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Transdermal fentanyl and its use in ovine surgery

Chris Christou *, Rema A. Oliver, John Rawlinson, William R. Walsh

Surgical and Orthopaedic Research Laboratory, Prince of Wales Clinical School, University of New South Wales, Level 1 Clinical Sciences Building Avoca St, Randwick 2031 Australia

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ABSTRACT

Fentanyl delivered via a transdermal patch has the potential to decrease the need for post-operative handling of sheep undergoing surgical procedures. Two studies were performed to test: (1) the ideal timing for the application of pre-emptive analgesic patches and (2) the efficacy of a 2 μg/kg/h dose, as extrapolated from other species.

The first study had sheep divided into two groups. Group 1 had a fentanyl patch applied for 24 h prior to a patch change and group 2 had a fentanyl patch applied 72 h prior to a change.

The second study applied the results obtained in the first and tested the efficacy of 2 μg/kg/h as an effective dose in an orthopaedic surgical environment.

Results indicated that the ideal time for pre-emptive fentanyl patch administration is 24–36 h prior to surgery and that 2 μg/kg/h is an effective minimum therapeutic dose rate for the use of fentanyl as an analgesic in an orthopaedic surgical environment.

1. Introduction

With the use of sheep as pre-clinical orthopaedic research models gaining momentum, the ethical considerations regarding their husbandry and the control of pain becomes paramount. The Australian code for the care and use of animals for scientific purposes states "The use of local and general anaesthetics, analgesics and sedatives must be considered as part of a plan to manage pain and distress, and such use should at least parallel their use in current veterinary or medical practice."(Australian Government, 2013)

The definition of pain has been debated philosophically over the ages and has changed as knowledge has increased. Pain has been described as an unpleasant sensory or emotional experience associated with actual or perceived tissue damage (Rollin, 1999).

Pain can arise from two physiological processes, tissue damage and the associated release of prostaglandins and other inflammatory cytokines, and from direct nerve damage or stimulation. Sensitisation to pain occurs as a result of a decreased threshold of nociceptor peripheral nerve terminals and an increased excitability of central neurones (Woolf and Chong, 1993). There are two major classes of systemic analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. NSAIDs assist with minimising the effects of the inflammatory cytokines in the peripheral tissues. Opioids work by increasing the threshold of excitability of the peripheral and central neurones (Lotsch et al., 2013). The daily need for injection of NSAIDs and the short 3–6 h duration of action for the commonly used opioids increases the demand of handling the sheep after any operative procedure which is expected to induce ongoing pain. This increased post-operative handling and injecting of the sheep does not only increase stress, it can also lead to further injury should the animal panic during the handling process. The effects NSAIDs can have on bone healing, via their anti-prostaglandin action, can also lead to complications in result reporting and is a significant consideration in fracture healing models (Barry, 2010; Pountos et al., 2012). The opioid mechanism of action is via receptors in the central and peripheral nervous system and therefore opioid analgesics have no direct impact on bone healing (Sehgal et al., 2011). Three major opiate receptor types are recognised within the central nervous system (CNS) and were named based on the compound that originally resulted in specific receptor binding. These are the mu (μ), delta (δ), and kappa (κ) opiate receptors that bind to morphine, dynorphin, and ketocyclazocine, respectively (Kukanich and Clark, 2012). mu-Receptor agonists are noted for their ability to produce profound analgesia with mild sedation (Hofmeister and Egger, 2004).

Fentanyl is an opioid analgesic developed as an alternative to morphine in 1960 in an effort to provide increased potency and fewer side effects (Stanley, 1992). Like morphine, fentanyl binds to mu receptors, but it has a potency 80–100 times greater than morphine (Ahern et al., 2009). The major drawback of opioid analgesics, however, is their short half-life after IV or IM injection which again raises the issue of increased post-operative handling.

Since 1991 fentanyl has become available as a slow release transdermal patch sold under the trade name Durogesic by Janssen

* Corresponding author. Surgical and Orthopaedic Research Laboratory, Prince of Wales Clinical School, University of New South Wales, Level 1 Clinical Sciences Building Avoca St, Randwick 2031, Australia. Tel.: +61 2 93824040; fax: +61 3 93822660.
E-mail address: c.christou@unsw.edu.au (C. Christou).

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Pharmaceuticals (Hofmeister and Egger, 2004). While developed for use in human medicine, fentanyl patches have also found favour as an off label analgesic in the veterinary world. Fentanyl has been studied in many species including dogs, cats, horses and sheep at a dose rate of 2 μg/kg/h (Ahern et al., 2010; Hofmeister and Egger, 2004; Orsini et al., 2006). A drawback of the fentanyl patch is its slow uptake to therapeutic levels following application (Ahern et al., 2010). In an effort to provide effective analgesia when required, that is intra and post operatively, the timing for the pre-emptive application of the fentanyl patches was investigated.

The use of pre-emptive analgesia to assist in the control of post-surgical pain is a concept that has been introduced and debated for many years; while no consensus has been reached, many studies show a beneficial effect (Mishra et al., 2013; Ong et al., 2005; Woolf and Chong, 1993). With the potential benefits of anticipating a noxious stimulus outweighing any contraindications, our studies aim to find an effective and practical regimen for the use of fentanyl patches in an ovine orthopaedic research situation. The optimal analgesic concentration of fentanyl in sheep has not been determined and all reported effective blood concentrations are based on extrapolation from other species (Ahern et al., 2010). In humans, Lane reported that the minimum blood concentration required to achieve effective analgesia is 1 ng/ml of blood (Lane, 2013), however Gourlay et al. have demonstrated it to be as low as 0.23 ng/ml in some human patients (Gourlay et al., 1988).

The aims of the studies were to evaluate the optimal pre-emptive regimen for the application of fentanyl patches in an effort to maximise post-surgical analgesia and to test the dose rate required to achieve effective analgesic effects in a surgical environment.

2. Methods

2.1. Study 1 – To determine optimal pre-operative timing of patch application

Ethical approval was gained from the Animal Care & Ethics Committee of the University of New South Wales (12/115A). Eight, 2 year old cross-bred Merino wethers were divided into pairs and acclimatised in their respective stalls (6 m^2) for 1 week prior to the study; the duration of the study was 6 days. The sheep were maintained on a diet of lucerne hay, chaff and water *ad libitum*.

The sheep were randomly allocated into 2 groups of $n = 4$, each group received two patches throughout the course of the study.

For group 1 the second fentanyl patch was applied 24 h, following removal of the first patch and for group 2 the second patch was applied 72 h after removal of the first (Fig. 1). No surgical procedures were performed as only the drug's absorption and elimination curve was investigated in this study.

One 100 μg/kg/h fentanyl patch was assigned to each sheep per application; given their weights were 85.9 kg ± 7.5 kg this produced a dose rate range of 1–1.6 μg/kg/h.

All patches were applied to the left antebrachium on the cranial aspect just below the elbow (Fig. 2). To apply the patches the sheep were manually restrained by one person placing one arm behind the rump and the other under the jaw, while using lateral pressure to constrain the sheep against the wall of the pen. Each leg was clipped with no. 40 clipper blades with care taken so as not to graze or cut the skin. The skin was cleaned with a 70% v/v chlorhexidine/alcohol solution and was allowed to fully dry before the patch was applied. Following patch application, the leg was then wrapped with a single layer of elastic conforming bandage (Vetrap, 3M) and this was held in place with sticking plaster (Tensoplast Vet, Smith & Nephew). This ensured good patch/skin contact with no slippage.

For blood sampling each sheep was held by the same means used for patch application; sampling was performed via jugular venipuncture using a 19G needle according to the time points described in Fig. 1; 4 ml of blood was collected into a plain vacuum blood tube (Vacutiner, BD Medical). The whole blood was allowed to stand for 10 min for the clotting process to begin, before being centrifuged at two times the force of gravity (2*g*) for a further 10 min. The serum was then extracted using a micropipette and placed into cryotubes for immediate freezing at −18 °C.

Fentanyl levels were measured in duplicate using a commercially available, human enzyme-linked immunosorbent assay (ELISA) Fentanyl kits (BQ Kits), according to the manufacturer's instructions. A negative and positive standard was provided with each kit. The negative standard was tested against normal sheep serum. The absorbance was read at 570 nm/650 nm using a microplate absorbance reader (Tecan Sunrise). Each sample was tested in triplicate, the ELISA results were collated and mean drug levels along with their SD were calculated based on conversion factors obtained from the negative and positive standards results.

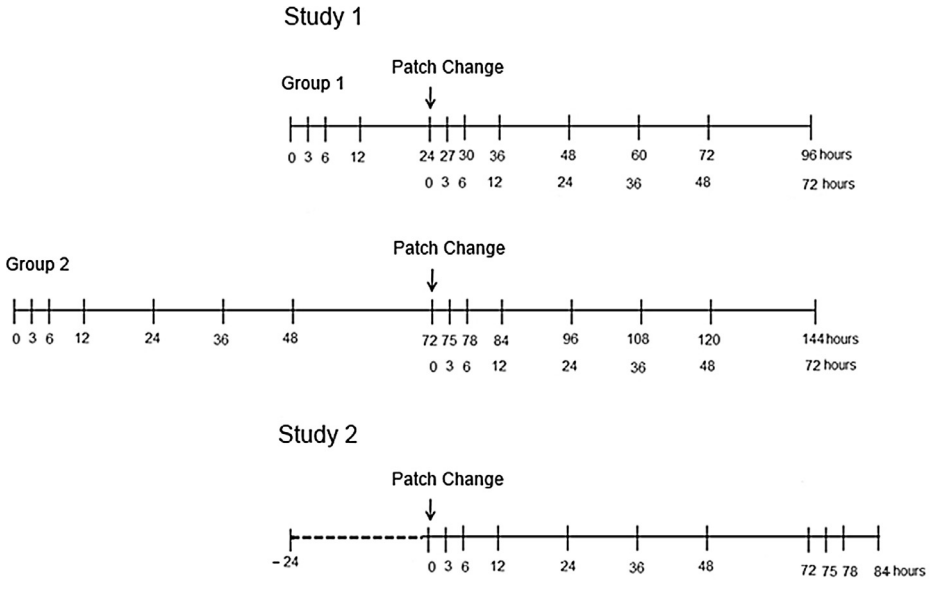

Fig. 1. Study designs – Timelines of the groups and their allocated blood collection times.