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5-Fluorouracil exacerbates cefepime-induced convulsions in pentylenetetrazol-kindled mice

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ABSTRACT

Objective: The antibiotics cefepime and meropenem are recommended for the treatment of neutropenia. However, cefepime has been found to be associated with both peripheral and central adverse events such as renal impairment and seizures, respectively. Previous studies showed that cefepime exacerbated convulsions in corneal kindled mouse models of epilepsy. However, its involvement in chemotherapy-induced side effects is unknown.

Methods: In this study, we examined the convulsive potential of cefepime (500 mg/kg) and meropenem (500 mg/kg) in pentylenetetrazol (PTZ)-kindled mice using an electroconvulsive shock test with low-intensity stimulus currents. Then, the effects of 5-fluorouracil (5-FU, 200 and 400 mg/kg, i.p.) treatment, a model of chemotherapy-induced side effects, were investigated in the PTZ-kindled mouse model.

Results: In fully PTZ-kindled mice, intravenous administration of cefepime (500 mg/kg) or meropenem (500 mg/kg) did not elicit any convulsions in the electroconvulsive shock test with low-intensity stimulus currents. In the PTZ-kindled mice treated with 5-FU (200 mg/kg), intravenous administration of cefepime (500 mg/kg) exacerbated the convulsions that occurred within 1 min in the electroconvulsive shock test, and the mice subsequently developed convulsive status epilepticus. However, intravenous administration of meropenem (500 mg/kg) did not produce such effects.

Conclusion: These findings suggest that the combination of 5-FU and cefepime exacerbates early-onset convulsive seizures and elicits delayed-onset convulsive status epilepticus. Additionally, 5-FU treatment increases the risk of induction of neurotoxic side effects by cefepime.

1. Introduction

Chemotherapy-induced neutropenia is a common complication in cancer treatment. Particularly, patients with febrile neutropenia should initially be administered empiric antibiotics intravenously in a hospital setting. Clinical practice guidelines recommend initial antibiotic monotherapy including a fourth-generation cephalosporin antibiotic (i.e., cefepime), a carbapenem (i.e., meropenem) or piperacillin-tazobactam (Tamura, 2005). A systematic review and meta-analysis showed that cefepime use is associated with increased mortality risk because of neurotoxic side effects, including seizures, non-convulsive status epilepticus and coma (Yahav et al., 2007; Grill and Maganti, 2008). Severe renal dysfunction or a previous diagnosis of epilepsy are reported to be significant risk factors for neurotoxic side effects of cefepime (Anzellotti et al., 2012; Lamoth et al., 2010; Payne et al., 2017; Tanaka et al., 2013). However, the effects of chemotherapy on the neurotoxic side effects of cefepime remain unclear.

Animal models of seizure and epilepsy are widely used in the identification of new antiepileptic drugs and the examination of neurotoxic side effect profiles of drugs (Klitgaard et al., 1998). Kindling is a phenomenon in which repeated application of an initially subconvulsive electrical or chemical stimulus such as pentylenetetrazol (PTZ) leads to the development of generalized seizures (Löscher, 2011). Previous studies have shown that intravenous administration of cefepime exacerbated convulsions induced by an electroconvulsive shock test with low-intensity stimulus currents in corneal electroshock-kindled mice. Additionally, the convulsive potential of cefepime is significantly higher than that of meropenem (Tanaka et al., 2014). In this study, to clarify the involvement of chemotherapy-induced side effects in cefepime-associated seizures, we examined the effects of 5-

Abbreviations: PTZ, pentylenetetrazol; 5-FU, 5-fluorouracil; $GABA_A$, gamma-aminobutyric acid A; NMDA, *N*-methyl-*D*-aspartate; TNF-α, tumor necrosis factor-alpha

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fluorouracil (5-FU) in PTZ-kindled mice using an electroconvulsive shock test. Moreover, we compared the convulsive potential of cefepime and meropenem in a model of chemotherapy-induced side effects.

2. Materials and methods

2.1. Animals

All animal care and experimental procedures were performed in accordance with the Guiding Principles for the Care and Use of Laboratory Animals adopted by the Japanese Pharmacological Society and were approved by the Ethics Committee for Animal Experimentation of Shujitsu University (approval code 025-002).

Male ICR mice were purchased from Shimizu Laboratory Supplies Co., Ltd. (Kyoto, Japan), and 150 mice were used in total. Animals were maintained in a temperature-controlled room (22 ± 2 °C) under a 12/12 h light/dark cycle with lights on at 08:00 h. Mice were housed from 4 weeks of age in standard-sized plastic cages (32 × 18 × 24 cm) with paper bedding (4–5 mice per cage). The mice were allowed free access to food and water except during experiments.

2.2. Drugs

Cefepime (Maxipime; Bristol-Myers Squibb, Tokyo, Japan) and meropenem (Meropen; Dainippon Sumitomo Pharma Co., Osaka, Japan) were dissolved in saline, and both antibiotics were injected intravenously into the lateral tail vein. The doses of cefepime and meropenem (both 500 mg/kg) were chosen based on those used by Tanaka et al. (Tanaka et al., 2014). The control group received only saline. PTZ (Sigma, St. Louis, MO, USA) and 5-FU (Kyowa Co., Tokyo, Japan) were dissolved in saline and administered intraperitoneally. All drugs were administered in a volume of 0.1 mL/10 g body weight.

2.3. PTZ kindling

Mice at 5 weeks of age were used for the PTZ kindling. The procedure for kindling seizures was similar to that described previously (Suemaru et al., 2018). PTZ kindling was induced by daily administration of PTZ (40 mg/kg, i.p.), 5 days per week for 13 days. The animals were observed for 20 min after injection. The seizure intensity score was determined using the Racine scale (stages 0–5) as follows: 0, no response; 1, ear and facial twitching; 2, myoclonic body jerks; 3, forelimb clonus, rearing; 4, clonic seizures, falling to one side; 5, generalized clonic seizures, falling on the back (Racine, 1972). "Fully kindled" was defined as the occurrence of three consecutive stage 4 or 5 seizures.

2.4. Proconvulsive test in PTZ-kindled mice

Mice fully kindled by PTZ were used for proconvulsive tests (Fig. 1). Proconvulsive activity was evaluated using an electroconvulsive shock test with low-intensity stimulus currents according to Tanaka et al. (2014). Saline drops were administered to the eyes before stimulation. The mice corneas were stimulated using a stimulator (SEN-3301 and SS-403 J; Nihon Kohden, Tokyo, Japan). Twenty-four hours before the test, corneal stimulations of 4.0 mA (60 Hz) for 3 s were used to confirm that kindled mice did not exceed stage 1 according to the Racine scale (Racine, 1972). On the day of the proconvulsive test, the kindled mice were injected intravenously with cefepime, meropenem or saline. Ten minutes after the injections, mice underwent corneal stimulation of 4.0 mA (60 Hz) for 3 s.

The first convulsion phase was observed for 1 min after stimulation, and the seizure intensity was scored using the Racine scale (stages 1–5). The second convulsion phase (convulsive status epilepticus) was observed for 30 min. Status epilepticus was defined as continuous seizures lasting more than 5 min. The seizure intensity of the second phase was scored using a modified Racine scale (stages 1–5) (Racine, 1972) as follows: 0, no response; 1, ear and facial twitching; 2, myoclonic body jerks; 3, clonus seizure; 4, tonic-clonic seizure; 5, generalized clonic seizure.

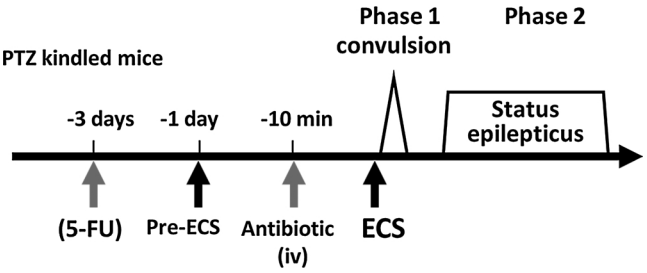

Fig. 1. Outline of treatment and the electroconvulsive shock (ECS) test schedule. Fully PTZ-kindled mice were administered 5-FU (200 mg/kg) intraperitoneally 3 days before a proconvulsive ECS test. In the 24 h before the test, PTZ-kindled mice received corneal stimulation with low-intensity stimulus currents (4.0 mA for 3 s), and mice that did not exceed stage 1 of the seizure intensity scale were used for the test. On the day of the proconvulsive test, the kindled mice were intravenously injected with cefepime (500 mg/kg), meropenem (500 mg/kg), or saline. Ten minutes after the injections, mice received corneal stimulation (4.0 mA for 3 s). Seizures began within 1 min (first convulsion phase), and the mice subsequently developed convulsive status epilepticus (second convulsion phase), which lasted at least 30 min.

2.5. 5-FU treatment

Mice treated with 5-FU were used as a model of chemotherapy-induced side effects. Fully PTZ-kindled mice or naive mice were administered 5-FU 3 days before the proconvulsive test. Naive mice were administered 5-FU at doses of 200 and 400 mg/kg (i.p.) to evaluate the dose-response effect of 5-FU. The dosages of 5-FU were chosen based on those used by Kojouharov et al. (2014). Fully PTZ-kindled mice were administered 5-FU (200 mg/kg, i.p.) 3 days before the proconvulsive test.

2.6. Statistical analysis

Data are presented as box-and-whisker plots depicting the median, interquartile interval and minimum and maximum values. Progression of the seizure intensity score during PTZ-induced convulsions is expressed as the mean ± standard error of the mean (SEM). Statistical analysis was performed using Statcel for Excel version 4 (OMS Publishing Inc. Japan) for Windows. Statistical significance tests of seizure scores were performed using the Kruskal-Wallis test followed by Steel's test, which is a multiple-comparison rank sum test for comparing treatments with a control (Steel, 1959).

3. Results

3.1. Proconvulsive test in PTZ-kindled mice

Repeated administration of a subconvulsive dose of PTZ (40 mg/kg, i.p., n = 10) induced kindling in mice as revealed by the progressive increase in seizure scores (Fig. 2). The effects of cefepime (500 mg/kg, i.v.) and meropenem (500 mg/kg, i.v.) in the proconvulsive test using fully PTZ-kindled mice are shown in Fig. 3. Corneal stimulation with low-intensity stimulus currents (4.0 mA) produced slight seizures with scores lower than those of stage 1 in the first convulsion phase of mice intravenously injected with cefepime (n = 24), meropenem (n = 11), or saline (n = 22). The median scores (interquartile range) were 0.25 (0.63), 0.25 (0.5) and 0.5 (1.0), respectively, and no significant difference was observed among the three groups. However, convulsive status epilepticus (second convulsion phase) was not evoked in the

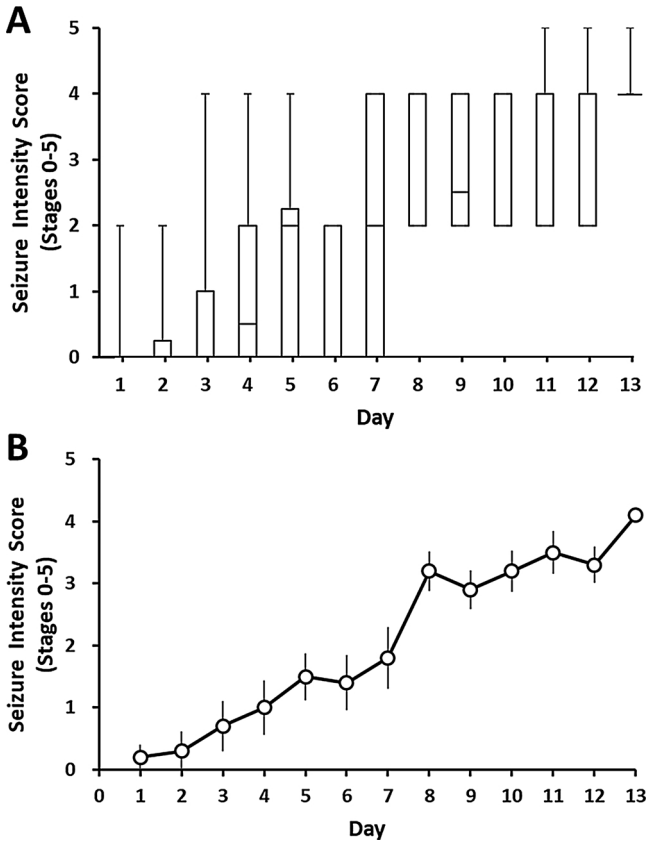

Fig. 2. Progression of seizure stages during PTZ-induced convulsions in mice. PTZ kindling was induced by daily administration of PTZ (40 mg/kg, i.p., n = 10). The seizure intensity score was determined using the Racine scale (stages 0–5). A; Seizure intensity score data are presented as box-and-whisker plots depicting the median, interquartile interval and minimum and maximum values. B; Each value represents the mean seizure stage ± SEM.

three groups.

3.2. Proconvulsive test in 5-FU-treated mice

Naive mice were administered 5-FU (200 and 400 mg/kg) or saline intraperitoneally 3 days before the proconvulsive test. Corneal stimulation with low-intensity stimulus currents elicited the first convulsion phase in a 5-FU dose-dependent manner, and a significant difference ($P < 0.01$) was observed in the score of the first convulsion phase between mice treated with saline [median (interquartile range), 0 (0.0), n = 10] and those treated with 400 mg/kg 5-FU [median (interquartile range), 1.3 (1.8), n = 10]. However, no significant difference was observed in the score between mice treated with saline and those treated with 200 mg/kg 5-FU [median (interquartile range), 0.3 (0.5), n = 10]. The second convulsion phase (convulsive status epilepticus) was not evoked in the saline or 5-FU-treated groups (Fig. 4).

3.3. Proconvulsive test in PTZ-kindled mice treated with 5-FU

The effects of cefepime and meropenem in the proconvulsive test using fully PTZ-kindled mice treated with 5-FU (200 mg/kg, i.p.) are shown in Fig. 5. Intravenous administration of cefepime (500 mg/kg) significantly ($P < 0.01$) exacerbated the first convulsion phase compared with the saline-administered control group. The median seizure scores (interquartile range) in the two groups that received saline (n = 14) and cefepime (500 mg/kg, n = 19) were 0.5 (0.7) and 2.0 (3.0), respectively. The short-term convulsions in the cefepime group were followed by convulsive status epilepticus (second convulsion phase). Some mice exhibited continuous convulsions lasting longer than 30 min. A significant difference ($P < 0.05$) was observed in the scores of the second convulsion phase between the saline [median (interquartile range), 0 (0), n = 14] and cefepime groups [median (interquartile range), 0 (3.0), n = 19]. Intravenous administration of meropenem (500 mg/kg) slightly increased the score of the first convulsion phase compared with that of the saline group [median (interquartile range), 0.5 (1.4), n = 10], but the difference was not significant. Moreover, intravenous administration of meropenem or saline did not evoke convulsive status epilepticus.

4. Discussion

Previously, we reported that intravenous injection of cefepime (250 and 500 mg/kg) dose-dependently exacerbated convulsions that occur within 1 min (first convulsion phase) following electroconvulsive shock with low-intensity stimulus currents in corneal kindled mice. However, meropenem (250 and 500 mg/kg) had no such effect (Tanaka et al., 2014). In this study, we examined the effects of cefepime and meropenem on PTZ-kindled mice using a proconvulsive test. Intravenous administration of cefepime (500 mg/kg) or meropenem (500 mg/kg) did not exacerbate the first convulsion phase. Kindling is a phenomenon in which repeated application of an initially subconvulsive electrical or chemical stimulus leads to the development of generalized seizures (Löscher, 2011). It is considered an animal model of complex partial seizures with secondary generalization (Löscher, 2011). Compared with acute seizure tests using naive mice, the corneal electroshock and PTZ-kindled mouse models are highly sensitive, and these are efficient screening methods for assessing potential antiepileptic drugs. Moreover, the corneal kindled mouse model has been found to be more sensitive than the PTZ-kindled mouse model. For example, the protective ED50 value of levetiracetam in the corneal kindled mouse model is markedly lower than that of the PTZ-kindled mouse model (Klitgaard et al., 1998). Therefore, the different results observed regarding the convulsive potential of cefepime in kindling models may be related to differences in seizure susceptibility.

In this study, we examined the effect of 5-FU treatment (200 and 400 mg/kg) as a model of chemotherapy-induced side effects. Naive mice treated with 5-FU at a dose of 200 mg/kg did not exhibit a significant increase in the score for the first convulsion phase in proconvulsive tests using low-intensity stimulus currents. However, treatment with 400 mg/kg of 5-FU significantly exacerbated the first convulsion phase that occurred within 1 min. It is well known that 5-FU

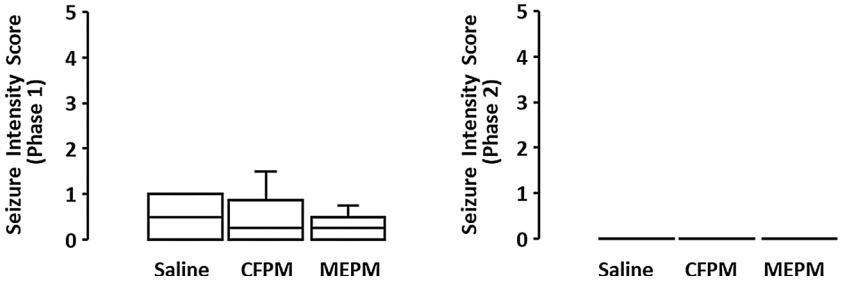

Fig. 3. Effects of cefepime and meropenem on electroconvulsive shock-induced convulsions in fully PTZ-kindled mice. Mice were injected intravenously with cefepime (500 mg/kg), meropenem (500 mg/kg) or saline. Seizure intensity score data are presented as box-and-whisker plots depicting the median, interquartile interval and minimum and maximum values. Saline (n = 22); CFPM, cefepime (n = 24); MEPM, meropenem (n = 11).

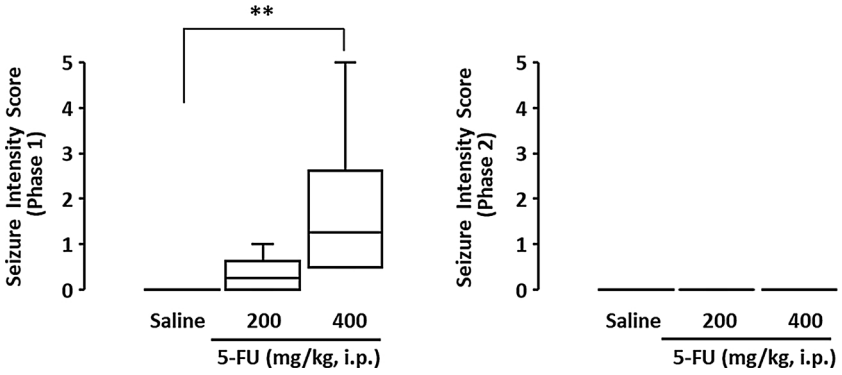

Fig. 4. Effect of 5-FU on electroconvulsive shock-induced convulsions in mice. Naive mice were injected with 5-FU (200 and 400 mg/kg, i.p.) or saline 3 days before the test (n = 10 for each group). Seizure intensity score data are presented as box-and-whisker plots depicting the median, interquartile interval and minimum and maximum values. ** $P < 0.01$, versus saline (Steel's test).

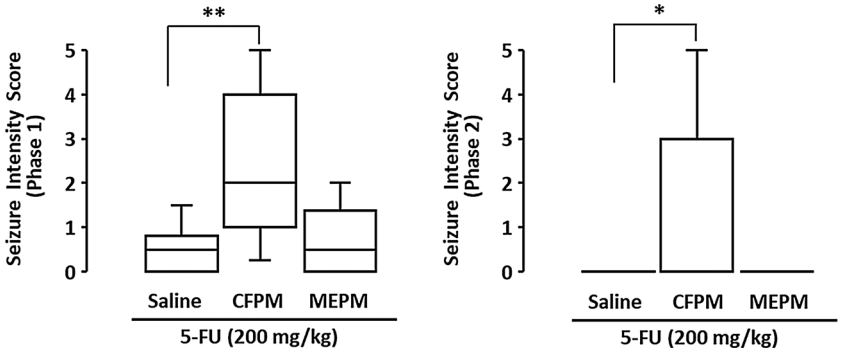

Fig. 5. Effect of cefepime and meropenem on electroconvulsive shock-induced convulsions in fully PTZ-kindled mice treated with 5-FU. Mice were administered 5-FU (200 mg/kg, i.p.) 3 days before the proconvulsive test. On the day of the test, mice were injected intravenously with cefepime (500 mg/kg), meropenem (500 mg/kg), or saline. Seizure intensity score data are presented as box-and-whisker plots depicting the median, interquartile interval and minimum and maximum values. Saline (n = 14); CFPM, cefepime (n = 19); MEPM, meropenem (n = 10). * $P < 0.05$ and ** $P < 0.01$, versus saline (Steel's test).

not only induces leukopenia but also induces intestinal mucositis (Huang et al., 2009). Previous studies have shown that peripheral inflammation increases seizure susceptibility via the induction of neuroinflammation including activation of microglia and production of proinflammatory cytokines in the brain (Ho et al., 2015; Riazi et al., 2008). Taken together, our findings suggested that 5-FU-induced side effects, including intestinal mucositis, may be responsible for the proconvulsive effect of cefepime in PTZ-kindled mice.

Cephalosporins, particularly cefepime, exert neurotoxic side effects including tardive seizures, myoclonus, seizure, non-convulsive status epilepticus and status epilepticus (Payne et al., 2017). Clinical studies have provided evidence that patients with renal failure or a previous diagnosis of epilepsy are significant risk factors for the toxic effects of cephalosporins. Previous experimental studies have shown that intracerebroventricular administration of cephalosporins including cefepime induces convulsions such as rolling, wild running and clonic type convulsions, which are typically observed 2–3 min after injection in mice. In this study, to investigate the effects of cefepime and meropenem in a chemotherapy-induced side effect model, PTZ-kindled mice were treated with 5-FU (200 mg/kg), which did not affect the proconvulsive test using low-intensity stimulus currents. The results of this study showed that intravenous administration of cefepime (500 mg/kg) exacerbated the convulsions that occurred within 1 min (first convulsion phase), and mice subsequently developed convulsive status epilepticus (second convulsion phase). However, intravenous administration of meropenem (500 mg/kg) did not elicit the second convulsion phase. Both cefepime and meropenem can cross the blood–brain barrier (Chang et al., 2001; Dupuis et al., 2000). Together, these findings suggest that the combination of cefepime and 5-FU elicits delayed-onset convulsive status epilepticus following the first convulsion phase in PTZ-kindled mice. However, electroencephalographic studies are needed to clarify the latency to seizure onset and status epilepticus duration (Phelan et al., 2015).

in vitro studies in mouse brain synaptosomes revealed that cephalosporins, including cefepime, have an affinity for gamma-aminobutyric acid A ($GABA_A$) receptors but not for *N*-methyl-*D*-aspartate (NMDA) receptors (Sugimoto et al., 2003). These data indicate that the ability to block $GABA_A$ receptors is involved in the generation of cephalosporin-induced convulsions. However, a recent study using the whole-cell patch-clamp method in rat cortex slices reported that cefepime and ceftriaxone are weak $GABA_A$ receptor blockers (Amakhin et al., 2018). Therefore, additional mechanisms are thought to be involved in cefepime-induced neurotoxic side effects.

As a possible mechanism, involvement of tumor necrosis factor-alpha (TNF-α) was considered. A single administration of ceftazidime, a third-generation cephalosporin, increased circulating concentrations of TNF-α in rats (Alkharfy et al., 2000). Neuroinflammation is widely recognized to play an important role in the development of epilepsy, and activation of microglia, astrogliosis, expression of proinflammatory cytokines, blood–brain barrier leakage and peripheral immune cell infiltration contribute to neuroinflammation (Hiragi et al., 2018; Vinet et al., 2016). In this study, we examined the effects of 5-FU using a PTZ-kindled mouse model. Previous experimental studies have shown that minocycline, an inhibitor of microglial activation, has a weak anti-epileptogenic effect in the PTZ-kindled mouse model and prevents an increase in TNF-α receptor mRNA in both the hippocampus and piriform cortex (Ahmadirad et al., 2014). Central antagonism of TNF-α using a monoclonal antibody or inhibition of microglial activation by intraventricular injection of minocycline prevented the increase in seizure susceptibility induced by peripheral inflammation (Riazi et al., 2008). Moreover, in a mouse model of intestinal mucositis induced by 5-FU, minocycline attenuated mucositis by blocking the expression of proinflammatory cytokines including TNF-α (Huang et al., 2009). Thus, the increase in TNF-α induced by cefepime and the increase in peripheral inflammation induced by 5-FU may be related in the mechanisms of cefepime-induced convulsion and convulsive status epilepticus. However, further studies will be needed to clarify the role of cytokines.

5. Conclusion

Our findings revealed that cefepime elicits delayed-onset convulsive status epilepticus following the first convulsion phase in a proconvulsive test in fully PTZ-kindled mice treated with 5-FU and that chemotherapy-induced side effects increase the risk of the induction of

neurotoxic side effects by cefepime.

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Declaration of Competing Interest

The authors claim no conflict of interest.

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