Potential mechanisms behind contrast medium-induced nephropathy

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 hemodynamics, 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 etiology. An increase in serum creatinine by more than 25% or 44 µmol/l (0.5 mg/100 ml, within 48 - 72 hours of contrast administration) is often taken as a marker for the occurrence of CIN. 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.

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. The incidence of nephropathy induced by low-osmolar CM is low in the general population and has been calculated to be less than 2%. 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% requiring transient dialysis or progress to end-stage renal disease.

Risk factors

By far the greatest risk of developing CIN is pre-existing renal impairment combined with diabetes, dehydration, or a combination of both. Remarkably, however,
diabetes mellitus per se without renal insufficiency is not a risk factor. 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.

Any condition associated with decreased effective circulating volume enhances vulnerability with regard to CIN. 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 high-osmolar CM. Unfortunately, though, patients with pre-existing renal impairments are to a large extent also the patients requiring angiography and in this subpopulation high doses of CM increase the risk for CIN.

**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. 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 1.3 mg/dl (113 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. 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.

Some comparative studies in patients with pre-existing renal impairment have shown similar susceptibility for CIN with both nonionic monomeric and nonionic dimeric CM, whereas other trials have concluded that iso-osmolar CM have advantages with regard to the occurrence of CIN in 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.

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. Oxygen delivery to the peripheral tissues can be impaired by CM due to an increase oxygen affinity of haemoglobin.

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. 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
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. 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, and suboptimal pulmonary perfusion-ventilation relationship.

Another study 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 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. 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. 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. 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.

Another explanation for the development of CIN is that hyperosmotic CM can also impair local pO2 more strongly than low-osmolar, and even high-osmolar CM. 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.

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. 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 rats and the afferent and efferent arteriolar vasoconstrictor response to NOS inhibition is impaired. 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 endothelial effects.

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

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. However, the role for adenosine in CIN may be considerably overestimated. For instance, in normal rats, A–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.

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

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) \( R = \frac{8\mu L}{\pi r^4} \) (\( \mu \) 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 resistance caused by capillary length. This is brought about by the Fåhraeus-Lindqvist effect and plasma skimming. The Fåhraeus-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 flow). In effect haematocrit is very low in these vessels.

The low haematocrit is further brought about by plasma skimming: The afferent arterioles are concentrated in the center 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 in 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 pO₂ 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. 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.

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.

References


