 CASE REPORT

Long duration anaesthesia in pigs with an infusion of alfaxalone and dexmedetomidine

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Abstract
Pigs are commonly maintained on total intravenous anaesthesia when used in comparative medical research to study controlled manual ventilation of the lung. In this case study, four pigs were anaesthetised with a total intravenous anaesthetic infusion of alfaxalone and dexmedetomidine for up to 24 h whilst being mechanically ventilated. Cardiovascular parameters, blood gas values and body temperature were minimally affected throughout the anaesthetic period. Additional analgesia is recommended when utilising this drug combination for procedures that involve noxious stimuli.

KEYWORDS
TIVA, pig, alfaxalone, dexmedetomidine

1 | INTRODUCTION

In respiratory research, the similarities between the pig and the human lung have made the pig a common model in comparative medical research studying ventilation and respiration (Judge et al., 2014). To facilitate research into critical care ventilators using pigs, intravenous infusions of anaesthetic drugs may be used to maintain pigs at an anaesthetic plane such that they can be intubated to allow mechanical ventilation. Alfaxalone is a neuroactive steroid that is commercially available in an unpreserved (Alfaxan®) and preserved (Alfaxan® Multi-dose) formulation that is registered for use in veterinary medicine as an intravenous induction and maintenance anaesthetic agent in dogs and cats. In pigs, alfaxalone has been used to induce and maintain anaesthesia and reported to have minimal cardiovascular effects at clinical doses rates (Bigby et al., 2017; Lervik et al., 2020; Santos Gonzalez et al., 2013). As such, alfaxalone is an alternative choice as an intravenous maintenance anaesthetic agent in the pig, particularly if there is a potential shortage of commonly used human drugs (e.g., propofol) such as during the COVID-19 pandemic. To the authors’ knowledge, the use of an intravenous infusion of alfaxalone and dexmedetomidine to maintain long duration anaesthesia (12–24 h) has not previously been reported in pigs.

2 | CASE REPORT

In a recent pilot study, a combination of alfaxalone (Alfaxan® Multi-dose, Jurox Pty Ltd., Rutherford, NSW, Australia) and dexmedetomidine (Dexdomitor, Jurox Pty Ltd.) was used to maintain long duration anaesthesia (12–24 h) in pigs that were mechanically ventilated to assess a rapid prototyped mechanical ventilator (Dhanani et al., 2020). All procedures were performed with approval from the University of Queensland Animal Ethics Committee (SVS/142/20).

Four female Large White (Sus scrofa domesticus) pigs aged approximately 10 weeks and weighing 35–40 kg were premedicated with intramuscular (IM) ketamine 10 mg/kg (Ketamil, Mavlab Pty Ltd, Slacks Creek, QLD, Australia), dexmedetomidine 10 μg/kg and methadone 0.25–0.4 mg/kg (Methodyne, Jurox Pty Ltd.). Once recumbent, anaesthesia was induced with isoflurane and oxygen delivered via a face mask connected to a circle system. The trachea was intubated with a cuffed endotracheal tube and anaesthesia initially maintained with isoflurane and oxygen. The auricular vein was catheterised and compound sodium lactate (Hartmann's Solution, Baxter Healthcare Australia, NSW), an isotonic crystalloid intravenous fluid, was administered intravenously at 3–4 ml/kg/h with intermittent bolus doses (10 ml/kg) administered to treat hypotension (defined as mean arterial pressure...
of 60 mmHg and below). The auricular artery was also catheterised to measure arterial blood pressure and the urinary bladder catheterised to permit continuous drainage of urine.

An hour after induction of anaesthesia, prior to the ventilator trial beginning, pigs were positioned in sternal recumbency, and inhalant maintenance anaesthesia was changed to total intravenous anaesthesia (TIVA) with a variable rate intravenous infusion of alfaxalone and dexmedetomidine using syringe drivers (Alaris® GH Plus, Becton Dickinson, Hamilton, QLD, Australia). Once pigs were judged to be adequately anaesthetised, controlled manual ventilation (CMV) was commenced using either a test prototype ventilator or a commercial ventilator (Ulco Campbell Ventilator EV500, Ulco Engineering Pty Ltd, Marrickville, NSW, Australia) over a 12- to 24-h period with an air and oxygen mixture. To test the functionality of the prototype ventilator, the ventilator settings were periodically changed. Further details regarding the ventilators are already described (Dhanani et al., 2020), and ventilator settings are reported in Table 2. Cardiorespiratory variables and clinical observations of anaesthetic depth were monitored continuously during the study using a multiparameter anaesthetic monitor (BM7vet, Bionet, Guro-gu, Seoul, Republic of Korea), and values were recorded every 5–10 min. Variables monitored included heart rate, arterial blood pressure, pulse oximetry, electrocardiogram, body temperature, end tidal carbon dioxide, palpebral reflex, eye position and jaw tone. Additionally, arterial blood samples were collected anaerobically every 2 h to measure pH, PaO2, PaCO2 and HCO3-

### Table 1

|                        | Pig 1 | Pig 2 | Pig 3 | Pig 4 |
|------------------------|-------|-------|-------|-------|
| Weight (kg)            | 40    | 38    | 35    | 35    |
| Median (min-max) alfaxalone infusion (mg/kg/h) | 5     | 4.65 (4–5.3) | 5.7 (2.9–5.7) | 5.1 (4.3–5.7) |
| Median (min-max) dexmedetomidine infusion (μg/kg/h) | 4     | 3.15 (1.1–5.3) | 3 (1.1–3.4) | 3 (3–4) |
| Intramuscular methadone (mg) | -     | -     | 21    | 21    |
| Duration of TIVA (hours) | 12    | 12    | 21    | 24    |

### Discussion

The median alfaxalone infusion rate in our study was comparable to other studies in pigs in which alfaxalone was infused alone (4.8 mg/kg/h) (Bigby et al., 2017). Similar alfaxalone infusion rates (5 mg/kg/h) in combination with ketamine 5 mg/kg/h and dexmedetomidine 4 μg/kg/h were reported in another study following premedication with ketamine and midazolam (Lervik et al., 2020). Both studies maintained anaesthesia for only 60 min, and it is likely that the pre-anesthetic drugs influenced drug infusion rates during the short anaesthetic period. For example, Bigby et al. (2017) observed that in some animals (3/9), endotracheal intubation was possible with the premedication only and no additional induction drug was required.

The protocol used in the present study was suitable for immobilising the pigs for mechanical ventilation but would not be suitable for noxious interventions. This is evidenced by most animals requiring additional alfaxalone or methadone when stimulated to position for radiographs. Interestingly, similar findings were reported during the previously described short duration alfaxalone and alfaxalone-ketamine-dexmedetomidine infusions with approximately 14%-35% of animals responding to epidural placement or dewclaw clamping, respectively (Bigby et al., 2017; Lervik et al., 2020). Alfaxalone is not an analgesic, and while information on dexmedetomidine in pigs is limited, it has been reported to provide significant analgesia when infused at 4 mcg/kg/h in combination with ketamine and propofol (Lervik et al., 2020). It is possible that increasing the dexmedetomidine infusion rate and perhaps the addition of an opioid to the infusion regime may have provided more consistent anti-nociception and a more balanced anaesthetic and analgesic technique.

Cardiovascular parameters monitored were within acceptable ranges for anaesthetised pigs, and mean arterial blood pressure did not fall below 60 mmHg in any animal despite periods of significant positive end expiratory pressure of up to 15 cmH2O and peak inspiratory pressures (PIP) often in excess of 25 cm H2O (see Table 2 for details). This is in agreement with other studies investigating the cardiovascular...
| Hour | Pig 1 | Pig 2 | Pig 3 | Pig 4 |
|------|-------|-------|-------|-------|
| 0    | 17    | 19    | 20    | 22    |
| 2    | 21    | 23    | 20    | 22    |
| 4    | 20    | 23    | 19    | 22    |
| 6    | 20    | 23    | 19    | 22    |
| 8    | 30    | 21    | 20    | 23    |
| 10   | 21    | 27    | 34    | 27    |
| 12   | 21    | 27    | 27    | 20    |
| 14   | 20    | 28    | 28    | 20    |
| 16   | 23    | 28    | 27    | 25    |
| 18   | 25    | 28    | 27    | 25    |
| 20   | 28    | 20    | 28    | 22    |
| 22   | 28    | 22    | 30    | 30    |
| 24   | 26    | 22    | 30    | 30    |
| 26   | 24    | 22    | 24    | 24    |

Table 2: Physiological Parameters at each blood gas sampling time point for four pigs maintained under total intravenous anaesthesia whilst mechanically ventilated.

| Ventilator settings | Blood gas | Cardiovascular | Other |
|---------------------|-----------|----------------|-------|
| Hour PIP RR TV FiO2 PEEP I:E ratio pH PO2 PCO2 HCO3- HR SAP DAP MAP SPO2 ETCO2 Temp |
| Pig 3 27 16 479 54 10 - 7.45 268 48 33.4 79 109 69 84 98 50 38.7 |
| Pig 4 23 24 375 49 10 1.15 7.46 243 45 32 83 99 55 73 99 50 38.8 |
| Pig 5 10 21 20 35 10 - 7.38 271 52 29.7 110 105 57 70 98 49 38.7 |
| Pig 6 20 23 350 54 10 - 7.49 267 44 33.5 110 129 79 97 97 50 39.1 |
| Pig 7 19 16 471 57 5 - 7.44 289 48 32.6 77 116 80 96 98 47 38 |
| Pig 8 22 20 430 47 5 1.97 7.46 232 47 33.4 83 116 76 94 99 53 38.8 |
| Pig 9 20 21 52 10 - 7.37 271 49 27.9 106 102 60 73 99 48 38.7 |
| Pig 10 20 21 53 - 7.46 267 48 34.1 101 122 74 92 96 51 38.3 |
| Pig 11 27 16 479 54 10 - 7.45 268 48 33.4 79 109 69 84 98 50 38.7 |
| Pig 12 23 24 375 49 10 1.15 7.46 243 45 32 83 99 55 73 99 50 38.8 |
| Pig 13 30 21 52 10 - 7.38 271 52 29.7 110 105 57 70 98 49 38.7 |
| Pig 14 20 23 350 54 10 - 7.47 263 48 34.9 105 131 79 98 95 52 39.2 |
| Pig 15 27 20 472 50 10 - 7.45 248 47 32.7 90 117 72 88 98 50 38.4 |
| Pig 16 24 22 375 49 10 1.82 7.46 253 45 32 79 105 58 76 99 48 38.6 |
| Pig 17 20 21 53 - 7.37 271 49 27.9 106 102 60 73 99 48 38.7 |
| Pig 18 20 21 53 - 7.46 267 48 34.1 101 122 74 92 96 51 38.3 |
| Pig 19 27 16 479 54 10 - 7.45 268 48 33.4 79 109 69 84 98 50 38.7 |
| Pig 20 23 24 375 49 10 1.15 7.46 243 45 32 83 99 55 73 99 50 38.8 |
| Pig 21 30 21 52 10 - 7.38 271 52 29.7 110 105 57 70 98 49 38.7 |
| Pig 22 20 23 350 54 10 - 7.47 263 48 34.9 105 131 79 98 95 52 39.2 |
| Pig 23 27 20 472 50 10 - 7.45 248 47 32.7 90 117 72 88 98 50 38.4 |
| Pig 24 24 22 375 49 10 1.82 7.46 253 45 32 79 105 58 76 99 48 38.6 |

Abbreviations: DAP, diastolic arterial pressure; ETCO2, end tidal carbon dioxide; FiO2, fraction of inspired oxygen; HR, heart rate; Hour, time from first blood gas sampling; I:E ratio, inspiratory to expiratory time ratio; MAP, mean arterial pressure; PEEP, peak end expiratory pressure; PIP, peak inspiratory pressures; PO2, partial pressure of oxygen in arterial blood; PCO2, partial pressure of carbon dioxide in arterial blood; RR, respiratory rate; SAP, systolic arterial pressure; SPO2, TV, tidal volume; oxygen saturation via pulse oximetry; Temp, temperature.

* Novel ventilator prototype failure.
effects of alfaxalone-based anaesthetic protocols in pigs (Duval et al., 2018; Ruane-O’Hora et al., 2011).

Previously, reports of alfaxalone (without preservative) infused alone or as part of a balanced anaesthetic technique in pigs have reported maintenance of anaesthesia for up to 60 minutes duration (Bigby et al., 2017; Duval et al., 2018; Lervik et al., 2020). To the authors knowledge, this is the first report of the preserved formulation of alfaxalone infused for 12–24 h to maintain anaesthesia in pigs. The formulation of alfaxalone used in the present study contains preservatives (ethanol, chlorocresol and benzethonium chloride); we are unable to rule out any possible toxicity or unforeseen effects these preservatives might have caused.

In conclusion, this study demonstrated that a combination of alfaxalone and dexmedetomidine is suitable to maintain long duration TIVA in pigs anaesthetised for controlled mechanical ventilation.

AUTHOR CONTRIBUTIONS
Formal analysis and writing—original draft: Irving Kat. Resources and writing—review and editing: Jayesh Dhanani. Investigation and writing—review and editing: Grant Whitten. Investigation and writing—review and editing: Nicholas Cowling. Conceptualisation, investigation, methodology, writing—original draft, and writing—review and editing: Wendy Goodwin.

ACKNOWLEDGEMENTS
The authors would like to thank Jurox Pty Ltd. for the generous donation of Alfaxan® Multidose for use in the trial.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

FUNDING INFORMATION
None.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.953.

ETHICS STATEMENT
The authors confirm that the ethical policies of the journal, as noted on the journal’s author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The study protocol was approved by the University of Queensland Animal Ethics Committee in accordance with the Australian code for the care and use of animals for scientific purposes.

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How to cite this article: Kat, I., Ahern, B. J., Dhanani, J., Whitten, G., Cowling, N., & Goodwin, W. (2022). Long duration anaesthesia in pigs with an infusion of alfaxalone and dexmedetomidine. Veterinary Medicine and Science, 8, 2418–2421. https://doi.org/10.1002/vms3.953