

Potential mechanisms behind contrast medium-induced nephropathy

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Abstract

How contrast medium-induced nephropathy (CIN) comes about is poorly understood, although CIN is a common cause of acute renal failure. Hitherto, the various studies performed have led to different interpretations and partially contradictory conclusions. This article aimed to review the mechanisms underlying CIN and to outline existing data obtained with the newer iodinated agents in patients with pre-existing renal failure. Osmolality, which has received considerable attention, is but one of several physico-chemical properties of contrast media (CM). The more recently developed iso-osmolar CM are dimers, not monomers as the widely used non-ionic low osmolar CM. Thus, in

spite of them being iso-osmolar, they have physicochemical features different from other CM, e.g. in terms of viscosity (> 5 fold greater than plasma viscosity), which may be of considerable pathophysiologic and clinical importance. Many experimental studies provide evidence for greater perturbation in renal function with iso-osmolar CM compared with non-ionic low-osmolar CM. Conversely, some clinical trials indicate an advantage of the iso-osmolar CM, although others do not. In this review, the possible causes of CIN are highlighted, including altered rheological properties, perturbation of renal haemodynamics, regional hypoxia, auto- and paracrine factors (adenosine, endothelin, reactive oxygen species) and direct cytotoxic effects. It is concluded that caution must be taken to avoid a false sense of security with the use of iso-osmolar CM.

Introduction

This review critically surveys recent clinical studies with regard to contrast medium-induced nephropathy (CIN) and focuses on mechanisms believed to mediate CIN, which implies impairment of renal function occurring within 3 days of the

intravascular administration of contrast medium (CM) and the absence of an alternative aetiology.^{1,2} An increase in serum creatinine by more than 25% or 44 $\mu\text{mol/l}$ (0.5 mg/100 ml, within 48 - 72 hours of contrast administration) is often taken as a marker for the occurrence of CIN.³⁻⁶ The serum creatinine concentration typically peaks on the second or third day after exposure to CM and usually returns to the baseline value within 2 weeks.^{7,8}

Generally, CIN is reversible. Nevertheless, the use of CM increases in-hospital morbidity, mortality and costs, in particular in those rare cases where dialysis is required. Thus, despite the small relative risk of developing adverse effects, CIN is the third leading cause of acute renal failure in patients who have been admitted, accounting for 10% of all cases.^{9,10} The incidence of nephropathy induced by low-osmolar CM is low in the general population and has been calculated to be less than 2%.^{11,12} In selected subgroups of patients, however, like those with pre-existing renal insufficiency or diabetes mellitus or a combination of both, the incidence is significantly higher, in the range of 12 - 50%^{10,13-17} requiring transient dialysis or progress to end-stage renal disease.¹⁸

Risk factors

By far the greatest risk of developing CIN is pre-existing renal impairment combined with diabetes, dehydration, or a combination of both.¹⁹ Remarkably, however,

Table I. Osmolality and viscosity for various CMs. Note differences in iodine concentrations

Generic name	Physicochemical properties of CM		
	Iodine concentration (mg/ml)	Viscosity (mPA'S at 37°C)	Osmolality (at 37°C mOsm/kg H ₂ O)
Iopamidol	300	5.25	636
Iopromid	300	4.6	610
Iohexol	300	5.7	690
Ioxaglate	320	7.5	600
Iomeprol	300	4.5	521
Iodixanol	320	11.4	290
Diatrizoat	292	4.0	1500
Iopentol	300	6.5	640
Iotrolan	300	8.1	320

diabetes mellitus per se without renal insufficiency is not a risk factor.¹⁵ Additional risk factors are: dosage of CM and type of CM, congestive heart failure, old age, hypertension, route of administration of CM, and the use of other nephrotoxic drugs.^{13,20}

Any condition associated with decreased effective circulating volume enhances vulnerability with regard to CIN.¹⁹ Of course, other causes of acute renal failure, such as atheromatous embolic disease, ischaemia, prerenal azotemia, sepsis, or other nephrotoxins should always be considered, particularly if CIN is suspected in a patient without known risk factors. For example, CIN might be mistaken for cholesterol crystal embolisation after intravascular catheterisation.

When comparing the renal effects of different vascular contrast agents in patients with normal renal function, there are inconclusive results in the literature. Patients with no pre-existing renal impairments have been shown to be highly resistant to CIN, even when using ionic high-osmolar CM.^{3,21} Unfortunately, though, patients with pre-existing renal impairments are to a large extent also the patients requiring angiography²² and in this subpopulation high doses of CM increases the risk for CIN.²³

Substance groups

For over 50 years the various available CM have been based on triiodobenzene. Their characteristics vary due to the osmolality and ionicity of the product. Earlier, during the time of high-osmolar CM (which have osmolalities approximately 6 times higher than plasma found in broad clinical use), it made sense to differentiate CM with regard to osmolality. However, already then it was obvious that many of the side-effects were actually caused by the electric charge. The current use of low-osmolar CM (which still have considerably higher osmolality than plasma) and iso-osmolar CM is widespread and it may be that the subdivision of CM according to their osmolality should be reconsidered. This is so since iso-osmolar CM are dimers, thus revealing greater viscosities than the monomeric low-osmolar CM (Table I). As

outlined below, this difference can be of importance for renal and systemic haemodynamics.

Clinical studies

Use of the more modern CM that are low- or iso-osmolar has reduced the likelihood of CIN compared with high-osmolar CM.

In a prospective, randomised study involving 1 196 patients undergoing angiography, Rudnick *et al.*⁵ found no differences in incidence of nephropathy between patients receiving iohexol (low-osmolar, 780 mOsm/kg H₂O) and patients receiving diatrizoate (high-osmolar, 1 870 mOsm/kg H₂O) among low-risk patients (patients without diabetes who had a baseline serum creatinine concentration of less than 1.5 mg/dl (133 µmol/l)). However, in patients without diabetes whose serum creatinine concentrations were higher than 1.5 mg/dl, the incidence of nephropathy was reduced from 27.0 to 12.2% with the use of iohexol.⁵ For patients with diabetes, the incidence was reduced from 47.7 to 33.3%. Overall, patients receiving high-osmolar CM were 3.3 times as likely to develop CIN as those receiving low-osmolar CM. For all practical purposes, all the newer low-osmolar or iso-osmolar agents are considered to be the agents of choice in patients at higher than usual risk for the development of CIN.¹⁹

Some comparative studies in patients with pre-existing renal impairment have shown similar susceptibility for CIN with both nonionic monomeric and nonionic dimeric CM,²⁴⁻²⁶ whereas other trials have concluded that iso-osmolar CM have advantages with regard to the occurrence of CIN in renally impaired patients.^{1,27} In particular Aspelin *et al.*¹ in the NEPHRIC study concluded that iohexol ($N = 65$) was significantly more nephrotoxic than the nonionic dimer iodixanol ($N = 64$) in patients with pre-existing chronic renal failure undergoing coronary or aortofemoral angiography. These results have received considerable attention due to the conclusions of the authors, but also due to some serious shortcomings of the study design. Previous studies have shown that critical factors for the susceptibility of CIN

are duration of diabetes, metabolic status and renal function before CM injection.⁸ The investigated groups in the study of Aspelin and co-workers¹ were significantly different in all of these parameters and thus the outcome of the study is more likely to reflect the differences of the studied populations rather than differences of the administered CM with regard to CIN. In addition, the hydration regimen was not pursued with vigour, as indicated by considerable variance in fluid intake.

The conclusion of the NEPHRIC study that the use of iso-osmolar CM, as opposed to low-osmolar CM, results in reduced incidence of CIN is not in line with our current understanding of CIN, as mentioned below, and contradicts studies in which the use of iso-osmolar CM conferred no advantage.^{28,29} In light of the controversy whether patients at risk actually benefit from iso-osmolar CM^{1,27} or not²⁴⁻²⁶ and the experimental data on physiologic/pathophysiological renal mechanisms that do not support any beneficial effects of iso-osmolar CM, the CM of choice still remains an open question.³⁰

Mechanisms of CIN

There is a particularly vulnerable kidney region in the deeper portion of the outer medulla. This is an area remote from the vasa recta that supply the renal medulla with blood. The reason for the vulnerability of the outer medullary portion of the nephron is the relative high oxygen requirements due to salt reabsorption. In this area of the kidney, the limbs of the loop of Henle exhibit hypoxic damage, for instance by perfusion with erythrocyte free solution.³¹ Oxygen delivery to the peripheral tissues can be impaired by CM due to an increase oxygen affinity of haemoglobin.³²

It is not fully clear what the underlying mechanism is with regard to CIN. Several suggestions have been put forward and it is widely held that a combination of various mechanisms need to act in concert to cause CIN.¹⁹ Among these mechanisms, a reduction in renal perfusion caused by a direct effect of CM on the kidney and toxic effects on the tubular cells are generally recognised as important. However, the pathophysiological relevance of direct effects of CM on

tubular cells remains disputed,¹⁹ as are the other proposed aetiologies.

By adding CM to the perfusate of the kidney, hypoxic injury to the region at risk is enhanced, probably by increasing renal vascular resistance.³³ It has been shown that an iso-osmolar dimer with high viscosity (iodixanol) compromises blood flow to all regions of the kidney to a greater extent than low-osmolar, and even high-osmolar CM.²⁹ However, it must be kept in mind that this decrease in perfusion was accompanied by profound systemic effects of iodixanol. Blood pressure in this study dropped considerably.²⁹ In fact, it is well known that local renal hypoxia can be aggravated by the systemic effects of some CM, such as transiently reduced cardiac output,³⁴ and suboptimal pulmonary perfusion-ventilation relationship.³⁵

Another study³⁶ supports the particular potency of dimeric CM in causing renal hypoxia – the iso-osmolar CM iotrolan was also found to impair local pO₂ to a greater extent than the low-osmolar CM iopromide.

The tubuloglomerular feedback (TGF) is a powerful mechanism in the control of renal vascular resistance and glomerular filtration and has often been taken as an explanation for the development of CIN. Specifically, it is believed that increased osmotic pressure brought about by CM elicits renal ischaemia.

The macula densa cells of the thick ascending limb mediate the TGF by sensing Na⁺, K⁺, and Cl⁻ concentrations in the tubular fluid via the Na⁺-K⁺-2Cl⁻ cotransporter. This transporter is effectively blocked by furosemide. The affinity for Cl⁻ is very low, so in a physiological setting there will always be enough Na⁺ and K⁺ to keep the system running; Cl⁻ is the limiting factor.^{37,38} A widespread explanation for the development of CIN is that hyperosmotic CM causes an increased osmotic gradient at the macula densa, which activates the TGF and subsequently compromises renal blood flow and glomerular filtration. Obviously, this chain of events is not a likely explanation for CIN, and this has been shown already by pioneer experiments with retrograde perfusions of the tubule. In this setting, osmolality has no effect on the TGF.^{37,38} The ruling out of the osmotic

diuresis theory is further supported by experiments using mannitol, an osmotic diuretic. Increases in osmolality, such as after mannitol infusion or after CM application, decrease NaCl concentration at the macula densa, however, simultaneously increasing tubular flow. Therefore, the resulting net change in the amount of NaCl passing the macula densa is negligible.³⁹ Moreover, furosemide, a known blocker of the TGF, does not decrease serum creatinine after application of CM, which is usually the parameter taken to indicate CIN.² Blocking the transport using furosemide should dramatically lower local oxygen consumption and alleviate the reduced oxygen supply. In fact, this has been demonstrated to occur in experiments in rats showing that outer medullary pO₂ is elevated after furosemide.⁴⁰ However, furosemide given just before angiography fails to limit increases in serum creatinine after CM application, indicating that yet other mechanisms are involved in CIN.²

Among the often-discussed mechanisms, endothelin and adenosine have received much attention. The effects of endothelin on vascular beds is very dependent upon the receptor subtype activation, but both subtypes of receptors (ET-A and ET-B) are thought to mediate the vascular actions of endothelins in human blood vessels.⁴¹

Endothelin has been suggested as a key element in the scenario leading to CIN because of the elevated endothelin levels in plasma and urine that are found after CM application.⁴²⁻⁴⁴ Further support for the role of endothelin in CIN is derived from the observed enhancement of endothelin transcription and release from endothelial cells in response to CM.⁴⁵ Finally, in patients with impaired renal function, the increase in endothelin after giving CM is exaggerated.⁴⁶ A potential beneficial effect of endothelin in preventing CIN may be mediated by the ET-B mediated effects, such as vasorelaxation. Thus, a selective ET-A receptor blockade could prove to be effective in the prevention of CIN. Indeed, a positive effect of ET-A selective blockade on the renal outer medullary hypoxic response to CM has been reported in the normal rat.⁴⁷ However, when both ET-A and ET-B receptors are blocked in humans

receiving CM, serum creatinine concentration rises to a greater extent than in patients receiving placebo and the CIN incidence is significantly increased in the patients who received combined ET-A and ET-B blockade.⁴⁸

Diabetes mellitus is among the most important risk factors for CIN and diabetics often have endothelial dysfunction of renal vessels. In this setting, NO is suppressed in the renal microvasculature which contributes to the endothelial dysfunction.⁴⁹ Superoxide is a scavenger of NO and may cause the attenuated NO activity found in the diabetic renal microvasculature. Indeed, superoxide production has been found to be increased in renal cortical tissue from diabetic rats⁵⁰ and the afferent and efferent arteriolar vasoconstrictor response to NOS inhibition is impaired.⁵¹ Taken together, superoxide, and perhaps other reactive oxygen species (ROS) may be crucial in the development of CIN. Since ROS are extracellular signalling molecules, they may be significant in mediating the part of the endothelin effects.⁵⁷

Due to the possible role of ROS in CIN, clinical trials have been undertaken to prevent CIN by scavenging ROS.⁵²⁻⁵⁵ In these trials, N-acetylcysteine was given and showed a positive outcome in four studies.⁵³⁻⁵⁶ However, this recommendation is by no means unequivocal.⁵⁷

In analogy to endothelin, a prominent role in causing CIN has also been suggested for adenosine. The renal vasculature of diabetics reveals an enhanced sensitivity to adenosine, thus it has been suggested that adenosine is a particularly important contributor to CIN in patients with this metabolic disorder.⁵⁸ However, the role for adenosine in CIN may be considerably overestimated. For instance, in normal rats,⁵⁹ A₁-receptor blockade fails to alleviate medullary hypoperfusion and hypoxia in response to CM. Moreover, the general reduction in renal plasma flow and GFR caused by CM is not attributable to enhanced adenosine action.⁶⁰

CM can also have direct cytotoxic effects on renal tubular cells. A perturbation of mitochondrial enzyme activity and mitochondrial membrane potential is found under ex vivo conditions in a proximal tubule cell line.⁶¹ Notably, low-osmo-

lar monomeric CM cause less damage than iso-osmolar dimeric CM and ionic compounds reveal the most profound effect.⁶¹ In the more distal segments of the kidney, CM can cause apoptosis, as indicated in another cell line model.⁶² Apoptosis may be brought about by hypoxic damage⁶³ and by a direct influence on these cells.⁶²

A quite simple mechanism that seems to be of paramount importance for the development of CIN has hitherto attracted rather little attention: the rheological properties of CM. The viscosity of the fluid is of particular importance with regard to the renal vascular bed, since the length of the capillaries that supply the renal medulla with blood are extremely long. Although the vasa recta have the same diameter as usual capillaries, they are several cm long. This increases vascular resistance, as indicated by Poiseuille's law: (Equation 1) $R = \eta \cdot 8 \cdot l / \pi \cdot r^4$ (η is viscosity, l refers to the length of the vessel and r is the radius).

The viscosity of the blood flowing through the vasa recta is maintained very low in order to minimise the large resistance caused by capillary length. This is brought about by the Fåhræus-Lindqvist effect and plasma skimming. The Fåhræus-Lindqvist effect guarantees that blood viscosity in the capillary is very low. In fact, it is not much higher than plasma viscosity. This is so due to the high-flow velocity of the erythrocytes flowing through capillaries (single line flow). In effect haematocrit is very low in these vessels.

The low haematocrit is further brought about by plasma skimming: The afferent arterioles separate from the interlobular arteries at a right angle. Since the erythrocytes are concentrated in the centre of the interlobular arteries (laminar flow), the plasma-rich blood near the endothelium is skimmed off into the juxtamedullary afferent arterioles.

Taking these general considerations into account, it is clear that iso-osmolar CM are not a priori superior to low-osmolar agents, since the dimeric iso-osmolar CM have very high viscosities. Therefore, iso-osmolar CM should impair renal medullary blood flow to a greater extent than low-osmolar agents, which indeed seems to be the case, as indicated by the

particularly reduced pO_2 levels caused by iso-osmolar CM (Fig. 1).

Augmented fluid viscosity caused by dimeric iso-osmolar CM may be of even more importance in the renal tubule. Under normal conditions, tubular fluid is of lower viscosity than plasma, as the ultrafiltrate contains very few plasma proteins. Use of dimeric iso-osmolar CM will increase tubular fluid viscosity dramatically and thereby increase the resistance to flow in renal tubules.⁶⁴ In consequence, renal interstitial pressure may take on values as high as 50 mmHg (Fig. 2). Such pressure will dramatically decrease renal medullary flow and decrease GFR. Volume expanding the patient before application of CM will markedly alleviate this effect since the CM will not become as concentrated in the renal collecting ducts. This may be the mechanism responsible for the generally accepted best way to prevent CIN: periprocedural hydration.^{2,65,66}

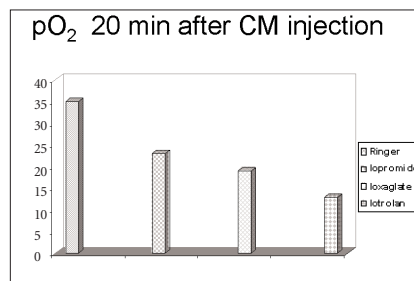


Fig. 1. Medullary hypoxia induced by CM compared with Ringer's solution. Reduction in pO_2 is greatest for Iotrolan (iso-osmolar non-ionic dimer) followed by Ioxaglate (low-osmolar ionic dimer). Iopromide (low-osmolar monomer) had the least effect of the CM. Data from Liss *et al.*⁶⁶

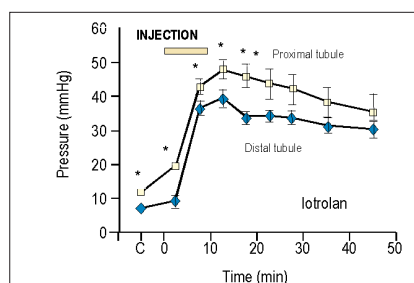


Fig. 2. Renal tubular pressures after injection of an iso-osmolar non-ionic CM, Iotrolan. (Data from Ueda *et al.* *Acta Radiol* 1998; **39**: 90 - 95).

Conclusions

The current understanding of CIN development now includes the rheological

properties of a fluid. Resistance depends on fluid viscosity, not osmolality (Poiseuille's law). Thus, perhaps too much attention has been directed to the osmolality of different CM, while neglecting the impact of other physicochemical properties. Well-controlled animal studies cannot confirm that iso-osmolar CM are superior with regard to the occurrence of CIN. The contrary seems to be the case.

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