Contrast medium-induced nephropathy: critical review of the existing clinical evidence

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Contrast agents have evolved remarkably since their use was first considered in 1896, shortly after the first description of X-rays by Roentgen. First attempts include sodium iodide, among many other both simple and complex compounds. By the 1950s, using both science and trial-and-error, radiographic contrast agents had evolved to ionic monomers (e.g., Conray, Renografin, Urografin) that consist of a fully substituted benzene ring with three attached iodine atoms to impart radio-opacity, and a dissociating side chain. The osmolality of this class of contrast agents is in the range of 1200–2000 mOsm/kg. In the late 1970s, to address concerns relating to hypertonicity and related toxicity, Almen developed the first non-ionic monomer, a contrast agent with identical radio-opacity but, because there was no longer a dissociating side chain, with markedly reduced osmolality. These were released in the 1980s and have been in wide use since then. Simultaneously, an ionic dimer was developed, with similarly decreased osmolality. This osmolality was closer to that of blood (~300 mOsm/kg), and led to less discomfort and a marked decrease in the incidence of at least minor adverse events. In the 1990s, two non-ionic dimeric contrast agents were developed. Currently, only one is commercially available for intravenous application in Europe and the USA. This is iodixanol. Since this is a non-ionic dimeric contrast agent with six iodine atoms per molecule, rather than three as in the non-ionic monomer, its osmolality is theoretically decreased by 50%, and is close to that of blood. In theory, this has led to a further decrease in adverse events. With lower osmolality and a decrease in the incidence of at least minor adverse events, there has been increasing focus on events that may have clinical significance. Contrast nephrotoxicity is one such area of concern. It has generated much interest over the last few years, for several reasons: first, it is potentially a significant clinical concern. Secondly, with the ageing of the population, the incidence of renal dysfunction is increasing. Simultaneously, the utilization of contrast agents is increasing markedly. A final, very important consideration is that, as a number of recent papers have suggested, the incidence and severity of contrast medium-induced nephropathy (CIN) can be decreased. With this in mind, it is important to review the available data regarding all aspects of CIN.

CIN goes by many different names: contrast nephropathy, contrast nephrotoxicity, contrast media nephropathy, contrast agent nephropathy, radiocontrast-induced nephropathy, and others. The multiplicity of names is, perhaps, emblematic of the level of understanding of this entity. Accompanying this lack of a clear name is lack of a clear definition of the entity. The definitions that have been used include a 50% increase in serum creatinine, a 25% increase in serum creatinine, a 0.5 or 1.0 mg/dl increase in serum creatinine or a percentage decrease in actual or calculated creatinine clearance. As will be discussed subsequently, it is important to unify the definition of CIN, as it is important to define the best name for it. In this review, this entity will be referred to as contrast medium-induced nephropathy (CIN), but a universally acceptable definition is more difficult to arrive at. The most apt definition currently is probably a defined decrease in calculated creatinine clearance.

The history of CIN is interesting. It was perhaps first described in 1955 by Alwall et al., in an article describing the course of renal failure after intravenous urography [1]. In 1968, the entity had achieved sufficient importance to be discussed in an article in the New England Journal of Medicine [2]. An influential article in 1978 [3] described renal failure following major angiography, and was perhaps the first to indicate that the key risk factor was the presence of underlying renal dysfunction. Subsequent articles [4,5] suggested that CIN was one of the major causes of in-hospital renal failure.

The incidence of CIN is difficult to define, since it is a function of its specific definition and the presence or absence of risk factors. There are several important...
risk factors including diabetes mellitus, concomitant nephrotoxic medications, the general hydration status of the patient and the amount and type of hydration that is given before contrast administration. Other important considerations are whether or not prophylactic measures (i.e. medications) are utilized and what these are, the type of contrast agent, the volume of contrast agent utilized and the route of administration. As will be stressed subsequently, the primary and probably requisite risk factor is the presence of underlying renal dysfunction; it is likely that CIN occurs only if renal function is abnormal. Since serum creatinine is dependent on age, sex and muscle mass, it is not necessarily a particularly accurate reflector of true renal function. Calculated creatinine clearance is probably more accurate in this regard. True creatinine clearance is very difficult to obtain, due to the need for complete urine collections. Calculated creatinine clearance, however, has been validated [6,7] and is in fact now being reported routinely by many laboratories. It is probably the single best predictor of the risk of CIN.

Dehydration is a major dependent risk factor. It must be kept in mind that dehydration is not only related to lack of oral intake. It may also be a function of decreased intravascular volume, as in post-operative patients or with large volume blood loss. Diabetes mellitus is another major risk factor. Data [8] suggest that diabetes by itself is not an independent risk factor but, in conjunction with underlying renal dysfunction, it increases the risk of developing CIN. Another conditional risk factor is compromised renal perfusion, as can occur in severe congestive heart failure or during surgery. Other risk factors include nephrotoxic medications, such as gentamycin, high-dose non-steroidal anti-inflammatory drugs (NSAIDs) and certain chemotherapeutic agents.

Several studies have examined the impact of gender on CIN. In one study [9], there was a higher incidence of CIN in females than in males. When patients were matched for renal dysfunction, however, there were no gender differences in overall mortality or in major adverse cardiovascular events. In this study, as in others, the best independent predictor of CIN was an elevated serum creatinine; secondary predictors were the presence of diabetes, increasing age and New York Heart Association Class IV status. In another study [10], comparing patients who did not have renal insufficiency at baseline but developed CIN, the risk of major adverse cardiovascular events or death was increased in females relative to males. In comparing males and females who had underlying chronic renal insufficiency and then developed CIN, however, the risk of a major late adverse event was not significantly different. It is important to remember, however, that with serum creatinine and age equal, the glomerular filtration rate (GFR) will be lower in women than in men, and may be substantially reduced from normal (i.e. well below 60 ml/min) even in the presence of normal serum creatinine.

Due to the varying definitions utilized and the varying patient profiles in different studies, it is difficult to describe accurately the natural history of CIN. Overall, CIN appears to be characterized by an immediate decrease in creatinine clearance. There is in general an accompanying, although delayed, increase in serum creatinine which begins on day 2 following contrast administration and becomes maximal at days 4–7. There is in general a return to baseline over 7–21 days. It must be kept in mind that a permanent alteration in renal function is rare and is most likely to be seen in patients with severe underlying renal dysfunction [11]. Guiterrez et al. examined the pattern of serum creatinine in acute CIN [12] and found that the best predictor of this evolution was baseline calculated creatinine clearance. They also found that the best predictor of the rate, severity and duration of increase in serum creatinine after contrast administration was the baseline renal function.

Although end-stage renal disease is rare after contrast administration, it does occur. Hou et al. [5] noted an overall 4.9% in-hospital incidence of renal insufficiency (from all causes). They further noted a 64% mortality rate if there was a >3 mg/dl increase in serum creatinine. This poor prognosis in patients who develop an acute, marked increase in serum creatinine has also been noted in other studies. In CIN specifically, dialysis was necessary in eight of 514 patients with an elevated serum creatinine at baseline [11]. Dialysis was acute in five patients, but was required permanently in three. It is important to note that dialysis was necessary in none of the 682 patients with normal creatinine who underwent coronary angiography. In another study [13], nine of 59 patients examined who had diabetes mellitus and a mean serum creatinine of 5.9 mg/dl required one or more haemodialysis sessions, but in none of these patients was permanent dialysis needed. In a more recent study, the overall incidence of CIN was 6% (seven of 114) [14]. In four of these patients, serum creatinine returned to the elevated baseline levels. Dialysis was required in none, although three (almost 3%) did have permanent elevation in baseline serum creatinine.

Other studies have examined the late risk after CIN. In one recent study, 3.5% of 5967 patients with a normal serum creatinine at baseline who underwent cardiac catheterization had an increase in serum creatinine of ≤15% [15]. This rise predicted 1 year morbidity and mortality and the need for cardiac revascularization. It must be kept in mind, however, that although serum creatinine was normal at baseline in these patients, renal function was almost certainly not. Since both GFR and creatinine production decrease with age, a normal serum creatinine in an elderly patient generally correlates with a moderate to marked decrease in true renal function. In another, earlier study, Levy et al. [16] noted a mortality of 34% in hospitalized patients who developed CIN, vs 7% mortality in controls. Although questions clearly remain about incidence and severity, it is clear that if CIN develops, it is a significant clinical concern and bespeaks a poor prognosis.

Since the 1970s, many approaches have been utilized to try to prevent the development of CIN. In 1972,
for example, Morris et al. [17] recommended mannitol infusion to restore and maintain glomerular filtration during renal hypoperfusion. Subsequently, mannitol was relatively widely used in an attempt to prevent CIN. Simultaneously, many investigators felt that the use of a diuretic such as furosemide, by increasing urine volume and, therefore, at least in theory, increasing the rate of excretion of contrast, would lessen the risk of CIN. In an important study published in 1994, Solomon et al. [18] examined the use of mannitol, furosemide and saline and their effects on renal function following contrast-enhanced cardiac catheterization. They found that hydration with half normal saline led to a relatively low incidence of CIN, infusion of mannitol did not alter the incidence, and furosemide actually increased the incidence. This led to the elimination of use of furosemide and mannitol for the most part, and the wide realization that saline hydration was important. Although many investigations on CIN were carried out subsequently, both in animal models and in humans, it was not until the publication of an article by Tepel et al. in 2000 [19] that good evidence emerged that it may be possible to decrease the incidence of CIN. This has led to many subsequent investigations utilizing various approaches.

With the beginning of widespread utilization of lower osmolality contrast agents (LOCM, low osmolality contrast media), as compared with high osmolality contrast agents (HOCM), in the 1980s, concerns centred on whether or not there was a difference between the two classes in the incidence of CIN. In 1993, a meta-analysis [20] suggested that in considering patients with and without renal dysfunction at baseline, there was a minor but not statistically significant difference in the effect on renal function favouring LOCM over HOCM. In patients with an elevated serum creatinine or decreased GFR, however, there appeared to be a statistically significant decrease in incidence. A large study published in 1995 examined the differences between a non-ionic monomer and an ionic monomer in >1000 patients undergoing cardiac catheterization [11]. The incidence and the differences depended on the definition utilized. This study attempted to utilize actual creatinine clearance as well as serum creatinine, but the former was not found to be helpful, probably because of both incomplete collections and incomplete reporting. Using a definition of CIN as a ≥25% increase in serum creatinine, the risk of CIN was examined as a function of contrast agent type, the presence or absence of diabetes mellitus and the presence or absence of elevated baseline serum creatinine. In patients who did not have diabetes and with a normal serum creatinine, CIN did not occur with either class of contrast agent. In patients with normal serum creatinine, with or without diabetes, the incidence of CIN was the same with both contrast agents, at 0.6%. None of these patients had clinically significant events related to the development of CIN. There was, however, a difference among patients with elevated serum creatinine. This difference was clinically significant for patients with the presence of insulin-dependent diabetes mellitus, with an incidence of 27% utilizing an ionic monomer (HOCM) and 11.8% utilizing a non-ionic monomer (LOCM). In another study [21], using as the criterion for CIN an absolute increase in serum creatinine of 0.5 mg/dl, in the group that received a non-ionic monomer (LOCM) and had a mean baseline serum creatinine of 1.8 mg/dl, the incidence was 8%. In the group studied with an ionic monomer (HOCM) and a mean baseline serum creatinine of 1.9 mg/dl, the incidence was 19%, a statistically significant difference. Another prospective randomized study, including patients with and without underlying renal dysfunction [22], showed no difference in nephrotoxicity between a non-ionic and an ionic monomer. As noted, the question of whether or not there is a clinically significant difference between these two classes of agents remains somewhat unclear. The data seem to suggest that there is a significant difference primarily in patients with an elevation in serum creatinine prior to contrast injection, particularly with markedly elevated serum creatinine and with co-existent diabetes.

The next question that arises is whether or not there is a difference between non-ionic monomers and the non-ionic dimer. In the Chalmers and Jackson study, however, there was a lower incidence of CIN with ioxidanol only using a definition of a 10% increase in serum creatinine. This is a definition that is not generally used. Using the far more common definition of a 25% increase in serum creatinine, there was no difference between the two agents [23]. The data in this regard are not conclusive. Two studies suggested that the incidence of CIN was significantly lower with ioxidanol than with iohexol [23,24]. Three other small studies, however, using other non-ionic monomers, showed no difference [25–27]. In a somewhat larger and better controlled study, NEPHRIC [24], Aspelin et al. prospectively evaluated 129 patients with diabetes mellitus and an elevated serum creatinine ranging from 1.5 to 3.5 mg/dl who underwent coronary or peripheral angiography. They found that the mean peak increased creatinine on days 3–7 was 0.13 mg/dl with ioxidanol and 0.55 mg/dl with iohexol, the non-ionic monomer. The incidence of creatinine increase of >1 mg/dl was zero among the 64 patients studied with ioxidanol and 10 among the 65 patients (15%) studied with iohexol. On the other hand, a small study in patients with mildly or moderately elevated serum creatinine who were undergoing intravenous urography showed no difference between ioxidanol and iopamidol [25]. In a very small study, Kohemainen and Soiva [26], found no difference between ioxidanol and another non-ionic monomer, iobitridol, in the incidence of CIN, utilizing definitions of either 0.5 mg/dl increase in serum creatinine or a >25% decrease in creatinine clearance. There were, however, only 25 patients per group, all patients who underwent contrast-enhanced computed tomography (CT) examinations. In still another study that has been presented but not yet published [27], 102 diabetic patients had a serum creatinine that was ≤2 mg/dl; there was no difference in nephrotoxicity between ioxidanol and iopamidol.
At this time, it is impossible to determine whether or not iodixanol offers benefits compared to specific non-ionic monomers. In the direct comparisons available, it appeared to be superior to iohexol in two studies, but was equivalent to three other non-ionic monomers in three other studies. If the results with iodixanol from various prospective randomized studies are compared with the results with other agents, from other randomized prospective studies, a wide range of results is seen. Figure 1 shows a comparison of the incidence of CIN with iodixanol and several non-ionic monomers. The data for this figure were taken from various randomized, double-blind comparisons of contrast agents or from the control arm of randomized studies of the preventive effect of vasodilators or antioxidants. All patients in these studies were reported to have been adequately hydrated and all studies involved intra-arterial administration of the contrast material. CIN was defined as an increase in serum creatinine of ≥0.5 mg/dl or a relative increase >25% over baseline at 48–72 h after contrast administration. CIN occurred with a frequency of 3–33% in studies with iodixanol, 21–26% in studies with iohexol, 6–12% with iopamidol, 16% with iomeprol and 11% with iopromide. Perhaps this is a function of the specific non-ionic monomer with which the dimer is compared, and it may depend on the incidence and severity of risk factors in the groups of patients comprising the various studies as well as the various ways of defining CIN that were used in the different studies. So far, it is not clear that an accurate comparison can be made, since the relevant variables, including calculated creatinine clearance, route of contrast administration, dose of contrast administration, presence or absence of diabetes mellitus, nature of pre-hydration and presence or absence of other risk factors, are neither uniform nor necessarily clear in the various studies. What is clear, however, is that further studies are necessary.

Many other approaches have been investigated in attempts to decrease the incidence and severity of CIN. Several looked at the use of fenoldapam, a dopamine A1 receptor agonist, which has been hypothesized as being helpful since it causes post-glomerular vasodilatation. Although small non-randomized studies were optimistic, a relatively large, prospective randomized study has shown that fenoldapam does not ameliorate CIN [28]. Theophylline has been used as an adenosine antagonist, and may thus block the renal vasoconstrictive effects that adenosine causes, primarily in the efferent arterioles. In one study of patients with azotaemia who were undergoing coronary angiography, it was shown to have a protective effect [29], and a recent meta-analysis suggests that it may be helpful [30]. It must be given intravenously, however; patients require close monitoring, and the toxic to therapeutic ratio is narrow, so further studies are needed to determine its efficacy, safety and utility. In one study, the nitric oxide substrate L-arginine was used, on the theory that CIN is related to impaired endothelial function, but it did not have a protective or ameliorating effect [31]. Captopril, an angiotensin-converting enzyme inhibitor, has been used in one positive but small study [32], and a prostacyclin analogue has been used in another [33]. The results with both agents must be considered preliminary and inconclusive.

Perhaps the most widely investigated agent is N-acetylcysteine (N-AC). This is a medication that has been widely available and widely utilized for treatment of acetaminophen toxicity. Its mechanisms of action is 2-fold. It appears to be a free radical scavenger and it also stimulates endothelial nitric oxide synthase production, and therefore is thought to cause intra-renal vasodilatation. Although it is important to stress that the aetiology of CIN remains unclear, and physiological responses in humans appear to be different from those in the various animal models, it is possible that the mechanism relates to hypoxia at the cortico-medullary junction, with the consequent production of reactive oxygen species. If this is what...
actually occurs, then a free radical scavenger may in fact be helpful. N-AC has been given in various ways. Most often in these studies, 600 mg has been administered orally twice a day beginning on the day prior to and continuing on the day of contrast administration. It has also been used intravenously in various approaches, including an infusion of 150 mg/kg over 30 min before contrast administration followed by 50 mg/kg over 4 h [34]. The evidence regarding the efficacy of N-AC is conflicting but generally positive. One meta-analysis concluded that the data did not support effectiveness [35] and another concluded that it did [36]. On the plus side, N-AC is inexpensive, easy to administer and is safe. On the other hand, it is not readily available for intravenous administration, its mechanism of action is not clear and, as the conflicting results of the metaanalyses show, it is not certain that it is effective. Hydration clearly plays a major role in the prevention of CIN, and has recently generated substantial interest. One study compared intravenous hydration with normal saline for 24 h, beginning 12 h prior to contrast administration, with routine oral hydration, and found the former to be more effective [37]. Another compared normal with half normal saline, both beginning either the morning of or immediately before contrast administration, and found normal saline to be more effective [38]. Finally, a recent investigation evaluated the incidence of CIN in a randomized study comparing hydration regimens of normal saline and sodium bicarbonate. In this relatively small study, sodium bicarbonate had a protective effect [39]. Because of the safety, low cost and convenience, the use of sodium bicarbonate, again not completely proven, is clearly appealing.

Many questions remain concerning CIN, despite the extensive literature and many studies. Only a few conclusions can be reached: it is thought to be clinically important, it can be associated with a poor prognosis independent of other risk factors although its course is generally benign, it occurs only in patients with some degree of renal compromise, the pathogenesis remains unclear, hydration is important in preventing or ameliorating it, and different contrast agent classes or even specific agents may be associated with different degrees of nephrotoxicity. Finally, there are a number of promising approaches to decrease the incidence and severity of CIN, namely N-AC, theophylline and hydration with sodium bicarbonate. At this time, no single approach has been shown conclusively to be effective. Further clinical investigations are necessary regarding this important but incompletely characterized entity.

Conflict of interest statement. None declared.

References

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