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The dose of iodinated contrast required for a CT scan is below the toxicological threshold of concern for nephrotoxicity: a toxicological perspective

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ABSTRACT

Background: Observational and retrospective studies have demonstrated an apparent association between administration of intravenous contrast and subsequent development of acute kidney injury (AKI). This condition is termed contrast associated acute kidney injury (CA-AKI). The CA-AKI literature has focused on contrast administration in the setting of percutaneous coronary intervention (PCI) rather than computed tomography (CT).

Discussion: The dose of contrast for PCI is significantly higher than that for CT, and extrapolating the risks of a medicine at high dose to low dose may imply a risk that does not exist. Multiple recent studies (notably Hinson 2017, Aycock 2018, and Ehmann 2023) assessing the relationship between AKI and low-dose contrast administration, i.e., that required for CT, found no association with renal injury.

The degree of toxicity of any substance exists on a continuum, and there is a dose below which there is no toxicity, called the toxicological threshold of concern (TTC). There is sufficient evidence to imply that the contrast doses for a single CT scan is below the TTC. Since the maximum typical contrast dose for a single CT is 120 mL of a 350 mg/mL solution, this dose appears to be below the TTC.

Conclusion: The dose for CT scan is a fraction of that for PCI, and while there may be a small risk of CA-AKI with doses required for PCI the literature indicates there is minimal risk of CA-AKI with the contrast dose required for a CT, indicating a toxicological threshold of concern of 120 mL. Simply put, the 200-900 mL of contrast required for PCI might cause CA-AKI, whereas no evidence suggests the 60-120 mL of contrast required for a single CT scan would.

1. Introduction

Observational and retrospective studies have demonstrated an apparent association between administration of intravenous contrast and subsequent development of acute kidney injury (AKI) [1]. This condition is termed contrast associated AKI (CA-AKI). The foundational literature on CA-AKI is problematic for several reasons. First, retrospective studies that examine IV contrast administration are implicitly confounded by other disease states that necessitate contrast enhanced imaging. For example, certain forms of infection or hemorrhage, acute myocardial infarction, and thrombotic events may require IV contrast for diagnosis. These disease states are themselves independent causes of AKI, yet contrast administration is often required to diagnose them. Contrast is therefore associated with diseases that cause AKI, and is also associated with AKI without necessarily causing AKI. Second, the CA-AKI literature has focused on contrast administration in the setting of percutaneous coronary intervention (PCI) rather than computed tomography (CT). The dose of contrast for PCI is significantly higher than that for CT, and extrapolating the risks of a medicine at high dose to low dose may imply a risk that does not exist. Third, during the 1990s and early 2000s low osmolality nonionic agents (such as iohexol and iodixanol) have supplanted high osmolality ionic agents (such as diatrizoate and iothalamate) as a drug class [2]. Over the past decade, multiple studies assessing the relationship between AKI and low-dose contrast administration, i.e., that required for CT, found no association with renal injury [3–5].

Physician concern for CA-AKI has led to suboptimal risk benefit assessments. The belief that contrast enhanced CT can cause CA-AKI may defer or delay CT, which may lead to missed or delayed diagnosis of life or limb threatening conditions. Necessary CT scans may be delayed pending measurement of creatinine concentration, and physicians may even be inappropriately blamed for causing CA-AKI in patients who developed renal injury due to reasons other than contrast administration.

2. Discussion

The degree of toxicity of a substance exists on a continuum, and there is a dose below which there is no toxicity. This is called the toxicological threshold of concern (TTC) (Fig. 1). For example, drinking 1 L of water is below the TTC, however rapidly drinking 10 L of water may lead to hyponatremia, cerebral edema, seizures, and death. Similarly, the

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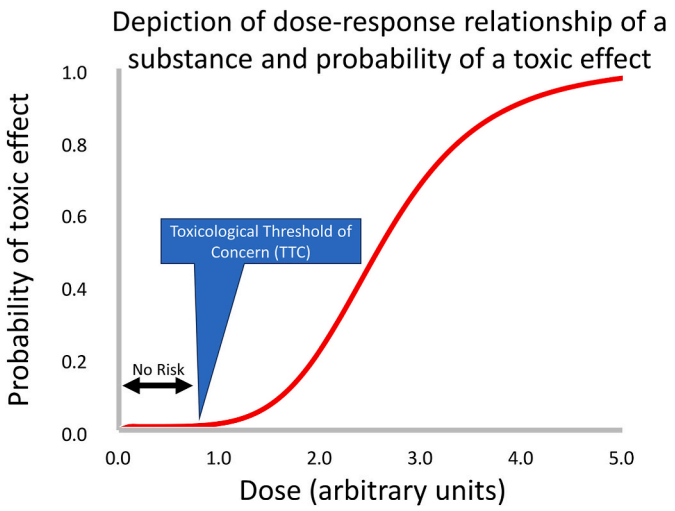

Fig. 1. Conceptual representation of the dose-response relationship for a toxic substance. The initial plateau from the abscissa to the TTC represents doses which have virtually zero risk of toxicity.

human body generates a low concentration of cyanide as a normal metabolic waste product, however only when one receives a dose of cyanide above the TTC is there any toxic effect. The TTC exists for all substances, including iodinated contrast [6].

A relationship between the dose of iodinated contrast and the risk of AKI, or an increase serum creatinine 25% or 0.5mg/dl from baseline, in patients receiving PCI was shown by Mehran and Nikolsky [7]. The study demonstrated a relationship wherein the odds of AKI were 1.46 for 200 – 400 mL, 1.98 for 400 – 600 mL, and 4.88 for above 600 mL of contrast [7]. A 2024 study examining contrast dose reduction in PCI substantiated the relationship between CA-AKI and high dose contrast by further demonstrating that reducing the contrast dose from 160 ± 23 mL to 95 ± 30 mL reduced the risk of AKI [8]. In both studies, risk increased for patients receiving a dose above 100 mL of contrast which is greater than what is administered for a CT scan (Table 1).

Furthermore, some patients undergoing PCI receive up to 900 mL of 300-350 mg/mL contrast which is more than tenfold the dose administered for most CT scans. The difference is due to CT scans delivering a fixed dose according to study protocol, whereas in PCI the physician delivers as many 6 – 12 mL "squirts" as needed to complete the procedure. As a result, there is significant variation in contrast dosing for PCI but highly consistent dosing for CT.

Both CT and PCI typically use 300-350 mg/mL concentrations of contrast. The volume dose of iodinated contrast typically ranges from (60 – 100 mL) for CT and (200 – 600 mL) for PCI (Table 1). The minimum dose of contrast required for PCI is typically greater than the maximum dose administered for CT. This leaves the question of what is the value of the TTC, and whether the contrast dose for a CT scan exceeds it? Multiple studies have approached this question, notably Hinson 2017, Aycock 2018, and Ehmann 2023 [3–5].

In 2017, Hinson et al. published a propensity-matched retrospective study over a 5-year period comparing the development of AKI in patients who received contrast-enhanced CT (n = 7201), non-contrast enhanced CT (n = 5499), and patients who did not receive a CT (n = 5234). Defining AKI according to the Kidney Disease Improving Global Outcomes guidelines, they discovered that 6.7%, 8.9%, and 8.1% of patients in these groups developed AKI respectively, with no significant differences between groups. All patients received either iohexol or iodixanol intravenously with a maximum dose of 120 mL. There was no difference in subsequent development of chronic kidney disease, need for dialysis, or renal transplantation [3].

The following year, Aycock et al. performed a systematic review and meta-analysis examining outcomes in 107,335 patients who received contrast for a CT scan compared to those who did not receive contrast. Patients variously received ioxhexol, ioversol, iopromide iopamidol, iomeprol, iodixanol, iobitridol, or diatrizoate at doses which were not recorded in the study. The authors found no significant association in rates of AKI, need for renal replacement therapy, or all-cause mortality. The authors concluded that due to the similar rates of AKI in both groups that disease and patient specific factors were more likely the cause of AKI than contrast [4].

In 2023 Ehmann et al. published a retrospective entropy-balanced and propensity-balanced observational cohort study of 14,449 hospitalized patients already meeting criteria for AKI at the time of emergency department visit who did or did not receive contrast media. All patients received 70 - 120 mL of iohexol or iodixanol intravenously. They found no association between contrast administration and persistent AKI or need for dialysis [5].

While the exact numerical value of a TTC cannot be deduced from these studies, there is sufficient evidence to imply that the contrast doses for a single CT scan is below the TTC. The 2017 Hinson and 2023 Ehmann articles specifically examined doses of iohexol and iodixanol of up to 120 mL, and concluded no evidence of CA-AKI. The 2018 Aycock article did not specify contrast media dose information, however Table 1 indicates a typical dose of 100 mL for the CT studies included in the article. Since the maximum typical contrast dose for a single CT is 120 mL of a 350 mg/mL solution, this dose appears to be below the TTC.

Although examining large numbers of patients, the studies attempting to debunk CA-AKI are all retrospective in design. Even propensity balanced, "pseudo-randomized," and meta-analytical retrospective analyses are not able to replace a prospective RCT. There will always be imperfect knowledge until a prospective RCT is performed. Additionally, propensity matched retrospective studies may overlook subgroups which are ultimately underpowered to demonstrate a difference. It is conceivable that low dose contrast may cause AKI in patients with extremely low GFR, specific predisposing intrinsic renal diseases, type IV hypersensitivity reactions, or other unstudied groups.

This was apparent such that in 2023 Goulden et al. published another retrospective study examining the association of contrast with subsequent AKI at dosages required for CT scan. Goulden et al. stratified patients by D-Dimer just above or just below the threshold for CT pulmonary angiography to compare CA-AKI incidence in otherwise highly similar cohorts. Presumably, these groups are nearly identical and that a slight difference in D-Dimer concentration is unlikely to be clinically meaningful but will determine whether or not a patient receives a contrast dose. The authors still found no difference in CA-AKI rates [9].

Despite skepticism, there is a body of evidence that supports the concept and relevance of CA-AKI. Notably, the aforementioned Mehran and Nikolsky study as well as a study by Yuan et al. demonstrate a dose-response curve between contrast dose and risk of subsequent AKI [7,10]. Yuan et al. proposed a model with high sensitivity and specificity for contrast dosing in PCI. The authors proposed a safe contrast limit of 299.3 mL for the minimum model, and 367.6 mL for the full model. Demonstrating a dose response curve is strong evidence that a substance is potentially toxic. Nonetheless, the minimum safe dosages are well above the typical 120 mL maximum amount administered during emergency department CT scans.

An additional opposing view with regards to CT contrast dose being

Table 1
Contrast dose (mL and mg) for various studies using most commonly used concentration 350 mg/mL in adults. Adapted from Radiopedia.org.

Modality and body system	Dose range (mL)	Dose range (mg)
CT abdomen and pelvis	70 - 100 mL	24,500 - 35,000 mg
CT angiography of cerebral arteries	50 - 75 mL	17,500 - 26,000 mg
CT pulmonary angiogram	60 mL	21,000 mg
CT abdominal aorta	75 - 100 mL	26,250 - 35,000 mg
PCI coronary arteries	200 - 600 mL	70,000 - 210,000 mg

below a toxic threshold is the potential for contemporaneous absorption of oral contrast. Although typically oral contrast has a bioavailability below 1%, certain disease states such as inflammatory bowel diseases increase the bioavailability of enteral contrast agents [11]. It is therefore conceivable that a patient with increased intestinal permeability who received both intravenous and enteral contrast could receive a total dose above the TTC.

Another consideration is the possibility that CA-AKI follows a stochastic rather than a deterministic model for toxicity. The TTC model assumes a dose-response model with a threshold, i.e., a deterministic model. However certain poisons such as radiation may follow a stochastic model. For example, a single gamma ray or a single cigarette has a negligible but non-zero probability of causing cancer due to disruption of a single strand of DNA. It is conceivable that CA-AKI follows a stochastic model of disease, such as allergic reaction leading to glomerulonephritis or generation of reactive oxygen species [12]. Stochastic toxins are often difficult to study due to rarity, and even a study with a large number of patients has the potential to misattribute causation in a truly rare disease. Fortunately, the chances of developing disease from stochastic toxins like radiation and other carcinogens is proportional to the dose, e.g., a low radiation dose caries a lower probability of causing disease than a higher dose. Therefore, even if iodinated contrast has a stochastic component of nephrotoxicity, it would be so minuscule as to be undetectable among thousands of patients.

Accounting for these opposing viewpoints, we believe the available evidence overwhelmingly supports the concept that the contrast dose from CT in the ED is below the TTC for nephrotoxicity. In special cases such as receiving multiple CT scans within a short time period, or a CT followed by PCI, altered gut permeability, and unstudied populations, clinicians should consider risk on a case-by-case basis for their individual patients.

In a deterministic model, the risk of toxicity from any substance, including contrast, does not begin at the abscissa of the graph; it remains zero until reaching the TTC. Hospitalized patients develop AKI at the same rate whether or not they received contrast for a CT [3]. Multiple studies have thoroughly demonstrated that the contrast dose for CT does not cause renal toxicity, i.e., is below the TTC. Since the risk of contrast nephropathy from CT scan is undetectably low, it is impossible to further reduce the risk. Reducing a non-toxic dose to decrease toxicity is absurd, and only reduces the CT's benefit by decreasing diagnostic clarity.

This paper does not involve patient data and is therefore exempt from IRB approval.

3. Conclusion

As with any medicine, the dose of iodinated contrast makes a difference. The dose for CT scan is a fraction of that for PCI, and while there may be a small risk of CA-AKI with doses required for PCI the literature indicates there is minimal risk of CA-AKI with the contrast dose required for a CT, indicating a toxicological threshold of concern of 120 mL. Simply put, the 200-900 mL of contrast required for PCI might cause CA-AKI, whereas no evidence suggests the 60-120 mL of contrast required for a single CT scan would.

CRediT authorship contribution statement

Amylisa Phillips: Writing – review & editing, Writing – original draft, Conceptualization. **Adam Blumenberg:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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