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Contrast medium-induced nephropathy.
Aspects on incidence, consequences, risk factors and prevention

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Abstract: Contrast media-induced nephropathy (CIN) is a well-known complication of radiological examinations employing iodine contrast media (I-CM). The rapid development and frequent use of coronary interventions and multi-channel detector computed tomography with concomitant administration of relatively large doses of I-CM has contributed to an increasing number of CIN cases during the last few years. Reduced renal function, especially when caused by diabetic nephropathy or renal arteriosclerosis, in combination with dehydration, congestive heart failure, hypotension, and administration of nephrotoxic drugs are risk factors for the development of CIN. When CM-based examinations cannot be replaced by other techniques in patients at risk of CIN, focus should be directed towards analysis of number and type of risk factors, adequate estimation of GFR, institution of proper preventive measures including hydration and post-procedural observation combined with surveillance of serum creatinine for 1-3 days. For the radiologist, there are several steps to consider in order to minimise the risk for CIN: use of "low-" or "iso-osmolar" I-CM and dosing the I-CM in relation to GFR and body weight being the most important as well as utilizing radiographic techniques to keep the I-CM dose in gram iodine as low as possible below the numerical value of estimated GFR. There is as yet no pharmacological prevention that has been proven to be effective.

Key Words: contrast media, nephropathy, creatinine, estimated GFR, radiology, acute renal failure

Introduction

Iodine contrast media (I-CM) are used in conjunction with x-ray procedures to enhance differences between normal body structures and pathological lesions. Side-effects of I-CM are common, one of the most severe being impairment of renal function. This complication has been known as a clinical entity for a long time. As early as the 1950s it was recognized that I-CM, especially after repeated administration, could be nephrotoxic [1]. The introduction of so called "low-osmolar" I-CM, shown to be less nephrotoxic than "high-osmolar" agents [2,3], during the 1970s was thought to reduce or eliminate this complication. This was, however, not found to be the case.

For many years contrast medium-induced nephropathy has been one of the most common causes of in-hospital acquired acute renal failure [4]. Only lately has the medical community come to an understanding of the risk factors involved in CIN and how this is best handled. Now in the early 21st century we have witnessed an increasing number of CIN cases in elderly patients being subjected to more and more advanced radiological examinations and percutaneous therapeutic interventions using I-CM. These procedures include the frequent use and rapid development of multi-channel detector computed tomography (MDCT) with concomitant administration of relatively large doses of I-CM [5]. Thus, there is an obvious risk that more patients will develop impaired renal function as the number of I-CM-enhanced radiological examinations will increase. In this situation it is important both for the physician and for the radiologist to consider what type of preventive measures should be taken. This overview will discuss incidence, consequences, and preventive measures to be considered when I-CM are administered, intravenously or intra-arterial.

Incidence

There are several definitions of CIN based on relative or absolute increase of serum creatinine. The most frequently used definition is a new onset or exacerbation of renal dysfunction after I-CM administration without other identifiable causes in combination with a rise in serum creatinine of at least 25% [6]. CIN occurs in less than 5% of a general population but in 10-30% of patients with renal insufficiency [3, 7-9]. In spite of the low risk for CIN in the general population, the vast numbers of examinations performed worldwide (about 80 million doses in 2003) indicate that CM complications will still affect a large number of patients. Patients exposed to CM are increasingly elderly with multiple co-morbidities that put them at increased risk. In patients with both renal insufficiency and diabetes, the incidence has been reported to be as high as 50% [10]. Up to 5% of patients with impaired renal function may develop CIN requiring dialysis [3,11]. Studies on computed tomography have reported a 4 to 21% incidence of CIN in patients with reduced renal function (a mean value of 12%) when data was pooled [12,13]. In a retrospective study of 703 consecutive patients with suspected acute pulmonary embolism subjected to acute CT examinations, we found a similar incidence of CIN [14]. However, none of the patients developed oliguria or needed dialysis. It was noted that generalised arteriosclerosis was commonly noted in the group that developed CIN.

Consequences

The consequences of CIN are prolonged hospital stay, increased non-renal morbidity, and increased cardiovascular risk and mortality [15-18]. McCullough et al [16] found that in-hospital mortality following coronary intervention was 7% in patients who develop CIN and 36% who develop CIN requiring dialysis. In patients not developing CIN under similar circumstances the figure was only 1%. Long-term survival was significantly less in those patients developing CIN than in those with stable renal function after I-CM administration [18]. The prognosis was especially grim in patients developing acute renal failure requiring hemodialysis with only 18% two-year survival [16].

A prospective, single center trial demonstrated that patients with no sustained elevated serum creatinine within the first few days after elective coronary angiography, but who developed this at 30-60 days post procedure, had a high mortality rate at two years [19]. Thus, I-CM administration could have more serious consequences than a transient fall in renal function.

Risk Factors

There are several established risk factors for CIN (table I), the most frequently cited being pre-existing renal impairment, especially if combined with diabetes mellitus [20-22]. Diabetes mellitus per se is not a risk factor in patients with normal renal function. Dehydration, congestive heart failure, hypotension, advanced age, and administration of nephrotoxic drugs are other common risk factors. The risk of CIN increases exponentially with the addition of multiple risk factors [21,23]. The combination of impaired renal function, reduced plasma volume, and congestive heart failure makes the patient especially vulnerable to CIN. This situation is common among many elderly patients. Special groups of interest are renal allograft recipients and those with multiple myeloma. Whereas patients with a kidney transplant are prone to develop CIN (reported incidence of 23%) [24], a review of 476 well dehydrated patients with myeloma, having undergone contrast media examination shows that only 0.6 – 1.25% demonstrated CIN. These figures are only slightly higher than the general population and indicate that the risk is due to level of renal function rather than myeloma per se [25].

After identifying risk factors, different scoring systems have been proposed to predict the risk of CIN. Some studies [21,26] have shown good correlation between risk score and CIN after coronary interventions. Nyman et al. [12] proposed to relate the planned I-CM dose in gram iodine numerically to the glomerular filtration rate (GFR), i.e. gram-iodine/GFR ratio, to predict the risk for CIN. The gram-iodine/GFR ratio is directly correlated to plasma under the concentration-time curve (AUC), a fundamental measure of systemic exposure of a drug excreted by glomerular filtration, and has been advocated for dose optimisation to avoid toxic effects [27,28].

Table 1
Risk factors for contrast media-induced nephropathy

Non-correctable risk factors	Correctable risk factors
- Pre-existing renal failure	- Hypotension
- RF combined with diabetes mellitus	- Dehydration, Low plasma volume
- Congestive heart failure	- Nephrotoxic drugs
- Old age	- Volume and type of I-CM
- Renal transplantation	- Repeated examinations
	- Surgery early after administration of I-CM

Prevention

Once CIN has developed, the only course is to treat the symptoms. Consequently any interventions must be preventive and focus on the patient at risk. These include adequate evaluation of renal function, identification of risk factors, institution of prophylactic measures, proper choice of I-CM, limiting the I-CM dose, or choosing an alternative diagnostic method.

Renal function

When evaluating risk for development of CIN, the essential question is whether renal function is normal or not. Traditionally serum creatinine has been used as an endogenous marker of GFR. It is well known, however, that serum creatinine has severe draw-backs caused by factors influencing both creatinine generation (muscle mass) and elimination (tubular secretion). Thus, serum creatinine will frequently overestimate renal function and is unreliable for proper evaluation of risk status when I-CM is to be given. It is most notable in patients over 70 years of age where GFR may be reduced below 50 ml/min in spite of a normal serum creatinine. This discrepancy was found in 50% of cases and was due to age-related decrease in muscular mass (creatinine generation) [29].

To improve prediction of renal function, GFR can be estimated with one of several published prediction equations based on anthropometric and/or demographic data apart from serum creatinine. The Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD)

Study formulas are presently the most frequently practised [30,31] However, a new creatinine based formula has recently been developed that, at least in the Scandinavian-Caucasian population, performed better than the Cockcroft-Gault and MDRD equation [32].

Lately reports have shown that GFR estimated from equations based on serum concentration of cystatin C are reliable values. Serum levels of cystatin C are not dependant on muscular mass and not secreted by renal tubules, the two main draw-backs of creatinine. GFR prediction equations based on cystatin C have been demonstrated to give similar or better results compared to the best known creatinine based equations [33].

Simple methods for rapid estimation of GFR with acceptable accuracy are thus available. Estimation of GFR via prediction equations is also recommended by several guidelines [34,35] and the risk of CIN is considered increased when estimated GFR falls below 60 ml/min. Thus, it is important to abandon serum creatinine as a sole marker of renal function and to focus on the available methods whereby GFR can be estimated. Also note that the patient's absolute GFR in ml/min should be used when dosing drugs including I-CM [30]. Using relative GFR, i.e. normalisation to a certain patient size (most commonly 1.73 m^2 body surface area), will overestimate renal function in small individuals and underestimate it in large ones. It should, however, be noted that serum creatinine alone is a useful marker when following renal function after I-CM administration.

Consider alternative diagnostic methods

Alternative imaging techniques without I-CM should be considered in patients at risk of CIN. These include ultrasonography, CT without I-CM, magnetic resonance imaging (MRI) and scintigraphy. One should be liberal with performing CT without I-CM in risk patients before contemplating injection of I-CM since a non-enhanced CT is often satisfactory and can give adequate information for clinical decisions.

MRI may be performed with or without gadolinium (Gd) CM. The molecular doses of Gd-CM for MRI (0.1-0.3 mmol/kg) are generally much lower, roughly by a factor of ten, compared with the clinical doses of I-CM (30-90 gram iodine) used in radiographic examinations corresponding to 1-3 mmol non-ionic monomeric I-CM molecules per kg in an 80-kg person. The low doses of Gd-CM may explain their apparent non-nephrotoxic effects in certain studies [36]. However, recent studies also indicate a nephrotoxic potential of Gd-

CM, especially in patients with severe renal impairment (GFR <30 mL/min) [37-39], when injected in doses of 0.2-0.4 mmol/kg. Thus, the same preventive measures should be instituted in patients with renal impairment undergoing MRI with Gd-CM.

In addition, it has recently been reported that patients with renal failure (<15 mL/min) may develop nephrogenic systemic fibrosis (NSF) / nephrogenic fibrosing dermopathy (NFD), a delayed serious adverse reaction following examinations with Gd-CM [40,41]. The FDA advises careful examination of risks and benefits associated with using a gadolinium CM in patients with reduced GFR in light of recent reports of NSF/NFD following administration of these agents. They advise choosing an alternative imaging method and/or contrast agent whenever possible [42]. Furthermore it may be prudent to institute prompt dialysis in patients with GFR <15 ml/min if Gd-CM are clearly necessary

Adequate hydration

Hydration is an important part of preventing CIN. It restores effective blood volume and prevents renal vasoconstriction and renal medullary hypoxia induced by contrast media [43]. Trivedi et al. [44] prospectively studied patients undergoing coronary angiography and found that the incidence of CIN was lower in patients who received IV 0.9% sodium chloride (saline) compared to those who received oral fluids. Approximately 100 mL or 1.5 mL/kg of fluid per hour, preferably saline, is recommended for 4-12 hours before to 12-24 hours after the examination [45]. However, volume and infusion rate must be balanced considering the patient's fluid, cardiac, and renal status to provide for adequate diuresis without volume overload.

Intravenous infusion of sodium bicarbonate has been shown to be superior to saline for prevention of CIN in two prospective studies [46,47]. Although the mechanisms are unclear this interesting strategy may prove useful if confirmed in further studies.

Pharmacological prevention

Several trials have been performed to study the influence of different pharmacological agents to prevent CIN. Mannitol, furosemide, theophylline, dopamine, atrial natriuretic factor, and fenoldopam have been tested in clinical studies with no significant effect [34]. There are some data favouring the use of calcium channel blockers and theophylline for the prevention of CIN although their use is not widely accepted [48]. N-acetylcysteine (NAC) on the other hand is

frequently being used to prevent or reduce the risk of CIN. A prospective, though low powered, study showed a lower risk of rise in serum creatinine after oral administration of NAC compared to a control group receiving only hydration in connection with computed tomography [49].

The mechanism for a possible protective effect of NAC is unclear. A cytoprotective effect due to scavenger of oxygen free radicals has been suggested as well as a vasodilatory effect. Recent meta-analyses, however, have not proved NAC to be advantageous compared to hydration alone [50,51]. There are also results indicating that NAC has specific effects on renal creatinine unrelated to renal function, which could explain the positive findings for the drug [52]. Thus, although cost is low and side-effects limited, NAC cannot be generally recommended for the prevention of CIN.

Nephrotoxic substances

Nephrotoxic substances may enhance the risk of CIN [53]. Non-steroidal anti-inflammatory drugs (NSAID) and cyclooxygenase inhibitors inhibit vasodilatory prostaglandins and could have negative effects on renal function especially in the presence of dehydration. Ideally administration of nephrotoxic drugs including NSAID, certain antibiotics (aminoglycosides), and cytostatics (cisplatin) should be stopped for at least 24 hours prior to a CM examination in patients at risk of CIN.

Dialysis

Contrast media, being water-soluble and not bound to protein, are promptly eliminated from the blood during hemodialysis [54]. The effect is even more pronounced when membranes with higher sieving coefficients or of other materials are used (high flux HD, hemofiltration). Several studies have investigated the role of post-contrast hemodialysis for prevention of CIN. The results published to date have been negative [54,55]. Marenzi et al. examined patients with p-creatinine above 176 umol/L undergoing coronary angiography and randomised to either "on-line" hemofiltration or traditional preventive measures. [56]. Patients treated with hemofiltration before and immediately after intravascular I-CM injection showed significantly lower incidence of CIN, defined as a 25% rise in serum creatinine, than control patients. It is unclear whether the effect was due to I-CM elimination or to a better control of plasma volume. As hemofiltration lowers serum creatinine, the evidence for a protective effect is not solid and further studies using proper GFR measurements are awaited.

Type of iodine contrast medium

It is now well recognized that ionic monomeric "high-osmolar" I-CM (e.g. diatrizoate) developed 50 years ago are more nephrotoxic than today's non-ionic monomeric (e.g. iohexol, iopromide, etc.) and ionic mono-acidic dimeric (ioxaglate) "low-osmolar" I-CM or non-ionic dimeric "iso-osmolar" I-CM (iodixanol) [2,3]. Thus, low- or iso-osmolar CM should be used in patients at risk of CIN [35].

Two recent prospective randomised studies [57,58] and a meta-analysis [59] indicate that "iso-osmolar" I-CM is less nephrotoxic than "low-osmolar" I-CM in patients with diabetes mellitus and/or renal impairment. Speculations that the high viscosity of non-ionic dimers contributes to CIN have emerged from studies in rats [60] but could not be verified in a recent renal artery study of ischemic porcine kidneys [61]. Injections of a mean dose of about 70 mL iodixanol 320 mg I/mL directly into a renal artery occluded by a balloon caused no histomorphological changes and had no effect on GFR. These porcine results may be more relevant to humans than those studies done with rats, since anatomy and physiology of porcine kidneys are considered more like human kidneys than most other species.

Gadolinium contrast media should not be used for x-ray examinations

The apparent non-nephrotoxic effect of Gd-CM in MRI studies has encouraged many investigators to use Gd-CM as a substitute for I-CM in x-ray examinations including a variety of catheter-angiography procedures and CT [62,63]. However, the sole purpose for I-CM intended for radiographic examinations is to attenuate x-rays. In experimental porcine studies Gd-CM, especially of the "high-osmolar" type such as gadopentetate (1,96 Osm/kg H_2O), has proven far more nephrotoxic than "low-" and "iso-osmolar" I-CM when injected in equal volumes and concentrations resulting in the same radio density. There is also a clinical study demonstrating a more pronounced nephrotoxic effect of Gd-CM than I-CM [64]. In fact plasma hyper-osmotic Gd-chelates imply a 75-year step-back regarding x-ray attenuation/osmotic ratio and should be contraindicated as a substitute for "low-"and "iso-osmolar" I-CM in azotemic patients undergoes CM-based x-ray examinations.

Dosage of iodine contrast media

The dose of I-CM should preferably be adjusted to the level of renal function and number and

types of examinations. Renal function should be expressed in GFR and not solely based on serum creatinine, which severely overestimates renal function in elderly patients. Preliminary investigations indicate that the gram iodine dose should not exceed the numerical value of estimated GFR. Ideally it should be as low as possible below that threshold value [12]. If multiple risk factors are present, the risk of CIN will rise exponentially [21,23,65,66]. Dosing per kg body weight at CT will markedly reduce the doses in patients with low BMI without losing diagnostic information compared with those patients who have higher BMI. The dose may be further reduced by employing 80 kV instead of the routine 120 kV at CT in patients with lower BMI [67].

In patients at risk of CIN, multiple I-CM-based examinations and/or major surgery should be delayed for at least three days combined with surveillance of serum creatinine. If there is elevated creatinine indicating CIN, a further delay of at least 7 days until creatinine has returned to baseline value is preferable.

Algorithm

An algorithm for avoiding nephropathy after administration of contrast media was recently suggested based on level of renal function [35]. If estimated GFR is < 60 mL/min and an I-CM examination is necessary, a number of measures should be considered including iv volume expansion, the use of "iso-"or "low-osmolar" I-CM, and a limited I-CM dose. For those patients who have GFR < 30 mL/min, in addition to employing the above measures, hospital admission, nephrology consultation and close follow-up is recommended. Dialysis support, should renal failure develop, must also be considered.

Conclusions

In patients at risk of CIN where CM-based examinations cannot be replaced by other techniques, the physician should focus on analysis of number and type of risk factors, adequate estimation of GFR, institution of adequate preventive measures, including hydration and post-procedural observation, combined with surveillance of serum creatinine for 1-3 days. For the radiologist, several things must be considered. In order to minimise the risk for CIN, use of "low-or "iso-osmolar" CM, dosing the CM in relation to estimated GFR and body weight (CT) are the most important, including utilizing radiographic technique to keep the CM dose in gram iodine as low as possible below the numerical value of estimated GFR (see authors' guidelines). There is as yet no pharmacological preventive treatment

that has been proven effective but with careful pre-examination evaluation, the risks can be minimised.

Author's Guidelines

1- Serum creatinine requirements for predicting GFR with equations: Any patient with suspected or known renal disease/-surgery/-impairment, diabetes mellitus, congestive heart failure, age ≥70 years or any other obvious risk factor.

2- Examination technique in patients at risk of developing CIN: Apart from adequate prophylactic measures such as hydration the examination technique should be adjusted to keep the CM dose (gram iodine) as far below the numerical value of estimated GFR (ml/min) if an I-CM examination is deemed necessary:

a) Angiographic procedures [68]: 1) Stage diagnostic and therapeutic interventions, 2) by lowering x-ray tube kilo voltage in thin patients it is possible to decrease CM concentration for the same radio density, 3) perform selective renal or juxtarenal artery injections with plasma iso-tonic CM, 4) limit "unnecessary" runs (e.g. left ventriculogram during coronary procedures), excessive test "puffs" or film them to obtain a diagnostic run, 5) scrutinise every diagnostic run before additional ones, 6) use biplane equipment whenever possible, 7) exchange multiple oblique runs for manometry to evaluate stenotic segments, 8) replace aortic injections with selective and super-selective catheterisation whenever possible (e.g. single leg run-offs), 9) decrease CM dose by reducing abdominal aortic flow using bilateral thigh tourniquets ad modum, Farinas [69], 10) direct CM to diseased vessels by occluding run-off to "healthy vessels".

b) Computed tomography: 1) Perform CT without CM, 2) relate CM dose to body weight; e.g. 0.3-0.5 grams of iodine per kg depending on indication [12,70], 3) if possible use 80 instead of 120 kVp to reduce CM dose by a factor 1.6 for constant radiographic contrast [67].

Extra caution is warranted when performing angiographic renal and juxta-renal CM injections and in patients with non-steady state renal function, e.g. shock, sepsis, etc.

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