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Gadolinium-Based Contrast Agents in Kidney Disease: Comprehensive Review and Clinical Practice Guideline Issued by the Canadian Association of Radiologists

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Abstract

Use of gadolinium-based contrast agents (GBCAs) in renal impairment is controversial, with physician and patient apprehension in acute kidney injury (AKI), chronic kidney disease (CKD), and dialysis because of concerns regarding nephrogenic systemic fibrosis (NSF). The position that GBCAs are absolutely contraindicated in AKI, CKD stage 4 or 5 (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) and dialysis-dependent patients is outdated, and may limit access to clinically necessary contrast-enhanced MRI examinations. Following a comprehensive review of the literature and reported NSF cases to date, a committee of radiologists and nephrologists developed clinical practice guidelines to assist physicians in making decisions regarding GBCA administrations. In patients with mild-to-moderate CKD (eGFR ≥30 and <60 mL/min/1.73 m^2), administration of standard doses of GBCA is safe and no additional precautions are necessary. In patients with AKI, with severe CKD (eGFR <30 mL/min/1.73 m^2), or on dialysis, administration of GBCAs should be considered individually and alternative imaging modalities utilized whenever possible. If GBCAs are necessary, newer GBCAs may be administered with patient consent obtained by a physician (or their delegate), citing an exceedingly low risk (much less than 1%) of developing NSF. Standard GBCA dosing should be used; half or quarter dosing is not recommended and repeat injections should be avoided. Dialysis-dependent patients should receive dialysis; however, initiating dialysis or switching from peritoneal to hemodialysis to reduce the risk of NSF is unproven. Use of a macrocyclic ionic instead of macrocyclic nonionic GBCA or macrocyclic instead of newer linear GBCA to further prevent NSF is unproven. Gadopentetate dimeglumine, gadodiamide, and gadoversetamide remain absolutely contraindicated in patients with AKI, with stage 4 or 5 CKD, or on dialysis. The panel agreed that screening for renal disease is important but less critical when using macrocyclic and newer linear GBCAs. Monitoring for and reporting of potential cases of NSF in patients with AKI or CKD who have received GBCAs is recommended.

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Resumé

L'utilisation de produits de contraste à base de gadolinium (PCBG) dans les cas d'insuffisance rénale est controversée, car les risques de fibrose systémique néphrogénique (FSN) chez les patients atteints d'insuffisance rénale aiguë (IRA), de néphropathie chronique et dialysés inquiètent médecins et patients. L'avis selon lequel les PCBG sont absolument contre-indiqués chez les patients atteints d'IRA, de néphropathie chronique au stade 4 ou 5 (débit de filtration glomérulaire estimé [DFGe] $<$ 30 mL/min/1,73 m^2) et dialysés est dépassé et peut limiter l'accès aux examens par IRM avec injection de produit de contraste cliniquement nécessaires. Après un examen exhaustif de la documentation et des cas de FSN signalés à ce jour, un comité de radiologues et néphrologues a préparé des lignes directrices de pratique clinique pour aider les médecins à prendre des décisions concernant l'administration de PCBG. Chez les patients atteints de néphropathie chronique légère à modérée (DFGe $\geq$ 30 et $<$ 60 mL/min/1,73 m^2), l'administration de doses standards de PCBG ne présente aucun danger et n'exige aucune précaution additionnelle. Chez les patients atteints d'IRA, de néphropathie chronique grave (DFGe $<$ 30 mL/min/1,73 m^2) ou dialysés, l'administration de PCBG doit être déterminée au cas par cas et d'autres modalités d'imagerie doivent être utilisées chaque fois que c'est possible. Si le recours aux PCBG s'avère nécessaire, des produits plus récents peuvent être administrés. Le médecin (ou son délégué) doit alors obtenir le consentement du patient, après avoir avisé ce dernier du risque extrêmement faible (nettement inférieur à 1 %) de FSN. Une dose standard de PCBG doit être utilisée; il n'est pas recommandé de réduire la dose à la moitié ou au quart, ni de répéter les injections. Les patients dialysés doivent poursuivre leur dialyse. Toutefois, les données ne permettent pas d'établir que la mise en route d'une dialyse ou le passage de la dialyse péritonéale à l'hémodialyse puisse atténuer le risque de FSN. Les données ne permettent pas non plus d'établir que le recours aux PCBG macrocycliques ioniques plutôt qu'aux PCBG macrocycliques non ioniques ou que le recours aux PCBG macrocycliques plutôt qu'aux PCBG linéaires récents réduisent également le risque de FSN. Le gadopentétate de diméglumine, le gadodiamide et le gadoversétamide demeurent absolument contre-indiqués chez les patients atteints d'IRA, de néphropathie chronique au stade 4 ou 5 ou en dialyse. Le groupe d'experts admet qu'il est important, mais moins essentiel, de procéder au dépistage d'une maladie rénale s'il y a administration d'un PCBG macrocyclique ou linéaire récent. On recommande de faire le suivi des patients atteints d'IRA ou de néphropathie chronique à qui un PCBG est administré, afin de déceler et de déclarer les éventuels cas de FSN.

Key Words: Gadolinium; Guideline; Magnetic resonance imaging; Nephrogenic systemic fibrosis; NSF

Gadolinium-based contrast agents (GBCAs) have been in clinical use for decades and have an integral role in magnetic resonance imaging (MRI) examinations. In general, GBCAs have an excellent safety profile [1−7]; however, they have been identified as the causative agent in nephrogenic systemic fibrosis (NSF) [8]. Due to the associations between NSF in patients receiving GBCAs and renal impairment, the use of GBCAs has been considered absolutely contraindicated in patients with acute kidney injury (AKI), severe chronic kidney disease (CKD), and receiving dialysis [9−11]. Nevertheless, the vast majority of documented NSF cases have occurred in patients who received linear nonionic or older linear ionic GBCAs (often repeatedly or at higher-than-recommended dosage) [12]. The incidence of NSF has substantially decreased over the past several years, and this is attributed mainly to physician awareness and avoidance of GBCAs in at-risk patients, the use of newer macrocyclic and linear-ionic GBCAs, and avoiding repeat injections and greater than recommended dosing [12−14]. In Canada, for example, to our knowledge the last officially documented case of NSF occurred in a 70-year-old patient who received an unspecified GBCA in 2011 [15].

To address a disparity in Canadian guidelines regarding NSF and more recent literature evaluating NSF in macrocyclic and newer linear-ionic agents, updated guidelines were developed by a working group involving members of the Canadian Association of Radiologists (CAR) and the Canadian Society of Nephrology. The goals of the working group were to review the literature regarding the NSF safety profile of GBCAs that are currently approved for clinical use in Canada, and to recommend clinical practice guidelines for physicians when considering the use of GBCAs in at-risk patients, namely those with AKI, with severe CKD, or on dialysis (herein referred to simply as at-risk patients) (see Appendix 1). The purpose of these guidelines was not to exhaustively review the mechanisms of NSF or the biochemistry of gadolinium chelates in general, or address the recently described phenomenon of gadolinium deposition in the brain (which is being reviewed with guidelines formulated by a separate working group commissioned by the CAR); however, these concepts were considered and are addressed briefly herein. Data on the risk of GBCA allergic adverse events are not reviewed and are beyond the scope of this guideline but have been described elsewhere [16].

Background

GBCAs have been used in conjunction with MRI since the 1980s and have an overall excellent cumulative safety record [17,18]. The ideal GBCA has high relaxivity (to generate increased contrast on T1-weighted MR images), would require a low, nontoxic dose, and is well tolerated without any adverse immediate or long-term effects. GBCAs are derived and administered in a chelated form to minimize the amount of free gadolinium in the body [17−19]. GBCAs used clinically should have high stability to prevent dissociation of gadolinium and should be rapidly cleared and excreted from the body [17,18]. The stability of GBCAs