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RESEARCH PAPER

Endothelin receptor subtype A blockade does not affect the haemodynamic recovery from haemorrhage during xenon/remifentanil or isoflurane/remifentanil anaesthesia in dogs

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Abstract

Objective To test the compensatory role of endothelin-1 when acute blood loss is superimposed on anaesthesia, by characterizing the effect of systemic endothelin receptor subtype A (ET_A) blockade on the haemodynamic and hormonal responses to haemorrhage in dogs anaesthetized with xenon/remifentanil (X/R) or isoflurane/remifentanil (I/R).

Study design Prospective experimental randomized controlled study.

Animals Six female Beagle dogs, 13.4 ± 1.3 kg.

Methods Animals were anaesthetized with remifentanil 0.5 μg kg^{-1} $minute^{-1}$ plus either 0.8% isoflurane (I/R) or 63% xenon (X/R), with and without (Control) the systemic intravenous endothelin receptor subtype A antagonist atrasentan (four groups, $n = 6$ each). After 60 minutes of baseline anaesthesia, the dogs were bled (20 mL kg^{-1}) over 5 minutes and hypovolemia was maintained for 1 hour. Continuous haemodynamic monitoring was performed via femoral and pulmonary artery catheters; vasoactive hormones were measured before and after haemorrhage.

Results In Controls, systemic vascular resistance (SVR), vasopressin and catecholamine plasma concentrations were higher with X/R than with I/R anaesthesia at pre-haemorrhage baseline. The peak increase after haemorrhage was higher during X/R than during I/R anaesthesia (SVR 7420 ± 867 *versus* 5423 ± 547 dyne seconds cm^{-5}; vasopressin 104 ± 23 *versus* 44 ± 6 pg mL^{-1}; epinephrine 2956 ± 310 *versus* 177 ± 99 pg mL^{-1}; norepinephrine 862 ± 117 *versus* 195 ± 33 pg mL^{-1}, $p < 0.05$). Haemorrhage reduced central venous pressure from 3 ± 1 to 1 ± 1 cmH_2O (I/R, ns) and from 8 ± 1 to 5 ± 1 cmH_2O (X/R, $p < 0.05$), but did not reduce mean arterial pressure, nor cardiac output. Atrasentan did not alter the haemodynamic and hormonal response to haemorrhage during either anaesthetic protocol.

Conclusions and clinical relevance Selective ET_A receptor blockade with atrasentan did not impair the haemodynamic and hormonal compensation of acute haemorrhage during X/R or I/R anaesthesia in dogs.

Keywords anaesthesia, atrasentan, catecholamines, dog, haemorrhage, xenon.

Introduction

Acute blood loss is a potential trigger for transient or prolonged hypotensive episodes during surgical anaesthesia. An important effect of vasoactive hormones, such as epinephrine, norepinephrine, vasopressin, endothelins and angiotensin II, is to regulate vascular tone and systemic vascular resistance (SVR), to limit the decrease in arterial blood pressure and cardiac output, and to defend the perfusion of vital organs and tissues. Specifically, acute inhibition of angiotensin II receptors (subtype AT_1) exacerbates hypotension and impairs cardiac output in a model of acute haemorrhage in non-splenectomized dogs (Francis et al. 2004; Höhne et al. 2004). These deleterious effects have been observed in conscious and anaesthetized animals. Consequently, those patients who are treated with angiotensin II subtype AT_1 receptor antagonists are exposed to a high risk of hypotension during intraoperative blood loss. Another important vasoconstrictor mechanism is based upon activation of vascular endothelin receptor subtype A (ET_A). Endothelin receptor antagonists, such as bosentan, atrasentan, tezosentan, sitaxsentan or ambrisentan, have been clinically evaluated and are increasingly used to treat pulmonary hypertension or acute heart failure (Barst et al. 2004; Galie et al. 2005; Battistini et al. 2006).

The ET_A receptor antagonist atrasentan does not affect the blood pressure response provoked by induction and maintenance of xenon or isoflurane-based anaesthesia in dogs (Francis et al. 2006). However, the impact of endothelin receptor antagonists on the haemodynamic response to acute blood loss is a highly relevant, yet unexplored concern in clinical physiology and anaesthesiology.

The present study is part of a much wider investigation into the effects of ET_A receptor blockade, angiotensin II receptor blockade, or both; their influence in the response to haemorrhage and if these changes are altered by the anaesthetic regimen in use (Höhne et al. 2004, 2008; Francis et al. 2006, 2008). The series of experiments were designed so as to reduce the number of procedures necessary for any one dog, and therefore the results of one series of experiments have acted as controls for the next. The present study specifically asks if systemic ET_A receptor inhibition would affect the circulatory and hormonal response in anaesthetized dogs that had 20 mL kg^{-1} of blood withdrawn in <5 minutes, to mimic acute intraoperative bleeding.

Materials and methods

This study was approved (G 0424/99-04) by the Local Animal Protection Committee in accordance with the German Animal Protection Law and adheres to the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Research 1996).

Animal maintenance and dietary regimen

Healthy, pure-bred, 2-year-old, female Beagle dogs (mean body weight: 13.4 ± 1.3 kg) were kept under highly standardized environmental conditions (air-conditioned room at 21 °C and 55–60% humidity) and received a dietary regime which was standardized for feeding time, as well as sodium, potassium and water intake as described previously (Höhne et al. 2002; Francis et al. 2004, 2006). Dogs were examined for physical health and well-being every day, including body weight, body temperature and social behaviour. Eight days prior to the experiments, 80 mL of each dog's own blood was withdrawn via a foreleg vein and stored in a blood bag at 4 °C (Biopack Compoflex CPDA-1; Biotrans, Germany). Whenever blood samples were taken for analysis during the experiment, stored blood was used to replace the specific amount of blood immediately. There was an interval of 14–42 days between experiments in the same dog to avoid possible interactions between the different anaesthetics or latent effects from the haemorrhage and retransfusion. The animals had intensive training and were gradually familiarized with the staff, the experimental procedures, and with all interventions that had to be carried out while the dogs were conscious. By this means, no sedatives, with potential cardiovascular or other side effects, were required.

Instrumentation and monitoring

This study reports a total of 24 experiments that were performed on six dogs subjected to four different experimental protocols. Preparation of the dogs started at 07:30 hours. Body weight and temperature were recorded. Topical anaesthesia (Lidocaine gel 4%; B.Braun, Germany) was used to minimize any discomfort associated with the insertion of a self-retaining transurethral urine catheter. A venous cannula (Venflon 20 gauge; BD, Germany) was inserted percutaneously into a cephalic