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EXPERIMENTAL STUDY / DENEYSEL ÇALIŞMA


Dr. Semiha KURT

The Importance of Hypothermia in the Effects of Paracetamol on the Electrical Activity of the Brain in Pentylenetetrazole Induced Experimental Status Epilepticus in Rats

Pentilentetrazol İle Oluşturulan Deneysel Status Epilepitikus Modelinde Parasetamolün, Beyin Elektriksel Aktivitesine Olan Ektisinde Hipoterminin Yeri

Semiha KURT,[1] Hatice AYGÜN,[2] Şeyma ÖZSOY,[2] Betül ÇEVİK,[1] Dürdane AKSOY,[1] Orhan SÜMBÜL[1]

[1]Department of Neurology, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat, Turkey
[2]Department of Physiology, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat, Turkey

Summary

Objectives: Paracetamol is a commonly used analgesic and antipyretic agent. In studies investigating the effects of paracetamol on seizure activity, to our knowledge, the hypothermic effect has not been evaluated in studies investigating the hypothermic effects of paracetamol, its activity on seizures has not been evaluated. In this study, we aimed to evaluate the effects of paracetamol on seizure and intracranial temperature simultaneously in rats.

Methods: Status epilepticus (SE) was induced with pentylenetetrazole (PTZ). In the control group (Group I), SE was induced with PTZ and paracetamol was not administered. Paracetamol was administered in Group II and after 30 minutes, PTZ was injected. Paracetamol was injected immediately after PTZ injection in Group III. Electrocorticography recording was taken for 120 min in all groups and the intracranial temperature was measured.

Results: In groups given paracetamol, the spike frequency was significantly lower than that of the control group for 120 min. In paracetamol-treated groups (Groups II and III), the intracranial temperature statistically decreased from the baseline at 30 minutes and hypothermia developed. Both the spike frequency and the intracranial temperature in Group II were statistically significantly lower than those of Group III at 60th min while at the 120th minute, the values for Group III were determined to be lower than those for Group II.

Conclusion: The parallel decrease in spike frequency and intracranial temperature suggests that paracetamol reduces intracranial temperature to prevent epileptic activity. Rather than being a prodrug, paracetamol may be an effective drug in the treatment of status epilepticus.

Keywords: Epilepsy; hypothermia; paracetamol; status epilepticus.

Özet

Amaç: Parasetamol çok yaygın olarak kullanılan analjezik ve antipiretik bir ajandır. Literatürde parasetamolün nöbet aktivitesine etkisini araştıran çalışmalarda hipotermik etkisi değerlendirilmemiştir. Parasetamolün hipotermik etkisini araştıran çalışmalarda da nöbet üzerine aktivitesi değerlendirilmemiştir. Biz bu çalışmada, ratlarda parasetamolün nöbet ve ısı üzerine etkisini eş zamanlı değerlendirmeyi amaçladık.

Gereç ve Yöntem: Status epileptikus (SE), pentilentetrazol (PTZ) ile oluşturuldu. Kontrol grubunda (1. Grup) PTZ ile SE oluşturulup parasetamol verilmedi. 2. Grupta parasetamol 300 mg/kg i.p uygulandıktan 30 dakika sonra 60 mg/kg i.p. PTZ enjekte edildi. 3. Grupta parasetamol 300 mg/kg i.p uygulandıktan hemen sonra 60 mg/kg i.p. PTZ enjekte edildi. Tüm gruplarda 120 dk boyunca elektrokortikografi kaydı alındı ve intrakranyal sıcaklık ölçümü yapıldı.

Bulgular: Parasetamol verilen gruplarda spike frekansı, 120 dk boyunca kontrol grubuna göre anlamlı derecede daha düşüktü. Parasetamol verilen gruplarda (Grup 2 ve 3) intrakranyal sıcaklık 30. dakikadan itibaren istatistiksel olarak anlamlı derecede bazal seviyenin altına düşerek hipotermi gelişti. Ratlarda hem spike frekansı hem de intrakranyal sıcaklık parasetamolün önce uygulandığı 2. grupta 60. dakikada parasetamolün sonra uygulandığı 3. gruptan istatistiksel olarak anlamlı derecede düşükken; 120. dakikada ise 3. grupta 2. gruptan daha düşüktü.

Sonuç: Spike frekansında azalmayla intrakranial ısıdaki düşüşün paralel olması bize parasetamolün intrakraniyal ısıyı düşürerek epileptik aktiviteyi önlediğini düşündürmüştür. Parasetamolün bir ön ilaçtan çok, status geliştikten sonra statusu önlemede etkili bir ilaç olabilir.

Anahtar sözcükler: Epilepsi; hipotermi; parasetamol; status epileptikus.

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***Correspondence (İletişim)*:** Semiha KURT, M.D.
***e-mail (e-posta)*:** gsemihakurt@hotmail.com

Introduction

Epilepsy is a genetic or acquired chronic neurological disease characterized by recurrent seizures. Epileptic seizures occur with the deterioration of balance in the brain to increase excitation and/or decrease in inhibition.[1]

Status epilepticus (SE) is one of the neurological emergencies that arise from high rates of morbidity and mortality. Thus, it is necessary to start treatment quickly to prevent and minimize the development of cerebral damage. The incidence of status epilepticus (SE) is estimated to be between 10 and 41 per 100.000 in studies in the United States and Europe.[2] Anticonvulsant drugs cannot succeed in ending SE in 20% of the cases.[2] Other treatment options have recently become accessible for cases in which anticonvulsant treatments are not successful. Paracetamol is a widely used analgesic and antipyretic agent. Wallenstein reported that paracetamol at 150 to 450 mg/kg was effective in preventing seizure activity in both penicillin G and pentylenetetrazole (PTZ) induced epilepsy models.[3,4] In our previous study, paracetamol had no effect on the epileptiform activity at the dose of 100 mg/kg in the epilepsy model in rats by injection of 500 IU intracortical penicillin. However, 150 and 300 mg/kg i.v paracetamol was found to be significantly effective on epileptic activity.[5]

Temperature changes have significant effects on seizures and epileptic activity. In animal experiments, hyperthermia-induced by body temperatures of 39.5–42 °C facilitates epileptic seizure formation,[6,7] 28–31 °C hypothermia in humans[8,9] and in vivo animal studies[10,11] showed a significant reduction of epileptic activity. In a comparative clinical study on human, superficial body cooling, head cooling, nasopharyngeal cooling, paracetamol and barbiturate use were evaluated, and paracetamol was shown to decrease the intracranial temperature more significantly than other methods. In addition, paracetamol reduced head temperature more than rectal temperature.[12]

In the literature, the effects of paracetamol on seizure activity have not been evaluated in hypothermic effects. In studies investigating the hypothermic effects of paracetamol, its activity on seizures was not evaluated. In this study, we aimed to evaluate the effects of paracetamol on seizures and heat simultaneously in rats.

Materials and Methods

Animals

In our study, 30 male Wistar albino rats weighing 250±10 g and 2–3 months old were used for the experiments. All described procedures were approved by the local ethics committee of Tokat Gaziosmanpasa University (2015-HADYEK-46). The rats were kept under control in a fixed temperature room (20±3 ºC), in the 12-hour-12-hour dark cycle, and permitted free access to food and water.

Insertion of ECoG electrodes and cannulation process

The rats, which were fasted one day before the operation, were anesthetized with 90 mg/kg ketamine and 10 mg/kg xylazine and the scalp was opened with an approximately 3 cm long incision. Bregma was detected after the membrane on the bone tissue was cleared (reference point). Using a hand drill, a 1 mm wide drill bit was drilled into four separate points of the skull. In order to record the electrocorticogram in three of these holes, a stainless steel screw was placed in contact with the brain membranes. The stereotaxic coordinates using the bregma as a landmark were 2 mm anterior and 3.5 mm lateral for the frontal electrode, and 6 mm posterior and 4 mm lateral for the occipital. A reference electrode was implanted over the cerebellum. From the last remaining hole, an external cannula of 0.5 mm diameter was advanced to a distance of 1 mm (3.2 mm vertical from the bone, 1.1 mm posterior from the bregma, 1.5 mm lateral) for intracranial temperature measurement. Electrodes were fixed to the skull with dental cement.

To prevent infection, the animal was injected with intraperitoneal 50 mg/kg ampicillin-sulbactam twice daily for three days. To alleviate the pain, xylazine at a dose of 10 mg/kg was injected immediately after surgery and for 1 day at 8-hour intervals. After surgery, the animal was allowed to rest for one week.

Experimental design

Convulsions were induced by a single dose of PTZ (60 mg/kg intraperitoneally). Following the injection, animals were placed in 35x35x35 cm transparent glass cages and each animal was observed for 120 minutes and behavioral scoring was performed. A rat with five ictal episodes of severity at grade 3 and above was considered to be kindled.[13] After the 60 mg/kg PTZ injection, all rats developed generalized epilepsy with tonic-clonic contraction. The intracranial temperature was recorded simultaneously with ECoG recording. The experimental groups were constructed as follows:

Group I (control group) (Normal saline + PTZ): PTZ (60 mg/ kg, i.p.) was administered 30 minutes after the administration of normal saline (1 ml i.p.) and ECoG was recorded for 120 minutes. Two rats who died within the first 10 minutes were excluded from the study (n=8).

Group II (Paracetamol + PTZ): PTZ (60 mg/kg i.p.) was administered 30 minutes after the paracetamol injection (300

mg/kg, i.p.) and ECoG was recorded for 120 minutes (n=10). ECoG recording started with PTZ injection.

Group III (PTZ + Paracetamol): Paracetamol (300 mg/ kg, i.p.) was administered immediately after PTZ (60 mg/kg i.p.) administration and ECoG was recorded for 120 minutes (n=10). ECoG recording started with PTZ injection. The experiment timeline is shown in Figure 1.

The Physitemp Thermalert Monitoring Thermometer TH-5 (Physitemp; 07013 Clifton, NJ) recorded the intracranial temperature on the left cortices. The TH-5 system probe was used. The intracranial temperature was measured by passing the probe through the canal. First, basal intracranial heat was taken from each rat. The intracranial temperature was measured every 30 minutes after PTZ injection.

Electrocorticographic recordings and analysis

The baseline and subsequent ECoG recordings were recorded and stored online with the Mp150 data acquisition system. Data recorded with the Mp 150 system allows LabChart v7.3.7 (ADInstruments, Australia) to measure the frequency and amplitudes of epileptic spikes. In the data analysis menu of this analysis program, the threshold level was determined from the normal basal brain activity, from the option that allows the separation of epileptic spike-wave activity. In determining the threshold level, normal basal brain activity recorded before the epileptic activity was taken as a measure. In this way, the program allowed us to measure the frequency and amplitudes of spike waves with epilepsy. The total number of spike-wave discharges (SWDs) clusters per minute, the number of spikes in each set, the total SWDs clustering time and the average amplitudes of the spikes (peak to peak) were automatically calculated by the features of this software. This calculation was performed separately for the records obtained from all animals used in the experiment. Statistical analysis of the data obtained from the analysis was transferred to SPSS (v16.0) program. Behavioral analysis was performed simultaneously with ECoG recording. The statistics for behavioral scoring were performed using the scoring of the stage, the spike-stage relationship, myoclonic jerk percentage (convulsion of stage 3 and over) and myoclonic jerk latency. This calculation was performed separately for the records obtained from all animals used in the experiment. Data obtained from the study were transferred to SPSS (v16.0) program for statistical analysis. Behavioral analysis was performed simultaneously with ECoG recording. The statistics for behavioral scoring were performed using the scoring of the stage, the spike-stage relationship, myoclonic jerk percentage (convulsion of stage 3 and over) and myoclonic jerk latency. Representative ECoGs are presented all groups in Figure 2.

Statistical analyses

Statistical analyses of each parameter were performed using SPSS 16.0. First, the Kolmogorov-Smirnov test was applied to determine whether the data were consistent with the normal distribution. In the analysis of normally distributed data, the Post-Hoc Tukey test was used in cases where the variances were homogeneous and Post-Hoc Tamhane's T2 analyzeswere used in cases where the variances were homogeneous (One-Way Anova Post-Hoc Tukey/Tamhane Test). For the analysis of the data that did not comply with normal distribution, the difference between the groups was determined by the Kruskal Wallis variance analysis, and then the paired comparisons were made with the Mann-Whitney U test. Bonferroni correction was performed to determine p-value in non-parametric analyzes. The results are given as mean ± standard error of the mean (SEM). For all statistical tests, $p<0.05$ was considered statistically significant.

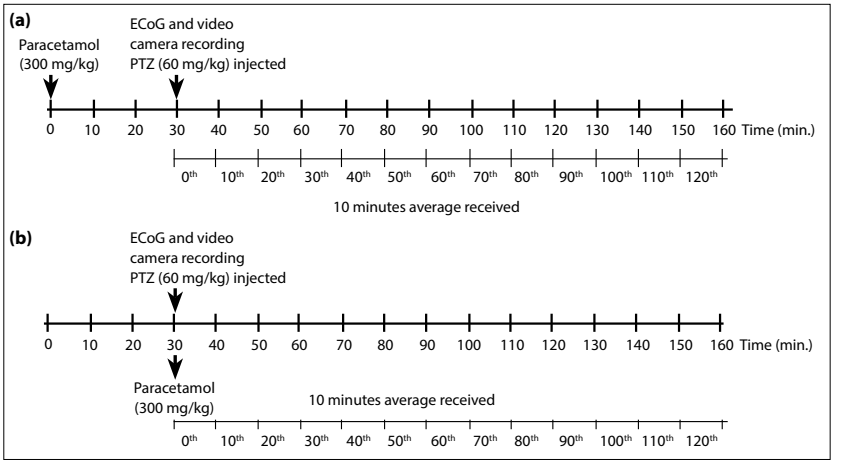

Fig. 1. Experiment timeline. Single doses of PTZ (60 mg/kg) intraperitoneally (i.p.) injection-induced epileptiform activity. **(a)** In the first set of experiments, 30 min after paracetamol injection, a dose of 60 mg/kg PTZ was the application and starting ECoG recording and video camera recording for 120 minutes. **(b)** In the second set of experiments, paracetamol (300 mg/kg) was applied then ptz was applied and and starting ECoG recording and video camera recording for 120 minutes.

Results

The spike frequency of the paracetamol groups (Group II and III) at 30th, 60th, 90th and 120th minutes was significantly lower than that of the control group (Group I). At the 60th minute of

recording, in Group II where paracetamol was administered before PTZ, the frequency of spikes decreased significantly compared to that of Group III in which paracetamol was administered after PTZ. At the 120th minute, there was a statistically significant decrease in the frequency of spikes in Group III compared to that of Group II (Fig. 3, Table 1).

At the 30th minute of the study, the seizure score was statistically significantly lower in Group II than the seizure score in the third group. The seizure scores at 60, 90 and 120 minutes were lower in the experimental groups than the control group (Fig. 3, Table 1).

The latency of the first myoclonic jerk formation was significantly longer in the paracetamol-treated groups than that of the control group (Fig. 4).

There was no statistically significant difference between the basal intracranial temperatures of the three groups (Fig. 5, Table 2). At the 30th minute after PTZ injection, a statistically significant increase was observed in the control group. This increase continued throughout the entire record. At the 60th minute of recording, in Group II where paracetamol was administered before PTZ, the intracranial temperature decreased significantly compared to that of Group III in which paracetamol was administered after PTZ. At the 120th minute, there was a statistically significant decrease in the intracranial temperature in Group III compared to that of Group II (Fig. 5, Table 2).

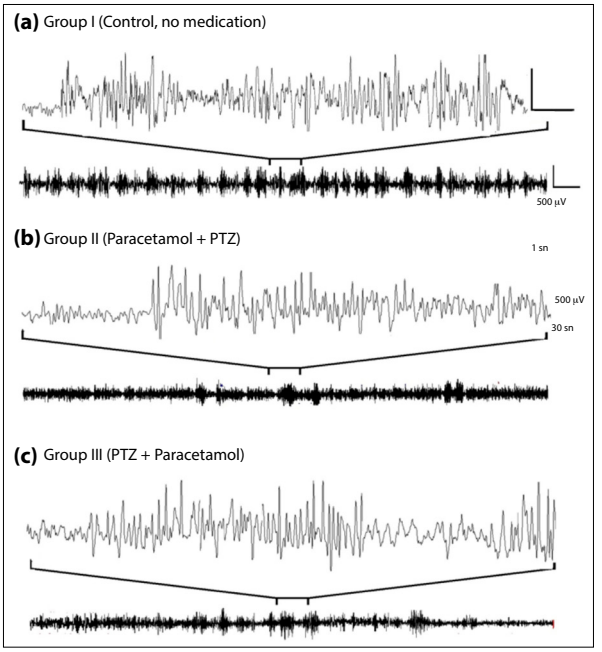

Fig. 2. Representative ECoGs are presented in all groups. **(a)** Intraperitoneally (i.p) injection of PTZ (60 mg/kg) induced epileptiform activity on ECoG. **(b)** Intraperitoneally administration of paracetamol, at a dose of 300 mg/kg, before PTZ injection, decreased the mean frequency of PTZ-induced epileptiform ECoG activity compared with control groups. **(c)** Intraperitoneally administration of paracetamol, at a dose of 300 mg/kg, after PTZ injection, decreased the mean frequency of PTZ-induced epileptiform ECoG activity compared with control groups.

Discussion

Paracetamol is the most widely used drug in the world. Paracetamol limits prostaglandin generation by cyclooxygenase (COX) not only in the central nervous system but also in the peripheral nervous system of human beings.[14] The effects of prostaglandins on seizures are still controversial. In addition to the preventive effects of seizures, there are also publications reporting that they cause seizures.[15]

In our study, 300 mg/kg paracetamol significantly decreased epileptic activity in rats before or after PTZ. It also reduced seizure scores and prolonged myoclonic jerk latencies. In a 1987 study, which was performed utilizing generalized and focal models of epilepsy arose from i.p. and intracortical penicillin G, the effects of paracetamol (i.p. 150–140 mg/kg), together with some other non-steroidal anti-inflam-

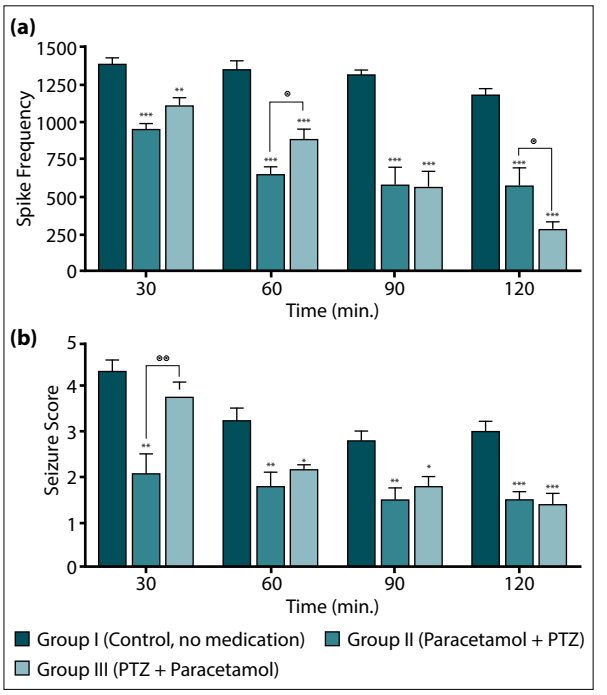

Fig. 3. Spike frequencies **(a)** and seizure scores **(b)** of groups. (*: p<0.05, **: p<0.01, ***: p<0.001) all groups compared to the control group (⊗: p<0.05, ⊗⊗: p<0.01) Group II compared to Group III.

Table 1. Evaluation of the seizure score and the total spike frequencies recorded in each group (mean ± SEM)

Time (min)	Group I (Control, no medication)		Group II (Paracetamol + PTZ)		Group III (PTZ + Paracetamol)	
	Spike frequencies	Seizure score	Spike frequencies	Seizure score	Spike frequencies	Seizure score
30	1380.83 ±45.36	4.33±0.24	952.00±38.92***	2.08±0.43**	1108.93±52.26**	3.75±0.33$^{⊙⊙}$
60	1350.08±54.70	3.24±0.28	654.50±50.22***/$^{⊙}$	1.80±0.30**	886.66± 67.64***	2.16±0.10*
90	1314.50±31.13	2.80±0.20	586.83±113.79***	1.50±0.25**	570.60±104.76***	1.80±0.20*
120	1179.66±41.23	3.00±0.22	582.50±112.65***/$^{⊙}$	1.51 + 0.18***	291.96±46.30***	1.40±0.23***

(*: p<0.05, **: p<0.01, ***: p<0.001) all groups compared to the control group. (⊙: p<0.05, ⊙⊙: p<0.01) Group II compared to Group III.

Table 2. Intracranial temperature (°C) values of groups (mean ± SEM)

Time (min)	Group I (Control)	Group II (Paracetamol + PTZ)	Group III (PTZ + Paracetamol)
0.	37.30±0.16	37.50±0.12	37.23±0.01
30.	38.25±0.39	35.90±0.02***	36.80±0.22**
60.	37.55±0.36	34.18±0.40***	35.66±0.06**/$^{⊙}$
90.	37.55±0.15	34.05±0.10***	34.78±0.31***
120.	37.55±0.15	34.40±0.26***	32.93±0.25***/$^{⊙⊙}$

(**: p<0.01, ***: p<0.001) all groups compared to the control group (⊙: p<0.05, ⊙⊙: p<0.01) Group II compared to Group III.

matory drugs were investigated. The findings showed that paracetamol reduced the frequency of seizure significantly, delayed or blocked spike activity and seizure onset and diminished ECoG voltage output.[4] Likewise, a study using an epilepsy model arose from PTZ found that paracetamol (300 or 450 mg/kg) was effective in reducing seizure frequency in rats.[3] In our previous study, paracetamol had no effect on the epileptiform activity at the dose of 100 mg/kg in the epilepsy model, which was created by injection of intracortical penicillin (500 IU). However, 150 and 300 mg/kg i.v paracetamol were found to be statistically significant on antiepileptic activity.[5]

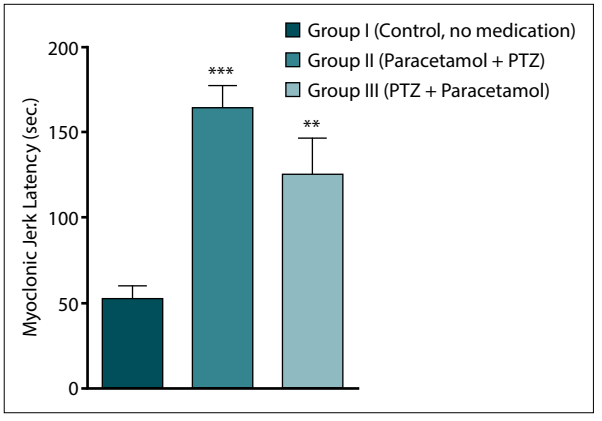

Fig. 4. Myoclonic jerk latencies of groups. Group I: 52.50±7.83 sec; Group II: 164.3±13.46 sec; Group III: 125.5±21.27 (**: p<0.01, ***: p<0.001) all groups compared to the control group.

In the rats of the control group (Group I), there was an increase in intracranial temperature after PTZ injection. In experimental status epilepticus (ESE) animal model and in humans with generalized status epilepticus, hyperthermia develops due to disturbances in temperature control. Although hyperthermia is considered to be due to intense muscle movements in generalized status epilepticus, the development of hyperthermia in monkeys even after complete muscle relaxation in ESE supports the idea that hyperthermia in ESE is due to impaired temperature control.[16]

In the groups given paracetamol (Group II and III), the intracranial temperature decreased significantly below the basal level after 30 minutes and hypothermia developed. Hypothermia has been shown to significantly reduce epileptic activity in

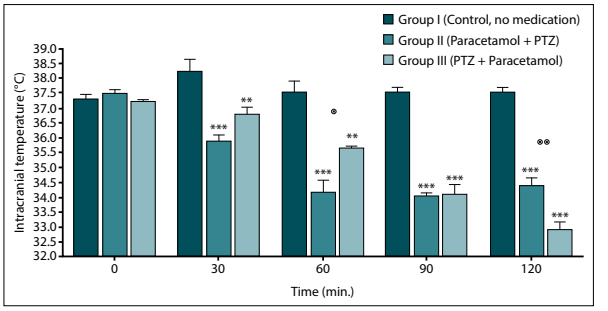

Fig. 5. Intracranial temperature values (°C) of groups. (**: p<0.01, ***: p<0.001) all groups compared to the control group (⊙: p<0.05, ⊙⊙: p<0.01) Group II compared to Group III.

humans[8,9] and in vivo animal studies.[10,11] Hypothermia was provided by focal, superficial or invasive methods in these studies. In a comparative clinical study, superficial body cooling, head cooling, nasopharyngeal cooling, paracetamol and barbiturate were evaluated and paracetamol was shown to decrease the intracranial temperature more than other methods. It was also found that paracetamol head temperature decreased more than rectal temperature.[12]

In our study, at the 60th minute of recording, in Group II, where paracetamol was administered before PTZ, the intracranial temperature decreased significantly compared to Group III in which paracetamol was administered after PTZ. At the 120th minute, there was a statistically significant decrease in the intracranial temperature in Group III compared to that of Group II (Fig. 5, Table 2). Spike frequencies in rats were similar to intracranial temperature and significantly lower in Group II at the 60th minute. The spike frequency was lower in Group III at 120th minute than the spike frequency in Group II. The decrease in the spike frequency and the decrease in intracranial temperature made us think that paracetamol prevented epileptic activity by decreasing intracranial temperature. In addition, at the 120th minute, both the spikes frequency and the intracranial temperature were significantly lower in Group III, suggesting that paracetamol that is effective in preventing the status epilepticus is a drug rather than a prodrug.

In a study by Espinosa Bosch et al.,[17] paracetamol concentrations were observed in the cerebrospinal fluid at 20 minutes following the infusion of paracetamol 1 gram. Paracetamol reduces fever within 30 minutes and antipyretic effect lasts at least six hours.[18] Paracetamol is a cheap, safe, and easy to use medicine. The additional benefit of paracetamol in SE will be very important. Therefore, there is a need for human studies in which paracetamol is used in the additional treatment of SE.

Ethics Committee Approval

Ethics committee approved.

Peer-review

Externally peer-reviewed.

Conflict of interest

The authors declare that they have no conflict of interest.

Authorship Contributions

Concept: S.K., H.A., Ş.Ö., B.Ç., D.A., O.S.; Design: S.K., H.A., Ş.Ö., B.Ç., D.A., O.S.; Supervision: S.K., H.A., Ş.Ö., B.Ç., D.A., O.S.; Materials: S.K., H.A., Ş.Ö.; Data collection &/or processing: S.K., H.A., Ş.Ö.; Analysis and/or interpretation: S.K., H.A., Ş.Ö.; Literature search: S.K., H.A., Ş.Ö.; Writing: S.K., H.A.; Critical review: H.A., Ş.Ö., B.Ç., D.A., O.S.

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