Physiology & Behavior 128 (2014) 114–118

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Comparison between the effect of propofol and midazolam on picrotoxin-induced convulsions in rat

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HIGHLIGHTS

- The time-course for the anticonvulsant effect of propofol and midazolam is shown.
- Midazolam was more effective than propofol against PTX-induced tonic seizures.
- Midazolam was also more effective than propofol in reducing PTX-induced mortality.

ARTICLE INFO

Article history:
Received 29 August 2013
Received in revised form 26 November 2013
Accepted 24 January 2014
Available online 8 February 2014

Keywords:
Clonic–tonic seizures
Intravenous anesthetics
Midazolam
Picrotoxin
Propofol

ABSTRACT

Propofol is a short acting intravenous anesthetic that has been used in the treatment of status epileptics. However, the occurrence of seizures in epileptic and non-epileptic patients during recovery from propofol induced anesthesia suggests that propofol may have proconvulsant effects. We have previously shown that propofol displays anticonvulsant effects against picrotoxin (PTX) induced seizures during its peak sedative effects. The purpose of the present study was to compare the time course of the effect of intravenous administration of various doses (2.5, 5, and 10 mg/kg) of propofol and midazolam on PTX-induced seizures in adult female Sprague–Dawley rats. The latency to onset of clonic seizures induced by intraperitoneal injection of PTX was significantly increased by the highest dose of propofol and all doses of midazolam, suggesting that both agents display anticonvulsant effects. The anticonvulsant effects of propofol (10 mg/kg) lasted about 20 min and PTX-induced clonic seizures were observed thereafter and peaked within 30 min post drug administration. Clonic seizures progressed rapidly to tonic seizures leading to high rate of PTX-induced mortality. In midazolam (10 mg/kg) treated rats, clonic seizures were observed 25 min after drug administration and the number of rats exhibiting clonic seizures was highest within 40 min. However, clonic seizures did not progress into tonic seizures and thus, PTX-induced seizure related mortality was significantly reduced. In conclusion, this study provides further evidence for the anticonvulsant effects of propofol and midazolam against PTX-induced seizures. Furthermore, the data of the current study showed that midazolam was more effective than propofol against PTX-induced tonic seizures.

1. Introduction

Propofol is a short acting intravenous anesthetic that is widely used for the induction and maintenance of anesthesia [19]. Although propofol has been successfully used in the management of status epilepticus [3,13,23], clinical reports indicated the occurrence of seizures, or seizure like phenomena, during or following recovery from propofol anesthesia [26]. Consequently, some controversy still surrounds the effects of propofol on seizure activity [24].

A large body of experimental data demonstrated that propofol was an effective anticonvulsant in different experimental seizure models [10,11,18]. Propofol was also an effective anticonvulsant in animal models of status epilepticus [2,27]. We have previously shown that the intravenous administration of propofol increased PTX seizure threshold in rabbits [9]. However, the effect of propofol on seizure activity was determined only at the time of peak sedative effect. Therefore, the present study was undertaken to evaluate the time course of the effects of intravenous administration of propofol on PTX-induced convulsions. Of particular interest was to determine whether propofol blocks the initiation and the progression of PTX-induced seizures during and following the emergence from anesthesia. Latency to seizure onset, seizure severity, and PTX-induced mortality

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http://dx.doi.org/10.1016/j.physbeh.2014.01.027
0031-9384/

were evaluated to determine the effectiveness of propofol against PTX-induced seizures. Another objective of the present study was to compare the effects of propofol with those of midazolam on PTX-induced seizures. Such comparison was made because the two rapidly acting intravenous anesthetic agents share several pharmacological properties; for example, both agents have been used in the management of status epilepticus [23]. They have also exhibited anticonvulsant activity against pentylenetetrazol-induced seizures [6,8,21], and picrotoxin-induced seizures [20]. In addition, the anticonvulsant actions of the tow agents have been demonstrated to have the ability to enhance the actions of GABA at the GABAA receptor [1,14,16]. Thus, comparing both agents' pharmacological properties could ultimately reflect on the choice of the best agent for the management of status epilepticus.

2. Materials and methods

2.1. Animals

Experiments were conducted in adult female Sprague–Dawley rats (230–250 g) as described in [10]. Animals were obtained from a local colony at the College of Medicine and Medical Sciences, Arabian Gulf University, Manama, Kingdom of Bahrain. Animals were housed in stainless steel hanging cages at room temperature (24 °C) and 12 h light:dark cycle. Rats were allowed free access to water and ground rodent chow except at the time of the experiments. All experiments were conducted between 9 am and 12 pm. All studies were performed under a protocol approved by the Research and Ethics Committee at the Arabian Gulf University, College of Medicine and Medical Sciences.

2.2. Chemicals

Picrotoxin (Sigma Chemical Co., St. Louis, MO, USA) was dissolved in saline and administered i.p. in a volume of 0.5 ml/kg body weight. Propofol was administered as a commercially available injectable emulsion (Diprivan 1%; Astra-Zeneca pharmaceuticals LP, Wilmington, DE) that contains soybean oil (100 mg/ml), glycerol (22.5 mg/ml), egg lecithin (12 mg/ml), and disodium edetate (0.005%). Midazolam was administered as a commercially available injectable solution (Dormicum, Hoffman-Laroche Ltd., Basel Switzerland). Both propofol and midazolam were administered intravenously in a volume of 1 ml/kg.

2.3. Induction of seizures and evaluation of anticonvulsant effects of propofol and midazolam

Picrotoxin (4 mg/kg) was administered i.p. 5 min prior to the administration of propofol or midazolam. Different groups of rats ($n = 10$ each) were administered various doses of propofol (2.5, 5, and 10 mg/kg) or midazolam (2.5, 5, and 10 mg/kg). The anesthetic agents were administered i.v. as a single dose through the dorsal tail vein via a 25G butterfly scalp vein cannula. Control animals received equal volume of saline.

Following drug treatment, individual rats were placed in Plexiglas cages, and were closely observed for the occurrence of behavioral seizures. The latency to onset of mild clonic seizures (rhythmic clonic movements of the forelimbs) was recorded. In addition, the occurrence of mild clonic and severe tonic seizures characterized by tonic extension of the hind limb was also observed. Each rat was scored once for the worst seizure behavior every 5 min for a 40 min duration and PTX-induced mortality in all groups was observed over a 2 hour period.

2.4. Statistical analysis

Significant differences between mean latencies of clonic seizures in treated and control groups were determined after analysis of variance (ANOVA) when the overall F ratio was significant at the $P < 0.05$ level. The least significant difference (LSD) test was used as the post-hoc test and the level of significance was corrected for the numbers of comparisons by the Bonferroni method. For evaluation of the effectiveness of various doses of propofol and midazolam in protecting rats against PTX-induced seizure related mortality, the median anticonvulsant dose of either drug required to protect animals from PTX-induced mortality in 50% of animals (ED_{50}) and its associated 95% confidence limits, were calculated using the method of Litchfield and Wilcoxon [17], using a commercial computer program (Minitab 14).

3. Results

3.1. Behavioral and sedative effects of i.v. administration of propofol or midazolam

Prior to testing the effects of propofol and midazolam on PTX-induced seizures, behavioral effects of the two agents were evaluated. The administration of 2.5 mg/kg of propofol did not induce any observable sedative effects. Rats receiving 5 mg/kg propofol were easier to handle and mildly ataxic. The highest dose of propofol induced sleep with loss of righting reflex. Loss of righting ability was assessed by placing the animal on its back after the injection of drugs, rats that were not able to right themselves within 5 s of this maneuver were considered to have lost their righting ability. The anesthetic and sedative effects of propofol were observed immediately after propofol administration.

The sedative effects of similar doses of midazolam were milder than those of propofol. However, all doses produced mild sedation characterized by a decrease of spontaneous activity in all the animals, as evidenced by a slowing of movement and decreased vocalizations when handled. A higher dose of midazolam (20 mg/kg) was required to induce loss of righting reflex. The sedative effects were observed immediately after i.v. administration of the drug. Based on these findings, we evaluated the effects of similar doses of the two agents (2.5, 5, and 10 mg/kg) on PTX-induced convulsions.

3.2. PTX-induced convulsion in control animals

The intraperitoneal administration of picrotoxin (4 mg/kg) in control rats produced a spectrum of seizures, including myoclonus and clonic and tonic seizures. Myoclonus, seizures involving head or whole body jerks, which was usually single, was the seizure type observed initially in all animals. Progressively, more severe seizures were observed including minimal clonus with rhythmic movements of the fore limbs, head or jaw, minimal tonic seizures consisting of tonic contractions of head, neck and trunk muscles, torsion of the trunk and usually brief loss of righting reflex, and maximal tonic seizures, characterized by the presence of tonic limb flexion or extension. Clonic seizures were observed within 8–12 min after i.p. injection of PTX. Mean latency to onset of clonic seizures was 10.2 min (see Fig. 1). The incidents of clonic seizures peaked within 15–30 min after PTX administration and usually progressed to severe tonic seizures. Seizures persisted through the first hour in nine out of ten animals. Maximal tonic seizures were associated with respiratory depression which caused death within 30–60 min after PTX treatment.

3.3. Effects of propofol and midazolam on latency of PTX-induced clonic seizures

The effects of i.v. administration of various doses (2.5, 5, and 10 mg/kg) of midazolam or propofol on latency to clonic seizures are shown in Fig. 1. Midazolam significantly increased the latency of clonic seizures in a dose dependent manner. By contrast, the effects of propofol