LETTER TO THE EDITOR

Concerns about ceftriaxone co-administration with calcium gluconate: a call for enhanced guidelines and awareness in clinical practice

Abdullah Khalil[1], Muhammad Haroon[1], Ahmad Raza[1], Shafaq Saleem[2,*], Daniyal Ishtiaq[3]

[1]Department of Medicine, Rawalpindi Medical University [2]Harvard Medical School, Boston, Massachusetts [3]Hospital Medicine, Albert B. Chandler, University of Kentucky

*Author for correspondence: e-mail: shafaqsaleem6@gmail.com

Abstract

Co-administration of IV Ceftriaxone with calcium-containing solutions causes insoluble precipitation, leading to severe vascular occlusion, renal injury, and fatal embolization, especially in neonates. This is commonly seen in overburdened healthcare settings like those in Pakistan, despite established safety warnings. Inappropriate prescribing and systemic oversights persist. Urgent action is required through updated clinical guidelines, enhanced provider education, mandatory packaging warnings, and improved adverse event reporting to prevent these fatal outcomes.

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Dear Editor,

The high number of deaths associated with coadministration of ceftriaxone and calcium containing solution is a critical problem of clinical practice. This problem is very important but frequently not paid attention to. It still happens even though there have been warnings. Regulatory authorities have taken steps to address the issue. It remains to be the leading cause of preventable illness and death especially in places where there are not enough resources. New evidence from 2025 shows that there is need to update clinical guidelines, improve healthcare provider education and reinforce safe drug administration practices.

Ceftriaxone is a third-generation cephalosporin. It is frequently used to treat infections like pneumonia, meningitis and sepsis. The physicochemical properties can affect its solubility. The chiral carbon centers in ceftriaxone may cause precipitates formation. Precipitates can be formed due to ceftriaxone mixing with calcium-containing IV solutions. This reaction can produce insoluble calcium-ceftriaxone complexes that have been linked to serious clinical outcomes. These outcomes include Stevens Johnson Syndrome (SJS), multi-organ failure and aplastic anemia [1].

Recent advances in analytical techniques have provided a better understanding of this risk. A 2023 study confirmed that mixing ceftriaxone with calcium solutions produces precipitates. The particles identified in the study were larger than 20 μm, which is considered large enough to block pulmonary capillaries. Raman spectroscopy was used to confirm the presence and characteristics of these particles [2].

Reports have also described crystal accumulation in the kidneys, biliary tracts and cardiopulmonary systems in pediatric patients. These findings are supported by data from the FDA Adverse Event Reporting System (FAERS). The data show that newborns are more at risk because their blood vessels are smaller [3,4].

Animal studies confirm that calcium-ceftriaxone precipitation can trigger acute kidney injury. The proposed mechanisms include activation of the NLRP3 inflammasome and increased oxidative stress [5]. A systematic review by Steadman et al. found that giving ceftriaxone with calcium carries a 4.7 times higher risk of embolic events compared with other cephalosporins such as ceftazidime [6].

Many studies have pointed out that guideline adherence is suboptimal for some time. The problem persists because of systemic failures. Overburdened public hospitals in countries such as Pakistan and India often face staff shortages and high patient volumes. Heavy workloads can lead to rushed and incompatible IV administrations.

A 2019 survey of healthcare workers found that ceftriaxone was prescribed incorrectly in 68.9% of cases [7]. The widespread use of ceftriaxone also contributes to the problem. Its broad antimicrobial activity and relatively low cost make it a commonly selected antibiotic in settings where treatment options are limited. This widespread use can increase the risk of inappropriate administration and misuse.

Immediate action is needed to reduce these harms:

- Healthcare institutions should ensure that the rules for giving ceftriaxone are followed. This includes making sure that it is never given with IV solutions that contain calcium.
- Simulation-based training on how drugs work should be part of medical and nursing schools especially in low and middle income countries.
- Manufacturers should add “red-box” warnings on ceftriaxone packaging to reinforce awareness.

- Pharmaceutical companies and healthcare institutions should be encouraged to report adverse events related to ceftriaxone and identify the most affected regions.

It is a failure to ignore known drug problems. These incidents should be prevented by using a careful and responsible approach. Officials, doctors and leaders should work to stop this completely preventable cause of death.

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