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Original Contribution

Analgesic effect and pharmacological mechanism of fentanyl and butorphanol in a rat model of incisional pain☆

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Abstract

Objectives: To explore analgesic effects of fentanyl and butorphanol on incisional pain in rats and to investigate the pharmacological mechanism of combination.

Methods: Seventy rats were randomly divided into control group (group N, n = 10), fentanyl group (group F, n = 30), and butorphanol group (group B, n = 30), to determine median effective dose (ED_{50}) in fentanyl and butorphanol. Another 50 rats were treated with both fentanyl and butorphanol (joint group) to quantitatively detect response rate of joint application. Ninety rats were randomly divided into 1/4 ED_{50} fentanyl (group 1, n = 30), 1/2 ED_{50} fentanyl (group 2, n = 30), and 3/4 ED_{50} fentanyl (group 3, n = 30), to detect the correlation between combined pharmacological effects of 2 drugs and their dose proportionality. Statistical analysis was performed using SPSS 17.0.

Results: Probit analysis revealed that ED_{50} of fentanyl was 4.1 μg/kg, whereas ED_{50} of butorphanol was 295 μg/kg. The qualitative response rate of combination (P_o) was 0.84, and expected qualitative response rate (P_e) was 0.75, with no statistical significance ($P = 0.3$). Furthermore, probit analysis showed that 155 μg/kg butorphanol with 1/4 ED_{50} fentanyl could reach experimental ED_{50} of combination of 2 drugs; 115 μg/kg butorphanol with 1/2 ED_{50} fentanyl could reach experimental combination ED_{50}; and 88 μg/kg butorphanol with 3/4 ED_{50} fentanyl could reach experimental combination ED_{50}.

Conclusion: Both fentanyl and butorphanol showed good analgesic effect on incisional pain in rats, but fentanyl was superior to butorphanol. The pharmacological mechanism of combination with ED_{50} of fentanyl and butorphanol showed independent joint action, and the combination efficacy was related to the dosage.

1. Introduction

Opioid analgesics, also called narcotic analgetics, are the most commonly used and the most important drugs in the treatment of moderate to severe pain, which produce the analgesic effect by activating the opioid receptor in vivo [1,2]. According to the different varieties of receptors in pharmacology, opioid analgesics can be mainly divided into

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3 types, including agonists (morphine and fentanyl), partial agonists (buprenorphine and meptazinol), and agonist/antagonist (butorphanol and dezocine) [3,4]. Opioid analgesics play an important role in the treatment of different levels of pain, but large dosage of opioid analgesics can cause stupor, coma, respiratory depression, and some other side effects [5-7]. Previous researches have illustrated that fentanyl, a derivative of phenyl piperidine, has powerful μ-receptor agonist and high lipophilicity, which may enhance transdermal absorption, with rapid action time but short duration [8] (http://www.google.com.proxy.its.virginia.edu/patents/US20140005617). Fentanyl is known as a potent opioid, approximately 75 to 100 times stronger than morphine [9]. Clinically, fentanyl is used to provide analgesia in the process of anesthesia induction during surgery as well as to reduce the hypertensive response in intubation [10]. On the other hand, it can increase the hypnotic function of propofol [11]. However, fentanyl may induce various clinical complications such as respiratory depression, nausea, dizziness, and vomiting [10,12-14]. Butorphanol, chemically classified to levorphanol, is a kind of lipid-soluble narcotic and has property of mixed agonist-antagonist with strong κ-receptor agonist and weak agonist activity of μ-receptor thereby resulting in sedative and analgesic properties without respiratory euphoria or depression [15] (http://www.hoajonline.com/jacs/2049-9752/2/1). Because of the antagonistic and narcotic agonist characteristics of butorphanol, it is frequently used for intraoperative analgesic as well as postoperative analgesia (http://www.hoajonline.com/jacs/2049-9752/2/2). Evidence supports the notion that butorphanol has a better safety and efficiency profile for low possibility to cause nausea, vomiting, respiratory depression, and perioperative amnesia as well as psychomimetic effects [16] (http://www.hoajonline.com/jacs/2049-9752/2/2).

Action mechanisms of analgesics differ from their different categories, thereby achieving anesthetic effect [17]. However, for some reasons, using a single analgesic is difficult to effectively control pain [18]. Combination of different classes of analgesics might offers more effective depressant effects at fewer dose of single treatment and with less side effect than single-agent drug being used, which could also decrease adverse dose-associated events [17]. The most ideal combination should not only enhance the efficacy of analgesic but also reduce side effects at the most extent compared with monotherapy [18]. Fentanyl has been indicated that it has efficacy of managing intense pain for short duration, which can combine with ketamine, another analgesic being widely applied in changing burn dressing to eliminate side effect of ketamine [19]. Butorphanol, defined as a synthetic opioid, has been observed that it can lead to decrease of heart rate, arterial partial oxygen pressure, and average pressure of arterial when applied alone; however, it frequently combines with medetomidine for the enhancement of sedative and analgesic efficacy, which indicates that butorphanol could strengthen medetomidine cardiovascular effect [20]. Although the study on fentanyl or butorphanol combined with other therapies or analgetics has been well documented, the combination of these 2 as well as the underlying mechanisms has been seldom analyzed and presented [15,21,22]. Under these circumstances, the present study was performed to explore the analgesic effects of fentanyl and butorphanol on incisional pain in the rat model and to discuss the possible reasons.

2. Materials and methods

2.1. Ethics statement

Approval was obtained for the study from the institutional Animal Ethics Committee of the First Affiliated Hospital of Liaoning Medical University. All experiments were conducted in strict accordance with the established Guide for the Care and Use of Laboratory Animals of the National Institutes of Health.

2.2. Study design

Seventy male Sprague-Dawley (SD) rats (weight, 100-140 g) were divided in 3 groups at random: control group (group N, n = 10), fentanyl group (group F, n = 30), and butorphanol group (group B, n = 30), which were used for determining the median effective dose (ED_{50}) in fentanyl and butorphanol. Next, another 50 male SD rats (weight, 112.87 ± 10.2 g) were treated with both fentanyl and butorphanol (joint group) to quantitatively detect response rate of joint application of fentanyl and butorphanol. At last, 90 male SD rats (weight, 100-140 g) were randomly divided to 3 groups: 1/4 ED_{50} fentanyl group (group 1, n = 30), 1/2 ED_{50} fentanyl group (group 2, n = 30), and 3/4 ED_{50} fentanyl group (group 3, n = 30), to detect the correlation between combined pharmacological effects of fentanyl and butorphanol in analgesia and their dose proportionality.

2.3. Model of incisional pain and test of paw withdrawal pressure threshold

All rats were anesthetized with 2% isoflurane. A 1-cm longitudinal incision was made through skin and fascia of the plantar aspect of the foot, beginning 0.5 cm from the proximal edge of the heel and extending toward the toes. After the hemostasis with gentle press, the wound was sutured with filament. After the surgery, the rats were allowed to recover for 15 minutes. Then the paw withdrawal pressure threshold was measured at the time of paw withdrawal. Three different loci on rat plantar were tested for 3 times at 5-minute intervals. Mean paw withdrawal pressure threshold (PWPT) was established by averaging the values of 3 tests and a cutoff of 50 g was used. If there was no response to cutoff more than 50 g, the pain threshold value was marked 50 g to avoid injury for rat hind paw. Rats were excluded by PWPT less than 15 g (approximately 1/10 of weight) 30 minutes before surgery or PWPT greater than 15 g 15 minutes after surgery.