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Effect of administration duration of low dose methotrexate on development of acute kidney injury in rats

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Background: Methotrexate (MTX) is currently utilized as a key drug in treatment of both malignant tumors and rheumatoid arthritis. However, MTX treatment is often associated with various side effects, such as pulmonary damage, hepatotoxicity and nephrotoxicity. Recent report also revealed that, even though total administered dosage of MTX was same, longer duration of MTX administration caused more severe adverse effect rather than short duration of its administration in clinical usage. Despite the importance of appropriate usage of MTX, the mechanism of kidney injury caused by the difference in duration of MTX administration remains still unknown. The aim of this research is to establish an animal model, which can be used to determine the effect of administration duration on MTX-induced kidney injury and explore the significant factor and mechanism responsible for MTX caused-kidney injury.

Methods: Male Wistar rats were randomly divided into 4 groups. MTX (25 mg/kg) was intraperitoneally injected by short or long administration duration. Short administration duration control group (saline, Short-Con) and MTX group (25 mg/kg MTX saline solution, Short-MTX) were administered by 1 injection at day 1. Long administration duration control group (saline, Long-Con) and MTX group (5 mg/kg MTX solution, Long-MTX) were administered by 5 injections from day 1 to day 5, once a day. Urine samples were collected from 24h before administration to the end. Serum and kidney samples were collected on day 7. Body weight, water intake and urine volume were recorded. Urea nitrogen and CRE were determined in serum and urine. HE staining and determination of kidney damage markers, kidney injury molecule 1 (Kim-1) and neutrophil gelatinase-associated lipocalin (N-gal) were conducted. Renal accumulation and urine excretion of MTX were determined by LC-MS/MS. 4-Hydroxynonenal (4HNE) and malondialdehyde (MDA) in kidney were determined.

Results and Discussion: We successfully established animal models to determine the effect of administration duration on MTX-induced kidney injury and evaluated the significant factor and mechanism responsible for MTX
caused-kidney injury. In Long-MTX group, body weight, water intake, and urine volume were significantly decreased. Urea nitrogen and CRE in urine were obviously decreased in Long-MTX group, while BUN and CRE in serum were increased in Long-MTX group. In addition, Long-MTX group showed the significant increase in both neutrophil gelatinase-associated lipocalin (N-gal) and kidney injury molecule 1 (Kim-1), kidney injury markers. Interestingly, renal MTX concentration in Long-MTX group was higher than those in Short-MTX group. Moreover, 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), reliable oxidative stress markers, were significantly increased in Long-MTX group. Those results suggest that the MTX accumulation in kidney by long-MTX administration caused kidney injury through an increase in oxidative stress.

**Conclusion:** In this study, we provided first hand evidence that longer duration of MTX administration caused more severe kidney injury in rat model. MTX accumulation in renal tissue by long-MTX administration caused kidney injury through an increase in oxidative stress. These findings may bring new insights into understanding of MTX-induced kidney injury, and may lead to clinical application for appropriate treatment with MTX.