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Pulmonary, Hepatic, and Renal Fibrosis due to Nitrofurantoin in Rat Pups

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Abstract

BACKGROUND/AIMS: Nitrofurantoin is a commonly used antimicrobial drug for treating and prophylaxis of uncomplicated urinary tract infections in both children and adults. Mild and severe adverse reactions to nitrofurantoin may occur with its acute and chronic use. We aimed to investigate nitrofurantoin-induced fibrosis in lung, kidney, and liver tissue.

MATERIALS AND METHODS: We investigated the fibrosis-causing effect of nitrofurantoin in a rat pup experiment designed as 3 groups taking water, 60 mg/kg nitrofurantoin and 120 mg/kg nitrofurantoin for 60, 90, and 120 days. Histopathological evaluation was performed to detect fibrosis in lung, liver, and kidney tissues.

RESULTS: Fibrosis was detected in lung, liver, and kidney tissues and increased with increasing drug dose and duration. The degree of fibrosis ranged from none to abundant in lung and kidney tissues, whereas there were none to mild fibrosis in liver tissues. Surviving rat pups were asymptomatic, but fibrosis was continuously increasing.

CONCLUSION: Pediatric patients receiving nitrofurantoin should be regularly monitored for systemic side effects, particularly pulmonary, renal, and hepatic fibrosis.

Keywords: Nitrofurantoin, fibrosis, lung, liver, kidney

INTRODUCTION

Nitrofurantoin, an antibacterial, has been commonly used for the treatment and prophylaxis of uncomplicated urinary tract infections (UTIs) for more than half a century. Although pulmonary and hepatic fibrosis are more common potential serious adverse reactions, renal, neural, and hematological side effects may also be seen in adults.[1-3] These side effects have also been reported as less common than in adults in the pediatric population.[4]

We aimed to investigate the fibrosis-causing effect of nitrofurantoin on the lung, kidney, and liver tissues of 3-19 weeks aged rat pups for 4 months starting 21 days after birth following weaning.

MATERIALS AND METHODS

Study Design, Sample Collection and Ethical Consideration

Sixty-four Wistar Albino rat pups were enrolled in the study after obtaining approval from the Near East University Institutional Ethics

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All rats were kept without food and water limitation in 21±3 °C temperature and 50±5% humidity.

Study groups were designed as three groups of rats containing both female and male genders mixed randomly. The control group consisted of 18 rats that were only given drinking water (group 1), the second group consisted of 24 rats that were given 60 mg/kg nitrofurantoin dissolved with 1:5 diluted dimethylsulfoxide (DMSO) (group 2), and the third group consisted of 22 rats that were given 120 mg/kg nitrofurantoin dissolved in 1:5 DMSO (group 3). Nitrofurantoin and drinking water were all administered at the same time daily to all gavage groups. All rats were 3 weeks old at the beginning of the study period and were weighed weekly until the end of the study. Each group was divided into three as 1/3 received medications for 60 days, 1/3 for 90 days and 1/3 for 120 days. Each 1/3 of all groups was dissected at the end of 60., 90. and 120. days (Figure 1). Serum samples were obtained and stored at -80 °C on 60., 90. and 120. days to measure blood nitrofurantoin levels by ELISA. Experiments were carried out at the Laboratory of Animal Experiments, Faculty of Veterinary Medicine.

Histopathological Evaluation

The lung, liver, and kidney were surgically removed and fixed in 10% neutral-buffered formalin solution. All materials were processed at the Medical Pathology Laboratory of the Faculty of Medicine. Approximately 3 mm thick incisions were made parallel to the specimens. Each group was sampled from different areas. Samples were routinely embedded in paraffin. Paraffin blocks were serially sectioned with an average thickness of 3-4 micrometers. Sections were stained with hematoxylin and eosin and examined under light microscopy. Two histological slides (4 fields in each) were evaluated for each block. We used a 0-4 scoring system for the histopathological evaluation of fibrosis (0: None, 1: Rare, mild, 2: Moderate, 3: Frequent, 4: Abundant).

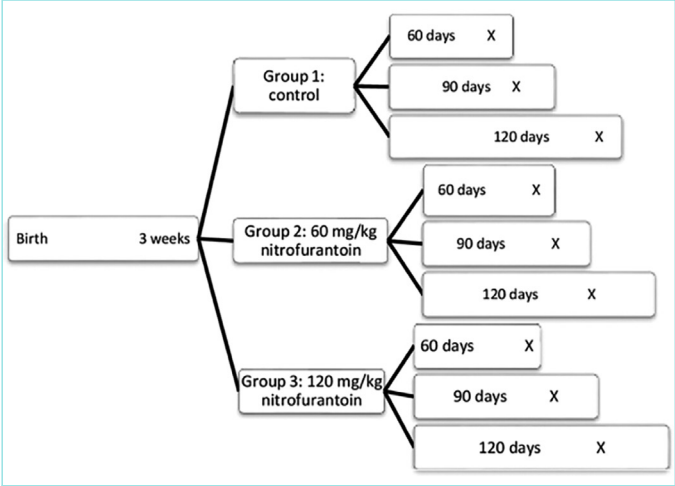

Figure 1. Study design.
X: Serum sample and lung, liver, kidney histopathology.

Statistical Analysis

The obtained data were tabulated in an Excel sheet, and statistical analysis was performed at the 95% confidence level. Descriptive statistics for the study variables were calculated (arithmetic mean and standard deviation). A two-way repeated measures ANOVA test was applied to assess the significance of differences. In cases of significance, Tukey's multiple comparison test was used to assess pairwise differences. GraphPad Prism (version 9.00 for Mac) was used for statistical calculations. The significance level was set as 0.05.

RESULTS

Comparison of the mean fibrosis scores of the lung, liver, and kidney tissue samples is presented on (Figure 2A-C). Histopathology of the lungs, liver, and kidney tissue is shown on (Figures 3-5).

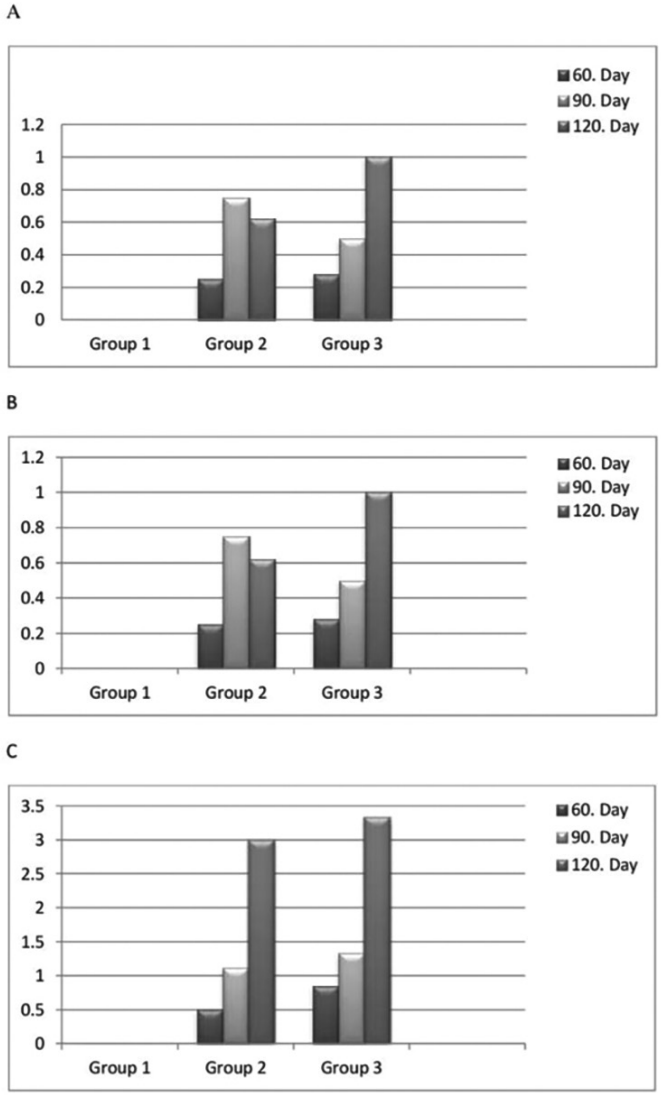

Figure 2. Relationship between nitrofurantoin exposure dose and duration with fibrosis scores in the (A) lung, (B) liver, and (C) kidney tissues.

Lung Tissues

Pathological examination of lung tissues from the first dissected group on day 60 of study revealed no fibrosis in group 1. There were mild fibrosis in 4/8 rats in group 2, although the result was not statistically significant when compared with group 1 (p=0.072). There were mild fibrosis in 7/7 rats in group 3, and this was higher than that in group 2 (p=0.05). Fibrosis in group 3 was much higher than group 1 with a statistically significant result (p<0.0001).

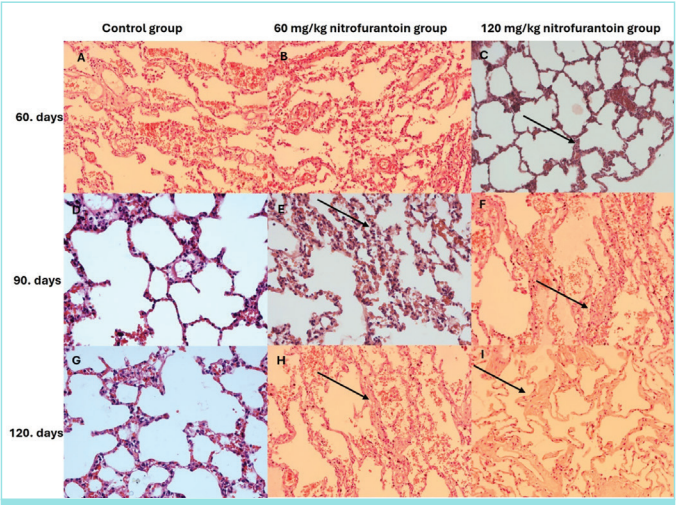

Figure 3. Histopathological lung tissue findings of control, 60 mg/kg and 120 mg/kg nitrofurantoin groups. Fibrosis areas are shown by arrowheads (100x hematoxylin eosin stain). (A) Normal lung tissue, (B) lung tissue without fibrosis, (C) mild fibrosis, (D) normal lung tissue, (E) mild fibrosis, (F) moderate fibrosis, (G) lung tissue without fibrosis, (H) moderate fibrosis, (I) abundant fibrosis in alveolar wall.

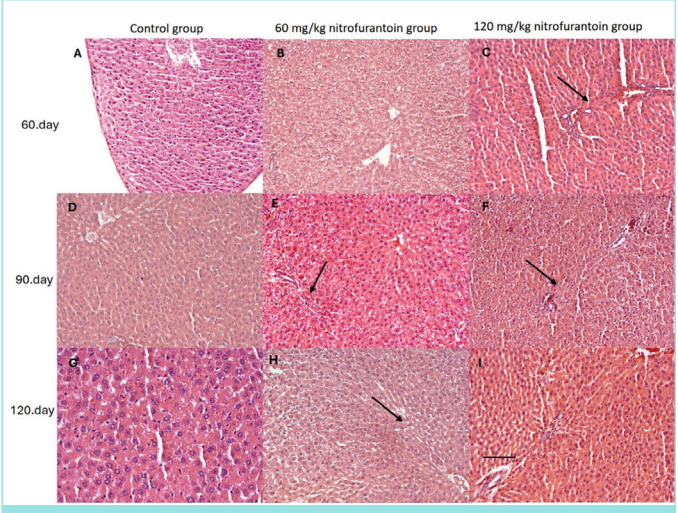

Figure 4. Histopathological liver tissue findings of control, 60 mg/kg and 120 mg/kg nitrofurantoin groups. Fibrosis areas are shown by arrowheads (100x hematoxylin eosin stain). (A) Liver without fibrosis, (B) normal liver parenchyma, (C) mild fibrosis in portal region, (D) normal liver parenchyma, (E) mild fibrosis, (F) moderate fibrosis, (G) normal liver parenchyma, (H) moderate fibrosis, (I) moderate fibrosis.

On day 90, there was no pulmonary fibrosis in group 1. In group 2, 7/8 rats had mild fibrosis, which was significantly higher than in group 1 (p=0.0003). In group 3, there were mild fibrosis in 3/6 rats and moderate fibrosis in 3/6 rats, which were statistically significantly higher than in group 1 (p<0.0001) and group 2 (p=0.014).

On day 120, no fibrosis was detected in group 1. In group 2, 5/8 rats had moderate fibrosis, and 3/8 rats had frequent fibrosis and results were was statistically significantly higher than in group 1 (p<0.0001). In group 3, there were frequent fibrosis in 4/6 rats and abundant fibrosis was observed in 2/6 rats, and the results were statistically significantly higher than in group 1 (p<0.0001) and group 2 (p<0.0001).

In group 2, fibrosis on day 90 (mean; 0.87) was higher than that on day 60 (mean=0.5) (p=0.11). Fibrosis detected on day 120 (mean; 2.3) was higher than that detected on day 90 (p<0.0001) and much higher than day 60 results (p<0.0001).

In group 3, fibrosis on day 90 (mean; 1.5) was higher than that on day 60 (mean; 1) (p=0.04). Fibrosis on day 120 (mean; 3.3) was higher than that on day 90 (p<0.0001) and much higher than that on day 60 (p<0.0001).

Liver Tissues

On day 60, no liver tissue fibrosis was observed in group 1. In group 2, there was mild fibrosis in 2/8 of the rats, and the result was not statistically significant compared with group 1 (p=0.579). There was mild fibrosis in 2/7 of the rats in group 3, but the results were not statistically significant compared with group 2 (p=0.99) and group 1 (p=0.49).

Results obtained on day 90 revealed that all 6 rats had no fibrosis in group 1. In group 2, 6/8 rats had mild fibrosis, which was more than in group 1 (p=0.001). Three/six rats of group 3 had mild fibrosis, and the results were not statistically significant compared with group 1 (p=0.08) and group 2 (p=0.59).

On day 120, there were no fibrosis in 6 rats in group 1 (p>0.99). Five/eight rats had mild fibrosis in group 2, and the results were statistically significant compared with group 1 (p=0.017). In group 3, 6/6 of the rats had mild fibrosis. Group 3 had higher fibrosis rates compared to group 1 (p=0.0001) and group 2 (p=0.22).

In group 2, hepatic fibrosis on day 90 (mean; 0.75) was higher than that on day 60 (mean; 0.25) (p=0.01). Fibrosis on day 120 (mean; 0.62) was more than that on day 60 (p=0.1) and less than that on day 90 (p=0.76).

Regarding group 3, fibrosis on day 90 (mean; 0.5) was higher than that on day 60 (mean; 0.28) (p=0.53). Fibrosis on day 120 (mean; 1) was higher than that on day 90 (p=0.05) and much higher than that on day 60 (p=0.002).

Kidney Tissues

On day 60, no kidney tissue fibrosis was observed in group 1. In group 2, 4/8 rats had mild fibrosis, which was higher than in group 1, but the result was not statistically significant (p=0.1). In group 3, 6/7 rats had mild fibrosis, which was higher than in group 1 (p=0.001) and group 2 (p=0.31).

On day 90, there were no signs of renal fibrosis in 6 rats in group 1. In group 2, 7/8 rats had mild fibrosis, and 1/8 rats had moderate fibrosis.

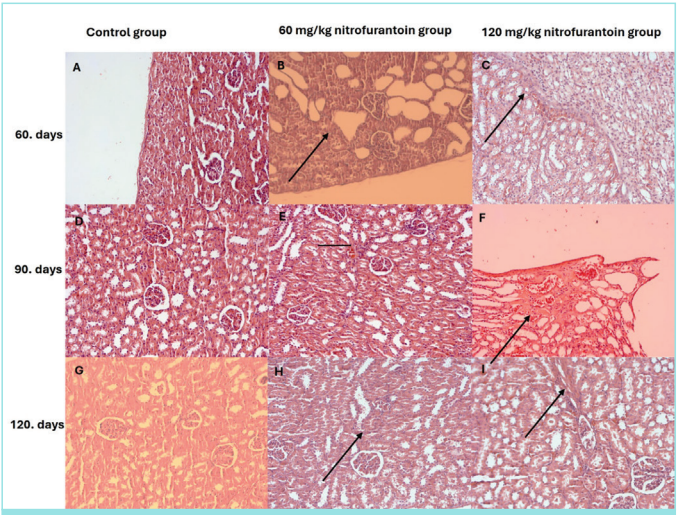

Figure 5. Histopathological renal tissue findings of control, 60 mg/kg and 120 mg/kg nitrofurantoin groups. Fibrosis areas are shown by arrowheads (100x hematoxylin eosin stain). (A) Kidney without fibrosis, (B) mild fibrosis, (C) mild fibrosis, (D) normal kidney parenchyma, (E) mild fibrosis, (F) moderate fibrosis, (G) Normal kidney parenchyma, (H) moderate fibrosis, (I) abundant fibrosis in parenchyma.

Results of group 2 were higher than those of group 1 ($p<0.0001$). In group 3, 4/6 rats had mild fibrosis and 2/6 rats had moderate fibrosis. This was higher than group 1 ($p<0.0001$) and group 2 ($p=0.76$).

Results of day 120 showed that 6 rats in group 1 had no fibrosis. In group 2, 4/8 rats had more frequent fibrosis, whereas 4/8 rats had more abundant fibrosis, and the results were higher than those in group 1 ($p<0.001$). In group 3, 4/6 rats had frequent fibrosis and 2/6 rats had abundant fibrosis. This was higher than in group 1 ($p<0.0001$) and group 2 ($p=0.0014$).

In group 2, fibrosis on day 90 (mean; 1,125) was higher than that on day 60 (mean; 0.5) ($p=0.007$). Fibrosis on day 120 (mean; 2.5) was more than that on days 60 ($p<0.0001$) and day 90 ($p<0.0001$).

In group 3, fibrosis on day 90 (mean; 1.33) was higher than that on day 60 (mean; 0.85) ($p=0.08$). Fibrosis on day 120 (mean; 3.33) was higher than that on days 60 ($p<0.0001$) and day 90 ($p<0.0001$).

There were three rat deaths (4.6%) in group 3, one on day 12, one on day 21, and one on day 26 of nitrofurantoin intake.

DISCUSSION

Nitrofurantoin, an old antibacterial, has regained interest in recent decades due to its efficient treatment results and almost no resistance rates, leading to its increased utilization for treating lower UTIs and prophylaxis of recurrent UTIs.[5]

Nitrofurantoin can lead to adverse reactions both in acute and chronic course. Adverse reactions reported in pediatric patients are mild gastrointestinal complaints beginning in the first week of nitrofurantoin treatment, including abdominal discomfort, nausea, and vomiting (4.4% risk per year). Pulmonary side effects detected in 0.7% of children were mild acute pulmonary reactions or chronic interstitial pneumonitis that subsided after nitrofurantoin discontinuation. Hepatic side effects in 12 cases, 3 of whom died, were the most lethal side effects and occurred after 4 months of therapy, suggesting a dose-dependent mechanism with equal incidence in both genders.[4,6] One was a 16-year-old boy who developed and recovered from cholestatic hepatitis detected on biopsy 1 week after consuming the milk of a cow treated with parenteral nitrofurantoin.[7]

A 16-year-old girl with a history of thoracic laminectomy, paraplegia, and recurrent UTI died of fatal cholestatic hepatitis and acute respiratory distress syndrome 11 years after intermittent nitrofurantoin use.[8]

Pulmonary fibrosis was recently reported in a 6-year-old female patient who was on nitrofurantoin prophylaxis for 2 years. Fibrosis was detected by chest computed tomography (CT) and lung biopsy. The use of nitrofurantoin was stopped, and 35 mg/kg methylprednisolone for 3 days was continued with oral prednisolone for 2 months. Total resolution of the fibrosis was detected by CT and lung function tests after 17 months.[9]

A 7-year-old girl was administered nitrofurantoin for recurrent urinary incontinence for 30 months and developed respiratory failure and liver dysfunction. She was thought to have asthma and had been treated for asthma for a long time. Restrictive lung function test results, desquamative interstitial pneumonitis on lung biopsy, and severe hepatitis with portal fibrosis on liver biopsy were detected. After nitrofurantoin withdrawal and the initiation of 2 mg/kg prednisolone, liver test results normalized in 10 days. Prednisolone was tapered every 2 weeks. Chest CT scan and lung function were normal after 3 months.[10]

Renal fibrosis due to nitrofurantoin is not reported in children. However, adult cases of acute granulomatous and acute interstitial nephritis have been reported. A 76-year-old man who was administered nitrofurantoin for 2 weeks developed acute granulomatous interstitial nephritis. Renal function improved 6 weeks after withdrawal of nitrofurantoin.[11] Another adult patient developed acute renal failure due to nitrofurantoin-associated acute granulomatous interstitial nephritis. Renal function recovered after nitrofurantoin administration without the need for corticosteroids.[12] Acute interstitial nephritis related to nitrofurantoin was reported in a 57-year-old female patient after receiving nitrofurantoin for 5 days for UTI. She developed fever, eosinophilia, eosinophiluria, and hepatic and renal dysfunction. Fever subsided 1 day after nitrofurantoin withdrawal. Elevated urea, creatinine, and liver enzyme levels gradually normalized in 5 weeks. An allergic or immune mechanism was suspected.[13] A 68-year-old man who was given nitrofurantoin for prostatitis for 14 days was hospitalized with fever, hypertension, rash, leucocytosis, eosinophilia, microscopic hematuria, proteinuria, sterile pyuria, and increased blood urea nitrogen and creatinine. Three days after the nitrofurantoin withdrawal fever resolved, the rash faded. After 6 weeks, he was well, and all findings were normal. Acute interstitial nephritis is the most likely diagnosis.[14] We detected renal fibrosis in several rats, but we did not observe granuloma formation in our study. It may be useful to question previous nitrofurantoin use in chronic renal failure without an obvious cause.

Bioactivation and oxidative stress caused by nitrofurantoin play roles in hepatic and pulmonary adverse reactions shown by animal experiments. Antinuclear antibody and anti-smooth muscle antibody positivities in hepatic and lung tissue also suggest immune-mediated

reactions. The dramatic disappearance of findings associated with drug cessation and the onset of side effects associated with drug rechallenge also support an immunological mechanism. However, long-term adverse reactions suggest a dose-dependent phenomenon. Multiple mechanisms seem to be responsible for the adverse effects of nitrofurantoin.[3,15]

The majority of patients in the literature recovered after supportive treatment and cessation of nitrofurantoin, while some required corticostreoid administration, liver transplantation and some died.[3,6] Pulmonary, hepatic, and renal fibrosis are serious problems, especially in the chronic course of nitrofurantoin used for prophylaxis of UTIs.[1-3,13,14] A recent adult study reported not only hepatocellular injury due to short term (<7 days) nitrofurantoin use, but also hepatic fibrosis, nodularity and cirrhosis in long term use (>1 year) of the medication. Autoantibody production resembling autoimmune hepatitis, steroid requirement, liver transplantation, and mortality were also observed recommending periodical ALT monitorisation for those receiving nitrofurantoin.[16]

The relationship between renal and pulmonary fibrosis due to nitrofurantoin was not confirmed with tissue diagnosis before the current study. We obtained significant fibrosis despite the protective effect of DMSO, which is found to prevent drug-induced hepatic fibrosis in rats by blocking inflammation.[17] Fibrosis in lung, liver, and kidney tissues increased parallel to increased dose and prolonged duration of nitrofurantoin use. Pulmonary and renal fibrosis were more severe than hepatic fibrosis in the current study. Three rat deaths possibly due to toxicity were also observed in group 3. There were no symptoms of the surviving rat pups, but significant fibrosis was present. There were no deaths in group 2 however fibrosis was again continuing to increase in tissues. This may also be similar in children too. We do not detect fibrosis in asymptomatic patients because tissue biopsy is not routine for children receiving nitrofurantoin.

Study Limitations

Although we had planned, we could not measure serum nitrofurantoin concentrations to correlate with pathological severity because the ELISA kits could not be obtained at that time due to COVID-19 restrictions and lockdown of Cyprus island. On the other hand, serum nitrofurantoin levels were almost undetectable, with a maximum concentration of 1 mg/L, except in patients with renal failure. Therapeutic drug levels were observed mainly in the lower urinary tract.[5] Therefore, histopathological evaluation is of major importance for the detection of fibrosis and may not always be correlated with serum nitrofurantoin levels. Lack of gender comparison is another lack of the study; however, we did not expect a significant difference related to genders, as not reported in the literature. Fibrosis is more common in females, probably because of higher UTI rates in females.[13,18]

CONCLUSION

As a result, monitoring of pulmonary, hepatic, and renal functions is necessary in patients receiving both short-term and long-term nitrofurantoin prophylaxis or treatment to prevent severe adverse outcomes as early as possible. Nitrofurantoin use should be kept in mind as a potential cause of several systemic complications to be able to take advantage of symptom resolution by early withdrawal of the medication.

MAIN POINTS

- Nitrofurantoin is commonly preferred in recent years for the treatment and prophylaxis of UTIs as an efficient treatment option without resistance.
- Increased dose and duration of nitrofurantoin increased fibrosis in the lung, liver, and kidney tissue samples of rat pups.
- Although rarely observed, systemic side effects should not be missed in patients receiving nitrofurantoin.

ETHICS

Ethics Committee Approval: Sixty-four Wistar Albino rat pups were enrolled in the study after obtaining approval from the Near East University Institutional Ethics Committee of Animal Experiments (approval number: 2017/13-22, date: 03.05.2017).

Informed Consent: Patient approval has not been obtained as it is performed on animals.

Authorship Contributions

Surgical and Medical Practices: B.B., A.A., H.Ö., S.K., Concept: İ.B., A.S., S.K., Design: İ.B., A.S., N.B., S.K., Data Collection and/or Processing: İ.B., B.B., Analysis and/or Interpretation: İ.B., B.B., N.B., S.K., Literature Search: İ.B., Writing: İ.B.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Madani Y, Mann B. Nitrofurantoin-induced lung disease and prophylaxis of urinary tract infections. Prim Care Respir J. 2012; 21(3): 337-41.
2. Miskoff JA, Chaudhri M. Nitrofurantoin Toxicity: A Near Case of Mistaken Identity. Cureus. 2018; 10(9): e3315.
3. Kiang TK, Ford JA, Yoshida EM, Partovi N. Nitrofurantoin-associated lung and liver toxicity leading to liver transplantation in a middle-aged patient. Can J Hosp Pharm. 2011; 64(4): 262-70.
4. Karpman E, Kurzrock EA. Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. J Urol. 2004; 172(2): 448-53.
5. Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother. 2015; 70(9): 2456-64.
6. Uhari M, Nuutinen M, Turtinen J. Adverse reactions in children during long-term antimicrobial therapy. Pediatr Infect Dis J. 1996; 15(5): 404-8.
7. Berry WR, Warren GH, Reichen J. Nitrofurantoin-induced cholestatic hepatitis from cow's milk in a teenaged boy. West J Med. 1984; 140(2): 278-80.
8. Mulberg AE, Bell LM. Fatal cholestatic hepatitis and multisystem failure associated with nitrofurantoin. J Pediatr Gastroenterol Nutr. 1993; 17(3): 307-9.
9. Mikkelsen LF, Rubak S. Reversible lung fibrosis in a 6-year-old girl after long term nitrofurantoin treatment. BMC Pulm Med. 2020; 20(1): 313.
10. Hage P, El Hajje MJ. Nitrofurantoin-induced desquamative interstitial pneumonitis in a 7-year-old child. Pediatr Infect Dis J. 2011; 30(4): 363.

11. Korzets Z, Elis A, Bernheim J, Bernheim J. Acute granulomatous interstitial nephritis due to nitrofurantoin. Nephrol Dial Transplant. 1994; 9(6): 713-5.

12. Namagondlu G, Low SE, Seneviratne R, Banerjee A. Acute renal failure from nitrofurantoin-induced acute granulomatous interstitial nephritis. QJM. 2010; 103(1): 49-52.

13. Beigel R, Perets R, Mouallem M. Acute kidney injury, hepatitis, and CPK elevation associated with nitrofurantoin therapy. Am J Med Sci. 2009; 337(2): 132-3.

14. Kahn SR. Acute interstitial nephritis associated with nitrofurantoin. Lancet. 1996; 348(9035): 1177-8.

15. Suntres ZE, Shek PN. Nitrofurantoin-induced pulmonary toxicity. In vivo evidence for oxidative stress-mediated mechanisms. Biochem Pharmacol. 1992; 43(5): 1127-35.

16. Chalasani N, Li YJ, Dellinger A, Navarro V, Bonkovsky H, Fontana RJ, et al. Clinical features, outcomes, and HLA risk factors associated with nitrofurantoin-induced liver injury. J Hepatol. 2023; 78(2): 293-300.

17. Nakamuta M, Ohta S, Tada S, Tsuruta S, Sugimoto R, Kotoh K, et al. Dimethyl sulfoxide inhibits dimethylnitrosamine-induced hepatic fibrosis in rats. Int J Mol Med. 2001; 8(5): 553-60.

18. Mir E, Malik JA, Lone SA, Mohi-Ud-Din R, Khalil M. Spontaneous resolution of nitrofurantoin-induced chronic pulmonary toxicity presenting with respiratory failure. Adv Respir Med. 2017; 85(6): 333-8.