Experimental Gerontology 46 (2011) 65–72

Contents lists available at ScienceDirect

Experimental Gerontology

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

Effects of chronic fentanyl administration on physical performance of aged rats

Jeremiah D. Mitzelfelt [a], Jameson P. DuPree [b], Dong-oh Seo [b], Christy S. Carter [b,c], Drake Morgan [a,b,*]

[a] Department of Psychiatry, University of Florida College of Medicine, Gainesville, FL, USA
[b] Institute on Aging, University of Florida College of Medicine, Gainesville, FL, USA
[c] Department of Aging and Geriatric Research, University of Florida College of Medicine, Gainesville, FL, USA

ARTICLE INFO

Article history:
Received 13 May 2010
Received in revised form 4 September 2010
Accepted 7 October 2010
Available online 15 October 2010

Section Editor: Christian Humpel

Keywords:
Locomotor activity
Rotarod
Grip strength
Body composition
Osmotic minipump

ABSTRACT

There is growing concern over the increasing use of opioids to treat chronic pain in the elderly primarily because of the potential increased sensitivity to the adverse side effects. Here, we use a preclinical model (male Brown Norway X F344 rats aged 12, 18, 24, and 30 months) to describe the outcome of chronic fentanyl administration (1.0 mg/kg/day) on various physiological and behavioral measures. Continuous fentanyl administration resulted in an initial decrease in food consumption, followed by the development of tolerance to this effect over a 4-week period and a subsequent increase in food consumption during withdrawal. This change in food consumption was associated with decreases in body weight (predominantly due to a loss of fat mass) that was maintained through early withdrawal. After 1 month of withdrawal, only the 12-month old animals had fully regained body weight. Fentanyl administration resulted in a decrease in grip strength and an increase in locomotor activity that did not differ across age groups. There was no effect of fentanyl administration on rotarod performance. These results demonstrate that while there is a delayed recovery of body mass with age, the observed changes in behavioral responses are uniform across ages.

1. Introduction

Opioids have been used to treat essentially every type of pain in humans, including acute and chronic pain, for pre-, peri-, and post-surgical situations, for both cancer and non-malignant conditions, and their use is increasing and becoming more widely accepted (Atluri et al., 2003; Bell et al., 2009; Benyamin et al., 2008; Brixner et al., 2006; Garcia del Pozo et al., 2008; Pergolizzi et al., 2008; Trescot et al., 2008). This is especially relevant to the aged population where chronic pain due to diffuse conditions (Delgado-Guay and Bruera, 2008; Fine, 2001, 2004; Pergolizzi et al., 2008) such as neuromuscular pain (Helme and Gibson, 2001; Thomas et al., 2004) and arthritis (Donald and Foy, 2004), and to disease-related conditions such as cancer (Potter and Higginson, 2004; Rao and Cohen, 2004) is more prevalent, with estimates of as many as 40% of aged individuals in the community (e.g. > 50 years of age) and 80% in nursing homes (mean age of 75 years) reporting pain that interferes with daily functioning (Fox et al., 1999; Gagliese, 2009; Rustøen et al., 2005; Scudds and Robertson, 2000; Thomas et al., 2004; Zarit et al., 2004). Unfortunately, this pain is often undertreated in aged individuals (Auret and Schug, 2005; Bernabei et al., 1998; Chodosh et al., 2004; Gianni et al., 2010; McNeill et al., 2004). This problem is due in part to the fact that physicians are often reluctant to prescribe opioids to the elderly, given that the full spectrum of adverse side effects (e.g. nausea, constipation, and sedation) (Benyamin et al., 2008; Byas-Smith et al., 2005; Herndon et al., 2002; Swegle and Logemann, 2006) in this particular population is not known (Hutchinson et al., 2007; Lin et al., 2007; Thomason et al., 1998; Wilder-Smith, 2005).

Long-term studies of aging in the human population can be difficult and costly. However, preclinical studies have demonstrated that various behavioral and physiological measures in animals can function as correlates to human measures of declining physical function (Carter et al., 2002; Moser, 2000). These tests evaluate not only basic health metrics such as body weight and composition (fat mass versus muscle mass), but also physical performance measures related to muscle strength, agility, and overall activity. The purpose of the present study was to apply these evaluation tools to study the effects of chronic opioid administration and withdrawal on physical function in rats of various ages. While there are numerous opioids that are used for the treatment of pain, fentanyl is increasingly used for a wide range of conditions including epidural anesthesia, chronic back pain, and cancer pain (Bhambhani et al., 2010; Bell et al., 2009; de Leon-Casasola, 2008; Hong et al., 2010; Manchikanti and Singh, 2008; Pergolizzi et al., 2008; Rauck et al., 2010), and the development of novel formulations and delivery systems such as the transdermal patch makes fentanyl easy to administer chronically in outpatient situations (Grape et al., 2010). In the current study, fentanyl was continuously administered at a dose of 1.0 mg/kg/day for 28 days via osmotic minipumps, as this dosing protocol has previously been shown to produce antinociception (i.e. pain relief) in rats across a wide age range (Morgan et al., 2008; unpublished data). Increased

* Corresponding author. Department of Psychiatry, PO Box 100183, University of Florida College of Medicine, Gainesville, FL 32610, USA. Tel.: +1 352 273 5732; fax: +1 352 273 5737.
E-mail address: drakem@ufl.edu (D. Morgan).

0531-5565/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.exger.2010.10.004

understanding of how age influences the effects of opioids can result in minimizing adverse outcomes, and consequently lead to more effective pain management in the elderly.

2. Materials and methods

2.1. Animals, treatment conditions, and experimental design

Male Fisher 344 x Brown Norway rats, obtained from the National Institute of Aging colony at Harlan Industries (Indianapolis, IN) across four age groups (12, 18, 24, 30 months of age during baseline testing) were used in the present study. This range of ages represents adulthood, middle-age, pre-senescent and senescent portions of the lifespan. Animals were individually-housed in a temperature- and humidity-controlled colony room with a 12-h light/dark cycle (lights on at 6 AM) with food and water available ad libitum. All surgery and testing was performed during the light cycle. Animals were cared for in accordance with the regulations of the IACUC and with the "Guide for the Care and Use of Laboratory Animals" (ILAR, 1996). In addition, animals were assessed on a weekly basis for signs of overt health problems with measures including, but not limited to, sudden decline in body weight, redness around the eyes and nostrils, ruffled coat, open sores on the tail, and haunched posture.

The experimental timeline is shown in the Table 1. In brief, upon arrival in the colony, the animals were given 2 weeks to acclimate before baseline testing began for body composition, grip strength, and open field with 2–3 days between each test. Animals within each age group were then randomized to receive osmotic mini-pumps containing either fentanyl ($n=32$) or saline ($n=36$). After 4 weeks of drug administration pumps were removed. In the end, 27 fentanyl- and 35 saline-treated animals completed the entire study (12 months: 5 fentanyl, 9 saline; 18 months: 9 fentanyl, 9 saline; 24 months: 7 fentanyl, 9 saline; 30 months: 6 fentanyl, 8 saline). Six animals did not complete the experiment presumably due to an adverse interactions between fentanyl and isoflurane. Of primary interest were the behavioral and physiological effects of fentanyl at approximately 1 week and 1 month of chronic fentanyl administration. These time points were chosen to be analogous to either short-term treatment regimens related to surgery or outpatient clinical situations, or longer-term disease conditions associated with chronic pain. For ease of description, these time points are referred to as "early" and "late" periods of chronic drug administration or withdrawal. Behavioral tests were conducted on different days, and the order of animal testing was counterbalanced across ages. In general, the duration of the testing was less than 3 h, and was conducted in the middle of the light/inactive phase.

Table 1
Timelime of experimental events.

Phase	Day	Experimental event
Baseline	0	Arrival in lab
	14–42	Open field, grip strength, TD-NMR, Rotorod, food consumption, and body weight measures
Drug/saline administration	0	Implant pump
	7	Body weight, food consumption, Rotorod
	8	TD-NMR
	10	Open field
	11	Grip strength
	21	Rotarod
	22	TD-NMR
	24	Open field
	25	Grip strength
	28	Food consumption, body weight
Withdrawal	0	Remove pump
	6	Body weight
	7	Food consumption, TD-NMR
	21	Rotarod
	22	TD-NMR
	24	Open field
	25	Grip strength
	28	Food consumption, body weight

2.2. Surgery and drug delivery

Osmotic mini-pumps (Model # 2ML4, Alzet, Durect Corp., Cupertino, CA) containing fentanyl or saline were implanted subcutaneously in the right hindquarter of animals while maintained on isoflurane anesthesia (1.5% at 1.0 L/min O_2). Mini-pumps delivered fluid at a rate of 2.58 μl/h for 28 days. Fentanyl was delivered at a dose of 1 mg/kg/day. Four weeks after pump implantation, animals were anesthetized and the pumps removed.

2.3. Behavioral and physiological testing

Food consumption. Twenty-four hour food consumption data were collected at 7 and 28 days after pump-implantation.

Body weight and composition. Body weight was measured weekly for all animals. Determination of body composition was assessed by time domain-nuclear magnetic resonance (TD-NMR) using a Minispec analyzer (Bruker Optics, The Woodlands, TX). TD-NMR testing allows for rapid (approximately 1 min) assessment of body composition in awake, restrained animals. Absolute values for fat, lean, and fluid mass were recorded. At each time point, each animal was tested twice and the average of those results is reported.

Open-field activity. Animals were placed into Plexiglas open-field testing chambers (690 cm × 555 cm) for 5 min and movement was tracked using an overhead camera and computer software (EthoVision, Noldus Information Technology, Wageningen, Netherlands). General activity levels were determined by assessing the total distance traveled. The amount of time spent along the margin of the open field as opposed to the center was taken as a measure of anxiety. The margin was defined as a 3-cm wide strip around the outside of the box.

Grip strength. Forelimb grip strength was measured using a Chatillon force gauge (Ametek, Largo, FL). Animals were placed so their forepaws were on a wire grid connected to the force gauge. Animals were then pulled away from the wire grid, while the force meter recorded the maximum force exerted on the wire grid. Animals were given three consecutive trials, and the maximum force was taken as a measure of grip strength.

Rotarod. Agility and balance were tested using a Rotamex® rotarod device (Columbus Instruments, Columbus, OH). Animals were given 2 days of training, in which they were placed on the 3.5 inch rotarod turning at a rate of 4 rpm. Animals falling in less than 30 s were placed immediately back on the drum for another trial with a maximum of three trials and a time limit of 60 s. Two days after the second training session, baseline performance was assessed. Animals falling prior to 60 s were immediately given a second trial, and trials were a maximum of 300 s in duration.

2.4. Statistics

For baseline assessments, one-way ANOVA with age as a factor was used. In cases of unequal variance and non-normal data, a Kruskal–Wallis one way analysis of variance on ranks was performed. For drug administration and withdrawal data, primary statistical analysis consisted of separate two-way repeated measures ANOVA comparing age and treatment phase within each drug group. Subsequent statistical analyses consisted of two-way ANOVA comparing age and drug group for each phase of testing (i.e. early drug, late drug, early withdrawal, and late withdrawal). Student–Newman–Keuls post-hoc tests were performed where appropriate. Differences were considered statistically significant when p-values were less than 0.05. All statistical tests were performed using SigmaStat version 3.11 (Systat Software, Inc, San Jose, CA).