Iopromide 1 week after administration. But no significant difference is seen in mean value of creatinine between Iohexol and Iopromide 72 hours after administration. Histomorphological changes showed moderate necrosis of the renal tubules which appeared severe with Iohexol after 1 week.

Conclusion: The findings of the study showed Iopromide have the least effect on the kidney when compared with Iohexol at different dose levels.

Keywords: Histomorphology, Iohexol, Iopromide, Renal Function, Wistar Rats, Contrast Agent

Introduction

An important potential side effect of iodinated contrast administration is contrast induced nephropathy (CIN), defined as reduction in renal function induced by contrast media within three (3) days of intravascular administration in the absence of any other etiology [1,2]. CIN is an important cause of hospital acquired renal failure. Prevention is therefore necessary to avoid the substantial morbidity and mortality that sometimes occur with CIN [3]. The identification of conditions that represent the risks for the development of CIN is of major importance in the prevention of CIN. Several studies have shown associated increased risk of contrast induced nephrotoxicity especially with high osmolar contrast media [4].

The precise mechanism of CIN is not entirely clear, but leading theories showed that CIN results from hypoxic injury of the renal tubules induced by renal vasoconstriction or by direct cytotoxic effects of contrast media [5, 6]. Alternatively some experts have argued that CIN occurring after intravascular administration of contrast media is caused by coexisting risk factors and is only coincidentally related to the contrast media, especially if contrast media are administered intravenously. Regardless of the precise etiology, the development of CIN after use of intravascular contrast media remains a major concern [7].

It is commonly presumed that contrast media of the same group category such as nonionic low osmolar contrast media have comparative similar effect and risk of complications to kidney function and morphology when administered intravenously, but however there are little direct comparative studies to support these assumptions [8, 9]. This study

therefore compared the effect of intravenous administration of Iohexol and Iopromide on kidney function and histomorphology of 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 renal function such as urea and creatinine. The kidney 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 kidney 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 kidney 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. 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 creatinine. However, creatinine value was significantly higher ($P < 0.05$) in the iohexol groups (7, 8, and 9) than in the iopromide groups (10, 11, and 12) after 1 week of administration (Table 1).

Histopathological alterations

Pathological findings for the kidney are summarized in table (2). Normal kidney tissues were seen in control group and 72 hours after administration of iohexol and iopromide and low-high doses. Moderate necroses of the tubules were noted in iopromide at medium and high doses when compared with iohexol groups which showed severe necroses of the renal tubules at the same dose level after 1 week of administration.

Table 1: Comparison between Iohexol and Iopromide at Different Dose Levels after Intravenous Administration (IVA).

Animal Groups	Urea (mmol/L)	Creatinine (mmol/L)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)
			After 72 hours			
Group 1 & 4 (Low Dose)	1.00	0.10	1.00	1.00	1.00	0.00*
Group 2 & 5 (Medium Dose)	1.00	1.00	1.00	0.52	1.00	1.00
Group 3 & 6 (High Dose)	1.00	0.63	0.21	1.00	0.15	1.00

Animal Groups	Urea (mmol/L)	Creatinine (mmol/L)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)
			After 1 week			
Group 7 & 10 (Low Dose)	0.26	0.01*	0.26	1.00	0.03*	0.00*
Group 8 & 11 (Medium Dose)	0.59	0.01*	1.00	1.00	1.00	0.73
Group 9 & 12 (High Dose)	1.00	0.00*	1.00	0.11	1.00	0.15

Table 2: Summary of Histological Findings of kidney 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	Normal	Normal
	1 week after IVA	
Low	Normal	Normal
Medium	Severe necrosis of renal tubules	Moderate necrosis of renal tubules
High	Severe necrosis of renal tubules	Moderate necrosis of renal tubules

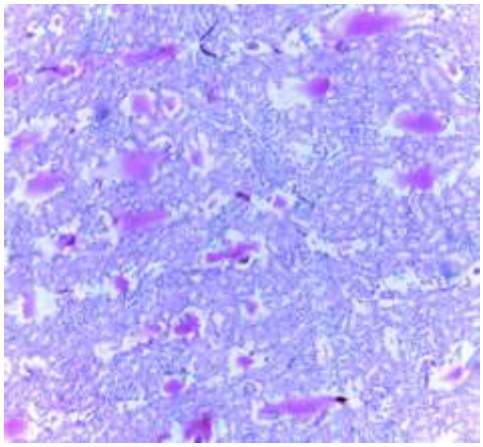

Fig 1(a)

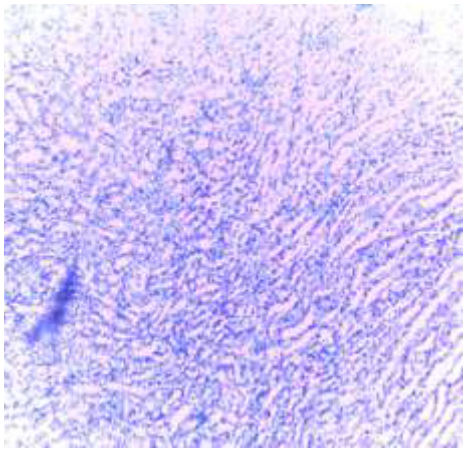

Fig 1(b)

Fig 1: Severe necroses of the renal tubules (a) in iohexol group and (b) Moderate necrosis of the renal tubules in iopromide group 1 week after intravenous administration

Discussion

Contrast induced nephropathy is a substantial cause of morbidity and mortality and the third most common cause of renal dysfunction by hospitalized patient (Nash et al. 2002). Prevention of the incidence of contrast induced nephropathy is therefore of great clinical relevance and value and previous studies have attempted to compare the effect of different types of low osmalar contrast media on renal functions [10, 11].

Once a decision had been reach to administer intravenenous contrast media to patient, some important factors to consider in order to minimize

the incidence of contrast induced nephropathy is the type and amount of contrast to be administered [8]. It is a general presumption that the risk of developing CIN increases with dose and that contrast of the same group category such as nonionic low osmolar contrast media have comparable similar effect and risk of complications [12, 13].The real risks for CIN are represented by pre-existing renal impairment, dose, route of administration, salt depletion and dehydration, advanced age etc. As of the time of writing and as far as we know no previous studies had strictly assessed and compare the effect of iohexol and iopromide on histomorphological and renal function in rats.

A comparative study of the effect of iohexol and iopromide on renal function by Jonathan et al showed CIN rates were not statistically different using any definition. Although the study result were unable to show absolute non- inferiority of iohexol compared with iopromide because of a very small difference in mean serum creatinine from baseline, this difference is likely of minimal or no clinical importance in outpatients undergoing CT with low risk for CIN. The mean change in serum creatinine from baseline was done maximally on day 3 which is equivalent to 72 hours after intravenous administration of the contrast agents [8]. This result agrees with the findings of this present study 72 hours after administration of contrast. Though, the study by Jonathan never studied change in serum creatinine after 1 week, our findings in this study showed significant increase in mean serum creatinine after 1 week of intravenous administration of iohexol when compared with iopromide.

Similarly a meta-analysis was carried out on the comparative effects of different contrast media on the kidney through 2014. The independent reviewers identified related articles on randomized control trials that reported CIN related outcomes in patients after receiving low osmolar contrast media as well as iso-osmolar contrast media. A head to head comparison of one LOCM with another LOCM was done in 856 patients from five randomized control trial. The LOCM that were found in the meta-analysis includes iohexol, iopamidol, iopromide among others. The study no statistically significant or clinically important difference between study arms in the incidence of CIN (or related measures of a change in renal function), and the overall analysis did not suggest that any one LOCM was superior to another [7]. The finds disagree with our results which found statistically significant difference between iohexol and iopromide after 1 week of administration.

In conclusion, our study was able to show that iopromide had the least nephrotoxicity when compared with iohexol after 1 week of intravenous administration, but appeared relatively non toxic within 72 hours. Thus, when administered intravenously, iopromide appeared to have the least adverse effect to the kidney compared to iohexol in this study in the long end.

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