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Short Communication

Ceftriaxone calcium crystals induce acute kidney injury by NLRP3-mediated inflammation and oxidative stress injury

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INTRODUCTION

Drug-induced renal calculi represented 1–2% of the total number of renal calculi analysed in specialised laboratories (Araz et al., 2007). Historically, sulfonamides were the first drugs implicated in renal calculi formation and acute renal failure (ARF) episodes early after their use in humans (Cristol et al., 1996). The true prevalence of drug-induced renal calculi was likely to be underestimated in most studies. Ceftriaxone, a third-generation cephalosporin, was widely used because of its broad spectrum, long plasma half-life and relatively few adverse effects (Chang et al., 2014). However, in combination with calcium ions, this drug could form a poorly soluble ceftriaxone-calcium salt which was also known as urolithiasis (Daudon et al., 2018). Although its incidence was relatively rare, ceftriaxone-induced urolithiasis tended to lead to acute kidney injury (AKI). Our previous systematic review demonstrated the incidence of impaired renal function in patients with ceftriaxone calculi was 72.7% which was much higher than other types of stones (Dursun et al., 2015). However, ceftriaxone-induced urolithiasis and the subsequent AKI were often overlooked in clinical practice. Under the circumstances, this particular type of urolithiasis should be given special attention and the underlying mechanisms should be well understood.

Previously, we found that besides urinary obstruction, which was well known, ceftriaxone induced crystalline nephropathy also contributed to nephrolithiasis-associated AKI. But the specific mechanism remained unclear.

As reported, NLRP3 was a crucial pattern recognition receptor and played pivotal roles in host defense against pathogens. In fact, NLRP3 activation has been demonstrated to have a contribution to multiple disease by increasing IL-1β and IL-18 secretion and amplifying the inflammatory response, including acute lung injury and acute liver failure (Feng et al., 2019). Evolving data suggested that the downstream IL-1/18 axis contributed to acute and chronic inflammation and tissue remodeling in the kidney (He et al., 2014). Our study defined the relative importance of the inflammasome in specific ceftriaxone calculi-induced AKI and suggested further study to get the therapeutic opportunities afforded by targeting the inflammasome.

Acute kidney injury was also associated with ROS production and impaired antioxidant activity (Palipoch, 2013). Kidney damage in oxidative stress (OS)-related AKI was associated with increased ROS/RNS production, leading to oxidation of several macromolecules (e.g. protein, DNA and lipid). Production of lipid peroxidation (LPO) in OS-related AKI resulted in large production of secondary products such as malondialdehye (MDA) and 4-hydroxynonenal (Schmutz et al., 2011). OS was one of the most important factors contributing to AKI by increasing production of oxidants, particularly ROS and RNS and/or ineffective/insufficiency of endogenous antioxidant defence system (Zhang et al., 2016). Our study found that markers of oxidative stress such as ROS, MDA, and H2O2 were significantly increased in the animal model of ceftriaxone calculi-induced AKI, and similar changes were also observed in HK-2 cells. Moreover, we showed here that ceftriaxone calcium crystal stimulation increased Nrf2 levels in the nuclei, as well as HO-1 and NQO1 protein and mRNA levels, which was indicative of a stress response.

CONCLUSION

In summary, we have developed an animal model of ceftriaxone calcium crystal nephropathy with development of renal failure and death. Using this model, we demonstrated that NLRP3-mediated inflammasome and oxidative stress injury are of major importance in the pathogenesis of ceftriaxone calcium crystal-induced AKI. This work emphasized the potential value of anti-inflammatory and antioxidant therapies in ceftriaxone

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calcium crystal nephropathy. Future studies was highly warranted.

CONFLICT OF INTEREST

None declared

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