The Veterinary Journal 236 (2018) 12–22

Contents lists available at ScienceDirect

The Veterinary Journal

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

Review

A review of factors affecting analgesic selection in large animals undergoing translational research

R.E. Clutton

The Wellcome Trust Critical Care Laboratory for Large Animals, Roslin Institute, Easter Bush Veterinary Centre, Roslin, Midlothian EH25 9RG, United Kingdom

ARTICLE INFO

Keywords:
Analgesics
Animal models
Pigs
Sheep
Translational research

ABSTRACT

The widespread physiological effects of pain in experimental animals are likely to reduce the validity of data except when pain itself is studied. Appropriately prescribed analgesics will limit pain and improve the welfare of animals undergoing noxious experimental procedures. However, their injudicious use may also introduce variability in data and limit study reproducibility. Optimizing both animal welfare and the value of scientific data from experimental studies requires the ability to identify, quantify and treat animal pain by applying a knowledge of analgesic pharmacology that is sympathetic to study objectives. This review first examines the reasons for promoting analgesic use in translational animal research and, in focussing on pigs and small ruminants, then identifies factors that should be considered when devising analgesic plans.

Introduction

Animal models in translational research

Translational research applies the outcome of basic scientific research to the treatment or prevention of human disease. This "bench-to-bedside" approach has been formalised into nine elements several of which may involve animals for experimental or regulatory purposes (Cooksey, 2006). The basic research and prototype discovery and design stages tend to involve rodents; larger animals are often involved in preclinical development. The animal species chosen depends on model validity and the research output, e.g., new drugs or vaccines, medical devices, diagnostic methods, surgical techniques (Roth and Tuggle, 2015). Increasingly, choice is being extended by the creation of genetically-edited animals (Nancarrow et al., 1993; Aigner et al., 2010). Similarities in whole body and organ size between humans, sheep and pigs, make production animal species popular in the development of medical devices and surgical methods, and in transplantation research (Klymiuk et al., 2010). This review will focus on analgesics in pigs and sheep.

Analgesics: role in pain management in animal models

Pain management involves its recognition, quantification and treatment. While there are non-pharmacological methods of treating pain (see later) this review focuses on the role and selection of analgesics. Analgesics have four major roles in animals involved in translational research: 1) pharmacokinetic/pharmacodynamic (PK/PD) studies of analgesic drugs; 2) incidental (non-experimental) pain management, e.g., bite-wounds in group-housed non-human primates; 3) reducing anaesthetic requirements in noxious procedures conducted under general anaesthesia; 4) reducing – ideally eliminating – post-procedural pain in recovery experiments, e.g., experimental surgery or physiological instrumentation, so that humane end-points (HEPs) are not exceeded. This article reviews points 3 and 4.

Analgesia; defence of use in animal models

An Ipsos MORI report[1] (2016) indicated that 71% of (UK-based) respondents considered animal use in research to be acceptable providing there was no unnecessary suffering. Suffering arising from pain may be alleviated by analgesics. The use of analgesics in research animals is justified on ethical, legal, medical and scientific grounds.

Analgesic use in laboratory animals is one of four elements of

E-mail address: e.clutton@ed.ac.uk (R.E. Clutton).

[1] See: https://discover.ukdataservice.ac.uk/catalogue?sn=8059.

https://doi.org/10.1016/j.tvjl.2018.04.006
1090-0233/

refinement, which along with *reduction* and *replacement*, constitutes the three "Rs" (Russell and Burch, 1959). The "3Rs" form a widely accepted ethical basis for animal use in research. Arguably, the ethical case for analgesic use in translational, rather than developmental research is stronger – particularly if the immediate human beneficiary of that research is likely to receive analgesics under similar circumstances. Failure to treat the translational animal model in the same way as the modelled human undermines model validity and is fundamentally unjust. Morton and Griffith (1985) point out that if animals are used to study human pain, then logically, it has to be taken that they similarly feel pain. Animals (Mogil et al., 2010) including pigs (Castel et al., 2014) and sheep (Wilkes et al., 2012) are used to study human pain.

Implementing the 3Rs is a major element of UK and EU legislation controlling research animal use, and project licence applications to conduct animal experiments in the UK must explicitly detail concordance with the 3Rs principle (Home Office (UK) 2014).[2] Therefore, consideration of analgesic use in proposed studies is a prerequisite to Home Office project approval. Similar consideration is promoted by Brambell's 5 Freedoms which assert that agricultural animal welfare is optimized by ensuring (amongst other things) freedom from: discomfort, pain, injury, disease, fear and distress (1965).

The ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines, introduced to 'maximise the output from research using animals by optimising the information that is provided in publications on the design, conduct and analysis of experiments' (Kilkenny et al., 2010) recommend the provision of precise details of the anaesthesia and analgesia used, including the drug formulation, and dose, site, and routes of administration.

Poorly managed acute (and chronic) pain in humans has widespread behavioural and physiological effects (Apfelbaum et al., 2003). There are reasons to assume the same is true in animals (Morton and Griffiths, 1985); see Tables 1 and 2. When present during data collection, pain reduces data quality by increasing variability and in reducing study "power", limits experimental reproducibility (Jirkof, 2017). The considered use of suitable analgesics will reduce pain during these periods and increase study power. Even permissible pain, i.e., that not transcending HEPs, may obfuscate physiological variables and invalidate study findings. The confounding effects of pain on study data may differ from the side-effects of analgesics (see below) but may be equally important in undermining their quality.

Analgesia; points against use in animal models

Analgesics produce effects beyond pain suppression (Table 2) which will increase variability in collected data and reduce study power. This concern has led to the limited use or exclusion of analgesics from animal studies (Fenwick et al., 2010). While pharmacological-mediated variability may be the lesser of two evils – being associated with lower pain levels – *any* loss of power means additional animals are needed to meet study objectives, so undermining *reduction*. This refinement vs. reduction conundrum means that the ideal analgesic protocol (drugs, doses and dosing patterns) should, where possible, be standardisable, and adequately control pain without producing side-effects (Jirkof, 2017).

Specific analgesics may be unsuitable in certain experiments because they directly affect study objectives, e.g., using non-steroidal anti-inflammatory drugs in inflammation models, or ketamine in NMDA agonist studies. Under these circumstances, analgesics with different pharmacodynamic properties must be used. Resistance to analgesic use also arises from concerns that describing new protocols in submitted articles may, in deviating from accepted methodologies, attract editorial criticism and delay, or prevent publication (Schofield and Williams, 2002). Concerns with accuracy in detecting pain (Hawkins, 2002) and a lack of knowledge about techniques assessing, monitoring and treating pain (Karas, 2006) also lead to analgesic under-prescription. Concerns with analgesic side-effects, which were commonly identified as reasons for withholding analgesics from animals e.g., Capner et al. (1999), are largely unfounded, having arisen from flawed scientific methodology, observer bias and misleading reportage (Clutton, 2010).

Reported use of analgesics in laboratory animals

Despite the benefits and requirements for analgesia in animal experiments, reports of their use in scientific articles is inadequate in detail and extent (Carbonne and Austin, 2016). Large animals are more likely to receive analgesics than rodents: Coulter et al. (2009) compared material published in 2000–2001 and 2005–2006 and found reported analgesic use was unchanged in experimental pigs (67%) but had increased in sheep (from 64 to 73%). However, whilst a study of analgesic use in laboratory pigs found 83% of 233 reviewed articles described use of drugs with analgesic properties, e.g., ketamine, only 37% explicitly described the prescription of postoperative analgesia (Bradbury et al., 2016).

Considerations in selecting analgesics in animal experiments

The analgesic plan

The PREPARE guidelines (Smith et al., 2018) list some pre-experimental requirements in formulating an analgesic plan: definition of a severity classification; identifying objective, measurable and unequivocal HEPs; and indicating primary and contingency methods for responding to impending HEPs e.g., increased analgesic doses, additional drugs, or euthanasia. PREPARE also requests that relevant details (drug type[s], dose [s], route[s] of administration, the time therapy begins and re-dosing frequency) of the proposed anaesthetic and analgesic plan be established *beforehand*. The proposed plan must be agreed between scientists (to ensure compatibility with study objectives), supervising veterinarians (to ensure efficacy), "named" personnel and, or the institutional Animal Welfare and Ethical Review Board (AWERB; to ensure regulatory compliance) and animal technicians (to ensure feasibility). Proposed plans will be scrutinized by the institutional AWERB (or Institutional Animal Care and Use Committee) who, in conjunction with additional specialists may approve, or recommend changes. In the UK, further amendments may be required by the Animal in Science Regulatory Unit before the project license is granted and the study allowed to proceed.

The reason why, and preference for scientists to adhere to established, published methodologies – including analgesic plans – must be appreciated. However, given that reported descriptions of pain management in many studies are either inadequate or absent (Richardson and Flecknell, 2005; Stokes et al., 2009; Bradbury and Clutton, 2016; Bradbury et al., 2016) material supporting maintenance of the *status quo* should be reviewed critically. Problems arising from the absence of adequate or convincing detail in published material may be resolved by contacting corresponding authors (Stokes et al., 2009; Bradbury and Clutton 2016). The case for withholding analgesics from animal experiments on scientific grounds should be made in writing to the appropriate ethical review process (Schofield and Williams, 2002).

[2] See: https://www.gov.uk/government/publications/operation-of-aspa.