Journal of Pharmacological and Toxicological Methods 80 (2016) 9–18

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

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

Successful implantation of an abdominal aortic blood pressure transducer and radio-telemetry transmitter in guinea pigs — Anaesthesia, analgesic management and surgical methods, and their influence on hemodynamic parameters and body temperature

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ARTICLE INFO

Article history:
Received 4 December 2015
Received in revised form 14 March 2016
Accepted 14 March 2016
Available online 16 March 2016

Keywords:
Anaesthesia
Analgesia
Arterial blood pressure
Cavia porcellus
Core body temperature
Guinea pig
Heart rate
Implantation
Methods
Radio-telemetry

ABSTRACT

Introduction: Guinea pigs (GPs) are a valuable cardiovascular pharmacology model. Implantation of a radio-telemetry system into GPs is, however, challenging and has been associated with a high failure rate in the past. We provide information on a novel procedure for implanting telemetry devices into GPs and we have measured the hemodynamics (arterial blood pressure, BP and heart rate, HR) and core body temperature (BT) in the 24 h after surgery.
Methods: Male Hartley GPs (Crl:HA, 350-400 g, 6.5 weeks, n = 16) were implanted with a radio transmitter abdominally and were then monitored continuously (HR, BP and BT) for 24 h after surgery.
Results: 13 of 16 GPs (81%) survived the surgery. Surgery duration was 94 min (min) (range: 76–112 min) and anaesthesia duration was 131 min (range: 107–158 min). GPs lost body weight until 2 days after surgery and then regained weight. Mean arterial BP increased from 33.7 mm Hg directly after surgery to 59.1 mm Hg after 24 h. HR increased from 206 bpm directly after surgery to 286 bpm at 8 h and fell to 251 bpm at 24 h after implantation. BT was 36 °C directly after surgery, fell to 35.4 °C until regaining of the righting reflex and then stabilized at 38.5 °C after 24 h.
Discussion: A high survival rate in telemetered GPs is possible. We achieved this through a procedure with minimal stress through habituation and planning, continuous warming during anaesthesia, an optimal anaesthetic and analgesic management, efficient surgical techniques and vitamin C supplementation.

1. Introduction

The guinea pig (GP) is a valuable small animal model for studying cardiovascular pharmacology, particularly when evaluating electrocardiogram-derived (ECG) parameters. GPs express the myocardial human-Ether-a-go-go Related Gene channel which rats do not. Its dysfunction or pharmacological blockade can cause the potentially fatal "long QT syndrome". Therefore, drug candidates can be tested for their effect on QT prolongation in the GP (Katagi et al., 2015). Also, compared to larger animal models, GP have a low body weight (BW) and hence need less test substance and have lower costs for their purchase and housing (Hess, Rey, Wanner, Steiner, & Clozel, 2007).

The direct, intravascular measurement of aortic blood pressure and the ECG using radio-telemetry has established itself as the model-of-choice for testing drug candidates for possible cardiovascular effects. It allows the acquisition of data from conscious, unrestrained animals, with little human influence and over long periods of time (Kurtz, Griffin, Bidani, Davisson, & Hall, 2005). Core body temperature (BT), locomotor activity and biopotentials (EEG, electromyogram; (Leon, Walker, DuBose, & Stephenson, 2004) can likewise be measured. However, abdominal radio transmitter implantation into GPs has proved to be very challenging and has been associated with high failure rates.

Guinea pigs are one of the most difficult rodents to anaesthetize safely (Schwenke & Cragg, 2004), with a limited choice of acceptable anaesthetics and the need for a well prepared surgery. The high surface to body volume ratio of the GP, combined with the inadequate thermoregulatory control mechanisms and the thermoregulatory depression of anaesthetics, causes a rapid BT loss during anaesthesia (Buchanan, Burge, & Ruble, 1998). Open abdominal surgery leads to a particularly fast temperature loss, making external body warming

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http://dx.doi.org/10.1016/j.vascn.2016.03.003
1056-8719/

essential (Kiyatkin & Brown, 2005). The body weight (BW) of GPs can vary widely as the intestinal filling accounts for up to 20–40% of the total BW, resulting in dosing inaccuracies of any injectable anaesthetic agent (Henke, 1998). The GP low resting mean arterial BP of 63 mm Hg (DePasquale, Ringer, Winslow, Buchholz, & Fossa, 1994)(DePasquale et al., 1994), the anatomically deeply embedded and fragile abdominal aorta (Provan, Stanton, Sutton, Rankin-Burkart, & Laycock, 2005) and the large caecum (Popesko, Rajtová, & Horák, 1992) additionally impede BP catheter placement into the abdominal aorta. Thus, multiple factors have contributed to the low success rate of this method in the GP.

During the implantation, the mentioned complications (multifactorial temperature loss, relatively risky anaesthesia, low arterial BP and fragile vascular structure) likely lead to changes in HR, BT and BP. So far, there is no data on the surgery's impact on the hemodynamic values in the first 24 h after radio transmitter implantation in GPs.

We provide a detailed description of a successful implantation approach into GPs, including anaesthesia, analgesia and surgical technique. We further report for the first time, data for BP, HR and BT during the critical first 24 h after abdominal surgery.

The following information can be utilized in any other abdominal surgery in the GP, both in experimental models and in curative approaches.

2. Methods

All experiments and procedures were performed in accordance with the German Animal Welfare Act (Art. 3 G v. 28.07.2014 I 1308) and the regional council for animal welfare.

2.1. Housing and acclimatization

Sixteen male Hartley GPs (Charles River Laboratories, Sulzfeld, Germany) (Crl:HA, delivery weight 350–400 g, average age of 6.5 weeks) were housed for 19 days prior to the radio-telemetry device implantation in groups of 2–3 in cages (EHRET TERULAN THF 1776) containing wooden bedding material (Lignocel FS14, Rettenmaier & Söhne, Rosenberg, Germany) and 2 red transparent plastic shelters.

Cage bedding changes were performed twice weekly. The GPs received 20 g/animal of pelleted, commercially available diet (3410 complete feed, KLIBA NAFAG, Provimi Kliba Sa., Kaiseraugst, Switzerland) and a large amount of autoclaved hay daily. Tap water was available *ad libitum*. The animal room was maintained at 20 ± 2 °C and 55 ± 10% relative humidity with an air change of at least 15 cycles/h. The light–dark cycle was 12:12, starting (5:30) and ending (17:30) with a dimmer phase of 30 min. For background acoustic habituation, radio music was simultaneously switched on and off with the lights. BW and the general condition of each animal were monitored daily. Beginning two weeks before the implantation, the animals were handled and acclimatized daily to being held, single housed for two hours in Makrolon® Type III cages with identical enrichment to their home cages and to being placed into the radio-telemetry data acquisition room. The GPs received 20 mg of Vitamin C in an aqueous solution orally for 7 days prior to and for 14 days after the implantation.

All habituation handling, medication, surgery and post-operative care was done by the same veterinarian.

2.2. Implantation of the radio transmitter system

Before the surgery, all electrical devices were checked for faultless function. On the morning of the surgery, the room and materials were arranged before the arrival of the animal.

The GP was removed from its home cage, weighed, examined clinically (checked for aberrant posture, behaviour, eyes, nose, fur), given the first oral dose of antibiotic dissolved in drinking water (enrofloxacin 10 mg/kg; for detailed medication and supplement list see Table 1) and singly placed into a Makrolone® III cage, containing cellulose bedding, 1 red shelter, pelleted food, autoclaved hay and a water bottle. The animal was then transported to the surgical preparation area.

After an average of 45 min after enrofloxacin medication, the GP was injected intramuscularly (i.m.; *m. semimembranosus/m. semitendinosus/m. biceps femoris*) with MMF (Henke, 2010; medetomidine 0.2 mg/kg, midazolam 1.0 mg/kg, fentanyl 0.025 mg/kg, see Table 1) and was returned to the cage until the righting reflex (RR, the animal rights itself when placed on its back) had disappeared. An additional one third of the initial MMF dose was given during the surgery to maintain surgical tolerance, which was assessed by evaluation of a mildly positive reaction to foot withdrawal (withdrawal of hind leg to a fingernail pinch on 1 toe with extended hind leg) and inguinal reflex (the hind leg is kicked as a response to a pinch in the inguinal region with a curved clamp up to the first catch). For surgical preparation the GP was then placed in dorsal recumbency on a heating mat, the abdominal and neck area was shaved

Table 1
Medication and vitamin supplement used for abdominal radio transmitter implantation and for pre- and post-surgical treatment in guinea pigs.

Purpose	Product name	Brand name/manufacturer
Anaesthesia-agonists	MMF = Medetomidine[1] 0.2 mg/kg + Midazolam[2] 1.0 mg/kg + Fentanyl[3] 0.025 mg/kg intramuscularly (i.m.) in mixed syringe	[1]DOMITOR®, 1 mg/mL, Orion Corporation, Espoo, Finland [2]Dormicum® 5 mg/mL, Roche Pharma AG, Grenzach-Wyhlen, Germany [3]Fentanyl®-Janssen 0.1 mg/2 mL, JANSSEN-CILAG, Neuss, Germany
Anaesthesia-antagonists	AFN = Atipamezole[4] 1.0 mg/kg + Flumazenil[5] 0.1 mg/kg + Naloxone[6] 0.03 mg/kg i.m. in mixed syringe	[4]ANTISEDAN® 5 mg/mL, Orion Corporation, Espoo, Finland [5]Flumazenil HEXAL® 0.1 mg/mL, HEXAL AG, Holzkirchen, Germany [6]Naloxon Inresa 0.4 mg/mL, Inresa Arzneimittel, Freiburg, Germany
Local anaesthetic	Lidocaine hydrochloride 0.9 mL/animal, subcutaneous (s.c.)	Xylocain® 1%, AstraZeneca, Wedel, Germany
Antibiotic	Enrofloxacin 10 mg/kg, oral (p.o.)	Enrotron® 100 mg/mL oral solution for drinking water dilution, aniMedica, Senden-Bösensell, Germany
Analgesia/anti-inflammation	Meloxicam 0.4 mg/kg, s.c./p.o.	Metacam® 2 mg/mL, Boehringer Ingelheim Vetmedica, Ingelheim/Rhein, Germany Metacam® oral suspension 1.5 mg/mL, Boehringer Ingelheim Vetmedica, Ingelheim/Rhein, Germany
	Metamizole 80 mg/kg i.m. p.o.	Novalgin® 1 g/2 mL, Sanofi-Aventis Deutschland, Frankfurt am Main, Germany Metamizol HEXAL® oral drops, 500 mg/mL, HEXAL AG, Holzkirchen, Germany
Supplement	Pure L-ascorbic acid 20 mg/day solved in sodium chloride solution, p.o.	Vitamin C Pulver, dm-Drogerie Markt, Karlsruhe, Germany