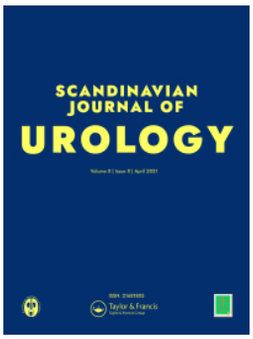
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ORIGINAL ARTICLE

Effects of N-acetylcysteine on radiocontrast nephropathy in rats

YAVUZ YENICERIOGLU[1], OSMAN YILMAZ[2], SULEN SARIOGLU[3], MURAT ORMEN[4], PINAR AKAN[4], ALI CELIK[1] & TANER CAMSARI[1]

[1]Nephrology Unit and the Departments of [2]Laboratory Animals, [3]Pathology and [4]Biochemistry, Dokuz Eylul University Hospital, Izmir, Turkey

Abstract

Objective. N-acetylcysteine (NAC) has yielded some promising results recently in the prevention of radiocontrast nephropathy (RCN). In this study, the structural and functional effects of NAC on RCN were analyzed. *Material and methods*. Twenty-eight Wistar rats were randomized into four groups, as follows: Group 1, controls; Group 2, contrast; Group 3, contrast+NAC; and Group 4, NAC. All rats were deprived of water for 24 h and then contrast medium (ioxoglate; 10 ml/kg) was administered to Groups 2 and 3. NAC (50 mg/kg) was introduced enterally to Groups 3 and 4 at a dose of 50 mg/kg in 0.5 ml of distilled water, in four sequential doses 12 h apart, starting after 12 h of water deprivation. After 4 days, rats were sacrificed. Creatinine clearance was calculated. The malondialdehyde (MDA) level was quantified in tissue samples. Slides stained with hematoxylin–eosin and periodic acid–Schiff were examined by means of light microscopy. Each tubular cross-section from all images was scored as either mild (preserved brush border, no necrosis), moderate (loss of brush border, no necrosis) or severe (loss of brush border accompanied by necrosis) and the frequencies of these lesion severities were compared. *Results*. Mean baseline serum creatinine levels and creatinine clearances were similar in all groups. Mean serum creatinine level increased significantly only in Group 2 (0.6 ± 0.1 vs 0.7 ± 0.2 mg/dl; $p < 0.05$). Tissue MDA levels were similar in all groups. Moderate ($13.8\% \pm 1.5\%$ vs $42\% \pm 1.4\%$; $p < 0.05$) and severe (0% vs $40\% \pm 2.1\%$; $p < 0.05$) lesions were significantly more frequent in Group 2 compared to Group 1. The frequency of severe lesions in Group 3 was found to be halved compared to that in Group 1 ($40\% \pm 2.1\%$ vs $20.2\% \pm 0.86\%$; $p < 0.05$). *Conclusion*. NAC protects the kidneys following exposure to contrast medium as it decreased the severity of tubular lesions in rats.

Key Words: *N-acetylcysteine, contrast, nephropathy, nephrotoxicity, radiocontrast, rat*

Introduction

Radiocontrast nephropathy (RCN) is defined as deterioration of renal function after administration of radiocontrast medium in the absence of any other explanation [1]. Although generally mild, it can occasionally lead to increased morbidity and mortality [2,3]. Several mechanisms for its pathogenesis have been proposed, including vasoconstrictive forces causing medullar ischemia, decreased production of local vasodilator prostaglandins [4], direct effects on renal tubular cells [5] and damage by oxygen radicals [6,7].

Despite intensive efforts there is still no universally accepted method for preventing RCN [8,9]. Aminophylline, calcium channel blockers, theophylline, atrial natriuretic peptide, mannitol, prostaglandins and endothelin antagonists have all been studied, but none showed satisfactory efficacy [10–16]. N-Acetylcysteine (NAC) is a novel candidate protector that has yielded promising results in some studies [17–23], although data obtained in others [24–27] failed to document its efficacy. Clinical and biochemical parameters were analyzed in the aforementioned reports but histological data were not presented. Therefore, we designed this study to analyze both the structural and functional effects of NAC on RCN in a rat model.

Material and methods

Twenty-eight female Wistar rats weighing 178–240 g were included in the study. To collect 24-h

Correspondence: Yavuz Yenicerioglu, Adnan Menderes Universitesi, Tıp Fakultesi Hastanesi, Nefroloji Bilim Dali, 09100 Aydin, Turkey. Tel: +90 256 4441256, ext. 378. Fax: +90 256 2144086. E-mail: yyenicerioglu@adu.edu.tr

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urine specimens, animals were individually housed in metabolism cages in a room maintained at a constant temperature (25°C). All rats were given unlimited access to standard rat chow and water excluding the 24-h period preceding the randomization procedure when all animals were deprived of water. Rats were weighed at the beginning of the study, at the end of the water deprivation period and before being sacrificed.

At the beginning of the study, rats were randomized into four groups, as follows: Group 1, controls; Group 2, contrast; Group 3, contrast+NAC; and Group 4, NAC. Baseline serum and 24-h urine creatinine levels were measured and creatinine clearances were calculated. After the 24-h water deprivation period, contrast medium was administered to Groups 2 and 3. Standard contrast medium (ioxaglate ionic dimer; 320 mg iodine/ml; Hexabrix®; Mallinckrodt, Guerbet, France) was administered through the tail vein at a dose of 10 ml/kg. Pure NAC (Toprak ilac, Istanbul, Turkey) was introduced to Groups 3 and 4 through a gastric tube at a dose of 50 mg/kg dissolved in 0.5 ml of distilled water, in four sequential doses 12 h apart. The first dose was given after 12 h of water deprivation. Groups 1 and 2 received 0.5 ml of distilled water in the same way. Group 1 received neither contrast medium nor NAC.

At the end of the 4th day, baseline laboratory examinations were repeated. The right and left kidneys were removed and reserved for histological examination and measurement of the malondialdehyde (MDA) level in the renal cortex, respectively. All rats were then sacrificed by means of hypovolemia. The study protocol is presented in Figure 1.

Inhalation ether anesthesia was used during i.v. interventions and nephrectomies. To avoid the risk of interference, synchronized anesthesia was administered to all four groups during administration of contrast medium.

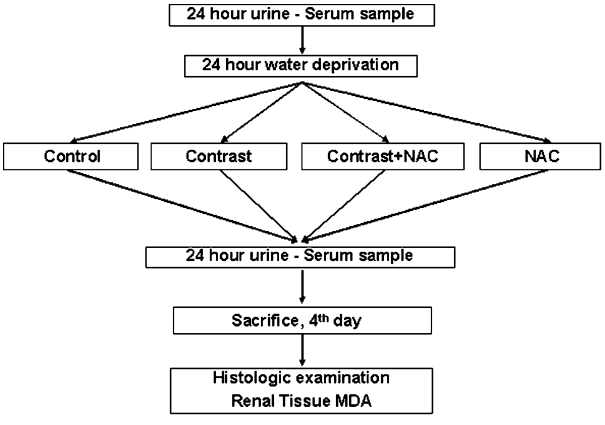


Figure 1. Summary of the study protocol.

RCN was defined as an increase in serum creatinine levels of >0.5 mg/dl or by a quarter of the baseline level.

The study protocol was approved by the Local Ethical Committee of Laboratory Animals at Dokuz Eylul University.

Pathology

The right kidney from each rat was sectioned horizontally through the renal pelvis immediately after excision of the organs in order to avoid autolysis. After 24 h, whole-surface sections (2-μm thick) were prepared and embedded in paraffin. Hematoxylin–eosin (H&E)- and periodic acid–Schiff (PAS)-stained sections (3-μm thick) were examined under light microscopy in order to identify all glomerular, tubular, interstitial and vascular lesions. For quantification of reversible and irreversible tubular injuries, PAS-stained sections were examined. The slide was lined with a marker prior to examination of five standard areas from different parts, as shown in Figure 2.

Digital images from selected areas were captured through a light microscope (Labophot-2; Nikon, Japan) at a magnification of $\times 20$ with a digital color video camera (WK-C220E; Hitachi, Japan) using image analysis software (Bs200D; BAB Muhendislik Muh. Mus. San. ve Tic. Ltd. Sti., Ankara, Turkey) and stored on a computer. Three cortical images were captured from each standard area, preferably periglomerular areas, making a total of 15 images from each case. The total test area for each case was 1.67×10^6 μm^2. For the grading of tubular injuries, the following scoring system was used for all tubular cross-section images: mild, preserved brush borders, no evidence of necrosis; moderate, loss of brush borders, no evidence of necrosis; and severe, loss of

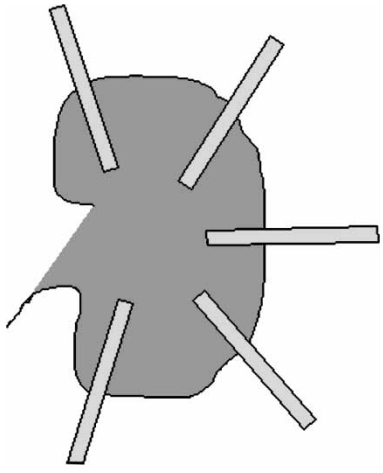


Figure 2. Selection of the five standard areas for defining tubular injury.

brush borders with tubular necrosis identified by means of changes such as karyorrhexis, karyolysis, pycnosis and/or denudation and/or tubulorexis. After scoring all tubules, the frequency of each score was calculated. The image analysis system was used for interactive marking and counting of tubular cross-sections.

Biochemistry

Serum and urine samples were stored at -85°C until the day of the study. Serum and urinary creatinine measurements were performed at once by the same physician with a Hitachi autoanalyser using the Jaffe method.

The left kidneys were used for cortex MDA level determinations. The renal artery was punctured, the kidney perfused with cold saline and then the renal artery and vein were ligated and nephrectomy was carried out. The renal cortex was dissected immediately, shaken in iced saline and dried with Watson paper. After weighing, tissue samples were frozen in liquid nitrogen and homogenized (90 times at a frequency of 800/min). The homogenate was then centrifuged at a frequency of 3000/min for 10 min at $+4^{\circ}$C and stored at -85°C. MDA levels were determined according to the method of Draper and Hadley [28].

Statistics

Data are presented as mean $\pm$ SEM. Wilcoxon rank tests and Mann–Whitney U-tests were used for intra- and inter-group analysis, respectively. Bivariate correlation analysis was used to test correlations. $p < 0.05$ was considered significant.

Results

All rats completed the study. Baseline serum creatinine and creatinine clearance levels were similar in all groups. RCN developed in only one (baseline creatinine 0.6 mg/dl; Day 4: 0.8 mg/dl) out of seven rats (14%) in Group 2. There was a significant increase in mean serum creatinine level only in Group 2 (0.60 ± 0.1 vs 0.70 ± 0.2 mg/dl; $p < 0.05$). Creatinine clearance did not change significantly (Table I).

When mean baseline body weights were compared, rats in Group 1 were heavier than those in Group 4. The mean body weights of rats in the other groups were similar to each other. After dehydration, the body weights of rats in all groups decreased significantly (Table II).

On microscopic examination, glomerular infiltration was not observed in any section, although scanty lymphocytes were present in the interstitium. Vascular structures were normal in all samples. Edema, vacuolization, loss of brush border and necrosis were observed in tubules. Tubulorexis, intratubular casts, regenerative atypia and mitosis were not present. The frequency of tubular lesions and renal cortical tissue MDA levels are presented in Table III and Figure 3.

Comparison of Groups 1 and 2

Baseline and Day 4 serum creatinine and creatinine clearance values were similar in the two groups. When tubular scores were considered, mild scores were predominant in Group 1 ($86.1\% \pm 1.5\%$ vs $16\% \pm 1.5\%$; $p = 0.001$), while moderate ($13.8\% \pm 1.5\%$ vs $42\% \pm 1.4\%$; $p = 0.001$) and severe (0% vs $40\% \pm 2.1\%$; $p = 0.001$) scores were more frequent in Group 2. Renal cortex MDA levels were similar in the two groups (Group 1, 2.06 ± 0.3 nmol/l; Group 2, 2.4 ± 0.6 nmol/l; $p < 0.05$).

Comparison of Groups 2 and 3

Baseline and Day 4 serum creatinine and creatinine clearance values were similar in the two groups. Mild tubular injury scores were significantly more frequent in Group 3 ($16\% \pm 1.5\%$ vs $37\% \pm 1.5\%$; $p = 0.001$). Moderate scores were similar in the two groups ($42.2\% \pm 1.4\%$ vs $42.2\% \pm 1.5\%$; $p > 0.05$). Severe scores were more frequent in Group 2 ($40\% \pm 2.1\%$ vs $20.2\% \pm 0.86\%$; $p = 0.001$). Tissue MDA levels were also similar in the two groups (Group 2, $2.4\% \pm 0.6\%$; Group 3, $2.9\% \pm 0.9\%$; $p > 0.05$).

Comparison of Groups 1 and 4

None of the parameters differed significantly between these two groups.

Discussion

Interest in NAC as a therapeutic agent has increased in recent years. The importance of oxidative damage in various diseases such as coronary artery disease, AIDS and adult respiratory distress syndrome is increasingly recognized, and agents with antioxidant properties hold great promise [29]. Oxidative damage is also important in the etiopathogenesis of renal diseases, including RCN. A protective effect of NAC in animals has previously been demonstrated [30–32] in gentamicin-, cyclosporin- and cadmium-induced renal damage. Additionally, some uncontrolled human data [33] suggest that NAC may improve renal function in hepatorenal syndrome.

Table I. Serum creatinine and creatinine clearance at baseline and Day 4.

	Serum creatinine (mg/dl)			Creatinine clearance (ml/min)		
Group	Baseline	Day 4	*p*	Baseline	Day 4	*p*
1	0.58±0.02	0.61±0.01	NS	0.59±0.07	0.67±0.10	NS
2	0.60±0.10	0.70±0.20	0.02	0.54±0.04	0.51±0.04	NS
3	0.64±0.02	0.64±0.03	NS	0.50±0.04	0.47±0.02	NS
4	0.60±0.01	0.64±0.02	NS	0.47±0.03	0.47±0.06	NS

Conflicting data have been obtained concerning the prevention of RCN by means of NAC. Although it was suggested in some studies [17–23] that it is beneficial, other authors [24–27] failed to document its efficacy.

Tepel et al. [17], in a placebo-controlled clinical study, reported that renal function could be preserved in patients with underlying renal dysfunction undergoing contrast-enhanced CT by administering NAC (600 mg twice daily for 2 days). In that study, serum creatinine was found to increase by 0.2 mg/dl in the placebo group, whereas it decreased by 0.4 mg/dl in the NAC group, and this difference was significant. It was difficult to explain this result solely on the basis of antioxidant properties as renal function was not only protected but actually improved. Vasodilator mechanisms may have played a role. Another possible explanation, namely interference of NAC dissolved in serum with measurement of serum creatinine levels, was ruled out by the authors.

In another double-blind, placebo-controlled study in patients with renal dysfunction undergoing cardiac catheterization [18], serum creatinine levels decreased significantly in the NAC group, but did not change in the placebo group. Possible effects of NAC on tubular creatinine secretion were discounted by a failure to observe changes in serum blood urea nitrogen levels. Therefore, the mechanism by which the serum creatinine level decreased in the NAC group remained obscure.

With the exception of the RAPPID study, in all studies that yielded positive results, NAC was administered by the oral route. In the RAPPID study [22], the i.v. route was used (150 mg/kg NAC in 500 cm^3 of saline over 30 min just before contrast medium administration, followed by 50 mg/kg NAC in 500 cm^3 of saline over 4 h). Other authors [19–21] have reported similar outcomes regarding the prevention of RCN by NAC. All the studies [17–23] supporting the administration of NAC showed decrements, which probably contributed to the statistically significant differences in serum creatinine levels.

In contrast to previous studies, Durham et al. [26], in a placebo-controlled, randomized trial, reported that NAC (1200 mg given 1 h before and 3 h after angiography) was not effective in the prevention of RCN after cardiac angiography in patients with baseline creatinine levels >1.7 mg/dl. The hydration protocol and the amount of contrast medium given were similar to those in the study of Tepel et al. [17]; however, the NAC protocol was different. Considering the pharmacokinetic data, although it sounds reasonable to give NAC 1 h before angiography, it is not clear whether NAC itself or a metabolite of it is responsible for the favorable effects. Similarly, Vallero et al. [24] reported that no advantage was obtained with NAC in patients with normal or mildly elevated serum creatinine levels who underwent coronary angiography or angioplasty. In that study, although the dose and schedule of NAC were the same as those used by Tepel et al. [17], more contrast medium was used (203 vs 75 ml). Therefore, the relatively lower dose of NAC per volume of contrast medium may have led to an unopposed toxic insult.

In another prospective randomized study, Allaqaband et al. [25] reported that use of NAC+saline, fenoldopam+saline and saline alone resulted in similar outcomes in the prevention of RCN in patients undergoing coronary procedures. Similarly,

Table II. Body weights and urine volumes of the rats.

	Body weight (g)			Urine volume (ml/day)		
Group	Baseline	After dehydration	*p*	Baseline	Day 4	*p*
1	208.1±5.1	200.7±5.1	0.017	10.8±2.2	12.3±2.3	NS
2	208±7.3	202±7.2	0.018	8.3±1.3	10.8±2.3	NS
3	200.7±3.08	183±3.8	0.018	9.39±0.74	11.11±0.93	NS
4	194.5±4.8	184±5.6	0.018	7.1±0.8	9.2±1.6	NS

Table III. Frequency of tubular injury scores and renal cortex MDA levels.

	Tubular injury score (%)			
Group	Mild	Moderate	Severe	MDA (nmol/l)
1	86.2±1.5	13.8±1.5	0	2.06±0.3
2	16±1.5*	42±1.4*	44±2.1*	2.4±0.6
3	37±1.5**	42.2±1.5**	20.8±0.86**	2.01±0.15
4	85.5±1.2	14.2±1.2	0.3±0.16	1.6±0.1

*p <0.05 vs Group 1; **p <0.05 vs Group 2.

in a study presented by Boccalandro et al. [27], in which they used a higher dose of contrast medium than Tepel et al. [17] (192 vs 75 ml), no benefit of NAC was documented.

In this study, we observed that NAC administered with contrast medium decreased the frequency of severe tubular scores twofold compared to administration of contrast medium alone. This is the most important finding of our study, namely the fact that NAC provides renoprotective effects against contrast medium. This is the first report concerning the beneficial effects of NAC on RCN at the tissue level.

As the administration of contrast medium in the absence of an accompanying renal insult does not reliably induce acute renal failure, a simultaneous renal insult was generally applied in previous studies [34–36]. In our study, we deprived rats of water for 24 h and used an ionic contrast medium so as to achieve sufficient renal damage [8,9]. Using this regimen, acute tubular necrosis developed in ≈40% of tubules in the contrast group and in none in the control group, documenting that nephrotoxicity had occurred. However, the increases in serum creatinine levels observed were lower than we expected, probably due to preservation of ≈60% of nephrons even in the contrast group. The observation of a similar distribution of tubular injury scores in the control and NAC groups suggests that NAC has no nephrotoxic effects at the administered doses.

The pathogenesis of RCN is not completely understood. There is some evidence suggesting that renal vasoconstriction and tubular toxic damage are the main operating mechanisms. Contrast infusion causes brief, transient increases in renal plasma flow and glomerular filtration rate, followed almost immediately by a sustained decrease in both of these parameters [37–39]. These hemodynamic changes are caused by release of vasoactive mediators in the kidney. Renal tubular toxic damage may also be directly induced by contrast medium. Specifically, reactive oxygen species have been implicated as a contributory factor in RCN [6,7,40]. Lipid peroxidation and tubular oxidative damage presumably could lead to transient renal dysfunction.

Most of the beneficial effects of orally administered NAC are theorized to be a result of its ability to either reduce extracellular cystine to cysteine or to be a source of SH metabolites. As a source of SH groups, NAC can stimulate glutathione (GSH) synthesis, enhance glutathione-S-transferase activity, promote detoxification and act directly on reactive oxygen radicals [29]. The mechanism of RCN prevention by NAC is not clear at present. Interference with serum creatinine determination [17] and increased tubular secretion of creatinine [18], which may misleadingly suggest renal protection, were discarded as theories in previous studies.

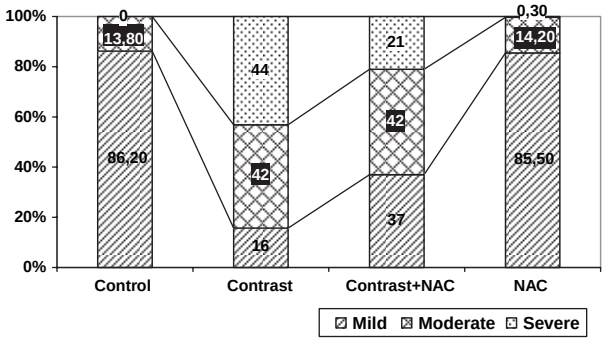


Figure 3. Frequency of tubular lesions.

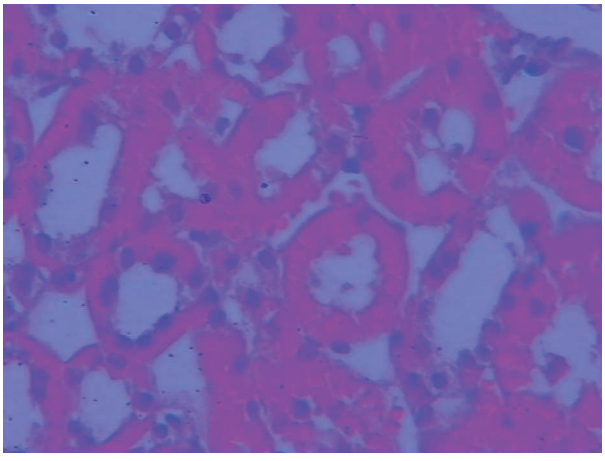


Figure 4. Thinning of proximal tubular epithelial cells and loss of nuclei with karyolysis or karyorrhexis in a rat in the contrast group. H&E staining; original magnification ×40.

Regarding the prevention of renal injury due to other toxic insults by NAC, the proposed mechanisms mainly involve its antioxidant effects, based on the observation of a decrease in lipid peroxidation end-products and increased tissue glutathione levels. Tariq et al. [31] reported that NAC, co-administered with cyclosporin, increased tissue glutathione levels and prevented an increase in serum creatinine and renal damage accompanied by decreased tissue lipid peroxidation products. However, other authors postulated that vasoactive mechanisms may play a role, at least in part. Some animal data have demonstrated that pretreatment with NAC protects against decreased renal perfusion and increased serum oxidant stress markers after inferior vena cava occlusion. The process was suggested to occur via NO-related mechanisms, as it could also be prevented by co-administration of N(G)-nitro-L-arginine methyl ester (L-NAME), an NO synthesis inhibitor [41]. Additionally, the renal vascular response to acetylcholine after renal ischemia was preserved in a group pretreated with NAC, in contrast to the situation in a control group and in a group administered L-NAME [41]. However, certain mechanisms of NAC on prevention of ishemia-reperfusion injury are still obscure. Conesa et al. [42], in a rat ischemic renal failure model, reported that NAC ameliorated the renal failure and outer medullary vasoconstriction induced by inferior vena cava occlusion. These effects seemed to be dependent on the presence of NO, as they could be abolished by administration of L-NAME. Other authors [43,44] reported that NAC also enhanced endothelium-dependent vasodilation in coronary, peripheral and mesenteric vessels.

In a recent animal study by Emch & Haller [45], the effects of pretreatment with NAC and theophylline, either alone or in combination, on the development of renal tubular vacuolization after iohexol administration was researched. The authors reported that neither NAC nor theophylline, either alone or in combination, were beneficial. In that study, NAC was administered at a dose of 4 mg by oral gavage every 12 h as three doses before and one dose after contrast medium injection. The relatively lower dose of NAC compared to that used in our study (50 mg/kg; $\approx$10–12.5 mg/rat twice daily for 2 days) may explain the failure to observe a beneficial effect.

Taking all the above data together, it seems that renal injury caused by contrast medium may be prevented by pretreatment with NAC. However, it is difficult to explain the exact mechanism of action. Scavenging oxidants may be one explanation. However, the fact that serum creatinine concentrations were lowered in comparison to baseline values in clinical studies suggests that other mechanisms operate in addition to antioxidant effects. The decreased serum creatinine levels, i.e. increased glomerular filtration rates, observed in the group pretreated with NAC leads to consideration of vasoactive processes. Similarly, the failure to observe changes in renal cortex MDA levels in our study argues against antioxidant mechanisms, although this result may have been due to the small number of rats studied. Research on vasoactive mechanisms was beyond the scope of this study.

Conclusions

NAC protects the kidneys from tubular lesions following exposure to contrast media in rats. The mechanism(s) of this action is obscure. However, there may be an interplay between the antioxidant and endothelial function-preserving properties of NAC.

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