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RESEARCH PAPER

Haemodynamic differences between pancuronium and vecuronium in an experimental pig model

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Abstract

Objective To compare baseline cardiovascular function in anesthetised pigs using either pancuronium or vecuronium as a neuromuscular blocker.

Study design Retrospective, non-randomized comparison.

Animals Norwegian Land Race pigs (*Sus scrofa domesticus*) weighing mean 42 ± SD 3 kg.

Methods One hundred and sixteen animals from four different research protocols premedicated with identical doses of ketamine, diazepam, atropine and isoflurane, and anaesthetised with pentobarbital, fentanyl, midazolam and N_2O were arranged into three uniform groups with respect to neuromuscular blocking agent: pancuronium bolus of 0.063 mg kg^{-1} followed by 0.14 mg kg^{-1} $hour^{-1}$ (n = 54), low-dose vecuronium 0.4 mg kg^{-1}/0.2 mg kg^{-1} $hour^{-1}$ (n = 29) and high-dose vecuronium 0.6 mg kg^{-1}/0.3 mg kg^{-1} $hour^{-1}$ (n = 33).

Results The majority of cardiovascular parameters demonstrated no significant differences between groups. For heart rate, there was an overall group difference, $p = 0.036$. Dromotropy was low in the pancuronium group, with an increased normalised PR-interval compared to the high-dose vecuronium group, median 0.200 interquartile range (0.190, 0.215) *versus* 0.182 (0.166, 0.199), $p < 0.05$. Left ventricular compliance was increased in pancuronium-treated animals, demonstrated as a reduction in the nonlinear end-diastolic pressure volume relationship β compared to both vecuronium groups, 0.021 (0.016, 0.025) *versus* 0.031 (0.025, 0.046) and 0.031 (0.022, 0.048), $p < 0.05$. The linear end-diastolic pressure volume relationship $EDPVR_{lin}$ was reduced as well in the pancuronium group, compared to the low-dose vecuronium group, 0.131 (0.116, 0.169) *versus* 0.181 (0.148, 0.247), $p < 0.05$.

Conclusions There are only minor haemodynamic differences when using pancuronium compared to vecuronium in the fentanyl-pentobarbital-midazolam-N_2O anesthetised domestic pigs. Furthermore, increasing doses of vecuronium have minimal haemodynamic effects.

Clinical relevance Experimental studies in pigs using either pancuronium or vecuronium as a neuromuscular blocking agent are comparable with regard to cardiac and haemodynamic performance.

Keywords cardiovascular, haemodynamic effects, neuromuscular blockers, pancuronium, pigs, vecuronium.

Introduction

In cardiac research, the *in vivo* large animal model is an important tool for translating knowledge from basic research into clinical trials and practise. Together with the possibility of using more invasive

techniques and methods developed for experimental research, one of the key points in such models is the standardization of the study population, allowing statistically powerful studies on relatively few subjects. Experimental cardiac research inevitably involves monitoring haemodynamic parameters as a way to evaluate cardiovascular performance. As anaesthetic agents have a particularly significant impact on the cardiovascular system, a strict standardised anaesthetic regime is essential for the predictability and stability of such research protocols.

In addition to analgesic and hypnotic agents, general anaesthetic protocols may also include neuromuscular blocking agents. These are used to facilitate endotracheal intubation, prevent involuntary muscular contraction and disturbance of surgical procedures, as well as to minimise shivering during tepid/hypothermic cardiopulmonary bypass. The two muscle relaxants studied, pancuronium (Pavulon; Organon, Norway) and vecuronium (Norcuron; Organon, Norway), are both non-depolarising neuromuscular blocking agents. Pancuronium has been previously demonstrated to possess stimulatory haemodynamic effects in man (Ferres et al. 1987; Sethna et al. 1987; Virmani et al. 2006) and animals (Domenech et al. 1976). In cardiac surgery and experimental settings, these effects are beneficial, and thus pancuronium has been used widely (Murphy et al. 2002). Vecuronium seems to have only minor cardiovascular implications across species (Booij et al. 1980; Chen et al. 1991; Husby et al. 1996), as well as in increasing doses in man (Chen et al. 1991; Husby et al. 1996), although parasympatholytic effects have been reported in dogs (Narita et al. 1992).

The use of muscle relaxants in experimental animal models is restricted, and should not be used unless the anaesthetic protocol has been meticulously evaluated without neuromuscular blocking agents in the species studied. This would ensure that sedation and analgesia is sufficient, thus preventing paralysis of the animal in a conscious/semiconscious state (Institute for Laboratory Animal Research 2010). An anaesthetic protocol allowing the use of muscular relaxation was documented prior to the introduction of muscle relaxants in our studies (Fannelop et al. 2004). Our research group has used pancuronium as a neuromuscular blocking agent in a porcine model related to tepid cardiopulmonary bypass, cardioplegic arrest and reperfusion, primarily to counteract the effects of shivering during controlled hypothermia. The instrumentation was identical in all included animals, intended for extensive evaluation of haemodynamic and cardiac function, together with load-independent variables describing systolic and diastolic function before and after cardiac arrest. As a result of pancuronium's deregistration in Norway in 2010, costs and supply has forced the use of vecuronium instead.

In this retrospective non-randomised study, we hypothesised that using vecuronium instead of pancuronium in pigs has only minor or no cardiac and haemodynamic influences on this experimental pig model, making such studies comparable.

Material and methods

Animals

From four experimental animal protocols with Norwegian Land Race pigs (*Sus scrofa domesticus*), the baseline cardiac and haemodynamic variables from a total of 116 pigs were compared. By combining baseline values from these studies, the large number of animals allows valid statistical evaluations without the need for separate animal experiments. The Norwegian State Commission has approved all experimental protocols (project No. 2004220, 20092088 and 20113923) that have been conducted in accordance with regulations of the European Communities Council Directives of 1986 and 2010. Animals were acclimatised for at least seven days in our animal facility under controlled lighting, humidity and temperature, and cared for under veterinary surveillance. The pigs were fed with a standard commercial young pig diet twice daily. Before the surgical procedure, animals were fasted overnight, but given free access to water.

Anaesthesia

All pigs were premedicated with ketamine (20 mg kg^{-1}), diazepam (10 mg) and atropine (1 mg) by intramuscular injection in the dorsal region of the neck and then weighed. Body surface areas (BSA) were calculated by the formula $BSA = k\,BW^{2/3}/100$, where BW is bodyweight in kilogrammes, and k for pigs is 9 $m^2\ kg^{-2}$. The pigs weighed (mean ± SD) 42 ± 3 kg with a calculated body surface area of 1.09 ± 0.06 m^2. During a short period of ventilation with oxygen and 3% isoflurane by mask, two ear veins were cannulated for administration of