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N-Acetylcysteine in the Prevention of Radiocontrast-Induced Nephropathy: Clinical Trials and End Points

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Key Words
N-acetylcysteine · Radiocontrast-induced nephropathy · Creatinine · Cystatin C · Glomerular filtration rate

Abstract
N-acetylcysteine (NAC) has been suggested to prevent radiocontrast-induced nephropathy (RCIN) in patients with a reduced renal function. However, clinical studies have not been demonstrating this effect consistently. Also, reviews and meta-analyses dealing with the question of prevention of RCIN by NAC have been controversial. Nearly all investigators used serum creatinine as surrogate end point of their trials, and changes in serum creatinine concentrations are thought to reflect the extent of renal injury as primary outcome. In a recent study, an effect of NAC on creatinine values and estimated glomerular filtration rate without any effect on cystatin C levels has been shown in volunteers with a normal renal function. Therefore, before renal protective effects of NAC in RCIN are proposed, any direct effects of NAC on creatinine, urea, and estimated glomerular filtration rate should be addressed. In future trials, the glomerular filtration rate should preferentially be measured directly, or at least additional markers of the renal function (e.g., serum cystatin C) have to be assessed. Furthermore, additional 'hard' end points, i.e., hospital morbidity, mortality, or dialysis dependency, should be considered in the design of future studies of RCIN.

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Introduction

Radiocontrast-induced nephropathy (RCIN) is defined as a sudden decline in renal function occurring after exposure to intravenous radiographic contrast agents that is not attributable to other causes. Typically, the serum creatinine level begins to increase 24–72 h after administration of contrast medium, peaks at 3–5 days, and requires further 3–5 days to return to baseline. In most studies, an acute radiocontrast-agent-induced reduction in the renal function was defined as an increase in the serum creatinine concentration of at least 0.5 mg/dl within 48 h after the administration of contrast agents.

Although several approaches have been explored to prevent renal contrast damage, RCIN continues to be a serious complication in patients with preexisting renal

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insufficiency. Effective regimens are still lacking, as the pathogenesis of radiocontrast-induced renal dysfunction is only partially understood.

Presently, hydration of the patient [1–3] and the use of small amounts of low-osmolar, nonionic contrast agents [4] are recommended. RCIN may be less likely to develop in high-risk patients, when iso-osmolar contrast medium is used rather than low-osmolar contrast medium [5]; however, further studies in support of this assumption are needed. Evidence from clinical trials did not sufficiently prove a beneficial effect of hemodialysis/hemofiltration or theophylline, aminophylline, prostaglandins, diuretics, dopamine, calcium channel blockers, atrial natriuretic peptides, endothelin receptor blockers, or mannitol to recommend the general use of one of these therapies or compounds [6–8].

The administration of N-acetylcysteine (NAC) seems to be an additional option to avoid renal injury, even if there are conflicting data about the additive protective properties of NAC when used in conjunction with hydration [9–19]. Interestingly, the advantage of NAC in most studies was based on a decrease in the serum creatinine concentration in patients exposed to contrast agents plus NAC, while often an unchanged serum creatinine concentration was observed after radiocontrast exposure in patients without NAC. In a recent study [20], we have shown that NAC led to a decrease in serum creatinine, while the serum cystatin C concentration did not change in volunteers with a normal renal function.

Thus, in the present review, we will first discuss the available evidence that NAC is able to prevent RCIN and secondly question whether the sole measurement of serum creatinine suffices as a reliable marker of the renal function in this setting.

N-Acetylcysteine

NAC is a thiol-containing compound which stimulates the intracellular synthesis of glutathione and enhances the glutathione S-transferase activity [21, 22]. NAC is supposed to have antioxidant properties because it suppresses plasma and tissue angiotensin-converting enzyme activities [23], attenuates cytotoxic properties of advanced glycation end products [24], and decreases homocysteine plasma levels [25]. NAC is demonstrated to act as an antioxidant only in oxidative stress conditions [26]. Some reports have shown that it can inhibit nuclear factor kappa B activation in renal mesangial and epithelial cells [27, 28].

In animal studies, nephroprotective properties of NAC have been demonstrated in ciclosporin-induced nephrotoxicity as well as in ischemia/reperfusion injury [29, 30]. In contrast, no benefits of NAC administration were found in a model of renal interstitial inflammation [31]. Moreover, at doses of 1.2 g daily, NAC may even exert pro-oxidative properties in subjects with normal intracellular glutathione levels [32].

By scavenging free radicals produced after contrast media administration, renal toxicity might be prevented by NAC [33]. The findings of Heyman et al. [34] in rats suggest that NAC-related protective properties during the evolution of acute renal failure may be mediated in part by dilation of the constricted renal vasculature. Previous studies already have described vasodilatory properties of NAC [34, 35].

NAC and RCIN

Although the concept of prevention of RCIN by NAC is favored by its simplicity and low cost, the role of NAC for the prophylaxis of RCIN has not been established definitively. To date, unfortunately only three trials [11, 14, 15] described the effects of NAC not only on serum creatinine but also on clinical end points. Kay et al. [11] investigated the effect of NAC on the length of hospital stay as a secondary end point and found a significant reduction of 12 h in patients given NAC. In another prospective, randomized, double-blind, and placebo-controlled study designed to evaluate the efficacy and safety of NAC in the prevention of RCIN in patients undergoing coronary angiography [14], there was no difference in length of stay, hospital charges, or serum creatinine changes between the NAC-treated and the control group. Goldenberg et al. [15] reported similar findings in patients with chronic renal insufficiency undergoing cardiac catheterization. The incidence of in-hospital adverse clinical events and the length of hospital stay did not differ between the NAC-treated and the control groups, and there were no differences in creatinine levels between the treatment groups.

In all other studies, due to the rare occurrence of severe clinical adverse events after radiocontrast administration, only surrogate markers of a reduced glomerular filtration rate (GFR), such as creatinine or urea, have been used as primary outcome, and renal injury has been accordingly extrapolated from changes in serum chemistry. This constitutes a major limitation of such studies. When reviewing the published studies to date, one has to keep in mind

that publication bias may well be present and that the comparability between trials is limited due to differences in baseline characteristics of the patients and in major study design details, particularly the severity of chronic renal insufficiency before the procedure and the amount of radiocontrast media.

Several meta-analyses of the presently available data concerning the role of NAC in the prevention of RCIN have been published during the last months. Birck et al. [19] in their meta-analysis studied seven randomized controlled trials comparing orally given NAC and hydration with hydration alone for preventing RCIN in a total of 805 patients with chronic renal insufficiency. The common end point of all these studies was a change in the serum creatinine concentration. A rise in serum creatinine >0.5 mg/dl was considered to indicate RCIN. Four studies [9–11, 36] showed a statistically significant reduction of the relative risk for the development of RCIN in patients given NAC, whereas the remaining three showed no significant benefit of preprocedural NAC [17, 18, 37]. By combining the effect sizes of these seven trials by a random-effects model, a significant relative risk reduction of 56% was seen in patients given NAC. Alonso et al. [38] and Findlay and Dwomoa [39] described nearly similar findings when performing meta-analyses of both seven blinded and unblinded randomized controlled trials, but in both analyses, there was a significant heterogeneity of the effect of therapy. Another recent meta-analysis performed by Pannu et al. [40] found only a borderline statistical significance of the efficacy of NAC for preventing RCIN. However, in this analysis, the effect of NAC was not statistically significant in several prespecified subgroup analyses, and the results were not robust to the addition of hypothetical new or unidentified randomized trials. In a further recently published meta-analysis of eleven studies [41], no benefit of NAC in reducing the risk of RCIN in patients with baseline renal dysfunction was found.

In a new experimental study performed by Emch and Haller [42], a method for preventing renal tubular vacuolization by administration of NAC prior to contrast medium administration was tested in rats. The occurrence of renal tubular vacuolization in the NAC-treated groups was similar to that in control groups.

In contrast to all other studies assessing the effects of orally administered NAC, a recent study [43] compared intravenous NAC and hydration given immediately before coronary angiography/intervention with hydration alone for the prevention of RCIN. In the NAC-treated group, the mean serum creatinine concentration decreased significantly from 1.85 to 1.77 mg/dl 48 h after contrast agent administration. In the group without NAC, the serum creatinine level increased slightly but not significantly. RCIN, defined in this study as an increase in the serum creatinine concentration by 25% occurred in 2 of the 41 patients in the NAC-treated group and in 8 of 39 patients in the group not receiving NAC ($p = 0.045$). After intravenous injection of NAC, however, 14.5% of the patients suffered flushing, itching, or rash.

Besides the question of the efficacy of NAC for RCIN prevention, it has to be asked whether the serum creatinine concentration is a reliable surrogate marker for the renal function at all. It is well known that the serum concentration of creatinine is determined not just by the GFR. Alterations in renal handling, i.e., tubular secretion and metabolism of creatinine, and methodological interference in its measurement may influence the serum concentration of creatinine. Due to dietary creatinine intake, tubular secretion of creatinine, and variations in the patient's muscle mass, the use of serum creatinine may inaccurately estimate the GFR.

Rickli et al. [44] recently compared serum cystatin C and serum creatinine to examine their kinetics after application of radiocontrast media in patients with a normal to decreased GFR. In this study, cystatin C achieved a maximum increase within 24 h after radiocontrast application, whereas serum creatinine started to increase at that time and continued to increase at 48 h. Cystatin C is suggested to be a potential early marker of nephrotoxicity.

In a recent prospective study [20], we have studied the potential effects of NAC on serum creatinine, independent of alterations in the GFR. For this purpose, volunteers with a normal renal function who did not receive radiocontrast media were enrolled. NAC was given orally at a dose of 600 mg every 12 h for a total of four doses. The serum levels of creatinine, urea, albumin, and cystatin C were determined before administration of NAC and 4 and 48 h after the last intake. Serum creatinine was measured both enzymatically and by the Jaffé method. The GFR was estimated (eGFR) on the basis of serum creatinine, urea, and albumin concentrations and weight, age, and sex, using the equation developed by Levey et al. [45]. There was a significant decrease of the mean serum creatinine concentration ($p < 0.05$) and a significant increase of the eGFR ($p < 0.02$) 4 h after the last administration of NAC, whereas the cystatin C concentration did not change significantly (fig. 1). The latter observation is not quite unexpected, as direct effects of NAC on the human renal function have not been reported yet. Taken together, two explanations for our findings are possible:

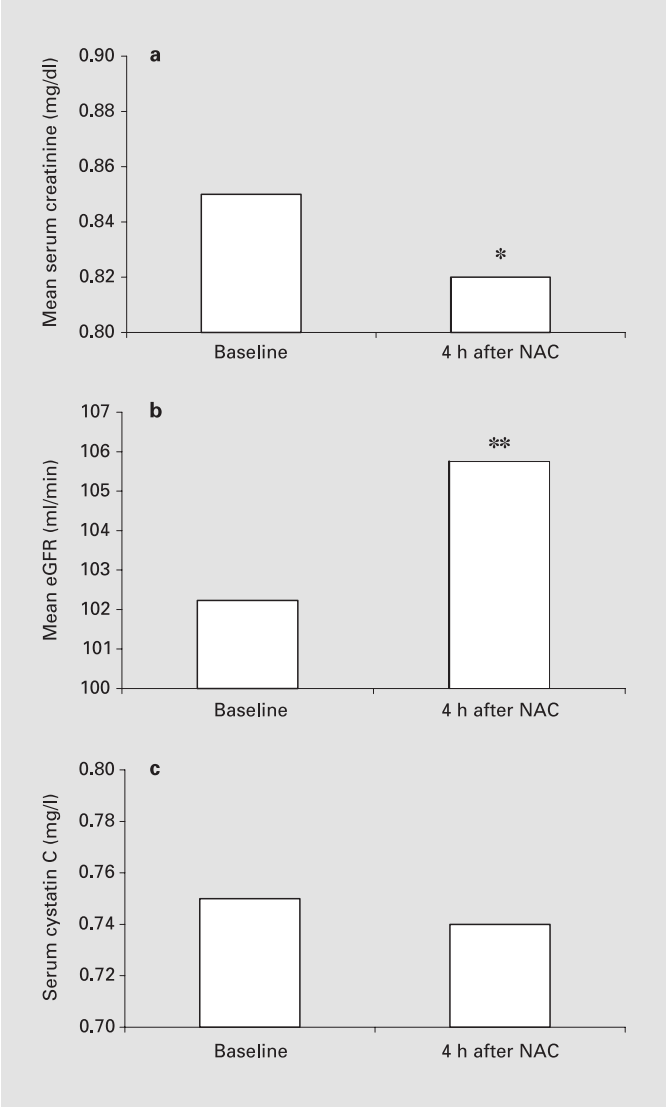

Fig. 1. Surrogate markers of the renal function. Mean serum creatinine (**a**), eGFR (**b**), and cystatin C (**c**) before (baseline) and 4 h after the last intake of NAC. There were a significant decrease of the mean serum creatinine concentration (* $p < 0.05$) and a significant increase of the eGFR (** $p < 0.02$) 4 h after the last administration of NAC, whereas the cystatin C concentration did not change significantly [20].

First, NAC truly improves the GFR, but cystatin C fails to detect such an improvement. This appears unlikely, since several studies comparing cystatin C and creatinine with the GFR employing the ^{51}Cr-EDTA clearance, the gold standard to measure the GFR, documented that cystatin C determination is superior to creatinine measurement [46–49]. Furthermore, contrary to the serum creatinine concentration, the serum cystatin C level is independent of age, sex, and muscle mass.

Second, NAC does not alter the GFR, but causes a decrease in the serum creatinine concentration through another mechanism. A number of reasons favor this assumption. Creatinine is predominantly but not exclusively eliminated by glomerular filtration. Especially in patients with an impaired renal function, the extent of tubular secretion may contribute significantly to the total creatinine excretion. Furthermore, the creatinine metabolism is affected by NAC either through direct activation of creatinine kinase or through reversal of inhibition by free radicals [50].

Although these data were obtained in healthy adults, it is likely that the underlying physiological mechanisms are the same in individuals with renal disease. In contrast, the effects of NAC on renal tubular creatinine secretion or muscle metabolism may be even more prominent in such patients. However, to prove the same effect in patients with an impaired renal function, further studies using a similar protocol without administration of contrast agents have to be done. Nevertheless, the data obtained in our study clearly cast some doubt on the present practice to administer NAC for protection from RCIN.

Conclusions

Efficacious and safe prevention of RCIN is expected to decrease morbidity, including the need for dialysis, and mortality during hospitalization and thus should reduce health care costs. So far, only hydration and the use of low-osmolar contrast media proved to be beneficial. When the role of NAC in human RCIN is studied, special attention must be given to the end point used to determine presence or absence of renal injury. The presently available data from human studies as well as the meta-analyses represent a special dilemma, as they show conflicting results, even for the most common surrogate end point serum creatinine. In a recent study [20], we have shown that NAC leads to a decrease of serum creatinine, but that another surrogate marker of renal function, serum cystatin C, does not change after NAC administration.

Therefore, it is suggested to assess hard clinical end points rather than solely changes in serum creatinine in future studies. If surrogate parameters of renal function are used to prove the protective effect of NAC, the study designs should preferably include direct GFR measurements or include at least another surrogate marker of the renal function, e.g., cystatin C.

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