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Title:
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Date:
2020-04-01

Citation:
Perera, M., Ischia, J., Bolton, D., Shulkes, A., Baldwin, G. S. & Patel, O. (2020). Experimental rat models for contrast-induced nephropathy; A comprehensive review. Journal of Nephropathology, 9 (2), pp.e12-e12. https://doi.org/10.34172/jnp.2020.12.

Persistent Link:
https://hdl.handle.net/11343/252008

www.nephropathol.com DOI: 10.34172/jnp.2020.12 J Nephropathol. 2020;9(2):e12

Journal of Nephropathology

Experimental rat models for contrast-induced nephropathy; a comprehensive review

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ARTICLE INFO

Article type:
Review

Article history:
Received: 4 November 2019
Accepted: 16 January 2020
Published online: 7 February 2020

Keywords:
Contrast-induced nephropathy
Contrast
Nephropathy
Kidney injury
Rat models
Animal models

ABSTRACT

Contrast-induced nephropathy (CIN) is an iatrogenic disease caused by the parenteral administration of iodinated contrast media (CM). A number of agents are currently being assessed to minimise or prevent CIN. Such agents are typically assessed using rat models. The aim of this study was to provide a comprehensive review of the rat models of CIN used in pre-clinical research. The MEDLINE, EMBASE, Web of Science and Cochrane databases were systematically searched. Articles reporting rat models of CIN were included for assessment. Study designs, contrast agents and outcome measures were assessed. Of the assessed studies, a majority report a requirement for pre-existing renal impairment prior to the administration of CM. Outcome measures are heterogenous between studies, but typically include assessment and quantification of serum biochemical markers, cellular oxidative stress and histopathological changes. The significant variation in methodology reported in the current literature highlights the lack of consensus. The use of a reliable pre-contrast insult appears critical to result in the development of contrast nephropathy. The use of acceptable outcome measures appears to include serum laboratory markers, quantification of reactive oxygen species (ROS) and objective histopathological outcomes.

Review

Implication for health policy/practice/research/medical education:
Contrast-induced nephropathy (CIN) is an iatrogenic disease caused by the parenteral administration of iodinated contrast media. A number of agents are currently being assessed to minimise or prevent CIN, of which initial assessment of these agents are typically assessed using rat models. We provide a comprehensive review outlining previously utilised rat models for the assessment of CIN. This paper is of benefit, as it highlights the different approaches to studying this model and provides a framework for future trials assessing novel agents.

Please cite this paper as: Perera M, Ischia J, Bolton D, Shulkes A, Baldwin GS, Patel O. Experimental rat models for contrast-induced nephropathy; a comprehensive review. J Nephropathol. 2020;9(2):e12. DOI: 10.34172/jnp.2020.12.

Introduction

Contrast-induced nephropathy (CIN) is an iatrogenic disease caused by the parenteral administration of iodinated contrast media (CM), usually in the context of diagnostic investigation or fluoroscopic therapies. Contrast medium used during computerised tomography provides significant improvements in image quality and interpretation. Various tissues exhibit and retain contrast to different degrees at distinctive time-points. The difference in CT attenuation allows better visualization of the tissue of interest during interpretation (1-4). Thus contrast agents can 1) increase the sensitivity of CT and enhance differentiation among different tissues, and 2) enable evaluation of tissue function (5). Historically, iodine (element 53) has been the most commonly utilized and researched element in CT imaging applications. To reduce toxicity, iodine is typically covalently bound with other agents, commonly as iodinated aromatics. Various functional groups may be added to the aromatic rings, which may alter the physical, chemical and pharmacological properties of the agent. Factors that may be altered include osmolarity, viscosity and concentration of iodine.

Advances in the availability, diagnostic ability and safety of computerised tomography (CT) have corresponded with its increasing use globally (6, 7). Accordingly, the use of CM within the healthcare sector is becoming increasingly prevalent. The clinical and economic burden

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of CIN is not insignificant. Contemporary incidence of CIN is currently reported as 5%-11% of hospital inpatients receiving CM (8, 9) and 1% of outpatients (10, 11). CIN represents the third most common cause of hospital-acquired acute renal failure (ARF) (12). CIN is objectively defined by the development of ARF within 24-72 hours of exposure to intravenous or intra-arterial iodinated CM. ARF is characterised by either an increase in serum creatinine (by 25%) or a decrease in the estimated glomerular filtration rate (to 30-60 mL/min). While complex, the pathophysiology relating to the development of CIN has been well documented. CIN occurs as a result of both the cytotoxic and osmolar properties of the CM. The cytotoxic properties of CM result in the interaction of various pathways that cause renal medullary hypoxia. The osmolar properties of the CM result in osmotic nephrosis and augment medullary hypoxia. As such, the key change that results in CIN is the process of renal medullary hypoxia (13-16). The outer medulla of the kidney is particularly vulnerable to hypoxia due to high oxygen requirements from salt absorption in the loop of Henle's thick limb and the S3 segment of the proximal renal tubules. To further compound this effect, the oxygen supply is compromised due to the significant distance between the descending vasa recta and outer medulla. Normal maintenance of medullar perfusion is dependent on descending vasa recta vascular tone, which is regulated by prostaglandins, nitric oxide and adenosine (15).

Given the significant morbidity and economic burden of CIN, there is considerable motivation either to develop a CM with fewer complications or to reduce the incidence of CIN. While limited reductions in risk of CIN have been observed with advances in pre-contrast hydration protocols and additional preventative strategies such as treatment with *N*-acetylcysteine (17), sodium bicarbonate (18, 19) or fenoldopam (20), none have achieved routine use in the clinic. Thus, there remains a need to identify further preventative measures that can reduce the short- and long-term effects of medullary hypoxia following CM administration. Attempts to reduce CIN have focussed on the development of iodinated CM contained in nano-particulates (21, 22), nanosuspensions (23-25), nanoemulsions (26, 27), nanocapsules (28) and liposomes (29). Furthermore, alternative CT attenuating elements, including lanthanide, gold or bismuth, are currently being investigated in contrast agents (5).

To investigate and develop these new contrast agents, there is a need for a robust small-animal model to assess the safety and efficacy of various agents. In the current literature, such small animal models are predominantly rat models. A systematic review of the current literature was therefore performed to assess current rat models for contrast-induced nephropathy.

Rat demographics

Most published rat-based models of CIN utilized either Wistar albino or Sprague-Dawley strains. Although significant heterogeneity was identified in gender and inclusion criteria, most studies utilized a single gender to reduce the effect of gender bias within the study. Among the studies included, there was no preponderance of either gender with 18 female and 23 male rat cohorts. Inclusion criteria varied significantly between studies, between ages of 10-30 weeks and weights of 150-350 gram. However, most studies used rats weighing between 250-300 g with no specified restrictions on age. Several series utilized age-based inclusion criteria, typically 16 weeks, representative of rats of adult status.

Pre-test conditions

Prior to the exposure to CM, series typically reported a brief period of pre-test acclimatization of up to seven days in total. Typically, rats were maintained on a 12-hour light/12-hour dark cycle at 22-25°C. It should be noted that in normal healthy animals, resistance to CIN is significantly high (30) and a single dose of CM does not produce reliable animal models of CIN. Therefore, pre-treating rats with 'insults' is typically required to augment the development of CIN in the respective rat models. Such examples of pre-contrast insults included dehydration, nephron reduction, or use of nephrotoxic compounds.

Several models reported dehydrating the rats for 24 to 48 hours prior to contrast administration (31-37). Efrati et al demonstrated that the renal physiological changes in response to CM are most pronounced in the dehydrated animal (38). The dehydrated state of rats at the time of CM administration acts synergistically with CM to promote renal medullary hypoxia thereby increasing the risk and degree of CIN. However, alternate metabolic and renal perfusion changes during the dehydrated phase may cause other detrimental effects on renal function and are a major limitation of this technique. Therefore, renal compromise post-contrast may not be totally attributed to CIN.

Pre-contrast nephron reduction has been reported to different degrees in previous models. Unilateral nephrectomy has been reported alone (39) or in conjunction with the addition of nephrotoxic medication (40). Further, Liu et al outlined results following a 5/6th nephrectomy model in Sprague-Dawley rats where the right kidney and 2/3rd of the left kidney were nephrectomised prior to CM administration (41, 42). Accordingly, 5/6th nephrectomy results in renal insufficiency and hypertension, which increases the susceptibility to CIN. Although this small animal model

is a reliable and suitable mimic of CIN, it is technically demanding and requires a high degree of surgical expertise (41). While the 5/6th nephrectomy model has been widely utilized to study alternate chronic kidney disease models, its use in assessing CIN has not been previously validated. Another method of preconditioning rats in preparation for CIN studies is the use of a brief period of bilateral renal arterial occlusion of up to 45 minutes. However, this model that has not been validated for use in CIN models in rat models (43).

Various nephrotoxic agents have been utilised to generate a pre-contrast insult. Such agents include cyclosporine, glycerol, cisplatin, and adriamycin (44-46). Su et al assessed the effect of contrast on artificially induced diabetic rats following streptozotocin therapy (47). It should be noted that the nephrotoxic effects of these agents may not be similar to human risk factors and may interfere with results. Furthermore, several series reported the use of nitro-L-arginine methyl ester (L-NAME) and/or indomethacin to induce hypertension and provoke CIN (48-56). Pre-treatment with L-NAME has been validated previously (51). Treatment with L-NAME results in rats that are chronically depleted of nitric oxide (48), and reproducibly impairs renal function following contrast when compared to control (50). The insufficiency of nitric oxide presumably results in defective vasodilation and aggravates intra-renal hypoxia and resulting CIN (51, 57). The use of L-NAME is cost-effective and simple and provides a reproducible injury model, and thus appears to represent a technique that is available for use globally.

Contrast media, dosing, and delivery

A number of commercially available CM have been utilized in CIN rat models (Table 1). CM dosing schemes were homogenous across all assessed studies with male and female rats receiving 10 mL/kg and 6 mL/kg of the selected contrast, respectively. Contrast medium was typically introduced under anaesthesia through injection into the tail vein (34,36,55,58-60), but other injection sites included the caudal vein (33), femoral vein (35), or intraperitoneally (61). Tail vein administration appears to be safe, effective and the most commonly utilized method for contrast administration.

Outcome measures

After administration, rats were typically fed *ad libitum*. In most studies the rats were sacrificed 48-96 hours, post-administration of CM. A number of outcome measures, which included evaluation of urine, blood, renal tissue and radiological features, were utilised in the assessment of CIN in rat models.

Biochemical studies and renal function assessment

Blood for determination of the renal function post-administration of the contrast medium was generally sampled between 9.00 and 10.00 AM to minimize circadian variation (36). Biochemical markers of renal function included serum creatinine, sodium and blood urea nitrogen. A few series assessed cystatin-C, which is a recognized marker of early ARF (62), through commercially available kits (34).

Urinary markers included urinary creatinine and sodium, which were generally evaluated with commercial spectrophotometric kits (32,33,60). Urinary neutrophil gelatinase-associated lipocalin and KIM-1 are relatively new biomarkers of acute kidney injury (63,64). These

Table 1. Contrast agents utilized in various rat models of contrast-induced nephropathy

Type	Generic name	Trade name	Manufacturer	[Iodine] (mg I/mL)	Osmolality (mOsm/kg)
Hypo-osmolar					
Non-ionic dimer	Iodixanol	Visipaque	GE Healthcare	320	290
Non-ionic dimer	Iotrolan	Isovist	Schering Healthcare	300	320
Non-ionic monomer	Iomeprol	Imeron	Bracco Imaging	300	521
Iso-osmolar					
Ionic dimer	Ioxaglate	Hexabrix	Mallinkrodt Imaging	320	580
Non-ionic monomer	Iopamidol	Isovue	Bracco Imaging	300	616
Non-ionic monomer	Iohexol	Omnipaque	GE Healthcare	300	640
Non-ionic monomer	Iopromide	Ultravist	Bayer Healthcare	300	610
Non-ionic monomer	Ioversol	Optiray	Covidien	300	650
Hyper-osmolar					
Ionic monomer	Iothalamate	Cysto-Conray II	Mallinckrodt Imaging	325	1843
Ionic monomer	Diatrizoate	Urograffin	Bayer Healthcare	306	1530

The concentrations of iodine in these agents are measured in mg of Iodine/ml (mg I/mL).

biomarkers have been used previously in other models of acute kidney injury (65,66), but only occasionally in CIN models (56,67).

Assessment of oxidative stress

The degree of intracellular oxidative stress can be determined by quantifying malondialdehyde (MDA), and the activity of antioxidants such as superoxide dismutase (SOD), renal tissue catalase (CAT) and glutathione peroxidase (GSH-Px) (32,33,36,58). The assessment of each of these variables has been validated in *in-vivo* and *in-vitro* models. MDA concentrations were measured by various methods, including the thiobarbituric acid reaction(32,60,68,69) and other commercially available kits (33). Typically, 0.5 gram samples of the kidney were taken and homogenized in 20 mM phosphate buffer. 10 uL of 0.5 M butylated hydroxytoluene per mL of homogenate was added and, after centrifugation, 200 uL of the supernatant from each homogenate was taken for reaction with the chromogenic reagent (36).

SOD enzyme activity was typically determined by inhibition of the production of superoxide (measured by reduction of nitroblue tetrazolium) by xanthine oxidase (32,68,70) . CAT activity was determined by measuring the decomposition of hydrogen peroxide at 240 nm (32,68,71). GSH-Px activity was determined by the production of glutathione disulphide, which was in turn measured with glutathione reductase by following changes in NADPH absorbance at 240-340 nm (32,71,72).

Several series determined the degree of apoptosis using a TUNEL assay, for example the ApopTag Plus Peroxidase In Situ Apoptosis Detection Kit. This assay is performed on frozen sections of the renal parenchyma and allows the measurement of DNA fragmentation by labelling the newly formed 3'-OH groups with digoxigenin-nucleotides, which are then detected with a specific antibody (41, 43,47,55,60,73). The specimens are incubated with the TUNEL reaction mixture, and TUNEL-positive cells are counted under a fluorescence microscope for quantitative assessment. This labelling technique allows for the objective measurement of cellular apoptosis which is characterised by this DNA fragmentation.

Of these measures of oxidative stress, none have formally been validated for use in the setting of CIN. Despite this deficiency, the most widely utilized methods include the quantification of MDA, and of apoptosis using the TUNEL assay.

Radiological assessments

Doppler flow of the kidney has been performed in a few studies to determine the microvascular blood perfusion through tissues (51,59,60). Despite this, this method has not been validated for use in such rat models and is a recognised limitation of such an outcome measure.

Multiple groups have reported the use of magnetic resonance imaging (MRI) to assess oxygenation changes following contrast administration (39,50,51). Intra-renal oxygenation changes have been assessed using blood oxygenation level-dependant MRI (50,51,57,74,75). MRI can also provide qualitative data on the presence and distribution of parenchymal abnormalities, or quantitative data on parenchymal percentage enhancement. However, MRI is expensive and not always accessible for kidney function analysis.

Renal histopathological examination

Histology was performed on formalin-preserved tissue embedded in paraffin wax. Histological assessment of slides stained with haematoxylin-eosin allows quantitation of the microscopic morphological changes associated with contrast injury. Such changes include vacuolization of the proximal and distal tubules, necrotic changes and medullary congestion (33,36). However, to date no validated scoring schemata has been used consistently through the included studies. Previously validated scoring systems including the Jablonski score (76) were not utilized. Despite this deficiency, an example of the most frequently utilized scales for renal damage and medullary congestion is outlined in Table 2 (47,58). Similar schemes for tubular necrosis were utilized in other studies (34,35, 49,68).

Conclusion

The significant increase in availability and use of CT imaging has resulted in an increased use of CM. Accordingly, a growing number of people are exposed to the potentially detrimental effects of CM. There has been a significant push to improve CM and identify agents that may reduce the risk of development of CIN. The

Table 2. Histopathological scoring scheme for renal necrosis and medullary congestion

Score	Renal necrosis	Medullary congestion
0	No Damage	No Congestion
1	Mild unicellular patchy necrosis	Mild: identification of erythrocytes by x400 magnification
2	Moderate damage less than 25%	Moderate: identification of erythrocytes by x200 magnification
3	Severe damage of between 25%-50%	Severe: identification of erythrocytes on x100 magnification
4	Very severe damage of >50%	Very severe: identification of erythrocytes on x40 magnification.

development of a robust rat model for CIN is essential for future research in this field. From the current intensive review, several key features have been identified that should be considered during the development of such models. The use of a reliable pre-contrast insult appears critical to result in the development of contrast nephropathy. The use of acceptable outcome measures appears to include serum laboratory markers, quantification of reactive oxygen species and objective histopathological outcomes.

Authors' contribution

MP and JI; data collection, manuscript production. DB, AS, GB and OP; supervision, manuscript correction. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the author.

Disclosures

There are no disclosures. The corresponding author is not a recipient of a scholarship. This paper is not based on any previous communication to a society or meeting.

Funding/Support

No funding support.

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