Prevention of contrast agent-induced renal impairment in patients with chronic renal insufficiency and heart disease by high-dose intravenous N-acetylcysteine: a pilot-ministudy

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Abstract

Background: Contrast-induced nephropathy is a relatively common complication occurring after various procedures requiringiodisze contrast agent injection, especially in patients with pre-existing renal failure.

Aim: This pilot study was designed to assess the effects of a high intravenous dose of N-acetylcysteine (NAC) on plasma creatinine concentration.

Methods: Twenty patients with pre-existing renal insufficiency were given NAC at a dose of 100 mg/kg. No contrast agent was given to 10 patients (Group A), whereas 10 patients received contrast at the time of coronary angiography (Group B). Changes in plasma creatinine were assessed at 3 hours and one day following NAC administration.

Results: In Group B, NAC prevented creatinine increase: baseline levels were 210.98±77.33 µmol/L, 200.26±71.94 µmol/L (NS) after 3 hours, and 203.80±83.94 µmol/L 24 hours later (NS). The following was seen in Group A patients: 201.21±42.28 µmol/L, 190.31±42.74 µmol/L ($p<0.01$), and 170.08±45.53 µmol/L ($p<0.01$), respectively.

Conclusion: The results of this study confirm the effectiveness of NAC in prevention of contrast agent-induced renal impairment. In addition, we demonstrated the beneficial effects of NAC on renal function in patients who were not exposed to contrast agent. This pilot study should provide the basis for more comprehensive research and, also, for safe clinical practice.

Key words: N-acetylcysteine, non-ionic contrast medium, nephropathy

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Introduction

The proportion of patients with various degrees of renal insufficiency scheduled for coronary angiography is not negligible. These are usually elderly patients who may have a number of comorbidities related to renal function: in particular diabetes mellitus and hypertension. Administration of contrast agents may result in significant deterioration of renal function. This deterioration, although usually reversible, may affect the metabolism of medications and undoubtedly affects the haemodynamic status of patients.

Contrast-induced nephropathy (CIN) may also have economic implications: it may prolong hospitalisation, or require additional therapies. CIN is a multidisciplinary problem involving clinical nephrology, interventional radiology and cardiology. It also attracts the interest of those involved in pharmacology and pathophysiology.

The first experimental study documenting the beneficial effect of N-acetylcysteine (NAC) on renal function at the time of ischaemic injury appeared in 1997 [1]. A landmark clinical study providing further insights into the role of NAC in CIN was published in 2000 [2]. To date, a host of studies have been conducted diffe-

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ring in various variables and providing inconsistent conclusions [3-7]. As we have performed several detailed studies on the effects of NAC on ischaemia/reperfusion injury in acute myocardial infarction, both in experiment and in clinical practice, we sought to assess the effects of this agent administered in a high intravenous dose to patients with pre-existing renal insufficiency and contrast agent administration at the time of coronary angiography [8-10].

Methods

Study design

This pilot study was not intended to enrol a large number of patients. It was only designed to test the hypothesis that the knowledge obtained in cardiovascular practice is also applicable to patients with renal disease. Our premise was based on the generally accepted fact that contrast agent administration to patients with renal insufficiency will increase creatinine levels (CIN induction by definition). Further, we sought to eliminate uncertainty related to the oral dose of NAC and therefore we chose a high dose administered intravenously, shortly before the invasive procedure, respecting the biological half-life of NAC which is approximately 2 hours [11].

Selection of patients

Twenty patients with a history of renal insufficiency were included. Their creatinine levels were >150 µmol/L (>1.7 mg/dL). Those on haemodialysis were not eligible given the different metabolism of drugs. Also excluded were patients receiving ACE inhibitors, which are known to affect renal function, as well as patients receiving dopamine. Ten patients underwent comprehensive cardiovascular examination but had no indication for coronary angiography (Group A). The other 10 subjects underwent coronary angiography with contrast injection (Group B). None of our patients had an acute coronary syndrome.

NAC administration

All patients (from both group A and group B) were given NAC i. v. at a dose of 100 mg/kg (ACC injekt, Hexal AG, Holzkirchen, Germany), with half of the dose administered as a slow bolus and the other half in an infusion of 200 ml of saline over 30 min. In those who underwent coronary angiography, the infusion had to be administered within 60 min. prior to the procedure. In this group, blood samples were collected on the day of the procedure for baseline creatinine level determination. Other blood samples were obtained 3 hours from NAC administration (approximately 2 h after coronary angiography), and on the next day. The physician performing coronary angiography was unaware of NAC administration to eliminate any bias in the selection and quantity of the contrast medium. Coronary angiography was performed using standard techniques. The selection of the contrast agent was fully at the discretion of the physicians performing coronary angiography. The following contrast agents were used: iopromide (Ultravist, Schering AG, Berlin, Germany), iomeprol (Iomeron, Bracco, S. p. A, Milano, Italy), iohexol (Omnipaque, Amersham Health, Cork, Ireland), and ioversol (Optiray, Mallinckrodt Medical Imaging, Dublin, Ireland).

All patients gave informed consent to undergo the procedure and the protocol of the study was approved by the local Ethics Committee.

Statistical analysis

Results are presented as mean ± standard deviation. Fisher's test was used to compare the two groups of patients. Quantitative parameters were compared using the t-test. Analysis of variance (ANOVA) with repeated measures and grouping factor was employed to compare inter-group differences. A p value <0.05 was considered statistically significant.

Results

Patient characteristics

Baseline characteristics of the patients including gender, age, weight and comorbidities are depicted in Table I and were similar in the two analysed groups. Creatinine levels in individual patients at different time points are given in Table II.

Creatinine concentration

All 20 patients tolerated NAC administration without any complications. Prior to the procedure, there were no differences in baseline plasma creatinine level in the two groups of patients (see Table I). At 3 hours after the administration of NAC, creatinine levels declined from 201.21±42.28 µmol/L to 190.31±42.74 µmol/L in Group A ($p<0.01$). A further decrease to 170.08±45.53 µmol/L was seen on the next day ($p<0.01$).

In Group B, NAC administration also led to a decrease in creatinine levels. However, the differences were not significant: 210.98±77.33 µmol/L to 200.26±71.94 µmol/L (NS) and 203.8±83.94 µmol/L (NS). The ANOVA test demonstrated an intra-group difference in trend ($p<0.01$), with a significant drop in creatinine noted in the group with contrast agent administration ($p<0.01$). Creatinine levels are shown in Figure 1 and the changes in this parameter in Figure 2.

Table I. Patient characteristics

Parameter	Group A (no contrast injection)	Group B (with contrast injection)	p
Number	10	10	NS
Male/Female	7/3	8/2	NS
Age [years]	71±8.11	75±7.46	NS
Body weight [kg]	74±13.53	73±8.88	NS
Hypertension	3/10	4/10	NS
Diabetes mellitus	1/10	3/10	NS
Coronary artery disease	8/10	10/10	NS
Baseline creatinine [µmol/L]	201.21±42.28	210.98±77.33	NS

Table II. Creatinine levels (µmol/L) in individual patients at different time points

Group A				Group B			
Patient	Baseline	3 hrs later	1 day later	Baseline	3 hrs later	1 day later	Cont/vol
1	242.0	227.9	217.1	156.8	145.3	144.0	Iom/100
2	221.3	218.3	196.9	207.2	210.2	220.0	Ioh/90
3	151.7	143.9	136.6	324.6	320.6	371.1	Iov/100
4	203.2	171.5	122.6	193.2	186.6	195.5	Iop/100
5	169.2	138.3	125.7	193.3	200.0	171.9	Iov/80
6	227.7	218.4	185.4	154.8	136.8	132.9	Iop/150
7	187.7	176.9	152.0	183.1	178.6	175.8	Iop/200
8	283.2	271.8	264.7	154.1	124.5	129.9	Iom/100
9	160.0	153.4	144.7	164.4	167.5	161.3	Iop/200
10	166.1	182.7	155.1	378.3	332.5	335.0	Iom/150
Mean	201.21	190.31	170.08	210.98	200.26	203.80	----------
±	42.28	42.74	45.53	77.33	71.94	83.94	----------

Abbreviations: Cont/vol. - type of contrast medium/corresponding volume of appropriate contrast medium. Iom - iomeprol, Ioh - iohexol, Iov - ioversol, Iop - iopromide

Discussion

Pathogenesis of CIN

The most common concept of pathogenesis of CIN is induction of ischaemia of the renal parenchyma. Experimental studies have shown that contrast agent administration results initially in short renal vasodilation followed by more pronounced vasoconstriction and decrease in glomerular filtration rate. This process is enhanced in hypovolemic animals [12]. This biphasic reaction has also been reported in humans, occurring approximately within 20 minutes of contrast medium injection. In cases where this process leads to the development of CIN, renal hypoperfusion becomes more pronounced [13]. CIN has been shown to be an independent predictor of one-year mortality in patients with coronary disease: one-year mortality of patients free of renal disease but with coronary disease was 5%, as high as 16.5% in those with renal disease not requiring dialysis, and over 44% in haemodialysis patients [14].

Response to contrast agents, their relationship with creatinine levels and development of CIN

Contrast medium injection will typically result in a rise, essentially non-significant, in plasma creatinine levels in all patients [15]. CIN should be considered in cases where creatinine levels increase by at least 25% of the baseline or in the presence of any increase in creatinine levels within 48 hours of contrast medium administration. The risk of CIN rises significantly with creatinine levels of 136 µmol/L (1.54 mg/dL) and higher [15]. Additional risk factors in patients with diabetes include a different pattern of intrarenal blood distribution and endothelial cell dysfunction with subsequent functional implications.

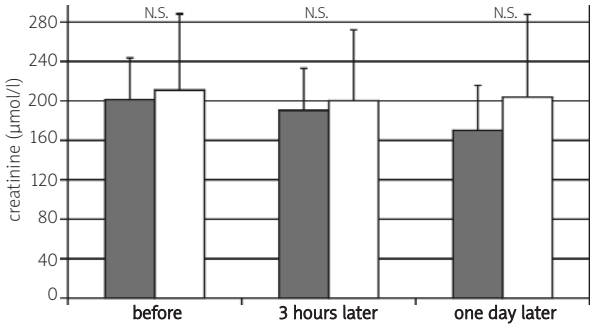

Figure 1. Comparison of mean creatinine levels measured at different time points in group A (dark bars) and group B (white bars)

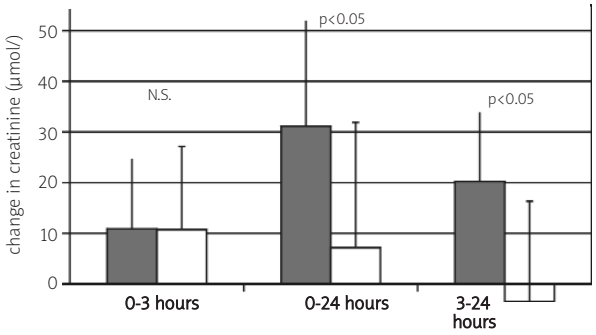

Figure 2. Comparison of mean changes in creatinine concentration measured at different time points in group A (dark bars) and group B (white bars). Changes [0-3, 0-24, 3-24] are calculated as the value obtained at the initial time point minus the value obtained at the following time point (positive difference means decrease, negative difference means increase)

Experience with NAC

The landmark studies of Di Mari et al. [1] and Tepel et al. [2] spurred increased interest in NAC in an effort to achieve a renoprotective effect. Tepel and coworkers re-examined the topic and demonstrated in 2003 the beneficial actions of NAC also in patients with end-stage renal failure. NAC also proved effective at a dose of 600 mg twice daily in dialysed patients [16]. Responding to studies not favouring the use of NAC, the above authors performed in 2004 an analysis of data from 19 studies and 5 meta-analyses, and concluded that the inconsistent results were due to the heterogeneity of patient populations. The conclusions continued to support hydration of patients and NAC administration, especially in advanced pre-existing renal impairment [3]. Inconclusive results, without a clearly identified determining factor, have also been reported by other authors [4, 5]. Still, some no longer see NAC as a controversial prophylactic agent but one to be appropriately used in emergency [6].

Importance of NAC dose

Shyu et al. have demonstrated that prophylactic oral administration of the antioxidant NAC along with hydration reduces renal damage induced by contrast agent in patients with chronic renal insufficiency undergoing coronary procedures. NAC was given orally at a dose of 400 mg twice daily to a cohort of 121 patients [17]. Tepel and Thomsen used a dose of 600 mg NAC taken orally twice a day [2, 8]. Likewise, Hoffman et al., though initially sceptical [7], later concluded that a dose of 600 mg twice daily for two days had beneficial effects, as indicated by a decrease in the plasma levels of creatinine and a rise in glomerular filtration rate [18]. Other reports confirmed the effects of NAC and even recommended its routine use [19-21]. Briguori et al. used even higher doses (1200 mg twice a day), finding them to be more effective compared to the 600 mg dose [22]. A meta-analysis of studies which included over 800 patients with chronic kidney disease showed that a combination of NAC with hydration reduced the incidence of CIN by 56% [23, 24].

Our study offers a novel look at the issue. It appears that NAC, when administered at extremely high doses, has a beneficial effect on renal function whether or not contrast agent has been used.

Conclusions

When given at high doses intravenously, NAC has a beneficial effect on creatinine levels in patients with chronic renal insufficiency, injected with a contrast agent. The efficacy of NAC was also impressive in a similar group of patients not receiving a contrast agent. This finding warrants future research in this multidisciplinary area.

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Wysokie dawki dożylnie podawanej N-acetylocysteiny w zapobieganiu nefropatii wywołanej środkami kontrastującymi – doniesienie wstępne

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Streszczenie

Wstęp: Nefropatia wywołana środkami kontrastującymi jest stosunkowo częstym powikłaniem procedur, w których wykorzystuje się kontrast, szczególnie u chorych z przewlekłą niewydolnością nerek.

Cel: To pilotowe badanie zostało zaprojektowane tak, aby zbadać wpływ wysokich, dożylnie podawanych dawek N-acetylocysteiny (NAC) na stężenie kreatyniny w osoczu.

Metodyka: Grupie 20 chorych z przewlekłą niewydolnością nerek podano dożylnie NAC w dawce 100 mg/kg. Spośród nich 10 chorych nie otrzymało środka kontrastującego (grupa A), natomiast pozostałych 10 otrzymało dożylnie kontrast podczas koronarografii (grupa B). Stężenie kreatyniny oceniano przed podaniem kontrastu oraz 3 godz. i 1 dobę po podaniu NAC.

Wyniki: W grupie B NAC zapobiegła wzrostowi stężenia kreatyniny; wstępne stężenie wynosiło 210,98±77,33 µmol/L wobec 200,26±71,94 µmol/L po 3 godz. (NS) i 203,80±83,94 µmol/L po 24 godz. (NS). W grupie A stężenie kreatyniny przed podaniem NAC wynosiło 201,21±42,28 µmol/L wobec 190,31±42,74 µmol/L po 3 godz. ($p<0,01$) i 170,08±45,53 µmol/L po 24 godz. ($p<0,01$).

Wnioski: Wyniki niniejszego badania potwierdzają skuteczność i bezpieczeństwo dużych dawek NAC w zapobieganiu niewydolności nerek wywołanej podaniem kontrastu. Dodatkowo wykazano korzystny wpływ NAC na funkcje nerek osób, które nie otrzymały kontrastu. To pilotowe badanie stanowi podstawę do przeprowadzenia dalszych prób nad protekcyjnym działaniem NAC u chorych z niewydolnością nerek.

Słowa kluczowe: N-acetylocysteina, kontrast, nefropatia

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