Renal haemodynamic alterations in contrast medium-induced nephropathy and the benefit of hydration

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Abstract

Though several suggestions have been put forward, the underlying mechanism of contrast medium-induced nephropathy (CIN) is not clear. Most probably, however, the culprit is a combination of various mechanisms working together to cause the development of CIN. The generally accepted main factors in the pathophysiology of CIN are the reduction in renal perfusion by contrast media (CM) combined with the toxic effects on the tubular cells. With regard to the literature, misconceptions are widespread when explaining the development of CIN, e.g. that osmolar challenge induces renal vasoconstriction due to the tubuloglomerular feedback mechanism (TGF). Although popular, this assumption is most probably false, since osmotic pressure is not the signal for the TGF. Much attention has been paid to reducing the osmolarity of CM further. In an effort to obtain iso-osmolar CM, dimers were formed. These CM have osmolarities in the near physiological range, but at the cost of increased viscosity. This seems to have adverse effects with regard to kidney haemodynamics. In contrast to the multifarious interpretations of CIN, it is generally accepted that hydration is effective in preventing CIN from occurring. There is no universally accepted explanation for the effect of hydration, but it may rely on enhancing renal medullary blood flow and reducing the viscosity of the fluid in the collecting duct.

Keywords: contrast medium-induced nephropathy; haemodynamics; hydration; tubuloglomerular feedback mechanism

Introduction

The term contrast medium-induced nephropathy (CIN) indicates an impairment of renal function occurring within 3 days following the intravascular administration of contrast media (CM), and the absence of an alternative aetiology [1,2]. A widely used marker for the occurrence of CIN is an increase in serum creatinine by >25% or 44 μmol/l (0.5 mg/100 ml) within 48–72 h of contrast administration [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 follows a benign course and only rarely necessitates dialysis. Nevertheless, use of radiocontrast media has been associated with increased in-hospital morbidity, mortality, cost of medical care and long admissions, especially in patients requiring dialysis.

The area at risk

An area remote from the vasa recta supplying the renal medulla with blood, the deeper portion of the outer medulla, is a particularly vulnerable kidney region. It is here that the thick ascending limbs of the loop of Henle exhibit hypoxic damage, e.g. when the kidney is perfused with erythrocyte-free medium [9]. The relatively high oxygen requirements due to salt reabsorption offer an explanation for the vulnerability of the outer medullary portion of the nephron. Kidney perfusion is very high for the cortex, but the medullary portions are maintained on the verge of hypoxia where pO2 levels can be as low as 20 mmHg [10]. This is a deleterious result for upholding the countercurrent mechanism for controlling urine excretion. By increasing renal vascular resistance, the addition of CM to the medium intensifies hypoxic injury to this region [11]. It has been shown that the iso-osmolar CM, ioxixanol, reduces blood flow to all regions of the kidney to a greater extent than low osmolar and even high osmolar CM [12]. Although this decrease in
perfusion was more likely to be due to the profound systemic effects of iodixanol (blood pressure also dropped considerably), studies have shown that iso-osmolar CM has adverse effects in terms of renal tissue oxygenation, when compared with low osmolar CM [13]. The osmolality of low osmolar CM is still about twice as high as that of plasma, but the fluid viscosity is considerably lower.

Adverse effects of different CM classes

The different physico-chemical properties may provide a key to understanding the various magnitudes of renal blood flow impairment caused by the different CM types. The numerous available CM are based on triiodobenzene. They are commonly grouped according to their osmolality and ionicity. High osmolar CM have osmolalities approximately six times higher than plasma, and were widely used for a time. It has become clear that many of the side effects were caused by the electric charge. Today it seems that this physico-chemical subdivision may actually require reconsideration: iso-osmolar CMs are dimers, and consequently have greater viscosities than the monomeric low osmolar CMs. This can have important implications for renal medullary perfusion and oxygenation [12].

Iothalamate, a high osmolar agent, strikingly reduces medullary $pO_2$ to about a third of control levels [13]. Remarkably, the iso-osmolar CM iotrolan impairs local $pO_2$ to a greater extent than the low osmolar CM iopromide [13]. The decrease in $pO_2$ by the CM iopromide failed to reach statistical significance. Obviously, osmolality does not explain the reduction in renal perfusion that is caused by CM. This exemplifies the shortcomings of classifying CMs simply by their osmolality.

CM and tubuloglomerular feedback (TGF)

Among the discussed causes of CIN are the marked diuresis that has been suggested to activate the TGF, which is a key regulator of kidney haemodynamics. Activating the TGF causes vasoconstriction of the glomerular afferent arterioles, therefore resulting in a decrease in the glomerular filtration rate (GFR) and an increase in renal vascular resistance (RVR). Speculation has implied that the TGF may be responsible for almost 50% of the increase in RVR induced by high osmolar ionic CMs. High osmolar CMs are thought to have a greater effect on the TGF. A common explanation for the development of CIN is that hyperosmotic CM cause diuresis, which activates the TGF and subsequently compromises renal blood flow and glomerular filtration [14]. However, this osmotic diuresis theory is not a likely explanation for CIN. The macula densa cells of the thick ascending limb sense $Na^+$, $K^+$ and $Cl^-$ concentrations in the tubular fluid via the $Na^+-K^+-2Cl^-$ co-transporter. Furosemide effectively blocks this transporter. 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. It is $Cl^-$ that is the limiting factor [15,16]. Pioneering experiments with retrograde perfusions of the tubule have already shown that osmolality has no effect on the TGF. With orthograde perfusion, quite a lot of transport occurs between tubular fluid and interstitium, and even non-ionic fluids occasionally may be able to elicit the TGF response. This would leave some room for a possible CM effect. In this case, however, other structural features would dictate the CIN potential of a particular CM, bypassing any reliance on its osmolality.

Experiments using mannitol, an osmotic diuretic, further support that the osmotic diuresis theory can be ruled out. Increases in osmolality, such as after mannitol infusion or after CM application, decrease NaCl concentration at the macula densa. However, this increase in osmolality also simultaneously increases tubular flow. Therefore, the resulting net change in the amount of NaCl passing the macula densa is negligible [17].

Finally, blocking the TGF by furosemide does not decrease serum creatinine after application of CM, which is usually the parameter taken to indicate CIN [2]. Consequently, combining these factors, the theory that the osmolality of a CM causes CIN via the TGF does not appear likely.

Hydration and the prevention of CIN

Unfortunately, the treatment procedures to prevent CIN have yet to be established. Several potentially successful approaches of CIN prevention have been reported, of which vigorous hydration may be the most important [18,19]. Other trials using diuretics, dopamine, calcium channel blockers, atrial natriuretic peptides and theophylline have yielded contrasting results [20–22]. For instance, acetylcysteine, a free radical scavenger, has been shown to be renoprotective in some studies [23–25], yet had opposite results in others [26].

Only periprocedural hydration is widely accepted to prevent CIN [2,27,28], and intravenous hydration seems to have better results than oral hydration. Further debunking conventional wisdom, the reason for the success of this manoeuvre is not related to an increase in renal blood flow or GFR [29]. Except in cases where the patient is severely dehydrated, volume loading has little effect on these haemodynamic measures. It appears more likely that renal medullary perfusion is increased when one is well hydrated. A selective increase in medullary perfusion is not readily detected by measuring total renal blood flow since only $<10\%$ of renal blood flow passes through the medulla.

Renal medullary blood flow increases during hydration due to the inhibition of vasopressin (Figure 1).
The vasa recta that supply the medulla with blood are among the vessels most sensitive to vasopressin [30,31]. Vasopressin levels become nearly undetectable below physiological plasma osmolarity, thus these vessels dilate in response to hydration. In consequence, the oxygen supply to the kidney regions at risk of CIN increases.

In addition to this vasopressin effect on renal medullary blood flow, autoregulation may not be present under conditions of hydration [32]. Thus, an increase in perfusion pressure would again lead to increases in blood flow to this region.

Besides the positive effects of hydration on renal medullary perfusion, there is a second factor that is important in preventing CIN. Low vasopressin levels will decrease the water permeability of the collecting ducts and enhance fluid excretion. Hence, CM in the distal portions of the tubular system are diluted. This will dramatically reduce fluid viscosity. As has been shown by Ueda et al. [33] (Figure 2), tubular pressures increase dramatically when given CM. This effect is particularly pronounced in CM with high viscosity (iso-osmolar CM). Indeed, urine viscosity increases markedly in response to iso-osmolar CM application (Figure 3 [34]). Since the distal portions of the kidney reveal a steep increase in pressure once CM are given, there appears to be an increase in tubular resistance at the most distal sections of the nephron. Hydration may markedly attenuate this effect by diluting the CM flowing through the collecting ducts. The dilution takes place because of the reduced fluid permeability of the collecting ducts when vasopressin levels are suppressed.

Conclusion

It is unlikely that CMs significantly decrease renal blood flow or glomerular filtration by virtue of their osmolality. From an experimental point of view, iso-osmolar CM cannot be considered at lower risk of CIN than low osmolar CM.

In an attempt to avoid the occurrence of CIN, hydration is of paramount importance and may overcome any smaller differences in injected CM osmolality or viscosity.

Conflict of interest statement. None declared.
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References


34. Ueda J, Furukawa T, Higashino K et al. Urine viscosity after injections of iotrolan or iomepral. Acta Radiol 1997; 38: 1079–1082