Clinical and Experimental Health Sciences

The Antiepileptic and Antidepressant-Like Effects Of Dexpanthenol in Female Swiss Albino Mice

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Received: 20.01.2021 **Accepted:** 23.12.2021

ABSTRACT

Objective: Oxidative stress is one of the main mechanisms of epilepsy and depression. Based on our information, behavioral effects of dexpanthenol in animals have not yet been demonstrated. Dexpanthenol itself is a topical medicine to restore skin barrier against infections caused by microorganisms which also stimulates the peristaltic movements in the gut when administered parenterally; however since it is cheap and easy to use with minor side effects, the main idea of the current research was to evaluate whether dexpanthenol has an antiepileptic and/or antidepressant-like effects.

Methods: A group of female Swiss albino mice (25-30 g) were injected with dexpanthenol (ip, N = 8) or saline (ip, N = 8), and 30 min later pentylenetetrazole (65 mg/kg, ip)-induced convulsions were determined for 30 min. In addition, another group of mice were again injected with dexpanthenol (500 mg/kg, ip, N = 8) or saline (ip, N = 8) and immobility time were evaluated in the forced swim test. Finally, mouse righting reflex test was used to assess the possible changes in motor coordination.

Results: Our data showed that dexpanthenol, at the dose of 500 mg/kg displayed significant antiepileptic and antidepressant-like effects without affecting motor behavior.

Conclusions: A common low-cost topical drug for various skin disorders that can also be given parenterally for motility regulation has an antiepileptic and antidepressant-like activity in mice.

Keywords: Epilepsy, Depression, Dexpanthenol, Mice

1. INTRODUCTION

Dexpanthenol, a precursor and alcohol analogue of D-pantothenic acid is a commonly used topical medicine to restore skin barrier against infections caused by microorganisms (1). There are several mechanisms how dexpanthenol shows its pharmacological activity, but the most common mechanisms are that dexpanthenol promotes cell proliferation and protects epithelium (2) which may contribute to inhibit oxidative stress (3, 4) and show anti-inflammatory activity (5). Moreover, dexpanthenol is readily oxidized to pantothenic acid in the mammalian cells which in turn stimulates the peristaltic movements in the gut. Thus, it has been a treatment option for adynamic ileus (6).

Epilepsy is a complex and one of the most common neurological disorders characterized by recurrent seizures; which affects approximately 70 million people worldwide (7). Even though there are various cellular mechanisms to understand the seizure susceptibility in mammals, one of the main mechanisms of epilepsy is the imbalance between excitatory and inhibitory neurotransmitter systems in the brain (8). Besides, more than 20% of the patients with epilepsy are refractory to current therapy options (9-11); therefore it is crucial to investigate new drugs and/or bioactive chemicals that have potential antiepileptic features with low adverse effects.

In addition to epilepsy, depression is one of the leading psychiatric and social problems in developing countries. Most patients with depression have been treated by classical antidepressant drugs, however 30% of the patients do not respond to those treatments (12), and yet the mechanisms underlying depression are still unclear (13). It is likely that, epilepsy is also related to depression since there are several

DOI: 10.33808/clinexphealthsci.865421

reports which clarify the emotional responses are much higher in patients with epilepsy (14, 15).

It has been well documented that sex hormones may change the effects of the drugs. For example, women are more susceptible to the analgesic effect of morphine, as well as the dermatological adverse effects of antiepileptic drugs; such as rash (16). Furthermore, women have higher risks for anxiety and depression (17, 18). Also, there are few studies showing the sex differences in seizure susceptibility in mice (16, 19, 20).

Based on our information, behavioral effects of dexpanthenol have not yet been investigated. Thus, the main idea of the current research was to evaluate whether dexpanthenol has an antiepileptic and/or antidepressant-like effects in young female *Swiss albino* mice.

2. METHODS

2.1. Animals

Female *Swiss albino* mice (25-30 g) purchased from the Experimental Medicine Research and Application Center (SUDAM) at the University of Selcuk were used in the experiments. They were randomly divided into 4 groups (1: saline + PTZ; 2: dexpanthenol + PTZ for epilepsy study; 3: saline alone and 4: dexpanthenol alone for depression study) and housed in a vivarium. Food and water were ad libitum. The ethical statement was approved by the University of Selcuk Animal Care and Use Committee (Protocol Number 2020/3).

2.2. Anticonvulsant-like Effects: The Pentylenetetrazole (PTZ)-induced Seizures

The GABA-A receptor antagonist PTZ has been a widely used chemoconvulsant for decades in rodent models of epilepsy (21). A single dose of PTZ (65 mg/kg, ip) (22) was injected in mice 30 min after dexpanthenol (500 mg/kg, ip) or saline administration. The effective dose of dexpanthenol was selected according to our previous studies and literature (5, 23, 24). After PTZ administration, mice were observed for 30 min and the onsets of myoclonic and clonic convulsions and the occurrence of tonic hindlimb extension were recorded. After the observation period, mice were euthanized by high dose of ketamine anesthesia.

2.3. Motor Behavior: The Righting Reflex

The mouse righting reflex test was performed just before the forced swim test whether dexpanthenol at the dose of 500 mg/kg altered motor behavior in mice. The test was modified from the protocol as previously described in detail (25). Briefly, 30 min after the dexpanthenol treatment, mice were put on supine position and observed for righting reflex within 5 sec for 3 consecutive episodes.

2.4. Antidepressant-like Effects: The Forced Swim Test

The forced swim test was carried out by using the protocol described previously (26, 27). Concisely, mice were individually placed into glass cylinders (19 x 15 x 9 cm) which contain 23–25 °C tap water 30 min after dexpanthenol injection. During the 6 min period, immobility behaviors were recorded. A decrease in the duration of immobility was considered as an antidepressant-like effect.

2.5. Drugs

Dexpanthenol (Bepanthen® 500 mg / 2 ml) was purchased from Bayer Pharmaceuticals (Turkey) and dissolved in saline. Intraperitoneal injections were given 30 min before behavioral tests in a volume of 0.1 ml / 10 g body weight.

2.6. Statistical Analysis

Results were presented as means ± S.E.M. Statistical analyses were performed by SPSS statistical software (Version 14.0, SPSS Inc., Chicago, Il). A non-parametric Mann-Whitney U test was used for analyzing the data. Significance was set at $P < 0.05$.

3. RESULTS

3.1. Effects of Dexpanthenol in PTZ-induced Seizures

The effects of dexpanthenol in PTZ-induced seizures are shown in Table-1. At the dose of 500 mg/kg, dexpanthenol significantly prolonged the onset of myoclonic (control: 42.50 ± 8.41 sec; dexpanthenol: 116.42 ± 14.68 sec, N = 8 for each group, $P < 0.05$; Mann-Whitney U test) and clonic convulsions (control: 71.13 ± 11.34 sec; dexpanthenol: 226.57 ± 28.35 sec, N = 8 for each group; $P < 0.05$, Mann-Whitney U test) respectively. None of the mice were died during the seizures, as well as none of them showed usually fatal tonic hind-limb extensions.

Table 1. *The onset of myoclonic and clonic convulsions in saline control and dexpanthenol groups*

Groups	Onset of Myoclonic Convulsions (sec)	Onset of Clonic Convulsions (sec)
Saline (N = 8)	42.50 ± 8.41	71.13 ± 11.34
Dexpanthenol (N = 8)	116.42 ± 14.68*	226.57 ± 28.35*

Dexpanthenol significantly prolonged the onset of the seizures ($P < 0.05$, Mann-Whitney U test) and showed antiepileptic-like activity.*

3.2. Effects of Dexpanthenol on Righting Reflex

Dexpanthenol, at the dose of 500 mg/kg, did not alter motor behavior. Righting reflexes were within 2 and 3 sec for all groups. Data not shown.

3.3. Effects of Dexpanthenol in Forced Swim Test

While the duration of immobility was found 161.13 ± 18.24 sec in control group, at the dose of 500 mg/kg, dexpanthenol significantly reduced the duration of immobility to 82.59 ± 10.18 sec and showed antidepressant-like effect (Table-2); P < 0.05, Mann-Whitney U test. Eight mice were used in each group.

Table 2. *The duration of immobility in saline control and dexpanthenol groups.*

Groups	Duration of Immobility (sec)
Saline (N = 8)	161.13 ± 18.24
Dexpanthenol (N = 8)	82.59 ± 10.18*

Dexpanthenol significantly reduced the duration of immobility (P < 0.05, Mann-Whitney U test) and showed antidepressant-like activity.*

4. DISCUSSION

Dexpanthenol, namely Bepanthen® has been widely used for various diseases since 1950s such as systemic lupus erythematosus (28), chronic bronchitis (29), dermatological lesions (30, 31), chronic constipation (6, 32), postoperative ileus (33), testicular atrophy (34), acute rhinitis (2) and pattern alopecia (3). It is a stable alcoholic analog of D-pantothenic acid which in turn metabolized to pantothenic acid in the cells (35). Because of its antioxidant activity, dexpanthenol could reverse the hepatotoxic and ototoxic effects of cisplatin, a commonly used anticancer drug (36, 37). Recently, the metabolite pantothenic acid has been shown to enhance glutathione and coenzyme A levels as well as ATP synthesis in the cells that are the major defense systems against oxidative stress (38).

In the present study, we investigated the anticonvulsant and antidepressant-like effects of dexpanthenol in the mouse pentylenetetrazole and forced swim tests, respectively. To our knowledge and literature, this is the first pharmacological and behavioral study which has revealed the neurological effects of dexpanthenol. Briefly, dexpanthenol, at the dose of 500 mg/kg, ip showed promising effects in epilepsy and depression without altering motor coordination. And, it is a low cost drug with minor side effects.

It has been well documented that oxidative stress plays a major role in epilepsy (39) and depression (40). Epilepsy-related mitochondrial dysfunction and brain damage were attributed to oxidative stress and neuroinflammation in animal studies (41, 42) which might be primary mechanisms for dexpanthenol. Unlike epilepsy, oxidative stress plays a dual role in depression. While it may cause depression, depression itself may cause oxidative stress (43). Evidence showed that dexpanthenol has an anti-inflammatory activity and significant effects for reducing oxidative stress markers (44). Therefore, our current data support the idea of the inhibition of oxidative stress-induced activity by dexpanthenol in the brain. In addition, few studies showed that oxidative stress associated pharmacological and physiological effects were higher in females (45, 46), however in an age-related sex differences in antioxidant activity study, it has been found that women show efficient antioxidant activity (47). Since there are main differences responding to oxidative stress between sexes, we decided to study with young female mice.

5. CONCLUSION

Our data suggest that dexpanthenol may be involved in central nervous system antioxidant activity and could be a potentially novel low cost antiepileptic and/or antidepressant agent. However further studies are needed to understand the cellular mechanisms of these effects.

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How to cite this article: Inan SY, Acikgoz Y . The Antiepileptic and Antidepressant-Like Effects Of Dexpanthenol in Female Swiss Albino Mice. Clin Exp Health Sci 2022; 12: 141-144. DOI: 10.33808/clinexphealthsci.865421