Neurotoxicity associated with colistin methanesulfonate treatment is enhanced by concomitant sevoflurane inhalation

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ABSTRACT

Colistin methanesulfonate (CMS) is a cyclic polypeptide antibiotic with neurotoxic side effects. Sevoflurane (Sevo), an inhaled anesthetic, is known to enhance the non-depolarizing effect of neuromuscular relaxants; however, its mechanism of action is unclear. In this study, we investigated the augmentation effect of Sevo on CMS-induced neurotoxicity. We prepared a sciatic nerve-skeletal muscle stimulation model using Sprague-Dawley male rats administered CMS with or without Sevo. The muscle contraction inhibition rate was determined from electromyogram measurements. Furthermore, we simulated the pharmacokinetics of CMS and colistin using previous reports, and the relationship between the effect of muscle contraction inhibition and pharmacokinetic parameters was evaluated. We observed a dose-dependent neuromuscular inhibitory effect of Sevo under CMS administration. The 50% inhibitory dose (ID₅₀) values for CMS and CMS+Sevo were 167 ± 12 and 85 ± 5 mg/kg, respectively. The combination of CMS with Sevo showed a 49% decrease in the ID₅₀ compared with CMS alone. The simulated area under the time–concentration curve (AUC) values for CMS and colistin administration in rats at 200 mg/kg were 219 and 16.0 mg·h/L, respectively. The predicted AUC values of colistin corresponding to the ID₅₀ at 0–45 min for CMS alone and CMS+Sevo were 12.0 and 7.0 mg·h/L, respectively. We revealed that the neurotoxic effect of CMS was enhanced by the concomitant use of Sevo. Based on the simulated AUC values, we concluded that this neurotoxic effect may also occur in clinical settings, and concomitant use of CMS and Sevo should be avoided.

1. Introduction

In 2019, the Centers for Disease Control and Prevention published an antibiotic resistance threat report that included several gram-negative bacteria and classified carbapenem-resistant Acinetobacter and Enterobacteriaceae as ’Urgent Threats’ and extended-spectrum β-lactam-producing Enterobacteriaceae and multidrug-resistant Pseudomonas aeruginosa as ’Serious Threats’ [1]. Consequently, colistin regained attention as one of the few treatment choices for multidrug-resistant gram-negative bacterial infection [2]. Colistin is classified as a polypeptide antibiotic, and its prodrug, colistin methanesulfonate (CMS), is used in clinical settings (Fig. 1). Colistin is a cyclic polypeptide antibiotic developed in Japan. Colistin was originally used as sulfate and hydrochloride, but CMS was developed as a derivative with low toxicity. CMS has been used in clinical practice since the 1950s, but antibiotics with lower toxicity, such as β-lactams, have been developed since then [3]. CMS injection was discontinued in Japan owing to a higher incidence of nephrotoxicity and neurotoxicity compared with that of other antibiotics [4]. However, given the recent emergent increase in multidrug-resistant gram-negative bacillus infections, CMS injection has drawn renewed attention as an important therapeutic antibiotic [5].

The major concerning adverse events related to colistin treatment are nephrotoxicity and neurotoxicity. Clinical symptoms reported for neurotoxicity include dizziness, muscle weakness, abnormal sensation of the face and periphery, partial deafness, visual disturbance, confusion, hallucination, and seizures [6]. Neurotoxicity from CMS use is less common than nephrotoxicity from CMS use; however, fatal neuromuscular blockade has been reported [7,8]. A case of neuromuscular blocking by the combined use of muscle relaxants and CMS has also been reported [9]. Therefore, it is important to elucidate the drug-drug interactions between CMS and other drugs that enhance neurotoxicity, to prevent fatal adverse effects from occurring.

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Muscle relaxants such as tubocurarine, suxamethonium, and botulinum toxin are listed on the package insert of CMS as being harmful because they may increase the risk of neurotoxicity when used concurrently with CMS [10]. Similarly, aminoglycosides, polymyxin B, and ether, which have a muscle-relaxing side effect, are also mentioned. In addition, inhaled anesthetics also suppress neuromuscular transmission [11]. It is also known that volatile anesthetics such as sevoflurane (Sevo), isoflurane, and desflurane potentiate the effect of non-depolarizing muscle relaxants. Both CMS and inhaled anesthetics interact with non-depolarizing muscle relaxants and enhance their effects; therefore, concomitant use of CMS and inhalation anesthetics may increase the muscle-relaxing side effect. The aim of this study was to evaluate the interaction between CMS and Sevo, an inhaled anesthetic commonly used in clinical practice, to treat multidrug-resistant bacterial infections safely.

2. Materials and methods

2.1. Materials

Colistin methanesulfonate (Fig. 1) was purchased from FUJIFILM Wako Pure Chemical Corporation (Biochemistry grade, Osaka, Japan). Urethane was purchased from Sigma-Aldrich (St. Louis, MO, USA). Sevoflurane was purchased from Pfizer Co., Ltd. (≥ 99.0 %, NY, USA).

2.2. Animals

Male Sprague-Dawley rats (weight: 270–330 g) were purchased from Sankyo Labo Service Co., Inc. (Tokyo, Japan) and housed in a room with a controlled 12-h day/night cycle, temperature (21–23 °C), and humidity (40–60 %). All animals were freely provided with water and standard chow (CE-2, Japan CLEA, Inc., Tokyo, Japan). All experimental procedures for the animals were performed according to protocols approved by the Institutional Animal Care and Use Committee of Keio University (approval number: 18054) and complied with the standards outlined in the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and the Guidelines for the Care and Use of Laboratory Animals at Keio University.

2.3. Sciatic nerve-skeletal muscle stimulation model

We used a sciatic nerve-skeletal muscle stimulation model to evaluate the effect of ganglionic blocking activity. The rats were cannulated into the cervical vein under urethane anesthesia (1.3 g/kg body weight, i.p.) to obtain the vascular route of administration for CMS before the model operation was performed. Six rats were randomly assigned to each experimental group by body weight; however, the number of rats included in the analysis was reduced to 4–6 due to excessive bleeding during cannulation or being unstable for electromyogram. A measuring electrode was set at the lower limb, and a reference electrode was set at the tail. Liquid paraffin was dropped in the operating region to prevent drying of the nerve and electrical leakage. Electrodes for electrocardiogram measurement were connected to the chest, and a reference electrode was set at the tail. A square-wave pulse (frequency: 0.1 Hz; width: 0.2 ms; output current: 0.1 mA) was applied to the sciatic nerve to induce an electrical leak. The timing for the electromyography program is shown in Fig. 2. Fifteen minutes after stimulation was performed, we confirmed the stabilization of muscle contraction; then, CMS (0–200 mg/kg) was slowly administered through the catheter for 20 s with or without Sevo (1 %), and the electromyogram and electrocardiogram were recorded for 45 min.

2.4. Calculation of muscle contraction suppression rate

Using LabChart, the measured waveform was rectified, and the muscle contraction force caused by a single square-wave stimulation was expressed as the maximum amplitude value (mV). The inhibition rate of muscle contraction (%) was calculated from the maximum amplitude value every 5 min. The maximum amplitude value 5 min before the administration of CMS was defined as the baseline control.

2.5. Dose-response curve generation

A dose-response curve was generated using JMP®. The y-axis is the percent inhibition of muscle contraction (%), and the x-axis is the dose. The dose at which 50 % inhibition of muscle contraction occurred (ID50) was determined from the simulation curve.

2.6. Simulation of pharmacokinetic parameters

The volume of distribution (Vd/F) and total clearance (CLtot/F) were determined by simulation using JMP®.

Fig. 1. Chemical structure of colistin methanesulfonate.
calculated based on the result of the pharmacokinetic evaluation reported previously [12]. We used the following equations to determine the parameters. Vd/F and CLtot/F were calculated using the mean values from each dose.

- ke = ln2/t1/2.
- AUC = Normalized AUC Dose/30.
- CLtot/F = Dose/AUC.
- Vd/F = (CLtot/F)/ke.

2.7. Pharmacokinetic simulation

The conversion ratio (fm) in the one-compartment model was fitted to simulate the CMS and colistin blood concentrations in rats, which was estimated to be 6.8 % based on the report by Li et al. (2004). The maximum concentration (Cmax) was determined by simulation. The area under the time–concentration curve (AUC) at 0–45 min (AUC0-45 min) was calculated using the trapezoidal approximation method with a simulated curve.

2.8. Statistical analysis

All statistical analyses were performed using R software (R; Vienna, Austria). The statistical analysis comparing the means of the groups was performed by an independent-samples Student’s t-test. A value of p < 0.05 was considered statistically significant.

3. Results

3.1. Longitudinal changes in inhibition of muscle contraction by CMS alone and in combination with Sevo

The electromyographic measurements for CMS alone and CMS in combination with Sevo are shown in Fig. 3. Under the present experimental conditions, there was no decrease in contractility due to muscle fatigue over time during the electromyogram observation period of 45 min (Supplementary Fig. S1). Furthermore, no suppression of muscle contraction was observed for the combined administration of CMS with 1 % Sevo (Supplementary Fig. S1). At doses of 12.5–50 mg/kg CMS in both groups, the electromyographic changes were similar to those seen with saline, and the inhibition of muscle contraction was generally less than 20 %. The inhibition of muscle contraction increased to 63 ± 29 % and 97 ± 1 % with 1 % Sevo and 100 mg/kg and 200 mg/kg CMS, respectively (Fig. 3B). The inhibitory effect of CMS on muscle contraction was significant with the 200 mg/kg dose of CMS alone (p < 0.05 vs. saline), but the 100 mg/kg dose of the combination treatment with CMS and Sevo had a significant inhibitory effect (p < 0.05 vs. saline). No significant electrocardiogram changes were observed for any of the doses (data not shown).

3.2. Dose-response curve

Fig. 4 shows the dose-response curve generated based on the muscle contraction inhibition rate 45 min after CMS administration, which showed the maximum effect. An increasing trend in the curve was observed from about 50–60 mg/kg in the CMS group and at about 40 mg/kg in the CMS–Sevo group. It was shown that the low doses of CMS–Sevo tended to have more of an inhibitory effect on muscle contraction of CMS alone, but this result was not significant (Fig. 4). The calculated ID50 was 167 ± 12 mg/kg in the CMS group and 85 ± 5 mg/kg in the CMS–Sevo group, indicating that the concomitant use of CMS with Sevo reduced the ID50 by 49 % (Table 1).

3.3. Predicted AUC of CMS and colistin for inhibition of muscle contraction

Table 2 shows the pharmacokinetic parameters calculated by simulating the pharmacokinetics of CMS and colistin using Phoenix WinNonlin™. Simulations of colistin produced in rats calculated at 6.8 % of the CMS dose administered indicated that the Cmax was about 20 times higher and the AUC0-45 min was about 13.7 times higher in CMS than in colistin (Table 2). Using these results and estimated pharmacokinetic parameters (Supplementary Table S1), the relationship between the AUC0-45 min and maximal contraction inhibition for CMS and colistin is shown in Fig. 5. The AUC0-45 min of the ID50 of CMS was 156 mg·h/L in the CMS alone group and 96 mg·h/L in the CMS–Sevo group, indicating that the ID50 was 59 % lower from the combined use of CMS and Sevo than from CMS alone (Table 3). The AUC0-45 min of the ID50 of colistin was 12.0 mg·h/L in the CMS alone group and 7.0 mg·h/L in the CMS–Sevo group, indicating that the ID50 was 42 % lower from the combined use of CMS and Sevo than from CMS alone (Table 3). The AUC0-45 min values for CMS and colistin exhibiting the maximum contraction inhibition in combination with Sevo were approximately 200 mg·h/L and 15 mg·h/L, respectively (Fig. 5).

4. Discussion

This study revealed that the combination of CMS and Sevo had a 49 % lower ID50 than CMS alone, which indicates that Sevo enhanced the
neuromuscular blocking effect of CMS and inhibitory effect of CMS on muscle contraction. The interaction mechanism of Sevo with non-depolarizing muscle relaxants constitutes clinically important information that is presented in the package insert. Nevertheless, Fukushima evaluated this interaction in a sciatic-skeletal muscle stimulation observation model and found that Sevo reduced the ID<sub>50</sub> of each non-depolarizing muscle relaxant by 20–30% [11]. In the present study, the reduction in the ID<sub>50</sub> of CMS by concomitant use with Sevo was greater than that reported by Fukushima et al. for the interaction with non-depolarizing muscle relaxants, suggesting that the enhancement of muscle relaxation in CMS by the concomitant use of Sevo may provide important information on drug interactions.

Two mechanisms have been proposed for the neuromuscular blockade effect by CMS [14]. The first is inhibition of acetylcholine (ACh) release by presynaptic action. A decrease in the concentration of ACh in the synaptic cleft inhibits synaptic transmission, resulting in muscle relaxation. The second is a biphasic action, which is a competitive blockade of ACh and colistin, followed by a prolongation of depolarization. In this experiment, the muscle contraction suppression rate showed a negative value before the muscle contraction inhibitory effect appeared, and thus the enhancement of muscle contraction was observed (Fig. 3). This causes colistin to bind to the nicotinic acetylcholine receptor (nAChR) at the end of the synapse, resulting in transient muscle contraction. This is due to the subsequent inhibition of synaptic transmission by desensitization. We believe that the result suggests the latter mechanism. Paul et al. reported that the non-depolarizing muscle-relaxing effect of Sevo is caused by its enhanced affinity towards antagonists for nAChRs [15]. Since Sevo enhanced the myorelaxant effect of colistin in the present experiment, it was inferred that colistin has antagonist effects on nAChRs and that Sevo enhanced its binding affinity. However, it is difficult to determine the mechanism of neuromuscular blockade from the results of this experiment, and in vitro membrane potential measurement and discussion based on changes in the endplate potential are necessary to elucidate the mechanism in detail.

There is a pharmacokinetic difference between humans and rats. CMS is generally administered intravenously for over 30 min in humans. In our rat study, CMS was rapidly (20 s) administered intravenously. However, pharmacodynamic evaluations in model animals are generally based on human exposure to the drug (AUC). Therefore, the doses used in this study are based on dose-equivalent studies in rats and humans [13]. The experimental dosing design was determined to achieve an AUC equivalent to colistin. Then, pharmacodynamic (neurotoxicity) and pharmacokinetic parameters were compared. Honore et al. reported that the onset of muscle relaxant effects as C<sub>max</sub> in humans increased when blood concentrations of colistin exceeded 8 μg/mL [8]. In the present experiment, the dose at which the blood colistin concentration exceeded approximately 8 μg/mL was more than 50 mg/kg (Table 2), which is consistent with the dose at which the muscle contractile inhibitory effect began to become enhanced in the analysis of the dose-response curve (Fig. 4). Because the pharmacokinetics and tissue transferability of Aldreb® differ between rats and humans, we used the AUC to evaluate the relationship between adverse drug reactions and muscle contraction inhibition in order to evaluate adverse drug reactions in terms of drug exposure. According to the interview form for Aldreb®, the AUC<sub>0-12 h</sub> of colistin after a single intravenous administration of 2.5 mg/kg CMS to healthy adults is 15.8 ± 6.5 mg h/L [16]. From Table 2, the AUC<sub>0-45 min</sub> of colistin in rats treated with 200 mg/kg CMS was 16.0 mg h/L. At this time, it is estimated that muscle contraction is suppressed by about 60% when CMS alone is administered, and about 97% when Sevo is used in combination with CMS. It has been reported that the conversion rate of CMS to colistin in the body is higher in humans than in rats. In humans, 30% of the CMS dose is converted to colistin [17], while the fm for rats is reported to be 6.8–12.5% [12,13], which is lower than the fm for humans. Therefore, because blood concentrations of colistin are higher in humans than in rats, it was thought that the AUC at which muscle relaxation occurs could be achieved with a smaller dose.

Colistin consists of a cyclic seven-membered peptide with a tripeptide side chain whose N-terminal is acetylated by a fatty acid and is positively charged. CMS consists of a sulfomethyl group attached to the primary amine of colistin and is negatively charged at physiological pH. It has been reported that its antimicrobial activity is due to electrostatic interactions between the positive charge of colistin and anionic lipopolysaccharide (LPS) molecules present in the outer membrane of target bacteria [18]. In addition, colistin itself is substituted for Ca<sup>2+</sup> and Mg<sup>2+</sup>.

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**Table 1**

| Dose (mg/kg) | CMS | CMS+Sevo |
|--------------|-----|----------|
| 12.5         | 40  | 14       |
| 25           | 81  | 27       |
| 50           | 161 | 55       |
| 100          | 323 | 110      |
| 200          | 645 | 219      |

**Table 2**

Predictive pharmacokinetic parameters of CMS or colistin.

| Dose (mg/kg) | CMS | CMS+Sevo |
|--------------|-----|----------|
| 12.5         | 40  | 14       |
| 25           | 81  | 27       |
| 50           | 161 | 55       |
| 100          | 323 | 110      |
| 200          | 645 | 219      |

Abbreviation: AUC area under the concentration-time curve, CMS colistin methanesulfonate.

Abbreviation: ID<sub>50</sub> 50% of inhibitory dose, CMS colistin methanesulfonate. Data are expressed as means±SEM. (n = 4–6).

**Fig. 4. Dose-response curve.** The dose-response curve was calculated based on the inhibition rate of muscle contraction 45 min after CMS administration. Data are expressed as the mean ± SD (n = 4–6).
Colistin sulfate at a dose of 10 mg/kg has an intravenous administration of 10 mg/kg colistin sulfate killed the rats. In a previous preliminary study on rats, ternary amine structures that are characteristic of drugs with dated. In addition, neither CMS nor colistin has the tertiary and qua - in negatively charged LPS, causing localized damage to the bacterial outer membrane. Its bactericidal activity is exerted through the efflux of intracellular substances by these actions. The detailed mechanism of colistin-induced nephrotoxicity is also unknown, but it is thought that the surfactant effect increases membrane permeability and induces cell lysis [6]. Damage to the proximal tubular cells is believed to occur at this time. However, since the carnitine/organic cation transporter is involved in the uptake into proximal tubular cells [19], colistin is thought to be the active agent in renal injury. However, the identity of the active substance that causes neuromuscular blockade is not elucidated. In addition, neither CMS nor colistin has the tertiary and quaternary amine structures that are characteristic of drugs with neuromuscular blocking action. In a previous preliminary study on rats, an intravenous administration of 10 mg/kg colistin sulfate killed the rats (data not shown). Colistin sulfate at a dose of 10 mg/kg has an AUC<sub>0→45 min</sub> of 11.8 mg·h/L, and it is estimated that a single administration of colistin sulfate produces a contractile inhibition of about 50%. In contrast, the 200 mg/kg CMS dose administered in this experiment did not cause death. Therefore, we believe that colistin has a muscle-relaxing effect, although the mechanism underlying this effect is not clear. The rate of hydrolysis of CMS to colistin in the body is higher in humans than in rats. Therefore, it is necessary to analyze the enhancement of muscle relaxation by the combination of CMS and Sevo in humans.

Sevo-induced muscle-relaxing effects are known to increase in a dose-dependent manner [13]. Since urethane anesthesia was used to create the model in this experiment, the combined use of Sevo tended to suppress circulation. Therefore, a 1 % concentration of Sevo was used so that the combined use of CMS with Sevo would not produce this effect. In general, Sevo should be used at a concentration of 4 % or less to maintain anesthesia in humans, and it is expected that the concentration of Sevo used in clinical practice is higher than that in this experiment. Therefore, there is a possibility that interactions occur more readily in clinical practice than they did in this experiment. Patients with impaired renal function are particularly susceptible to increased muscle relaxation. CMS is primarily excreted by the kidneys, but prolonged excretion leads to increased hydrolysis and increased colistin levels in the blood. Therefore, it is appropriate to discontinue CMS and consider other agents to avoid adverse events in patients scheduled for surgery. If CMS cannot be discontinued, intraoperative monitoring of muscle contrac - tility by muscle relaxation monitoring and Sevo concentration adjustments should be performed to avoid potentiation or prolongation of the muscle-relaxing effect.

One factor that may lead to underestimation of the muscle-relaxing effect in this experiment is the measurement time. The dose-response duration used was 45 min after CMS administration, which caused the suppression of muscle contraction to be maximized. If the measurement is continued after 45 min, it is possible that the suppression of contraction will increase further. However, in this model, square-wave stimulation was applied once every 10 s, and considering the decrease in muscle contraction force due to the accumulation of muscle fatigue, the measurement limit was set to 45 min from the results of preliminary studies. Therefore, it was considered that the dose-response curve might actually shift to the higher dose side (right) more so in clinical practice than under experimental conditions. In contrast, hypothermia is considered to be a cause of the overestimation of muscle relaxation. During hypothermia, muscle strength decreases with or without muscle relaxants, and the effects of muscle relaxants are enhanced and prolonged [20]. Although we did not record or control the body temperature of the rats in this experiment, all experiments were at least conducted under the same temperature conditions.

The results of this study showed that the neurotoxicity of CMS is enhanced by its concomitant use with Sevo, an inhaled anesthetic. Furthermore, we suggest that this effect may also occur at clinical doses in humans, hence concomitant use of CMS and Sevo should be avoided.

### Table 3

| Values of AUC<sub>0→45 min</sub> on inhibition of muscle contraction. | % 50 % inhibitory AUC<sub>0→45 min</sub> (mg·h/L) | AUC<sub>0→45 min, CMS</sub> | AUC<sub>0→45 min, colistin</sub> |
|---|---|---|---|
| CMS | 156.2 | 12.0 |
| CMS+Sevo | 96.1 | 7.0 |

CMS colistin methanesulfonate.
CRedit authorship contribution statement

Mai Gotoda: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. Yuki Enoki: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. Shino Shishido: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization. Kazuaki Taguchi: Conceptualization, Project administration, Supervision, Visualization. Kazuaki Matsumoto: Conceptualization, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.toxrep.2022.05.020.

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