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Effect of radiocontrast agents on release Of urinary endothelin in patients With chronic renal impairement

Thesis submitted for fulfillment of master degree in Internal medicine

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I dedicate his study to my;

Mother,

Father,

Husband

Sisters,

Brothers,

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Abstract

Endothelin has potent vasoconstrictor effect on various vessels, including the renal vasculature and is reported to induce hemodynamic changes similar to those induced by CM when infused into the renal artery. Furthermore, ET antagonists such as BQ123 can inhibit CM induced vasoconstriction in the kidney. Therefore, it is conceivable that is one of the important mediators of RCN

Key word

Urinary endothelia impairement

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List of Abbreviations

NO	**Nitric Oxide**
NSAIDs	**Non Steroidal Anti Inflammatory Drugs**
ACEI	**Angiotensin Converting Enzyme Inhibitors**
ARBS	**Angiotensin Receptor Blockers**
GFR	**Glomerular Filtration Rate**
EF	**Ejection Fraction**
LOCM	**Low Osmolar Contrast Medium**
HOCM	**High Osmolar Contrast Medium**
IOCM	**Intermediate Osmolar Contrast Medium**
CKD	**Chronic kidney disease**
DA2	**Dopamine Receptor 2**
DA1	**Dopamine Receptor 1**
PGE1	**Prostaglandin E1**
ET1	**Endothelin 1**
ET2	**Endothelin 2**
ET3	**Endothelin 3**
ETA	**Endothelin Receptor A**
ETB	**Endothelin Receptor B**
EFF	**Effective Filteration Fraction**
ESRD	**End stage renal disease**
GFR	**Glomerular filtration rate**
CM	**Contrast Medium**
RCN	**Radioconrast Nephropathy**
CIN	**Contrast Induced Nephropathy**
CVD	**Cardiovascular Disease**
ED	**Endothelial Dysfunction**
DM	**Diabetes Mellitus**
HF	**Heart Failure**
ECE	**Endothelin Converting Enzyme**

Introduction

Radiocontrast medium (CM) is one of the most common causes of hospital-acquired acute renal failure. Although the precise mechanisms of radiocontrast- induced nephropathy (RCN) remain unclear. The proposed mechanisms include direct nephrotoxicity and renal ischemia. Infusion of CM in the renal artery results in acute transient vasodilatation followed by sustained vasoconstriction.

Endothelin-1 (ET) has potent vasoconstrictior effects on various vessels, including the renal vasculature and is reported to induce hemodynamic changes similar to those induced by CM when infused into the renal artery. Furthermore. ET antagonists such as BQ123 and FR 13917 can inhibit Cm induced vasoconstriction in the kidney. Therefore, it is conceivable that ET is one of the important mediators of RCN.

Patients with pre-existing renal insufficiency, diabetes mellitus, congestive heart failure or dehydration are at high risk of RCN however the reason why impairment of renal function predisposes a person to develop RCN is not clear. In the present study, we measured the dynamic changes in the plasma and urinary excretion of ET after the infusion of CM, and investigated the role of ET in ECN by comparing patients with renal dysfunction and those with normal renal function.

Aim of the study:

Aim of study is to examine the role of endothelin in radiocontrast nephropathy in patients with normal renal function, patients with diabetic nephrophathy with normal renal function, patients with impaired renal function, and patients with chronic renal failure on dialysis.

Chapter I

Radiocontrast nephropathy

Contrast induced nephropathy

With the increasing use of contrast media in diagnostic and interventional procedures, nephropathy induced by contrast media has become one of the most common causes of hospital-acquired acute renal failure. It is also associated with a significant risk of morbidity and death.

The current understanding of the pathogenesis indicates that contrast-medium nephropathy is caused by a combination of renal ischemia and direct toxic effects on renal tubular cells. Patients with pre-existing renal insufficiency, diabetes mellitus and congestive heart failure are at highest risk.

Risk factors also include the type and amount of contrast medium administered. Therapeutic prevention strategies are being extensively investigated, but there is still no definitive answer. In this article, we review the current evidence on the causes, pathogenesis and clinical course of contrast-medium nephropathy as well as therapeutic approaches to its prevention evaluated in clinical trials.

Nephropathy induced by contrast media is a significant yet underestimated problem in clinical practice. With the increasing use of contrast media in diagnostic and interventional procedures over the last 30 years, this form of nephropathy has become the third leading cause of hospital-acquired acute renal failure, accounting for 12% of all cases ***(Rich MW et al., 2000).***

The risk of contrast-medium nephropathy continues to be considerable, despite the use of newer and less nephrotoxic contrast agents in high-risk

patients in recent years ***(Cox CD et al., 2004)***. Affected patients are at increased risk of morbidity and death. They may require short-term hemodialysis, which can extend their hospital stay and increase the risk of permanent impairment of renal function ***(Cox CD et al., 2004).***

We review recent evidence on the incidence of and risk factors for contrast-medium nephropathy as well as the current understanding of its pathogenesis and the therapeutic approaches to its prevention that have been evaluated in clinical trials.

Definition

Contrast-medium nephropathy is usually defined as impairment of renal function occurring within 48 hours after administration of contrast media ***(Rihal CS et al., 2002).*** It is manifested by an absolute increase in the serum creatinine level of at least 44 µmol/L,***(Tepel M et al., 2000)*** or by a relative increase of at least 25% over the baseline value***(Briguori C et al., 2002)*** in the absence of another cause. Because creatinine levels typically peak 3–5 days after administration of contrast media, ***(Rich MW et al., 2000).***

This definition may overlook a large group of patients in whom nephropathy develops up to a week after administration of contrast media. However, older, more conservative definitions have a lower sensitivity because they require greater increases in the serum creatinine level ***(Moore RD et al., 2004).***

The current definition, which requires smaller increases in serum creatinine, is therefore more sensitive for the diagnosis of contrast-

medium nephropathy associated with clinically important adverse short- and long-term outcomes ***(Morcos SK et al ., 2004)***.

Epidemiology

The rate of contrast-medium nephropathy reported in studies that included patients with pre-existing renal dysfunction or diabetes mellitus in whom a standard hydration protocol was not administered is between 12% and 26% ***(Lufft V et al ., 2002)***. Lower rates (3.3%) have been reported among patients without these risk factors ***(Rihal CS et al., 2002)***.

Experimental studies suggest that contrast-medium nephropathy results from a combination of renal ischemia and direct toxic effects on renal tubular cells.

Renal hemodynamic changes

Early trials showed a transient increase in renal blood flow after injection of contrast medium that lasted up to 20 minutes followed by a more prolonged decrease in blood flow that lasted 20 minutes to hours ***(Katzberg RW et al., 1989).***

Subsequent animal studies showed that contrast media were associated with epithelial cell necrosis, primarily in the thin ascending limb in the renal medulla. The extent of these histologic changes correlated with the magnitude of disturbance in rat renal function. The renal medulla is uniquely susceptible to ischemic injury, and contrast media may cause medullar hypoxia by shunting blood flow to the renal cortex ***(Heyman SN et al., 1994).***