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Chronic Use of the Synthetic Cannabinoid WIN 55,212-2 55 Modifies the Isoflurane-Sparing Effect of Morphine and Dexmedetomidine

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Simple Summary: The minimum alveolar concentration of isoflurane was determined in 32 rats to evaluate the interaction of isoflurane with morphine and dexmedetomidine in rats treated chronically with the synthetic cannabinoid, WIN 55,212-2. We believe it is necessary to study the effects of chronic cannabinoid consumption on the requirements of inhalation anesthetics for patients who are submitted to general anesthesia and to whom morphine and dexmedetomidine are administered. The sparing effect of morphine on isoflurane decreases and the sparing effect of dexmedetomidine on isoflurane increases in rats treated chronically with the synthetic cannabinoid, WIN 55,212-2.

Abstract: The effects of morphine (MOR) and dexmedetomidine (DEX) on the MAC of isoflurane were measured in rats chronically treated with the synthetic cannabinoid WIN 55,212-2 (WIN55). Methods: The MAC of isoflurane was determined in 32 male rats from expiratory samples at the time of tail clamping. The effects of morphine ($MAC_{(ISO+MOR)}$) and dexmedetomidine ($MAC_{(ISO+DEX)}$) on the MAC of isoflurane in untreated rats and rats treated for 21 days with WIN 55,212-2 ($MAC_{(ISO+WIN55+MOR)}$) and ($MAC_{(ISO+WIN55+DEX)}$) were measured. Prior to the administration of morphine and dexmedetomidine, the MAC of the isoflurane was measured in both untreated rats ($MAC_{(ISO)}$) and those treated with WIN 55,212-2 ($MAC_{(ISO+WIN55)}$). Results: The minimum alveolar concentration was measured as 1.32 ± 0.06 in the $MAC_{(ISO)}$ group and 1.69 ± 0.09 in the $MAC_{(ISO+WIN55)}$ group. The MAC of the $MAC_{(ISO+MOR)}$ group was 0.97 ± 0.02 (26% less than the control group, $MAC_{(ISO)}$). MAC was measured as 1.55 ± 0.08 in the $MAC_{(ISO+WIN55+MOR)}$ group (8% less than the $MAC_{(ISO+WIN55)}$ group), 0.68 ± 0.10 in the $MAC_{(ISO+DEX)}$ group (48% less than the control group, $MAC_{(ISO)}$), and 0.67 ± 0.08 in the $MAC_{(ISO+WIN55+DEX)}$ group (60% less than the $MAC_{(ISO+WIN55)}$ group). Conclusions: The administration of WIN 55,212-2 for 21 days increases the MAC of isoflurane in rats. The sparing effect on isoflurane of morphine decreases in rats chronically treated with the synthetic cannabinoid, WIN 55,212-2. Dexmedetomidine increases its sparing effect on the minimum alveolar concentration of isoflurane in rats chronically treated with WIN 55,212-2.

Keywords: minimum alveolar concentration MAC; isoflurane; dexmedetomidine; morphine; synthetic cannabinoid WIN 55,212-2; rats

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1. Introduction

In the year 2020, 209 million people had used cannabis. *Cannabis sativa* is the most popular illicit drug in the 21st century, and countries are increasingly legalizing its medicinal and recreational use. According to the World Drug Report 2022, published by the United Nations [1], cannabis remains the most widely used drug in the world. There is a great expectation that cannabis and its derivatives will be used for medicinal purposes in the treatment of chronic pain (particularly cancer) and pediatric seizure disorders, as an appetite stimulant, as treatment for spasticity in multiple sclerosis, for controlling nausea and vomiting in patients with HIV/AIDS, in the treatment neurodegenerative diseases, and, potentially, in the treatment of post-traumatic stress disorder and addictions to different substances. Multiple investigations are underway on the use of cannabis in the treatment of various human diseases [2–4]. It is currently considered that the increased use of cannabinoids, as an alternative, may help in lowering the excessive use of opioids. There is evidence that cannabinoids can help to reduce the opioid dosage necessary for generating analgesia [5], with one related study reporting a 64% decrease in opioid use [6]. Similarly, when cannabinoids and opioids were administered in conjunction, a decrease in pain of 27% was recorded with no changes in the opioid plasma concentration pharmacokinetics [7].

On the other hand, the administration of dexmedetomidine during general-anesthesia procedures decreases the opioid and hypnotic requirements (sparing effect), offers analgesic properties, decreases postoperative nausea, vomiting, and shivering [8], and exerts therapeutic effects with respect to perioperative stress, postoperative delirium, and neuroprotection. However, the reasons for this are still not entirely clear, and elucidation of these thus remains a focus of studies [9–11].

Therefore, given the high possibility that a chronic consumer of *Cannabis sativa*, or its derivatives, requires general anesthesia and dexmedetomidine or an opioid, we consider it important to study whether the isoflurane-sparing effects of morphine and dexmedetomidine, previously reported in the literature, are the same in cannabis users, given the lack of studies on this topic.

2. Materials and Methods

This study and its procedures (protocol number 3492/2013CHT) have been approved by the Faculty of Veterinary Medicine of the University of the State of Mexico.

Thirty-two rats weighing 310 ± 20 g were used and were housed in Plexiglas cages at an ambient temperature of 23 ± 2 °C. The animals had free access to water and food (Prolab1 RMH 2500, St. Louis, MO, USA).

Animals were handled according to the Guide for the Care and Use of Laboratory Animals [12].

2.1. Anesthetic Procedure

Anesthesia was induced by placing each rat in the induction chamber and delivering 5% isoflurane (Forane; Baxter Laboratories, Irvine, CA, USA) with an oxygen flow rate of 5 L/min. Once the animal was anesthetized, it was removed from the chamber and dorsally intubated. The oral cavity was opened, and the larynx was located using a laryngoscope. At this point, a flexible wire guide was inserted to direct the endotracheal catheter (16G Teflon catheter: Introcan; B-Braun, Sao Goncalo, Brazil) and was fixed to the maxilla.

The analysis of CO_2 corroborated correct placement of the catheter (BeneView T5, Mindray, Multi-Gas Offers, Shenzhen, China), which was connected to a T-piece breathing system with fresh gas flow of oxygen at 1 L/min. The anesthetic concentration was adjusted in light of the hemodynamic changes and palpebral reflexes during instrumentation. During the experiment, rats breathed spontaneously.

The dissection was carried out on the carotid artery for placement of the 24-gauge catheter (Introcan; B-Braun, São Gonçalo, Brazil), which was connected to a pressure transducer for continuous measurement of systolic, diastolic, and mean arterial blood pressures (SAP, DAP, and MAP, respectively) and heart rate (HR) (BeneView T5, Mindray, Shenzhen, China) as well as for the

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collection of arterial blood for analysis of blood gases (GEM Premier 3000; Instrumentation Laboratory, Seattle, WA, USA). A total of 0.3 mL of blood was obtained after determining the MAC to guarantee that each rat presented normal physiological parameters at that time. A caudal vein was catheterized for the administration of the drugs of each group. Inspired isoflurane (FiIso), end-tidal (FeIso) concentrations, end-tidal carbon-dioxide tension ($PEtCO_2$), and respiratory rate (RR) were continuously measured through endotracheal gas sampling (60 mL/min) via a catheter placed in the endotracheal tube at the level of the carina connected to an infrared gas analyzer (BeneView T5, Mindray, multi-gas offers, Shenzhen, China)

Through use of a warming system (Equator1, SurgiVet1, Smiths Medical PM Inc., San Clemente, CA, USA), we sought to maintain the rectal temperature between 37 and 38 °C.

2.2. MAC Determination

Prior to initiating MAC isoflurane determination, FeIso was adjusted to 1.3%, which is a value of isoflurane MAC that was previously reported [13]. This was maintained for 15 min to allow equilibrium to be established between alveolar gas, arterial blood, and the spinal cord [14]. Isoflurane MAC was obtained using the tail clamp method [15]. A painful noxious stimulus was applied with a hemostat clamped (8-inch Rochester Dean) on the tail at a specific end-tidal concentration. The tail was clamped to the first ratchet lock for 60 s or until a positive response was observed. The tail was always stimulated proximally to the previous test site. A positive motor response was considered if jerking or twisting motions of the head or body or movement of the extremities were observed. A lack of movement, muscle rigidity, swallowing, and chewing were considered negative responses; movement of the tail was not considered.

If the observed response was positive, the anesthetic concentration was increased by 10%, and if the response was negative, the concentration of the anesthetic was decreased by 10%. After an equilibration period of 15 min, the stimulus was applied again. The evaluation of the MAC was carried out twice on each rat by a person who was unaware of the treatment being administered.

Since the experiment was carried out at a height of 2680 m above sea level with an average pressure of 556 mmHg, the values of MAC of isoflurane were corrected to sea level using the formula (barometric pressure of location/760 mmHg) × obtained MAC value.

At the end of each experiment, animals were euthanized with intravenously delivered pentobarbital (Anestesal, Pfizer, Toluca, Mexico).

2.3. Experimental Design

The animals were randomly distributed into six groups (n = 8) using Excel 2007, Microsoft Office.

For the $MAC_{(ISO+MOR)}$ group, the measurement was performed 45 min after the administration of 3 mg/kg morphine i.v. (Graten, PiSA, Mexico). This is the optimal dose, which had been determined in a previous publication [16]. Prior to the administration of morphine, the MAC of isoflurane was measured ($MAC_{(ISO)}$).

For the $MAC_{(ISO+DEX)}$) group, the measurement was performed 30 min after the administration of a continuous intravenous infusion of 0.25 µg/kg/min dexmedetomidine i.v. (Dexdomitor, Zoetis, Mexico). This is the dose determined to be optimal in a previous publication [17]. Prior to the administration of dexmedetomidine, the MAC of isoflurane was measured ($MAC_{(ISO)}$).

The $MAC_{(ISO+WIN55+MOR)}$ group was intraperitoneally (i.p.) administered 1 mg/kg of WIN 55,212-2 (mesylate salt, Sigma-Aldrich, St. Louis, MO, USA) every 24 h (at 09:00 h) for 21 days, in accordance with Lawston et al. [18]. The measurement was performed 24 h after the last treatment (day 22); 45 min prior to MAC measurement, 3 mg/kg morphine was administered i.v. Prior to the administration of morphine, the MAC of isoflurane was measured ($MAC_{(ISO+WIN55)}$).

The $MAC_{(ISO+WIN55+DEX)}$ group was intraperitoneally (i.p.) administered 1 mg/kg of WIN 55,212-2 every 24 h (at 09:00 h) for 21 days. The measurement was performed 24 h after the last treatment (day 22), 30 min after continuous intravenous infusion of 0.25 µg/kg/min dexmedetomidine i.v. Prior to the administration of dexmedetomidine, the MAC of isoflurane was measured ($MAC_{(ISO+WIN55)}$).

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WIN 55,212-2 was suspended in a vehicle of 0.3% Tween 80 in saline (0.9%), as described by Tanda et al. [19]. Isoflurane MAC measurements were performed 24 h after the last treatment with WIN 55,212-2 (day 22).

2.4. Statistical Analysis

Statistical analysis was performed using Prism 6 (GraphPad Software, Inc., San Diego, CA, USA). The Shapiro–Wilk test was used for the assessment of data normality. Data are reported as mean ± standard deviation (SD). Analysis of variance was performed, and post hoc comparison of the groups was performed using the Holm–Sidak test. Values were considered statistically different when $p < 0.05$.

3. Results

The minimum alveolar concentration was measured as 1.32 ± 0.06 in the $MAC_{(ISO)}$ group and 1.69 ± 0.09 in the $MAC_{(ISO+WIN55)}$ group. These values coincide with those previously reported in [20]. MAC was measured as 0.97 ± 0.02 in the $MAC_{(ISO+MOR)}$ group (26% less than the control group $MAC_{(ISO)}$), 1.55 ± 0.08 in the $MAC_{(ISO+WIN55+MOR)}$ group (8% less than the $MAC_{(ISO+WIN55)}$ group), 0.68 ± 0.10 in the $MAC_{(ISO+DEX)}$ group (48% less than the control group $MAC_{(ISO)}$), and 0.67 ± 0.08 in the $MAC_{(ISO+WIN55+DEX)}$ group (60% less than the $MAC_{(ISO+WIN55)}$ group) (See Tables 1 and 2).

Table 1. Chronic use of the synthetic cannabinoid, WIN 55,212-2 55, modifies the isoflurane-sparing effect of morphine and dexmedetomidine.

Group	MAC%	SD	% MAC Increase (↑) or Decrease (↓)	*p*-Value	95% CI
$MAC_{(ISO)}$	1.32	0.06		-	1.27–1.37
$MAC_{(ISO+WIN55)}$	1.69 *	0.09	↑ 28%	<0.0001	1.61–1.76
$MAC_{(ISO+MOR)}$	0.97 *	0.02	↓ 26%	<0.0001	0.95–0.99
$MAC_{(ISO+WIN55+MOR)}$	1.55 +	0.08	↓ 8%	0.0094	1.47–1.62
$MAC_{(ISO+DEX)}$	0.68 *	0.10	↓ 48%	<0.0001	0.59–0.77
$MAC_{(ISO+WIN55+DEX)}$	0.67 +	0.08	↓ 60%	<0.0001	0.60–0.74

* Statistically significant compared with the control group, $MAC_{(ISO)}$ ($p < 0.05$). + Statistically significant compared with the control group, $MAC_{(ISO+WIN55)}$ ($p < 0.05$).

Table 2. Cardiorespiratory and temperature values of the different study groups.

Value	$MAC_{(ISO)}$	$MAC_{(ISO+WIN55)}$	$MAC_{(ISO+MOR)}$	$MAC_{(ISO+WIN55+MOR)}$	$MAC_{(ISO+DEX)}$	$MAC_{(ISO+WIN55+DEX)}$
Heart rate (bpm)	401 ± 8	403 ± 7	399 ± 8	401 ± 11	303 ± 16 *	297 ± 21 +
Mean arterial blood pressure (mmHg)	93 ± 8	90 ± 9	91 ± 7	92 ± 8	86 ± 7	84 ± 11
Temperature °C	37.7 ± 0.07	37.6 ± 0.12	37.2 ± 0.11	37.4 ± 0.09	37.4 ± 0.10	37.5 ± 0.08
pH	7.3 ± 03	7.3 ± 0.04	7.4 ± 0.02	7.3 ± 0.02	7.3 ± 0.06	7.3 ± 0.09
PaO_2 (mmHg)	301 ± 34	295 ± 8	299 ± 12	289 ± 10	291 ± 16	289 ± 13
$PaCo_2$ (mmHg)	37 ± 4	37 ± 1	38 ± 2	38 ± 4	32 ± 2	37 ± 7

* Statistically significant ($p < 0.0001$) compared with MAC_{ISO} group. + Statistically significant ($p < 0.0001$) compared with $MAC_{ISO+WIN55}$ group.

4. Discussion

In this study, we observed that the repeated administration of the synthetic cannabinoid WIN 55,212-2 55 for 21 days increases the MAC of isoflurane. This result coincides with those previously

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reported in [20]. According to the obtained results, morphine decreases the MAC of isoflurane by 26%, which coincides with results previously reported in the literature [16]. We also observed that the isoflurane-sparing effect of morphine is weaker in rats chronically treated with the cannabinoid. This can be a consequence of increased noradrenergic activity in the central nervous system due to the chronic administration of cannabinoids [21,22]. It is also interesting to note that there are reports of a cross-tolerance effect between opioid and cannabinoid compounds. The administration of Δ9-THC has been observed to induce tolerance of the analgesic and cardiovascular effects of morphine [23], and it was also reported that the chronic administration of morphine induces tolerance of the analgesic effects of Δ9-THC [24]. The mechanism by which this effect is generated is complex and remains unclear [25]. The decrease in the effect of morphine, observed as the lowering of the MAC of isoflurane in rats chronically treated with WIN 55,212-2, could suggest (in MAC terms) a cross-tolerance effect between cannabinoids and morphine.

Finally, we observed that the decreasing effects of the dexmedetomidine on the isoflurane MAC were maintained even in rats chronically treated with WIN 55,212-2. Dexmedetomidine, a subtype of nonselective α2-adrenoceptor agonist, is sympatholytic; it decreases central sympathetic activity and, significantly, reduces the circulating levels of catecholamines [26], and it decreases the halothane MAC by up to 90% [27]. Therefore, the mechanism by which dexmedetomidine decreases the requirements of inhalational anesthetics implies mechanisms other than the inhibition of noradrenaline in the central nervous system, since it has been demonstrated that the locus coeruleus is not the only site where α2-adrenoceptor agonists have anesthetic effects [28]. It is important to determine how the constant administration of a synthetic cannabinoid favors the effect of dexmedetomidine on the requirements of inhalational anesthetics. Unfortunately, our study did not allow us to determine this mechanism. Therefore, it is important to consider the possibility of modifying the anesthetic requirements of individuals who consume or are treated with cannabinoids. These patients may present different responses to the usual doses of morphine and dexmedetomidine during inhalation anesthesia.

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