REVIEW

Radiocontrast Induced Nephropathy

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In spite of improvements in chemical structure, contrast media assisted X-ray examination is still the third leading cause of hospital-acquired acute renal failure. An increase > 50% or > 88 μmol/L in S-creatinine is a clinically important acute renal failure. The peak in S-creatinine occurs within 2–5 days after exposure. The frequency of oliguria, transient or permanent haemodialysis is unknown.

The cause is a hypoxic tubular injury due to vasoconstriction with release of free oxygen radicals. Major risk factors are prior renal insufficiency and diabetes mellitus. Minor risk factors are congestive heart disease, dehydration, hypotension, hypoxia, amount of contrast, ionic and high osmolar contrast, repeated examinations at short intervals, abdominal examination, and perhaps age, smoking, hypercholesterolaemia, and use of Non-Steroidal Anti inflammatory Drug.

Prevention seems possible by omission or reduction of contrast, ameliorating predisposing factors, saline hydration 24 h before and after exposure, and 600 mg acetylcysteine orally twice daily 24 h before and after exposure. A three-day treatment with 20 mg nitrendipine daily, starting 1 day before examination may also be preventive.

The present research is unfortunately characterised by small numbers, lack of clinical important renal failure, and lack of long term results. The latter may be important after new data indicate that radiation may trigger a chronic oxidative process through a similar pathway.

Key Words: Contrast induced nephropathy; Definition; Cause; Risk factors; Prevention.

Introduction

Contrast nephropathy (CN) is a well-recognised complication of arteriographic procedures, but also of intravenous urography and Computed tomography-scans with use of intravenous contrast media.

The signs are mostly a mild deterioration of the renal function with transient proteinuria and signs of tubular damage.1

The numbers of contrast media-enhanced examinations are increasing. The annual sale of iodine for contrast media now represents 60 million doses a year worldwide. In spite of improvements in chemical structure, contrast media-enhanced examinations are still the third leading cause of hospital-acquired acute renal failure.2

Several potential preventive possibilities seem to exist. Consequently, a review of the causes and preventive strategies was made.

Methods and Material

The Pubmed database was searched for relevant publications. The first search terms were “Radiocontrast nephropathy and angiography and risk factors” limited by English and procedures studied above 100 and after 1980. Unfortunately, relevant papers were mostly from 1984–1996. The second search terms were “Radiocontrast nephropathy and angiography and pathogenesis” limited by English and after 1980. The third search terms were “Radiocontrast nephropathy and prevention” limited by English and clinical controlled trial and after 1980.

Definitions and Manifestations

CN can be defined as an acute impairment of renal function that follows exposure of radiocontrast enhanced examination and for which alternative explanations for renal impairment have been eliminated.13
The clinical presentation of CN is distinct, having a temporal relation between the performance of the contrast study in the high-risk patient and the onset of an increase in S-creatinine levels within the next 24 h–5 days. S-creatinine values greater than 50% of baseline, or rising by 88 \( \text{m}\text{mol/L} \) or more seem diagnostic. However, the definition varies (Table 1). The peak S-creatinine level occurs within 3–5 days of the contrast enhanced study. After the introduction of less nephrotoxic contrast media, the frequencies of oliguria, transient and permanent dialysis are mostly unknown. It was earlier reported to be approximately in 25–30 and 10–20%, respectively,\(^{14-16}\) and with the introduction of modern contrast agents probably reduced. However, the long term prognosis or whether radiological examinations without or with signs of CN cause a progressive degenerative process seems not have been described.

Monitoring S-creatinine is the most useful clinical procedure in high-risk patients after angiography.\(^{13}\) However, S-creatinine is probably not the best parameter since the renal function must be severely damaged before changes in S-creatinine is observed (Fig. 1). Besides S-creatinine, impaired clearance can also be studied by measuring carbamide, creatinine clearance, urinary creatinine, osmolarity, albumin, alanylamino-peptidase, N-acetyl-beta-glucosaminidase, and alpha-1-microglobulin.\(^{17,18}\)

CN also have a high incidence of cortical contrast retention that is detectable on non-enhanced computed tomography.\(^{19}\)

### Pathogenesis

Low oxygen tension normally exists in the outer renal medullar region, reflecting the sensitive regional oxygen supply and a high local metabolic rate and oxygen requirement, resulting from active salt reabsorption by medullary thick ascending limbs of Henle’s loop. Contrast agents markedly aggravate this outer medullary physiologic hypoxia\(^ {3} \) because they cause enhanced metabolic activity and oxygen consumption as a result of osmotic diuresis and increased salt delivery to the distal nephron because the regional blood flow and the oxygen supply actually increase in this area. It is believed that this may result from the activation of various regulatory mediators of outer medullary blood flow to ensure maximal regional oxygen supply in the distal nephron. This local vaso-motoric response seems to involve complex and dynamic interactions between glomerular, tubular and interstitial cells mainly caused by decreased production of nitric oxide, a vasodilator, and increased production of endothelin, a vasoconstrictor 10 times more potent than angiotensin II, vasopression and neuropeptide Y, making it the most potent endogenous vasoactive substance known.\(^ {4,5} \) The result of the haemodynamic changes is hypoxia with following oxidative stress and repair.

Adenosine, a renal vasoconstrictor is thought to play a role in CN,\(^ {5,7} \) Also, stimulation of the dopamine receptors and angiotensin II seems to influence.\(^ {3} \)

One putative pathway might be generation of free oxygen radicals.\(^ {8} \) Kidney cells can produce various free oxygen radicals,\(^ {9} \) antioxidants have proven beneficial in the treatment of experimental renal disease,\(^ {10} \) and nephrotoxic agents can reduce the content of antioxidants in the kidneys.\(^ {11} \) However, radiation of cells with 10 Gy has shown to lead to oxidative stress through a similar pathway, and recently, Robbins \textit{et al.} found in an animal study, marked dose–response

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### Table 1. Various used definitions of contrast induced nephropathy.

(1) An increase of greater than 50% in the S-creatinine level.
(2) An increase in S-creatinine of 88 \( \text{m}\text{mol/L} \) or more.
(3) An increase in S-creatinine of 44 \( \text{m}\text{mol/L} \) or more.
(4) An increase in S-creatinine, at least 25% over baseline, within 48 h of the contrast enhanced study.
(5) An increase in S-creatinine greater than 0.3 mg/dl (26.4 \( \text{m}\text{mol/L} \)) and greater than 20%, 1–7 days after radiological examination.

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*Clinical important acute renal failure.*
related signs of chronic oxidative DNA damage 24 weeks after radiation. Whether CN also causes a chronic oxidative damage is unknown.

**Contrast Agents**

The type and volume of contrast used are correlated with the risk of CN. Furthermore, abdominal aortic and cardiac examinations compared with peripheral arteriography are associated with a higher risk of CN.

The contrast agents are all watersoluble and build of tri-iodobenzenes devariates. According to the structure, they are separated into whether they are ionised, and whether the tri-iodobenzenes is a monomer or a dimer (consisting of two triiodbenzene cores). Each agent is made with various iodid-concentrations, and the osmolarity is proportional with this content. Furthermore, the osmolarity depends upon the number of particles in the solution. Consequently, ionised monomere agents have three times as high osmolarity as non-ionised monomere and ionised dimere with the same iodid-concentration. Non-ionised dimere have the lowest osmolarity. Various examples of contrast agents are listed in Table 2.

As mentioned, the agents cause enhanced metabolic activity and oxygen consumption as a result of osmotic diuresis. Consequently, the osmolarity and perhaps chemical structure of the agents must influence the potential nephotoxicity.

In a randomised trial, 249 subjects with prior renal insufficiency were randomised to receive high or low osmolar contrast. S-creatinine rose by at least 25% in 6.8% given high and 3.8% given low osmolar contrast ($p > 0.05$). Greater than 50% increase in S-creatinine was seen in 3.4% with high osmolar contrast (HOCM) and 1.5% with low osmolar contrast (LOCM) ($p > 0.05$). Risk factors were prior renal insufficiency and diabetes mellitus, but not with type of contrast. However, the sample size was obviously not powered to detect such a relatively small difference. In a large metaanalysis, 31 randomised trials studying LOCM versus HOCM were used. The pooled $p$-value was 0.02. Consequently, the difference seems small. However, among 25 trials with available data, the pooled odds ratio of a rise in S-creatinine level of more than 44μmol/L with LOCM was 0.61 (0.48–0.77) times that after HOCM. For patients with existing renal failure, this odds ratio was 0.50 (0.36–0.68), while it was 0.75 (0.52–1.1, $p > 0.05$) in patients without prior renal failure. Greater changes in S-creatinine level occurred only in those with existing renal failure and were less common with LOCM (OR: 0.44 (0.26–0.73). Consequently, the risk reduction with LOCM is considerable, especially in cases with existing renal failure.

Today ionised monomeric contrast media has been abounded. The non-ionic dimeric contrast media are isoosmolar to plasma cause even fewer haemodynamic side-effects and could in theory be less toxic. Experimental studies have suggested that non-ionic contrast agents are less nephrotoxic than ionic contrast agents. However, in a large randomised trial, Schwab et al. were unable to demonstrate a difference in the frequency of CN between patients receiving a non-ionic contrast agent and those receiving an ionic contrast agent.

However, in another randomised trial with 1196 patients with prophylactic hydration, the frequency of clinical important CN was 7% in patients receiving diatrizoate (ionic) compared to 3% patients receiving iohexol (non-ionic) ($p < 0.002$). The differences in CN between the two contrast groups were confined to patients with prior renal insufficiency alone or combined with diabetes. In a multivariate analysis, baseline S-creatinine, male gender, diabetes, volume of contrast agent, and prior renal insufficiency were independently related to the risk of CN.

**Table 2. Contrast agents for intravascular use.**

<table>
<thead>
<tr>
<th></th>
<th>Ionised</th>
<th>Non-ionised</th>
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<tbody>
<tr>
<td>Monomer</td>
<td>Amidotrizoate</td>
<td>Iobitridol</td>
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<tr>
<td>Diatrizoate (Abounded)</td>
<td>Iohexol</td>
<td>Iomeprazole</td>
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<td></td>
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<td>Iopamidol</td>
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<td>Ioversole</td>
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<td>Iotronide</td>
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<td>Dimer</td>
<td>Ioxaglinate</td>
<td>Iodixanol</td>
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<td>Iotrelane</td>
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Unfortunately, very few studies concerning frequency and risk factors with an acceptable large study group have been published after the introduction of the less nephrotoxic modern contrast media. However, the above mentioned randomised trial found the frequency of clinical important CN was 3–7% depending upon whether modern ionised or modern non-ionised agents were used. Nevertheless, the pathogenesis seems to be the same, and the lessons learned in the past concerning risk factors must be expected to persist. Irrespective of the exact frequency, two major risk factors have been identified: pre-existing renal disease and diabetes mellitus (Table 3). When renal insufficiency defined as elevated S-creatinine and
diabetes both coexists the risk of CN increases up to 10 times. Only a single large study have been unable to find elevated S-creatinine as a risk factor of CN.

Table 3. Studies concerning risk factors for contrast induced nephropathy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Contrast agent</th>
<th>n</th>
<th>Definition</th>
<th>Risk factors</th>
<th>Not risk factors</th>
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<tbody>
<tr>
<td>Parfrey20</td>
<td>N.A.</td>
<td>220</td>
<td>ΔSCr &gt; 25%</td>
<td>DM with</td>
<td>SCr or</td>
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<td></td>
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<td></td>
<td>SCr</td>
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<tr>
<td>Taliercio21</td>
<td>Iopamidol</td>
<td>307</td>
<td>ΔSCr &gt; 88 µmol/l</td>
<td>DM</td>
<td>Congestive heart failure</td>
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<td></td>
<td>Diatrizoate</td>
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<td>Contrast volume</td>
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<td>Number of exam</td>
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<tr>
<td>Moore22</td>
<td>Omnipaque</td>
<td>929</td>
<td>ΔSCr &gt; 44 µmol/l or ΔSCr &gt; 33%</td>
<td>DM</td>
<td>Furosemide,</td>
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<td>Atrophic disease</td>
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<tr>
<td>Lautin23</td>
<td>Diatrizoate</td>
<td>394</td>
<td>ΔSCr &gt; 26 µmol/l</td>
<td>DM</td>
<td>SCr or</td>
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<tr>
<td></td>
<td>Ioxaglate</td>
<td></td>
<td>ΔSCr &gt; 20%</td>
<td></td>
<td>DM</td>
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<tr>
<td></td>
<td>Iohexol</td>
<td></td>
<td></td>
<td></td>
<td>Scr</td>
</tr>
<tr>
<td>Gussenhoven24</td>
<td>Hexabrix</td>
<td>396</td>
<td>ΔSCr &gt; 10%</td>
<td>DM</td>
<td>Age &gt; 70</td>
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<tr>
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<td>Isopaque</td>
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<td></td>
<td></td>
<td>Hypertension</td>
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<td></td>
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<td>Vol. contrast &gt; 150 ml</td>
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<td></td>
<td></td>
<td></td>
<td>ΔSCr</td>
</tr>
<tr>
<td>Paredero15</td>
<td>N.A</td>
<td>400</td>
<td>ΔSCr &gt; 88 µmol/l or ΔSCr &gt; 50%</td>
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<td>ΔSCr</td>
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<td>Contrast volume</td>
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<td>Abd. aortic studies</td>
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<td></td>
<td>Congestive heart failure</td>
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<tr>
<td>Gomes14</td>
<td>Isopaque</td>
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<td>ΔSCr</td>
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<td>Conray 60</td>
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<td>DM</td>
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<td>Contrast volume</td>
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<td>Rich26</td>
<td>Diatrizoate</td>
<td>183</td>
<td>ΔSCr &gt; 44 µmol/l</td>
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<td>ΔSCr</td>
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<td>Iohexol</td>
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<td>Congestive heart failure</td>
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<td>Vol. Contrast &gt; 200 ml</td>
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<td>ΔSCr</td>
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<td>DM</td>
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<td>ΔSCr</td>
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ΔSCr: Elevated S-creatinine. DM: Diabetes mellitus. ΔSCr: Change in S-creatinine before and after examination. N/A: Not available.

Minor and Potential Risk Factors

Congestive heart failure is also often associated with CN, but with a lower risk than diabetes and elevated S-creatinine.
S-creatinine $^{14,15,21,25}$ (Table 3). Due to the hypoxic component in the pathogenesis, one ought to believe that chronic obstructive pulmonary disease are associated with CN. Apparently, it has not been investigated. Both hypotension and hypertension has been reported as a risk factor CN, while others could not. $^{21,24,25}$ Antihypertensive and nephrotoxic drug medication seems not to increase the risk of CN, neither does hyperuricemia, liver or allergic diseases. $^{22}$

Other studies found age to be a risk factor of CN, $^{14,15,27}$ while other have not. $^{21,23,26}$ The male gender is variably described associated with CN. $^{23,28}$

Independent risk factors for CN have also been reported to be S-albumin $<35$ g/L, S-sodium $<135$ mmol/L. $^{26}$

Furthermore, in a human clinical controlled study, smoking and nicotine were accompanied by significant acute changes in renal hemodynamics and albuminuria. Consequently, smoking before contrast radiation could increase the risk of CN. $^{38}$

Finally, hypercholesterolaemia aggravated CN in an animal study but human studies are missing. $^{39}$ Major, minor, and possible risk factors are summarised in Table 4.

### Prophylactic Possibilities

#### Omission

The most efficient prevention would of course be avoiding contrast enhanced X-ray examination, for example by using alternative imaging with ultrasound or MR-angiography/urography. If not possible, use of non-ionic dimere in low-osmolar concentrations would be less nephrotoxic because of smaller osmotic load and vasomotor alterations. $^{40}$

#### Identification and ameliorating of predisposing factors

According to the pathogenesis, predisposing factors must be optimised as heart failure, and salt, water, and blood depletion. Optimising of respiratory diseases, oxygen supply in cases with habitual low saturation, avoidance of non-steroidal anti-inflammatory agents which inhibits prostacyclin production could in theory lower the risk of renal medullary hypoxia.

#### Saline hydration

Eisenberg et al. reported in 1981, that 537 patients undergoing angiography did not experience any serious renal failure, and believed it was due to intravenous infusion 12–24 h before angiography. $^{39}$ The strategy and observation was followed by others, $^{42,43}$ but apparently never tried in randomised trials (hydration versus no hydration). In a randomised trial, it was proven that hydration could be taken per orally at home (1 l over 10 h), and followed by 6 h of intravenous hydration (0.45 normal saline solution at 300 ml/h) beginning just before contrast exposure. $^{44}$

Recently, a major randomised trial showed showed isotonic hydration was superior to half-isotonic hydration, and thus indirectly that hydration matters. $^{36}$

#### Forced diuresis

In another randomised trial, patients were randomly assigned to receive 0.45% saline alone for 12 h before and after angiography, saline plus mannitol, or saline plus furosemide. The mannitol and furosemide were given just before angiography. In 11%, S-creatinine increased more than 44 $\mu$mol/l compared with 28% in the mannitol group, and 40% in the furosemide group ($p = 0.05$). The mean increase in S-creatinine was significantly greater in the furosemide group than in the saline group. $^{45}$ Consequently, forced diuresis cannot be recommended.

#### Haemodialysis

In a randomised trial performing hemodialysis or not immediately after contrast exposure in 113 patients with prior renal insufficiency, haemodialysis did not diminish the rate of complications, including CN. $^{46}$ Similar findings were observed on two other randomised trials. $^{47,48}$ The finding seems logical, since the
main exposure must occur while the contrast enhanced examination occurs.

Renal vasodilators

Adenosine-inhibiting-renal vasodilators
Patients with diabetes or prior renal insufficiency have a higher sensitivity of the renal vascular musculature to adenosine. However, in a clinical controlled trial with 26 receiving 200 mg intravenous aminophylline, compared with 26 individually matched controls for baseline creatinine, diabetes mellitus and amount of contrast, there was no significant difference between cases and controls. However, 18 patients with prior renal impairment were randomised to receive a continuous infusion of aminophylline or placebo before and during the radiocontrast procedure. There was a persistent deterioration in renal clearance in those who received more than 135 ml of contrast media, but it was not prevented by the use of adenosine. However, the number of participants was small, especially if the frequency of CN is taken into account.

Another adenosine inhibitor, theophylline, have been tested twice: First in 78 intensive care unit patients who had 200 mg theophylline per 70 kg body weight intravenously 30 min before examination with more than 100 ml contrast medium. Despite the large number of risk factors, S-creatinine concentrations did not increase 24 and 48 h after the contrast enhanced examination. The study design is obviously debatable, but the results are nevertheless interesting. However, they are in contrast to a study where dopamine and without coexisting diabetes mellitus, and compared with a previously published cohort of similarly at-risk patients. The frequency of CN, defined as an increase in S-creatinine above 25%, 2 days after the angiocardiography was 13% in the group treated with fenoldopam, compared to an expected 38% (p<0.05). Obviously, the control group is debatable, and randomised trials are needed.

Prostaglandin E-1
One hundred and thirty patients with prior renal insufficiency were included in a study where the patients received one of three different doses of prostaglandin E-1 (10, 20, or 40 mg/kg body weight/min) or placebo intravenously over a time period of 6 h beginning 1 h prior to radiocontrast application. In the placebo group, the mean elevation of S-creatinine was markedly higher after the contrast infusion than those receiving prostaglandin-E-1. However, no clinically relevant changes were seen regarding the creatinine clearance. Thus, the results are promising but randomised studies with clinical important outcomes are needed.

Dopamine
Low-dose dopamine has a dilatory effect on the renal vascular musculature, but the effect of dopamine on renal blood flow in patients with chronic renal insufficiency is controversial. In a randomised controlled trial, 66 patients with prior renal insufficiency and/or diabetes mellitus were randomised to either 120 ml/day of 0.9% saline plus dopamine2 mg/kg/min (Dopamine group) or saline alone (Control group) for 24 h before and after examination. There was no significant difference in the change of creatinine between the two groups. However, subgroup analysis revealed that patients with peripheral vascular disease had a significantly higher increase in S-creatinine after the use of dopamine compared with controls.

In another randomised trial, patients with prior renal insufficiency were hydrated with 0.45% NaCl intravenously at 100 ml/h for 12 h and then randomised to either 0.45% NaCl intravenously at 100 ml/h or dopamine intravenously at 2 mg/kg/min for 2 h during and after cardiac catheterisation. CN was defined as a 25% increase of S-creatinine above baseline 48 h after radiocontrast examination. The frequency of CN was not different between the two groups but dopamine infusion was associated with a significant increase in renal blood flow throughout the examination.

In a third trial, 50 patients with prior renal insufficiency were randomised to receive either isotonic saline, or one of three renal vasodilator/diuretic drugs: dopamine, atrial natriuretic peptide (ANP), or mannitol by intravenous infusion. Diabetic patients exposed to one of the three drugs had the greatest

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increase in renal blood flow. The incidence of CN among the diabetics receiving those drugs was 83, 83 and 75%, in the dopamine, ANP and mannitol groups, respectively. In contrast, among the nondiabetics in each of those groups the incidence of CN was zero. In the saline control group, CN in the diabetics and nondiabetics were 43 and 38%, respectively. The findings were non-significant and the power of the study could be discussed: 50 patients to four groups. Nevertheless, in summary of the three trials, dopamine could seem to increase the renal blood flow but it does not provide protection against CN.55

Calcium-antagonists

One hundred and twenty one outpatients with normal renal function received a single dose of placebo or nitrendipine 10 or 20 mg nitrendipine perorally 1 h before the procedure. S-creatinine and U-albumin remained unchanged.17

In another study, 27 patients (15 diabetics and 12 non-diabetics) with normal to moderately reduced renal function were randomised to hydration or hydration combined with 10 mg oral felodipine (Plendil) 3–4 h before angiography. S-creatinine increased significantly in the felodipine group but not in the placebo group.56

In a third study, 42 patients were randomised to receive nifedipine 10 mg orally 1 h before examination or no treatment. The mean changes in S-creatinine were insignificant. In a fourth randomised study, 35 patients were randomised to a 3-day treatment with 20 mg nitrendipine daily starting 1 day before X-ray examination or placebo. Despite the fact that baseline renal function was significantly more compromised in the investigational group, the prophyllactic application of nitrendipine preserved the glomerular filtration rate, whereas control patients showed a significant (27%) reduction in GFR on day 2 after contrast-media injection (p < 0.001). Moreover, the increase in proteinuria and specific enzymuria was ameliorated by nitrendipine.57

Thus, calcium channel antagonists may protect against CN, but the treatment apparently needs to be started the day before, and continued two days after exposure. However, the results seem needed to be confirmed in other studies using clinical important acute renal failure as end-point and a larger sample size.

Angiotensin converting enzyme inhibitors

Pharmacological inhibition of angiotensin II using either angiotensin converting enzyme (ACE) inhibitors or more recently angiotensin receptor II antagonists have been shown to be effective in the treatment and prophylaxis of experimental CN.58

Antioxidants

N-acetylcysteine (NAC), the acetylated variant of the amino acid L-cysteine, is an excellent source of sulphydryl groups, and is converted in the body into metabolites capable of stimulating glutathione synthesis, promoting detoxification, and acting directly as free radical scavengers.59–62

Besides, the scavenging effect, NAC could also protect by inhibiting ACE, which has been shown to be involved in experimental CN (see above). In a combined animal and human study, conscious rats received NAC or placebo infusion. After 2 h of infusion, the ACE activity was reduced with 31%. In a following human study, isosorbide dinitrate (5 mg/h) was infused into six male volunteers for 48 h followed by NAC (2 g i.v. followed by 5 mg/kg/h) from 24 to 48 h. p-angiotensin II increased during the first 24 h and 2 h after NAC infusion (p < 0.05). The results suggest that sulphydryl supplementation modifies the function of the renin/angiotensin system in vivo, an effect probably mediated by inhibition of ACE activity.63

Finally, a randomised clinical trial of NAC versus placebo concerning CN have been reported; 83 patients with chronic renal insufficiency, who were undergoing computed tomography and had a nonionic, low-osmolality contrast agent, were randomly assigned either to receive NAC (600 mg orally twice daily) and 0.45% saline intravenously, before and after exposure, or to receive placebo and saline. Two percent in the acetylcysteine group versus 21% in the placebo group had an increase of at least 44 μmol/l in S-creatinine 48 h after exposure (p = 0.01). In the acetylcysteine group, the mean S-creatinine decreased significantly (p < 0.001), whereas in the control group, the mean S-creatinine increased nonsignificantly (p = 0.18).

Consequently, the results of this well-conducted study suggest that simple oral administration of acetylcysteine along with hydration prevents CN in patients with prior renal insufficiency.64 The weakness of the study seems to be that clinical important CN was not an end point.

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