An inhaler device using liquid injection of isoflurane for short term anesthesia in piglets

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Abstract

Objectives To test a novel inhaler for administering isoflurane (ISO) anesthesia to piglets during castration and other surgical procedures of short duration.

Study design Prospective, randomized study.

Animals Fifty-seven male piglets aged 6–10 days, body weight 1.1–3.5 kg.

Methods An inhaler was developed which consisted of a mask, center body with open-close valve, vaporization chamber with wick and injection port, and a rebreathing bag. Liquid ISO required for induction of anesthesia and surgery was calculated, based on a desired alveolar ISO concentration of 1.82%. Dose was calculated using a square root of time model and metabolic size (B.W.0.75). For practical use the calculated dose was expressed in relation to scale weight (kg). Isoflurane was delivered into the liquid injection port, followed by oxygen to fill the rebreathing bag and initiate vaporization. After the mask was fitted over the piglet’s nose, the sliding open-close valve was opened to allow respiratory flow to move gases in and out of the inhaler and rebreathing bag. Fifty-seven male piglets received anesthesia prior to castration. Morbidity and mortality were assessed relative to unanesthetized litter mates. Induction, recovery and total anesthetic times were measured. End-tidal CO2 was measured immediately after mask removal by capnography. Costs of equipment and anesthetic agent were calculated.

Results Mean induction time was rapid, 47.5 ± 8.7 seconds, generally with minimal or no struggling. Surgery usually lasted less than 30 seconds and was always completed prior to the 120 seconds allotted for induction and surgery. Anesthesia was adequate and recovery time was 122 ± 44 seconds. Total time from start to standing was 260 ± 51 seconds. The end-tidal CO2 was 5.2 ± 1.1 kPa (39.4 ± 8.4 mmHg). No morbidity or mortality was associated with either group. Inhaler construction costs were below $100, and liquid ISO cost ranged between $0.02 and $0.03 per piglet.

Conclusion and clinical relevance Isoflurane delivered in a novel inhaler has the potential to provide economical, safe, rapid anesthetic induction and safe, smooth recovery in piglets.

Keywords anesthesia, castration, isoflurane, piglets, surgery.

Introduction

In some European countries, castration of young farm animals may not be accomplished legally in the absence of analgesia or anesthesia. In the UK and Germany, anesthesia or analgesia must be provided for castration of piglets after the age of 4 weeks [UK, Protection of Animals (Anaesthetics)
Act, 1964; Germany, Animal Welfare Act of 1998; Art.5(3)1]. Similar or more stringent regulations exist in Norway. The European community has been far more aggressive in efforts to require anesthesia or analgesia in the castration of farm animals and have conducted more studies of the problem than in the USA. Various studies have examined general anesthetics, local anesthetics and the use of carbon dioxide to obtund the pain and distress associated with castration. (Haga & Ranheim 2005: Kohler et al. 1998: Thurman et al. 1991) Although similar legal constraints do not exist in the USA, there is growing awareness of the need to provide humane treatment for all animals. Animal welfare groups are increasingly concerned and some are very active in promoting the use of analgesics and anesthetics in all farm animals to reduce stress and pain associated with surgical procedures. However, at present, many commercial producers and farm operators in the USA do not embrace this position. Because pain relief is not required by law, some perceive it as unnecessary for routine husbandry procedures, especially in neonates and young animals of various food animal species. Other reasons cited for withholding anesthesia or analgesia include increased production costs and the extra time required for each procedure. Potential anesthesia-related morbidity or mortality is also a concern.

The goal of this study was to develop a safe, rapid, inexpensive method of anesthetizing neonatal piglets that might be acceptable in commercial or farm production operations. Inhalation anesthesia using isoflurane (ISO) delivered via a mask was selected because mask induction of general anesthesia with ISO is common in other species. Induction of anesthesia would be rapid if adequate inspired concentrations were administered. Given a brief surgical procedure, recovery would also be rapid, provided other parenteral drugs were not administered. For this purpose, a simple hand-held inhaler was designed to deliver the ISO and its suitability for use during castration of piglets evaluated.

Materials and methods

Piglets in this study were 6–10 days of age and weighed 1.1–3.5 kg. The 57 males to be anesthetized for castration were randomly selected from multiple litters in a swine farrowing unit. Piglets in this swine farrowing unit are usually castrated at approximately 1 week of age. Unselected littermates undergoing routine castration without anesthesia were used to compare morbidity and mortality rates. The Kansas State University Institutional Animal Care and Use Committee approved all animal procedures.

Inhaler design

Because total anesthetic time needed would be short, carbon dioxide absorption was not considered a necessity. Arterial carbon dioxide was not expected to rise to unacceptable tensions. Oxygen was incorporated into the inhaled anesthetic mixture to alleviate the possibility of hypoxemia during the anesthetic period.

The inhaler consisted of a mask, a center body with a sliding open-close valve, a vaporization chamber and a rebreathing bag (Fig. 1). Masks were clear plastic with rubber diaphragms suitable for small animals (MDS Matrix; mask 9380 5028, Orchard Park, NY, USA). The center body and open-close valve were machined from acetyl plastic round stock (Cope Plastics, Inc, Topeka, KS, USA). This material is inert in the presence of halogenated anesthetics. The open-close valve was operable with one hand. The proximal end of the center body was 15 mm ID to accept standard 15 mm OD mask fittings. The distal end was attached to a vaporization chamber machined of type 303 stainless steel. The chamber contained an internal cotton wick sandwiched between two layers of stainless steel fine mesh (Wire Cloth Mesh size 40; Small Parts Inc. Miami Lakes, FL, USA). Centered above the cotton wick on the side of the chamber, a nylon stopcock was fitted to function as an injection port to deliver liquid ISO onto the wick and to flush oxygen into the inhaler. The distal end of the vaporization chamber was 22 mm OD to accommodate attachment of a standard rebreathing bag (220 mL). The total internal volume of the mask, inhaler, and full rebreathing bag used in this study was 250 mL.

Calculations of liquid ISO requirement

All calculations of ISO volumes required for anesthesia were based on the metabolic size of the piglets (B.W.0.75) and utilized the square root of time model (Lowe & Ernst 1981) (Appendix 1). Calculations based on metabolic size were converted to scale weight to construct a field-useable table (Table 1) that listed a range of piglet weights and
the corresponding ISO volume for each weight increment. The target alveolar ISO concentration of 1.82% was based on a minimal alveolar concentration (MAC) value of 1.41% and a MAC multiple of 1.3.

To calculate the total liquid ISO requirement using the square root of time model, it was necessary to calculate a ventilatory prime dose, an arterial prime dose and a unit dose based on metabolic size (Lowe & Ernst 1981) (Appendix 1). The ventilatory prime dose is the amount of liquid needed to establish the target concentration of 1.82% ISO in the inhaler plus the piglet’s pulmonary functional residual capacity (FRC). The arterial prime dose is the amount of liquid needed to establish the desired ISO concentration in the circulating blood. The unit dose is the amount of liquid needed to maintain anesthesia for each square root of time increment.

The ventilatory prime dose, arterial prime dose, and unit dose were summed to determine the total liquid ISO necessary for each piglet weight class. The target alveolar ISO concentration of 1.82% could be maintained by administering supplemental unit doses according to the square root of time model. Because the surgery would be brief, it was estimated that only one unit dose would be needed.

### Experimental protocol

Herd caretakers selected piglets at random from each litter to be processed. Each piglet was weighed on a digital scale and its appropriate ISO dose determined from Table 1. Litter and pig numbers, noted by reading ear notches, were recorded with weights.

Castration of piglets was conducted in a room adjacent and open to the farrowing house. Room temperature was maintained between 20–21.7 °C. Piglets were studied on four separate days as litters and farrowing house scheduling permitted. Two
identical inhalers were used alternately. The inhaler in use was evacuated by compressing the rebreathing bag and the sliding open-close valve closed. The calculated dose of ISO was delivered into the inhaler through the liquid injection port with a glass microliter syringe (Model 1750 LT; Hamilton Company, Reno, NV, USA). Oxygen (40 mL second⁻¹) was flushed through the port until the rebreathing bag was full.

Each piglet was cradled under the anesthetist’s left arm, and the mask and inhaler were applied with the right hand. The open-close valve was immediately opened to allow the piglet to breathe through the inhaler. Clinical signs of anesthetic depth were continually assessed during anesthetic induction. Signs included ventilatory character, heart rate by palpation, eye signs and muscle relaxation. After ventilation became regular and the piglet relaxed, the piglet was placed in dorsal recumbency in a V-trough and positioned for castration. Castration was performed by trained herd caretakers. Castration was usually complete in <20–30 seconds. A surgical plane of anesthesia was established and provided optimal conditions for surgical castration.

Piglets placed in a box for recovery typically lay quietly for a short time and then rolled sternal and jumped to their feet. They had good mobility and the ability to walk with minimal ataxia as soon as they arose from the sternal or lateral position. Inductions were rapid, 47.5 ± 8.7 seconds, with minimal or no struggling. The duration of surgery was usually <30 seconds. Anesthesia was adequate and recovery was rapid, 122 ± 44 seconds. Total time from start to standing was 260 ± 51 seconds. The end-tidal CO₂ was 5.2 ± 1.1 kPa (39.4 ± 8.4 mmHg). There was no morbidity or mortality associated with either group.

**Results**

Anesthetic induction of piglets was easily accomplished. The mask fit snugly around the nose of each piglet and was well tolerated. The inhaler device was easily manipulated with the anesthetist’s free hand as piglets were gently cradled with one arm. Changes in ventilatory excursions were easily visualized by observation of the small rebreathing bag. A surgical plane of anesthesia was established and provided optimal conditions for surgical castration.

**Discussion**

The square root of time model (Lowe & Ernst 1981) can be used to provide quantitative, closed circuit, liquid injection anesthesia in horses and dogs; in these circumstances the measured end-tidal concentrations of anesthetic agent are reasonably predicted by the square root of time model (D.S. Hodgson, unpublished observations). Although end-tidal concentration of ISO was not measured in piglets in the current study, a surgical plane of anesthesia was rapidly attained and maintained for the 2-minute anesthetic period.

In many species, a MAC multiple of 1.3 is expected to produce a light surgical plane of anesthesia. MAC for ISO in young piglets has been reported by several
investigators. A study in 15 piglets 2–17 days old determined a MAC of 1.20% (Schieber et al. 1986).

However the investigators found marked intra-subject variability and that MAC increased with age. The stimulus for MAC determination in this study was both tail and toe clamp applied for 30 seconds. Another study determined ISO MAC to be 1.48% in 4 to 10-day-old piglets. (Lerman et al. 1990). Clamping the coronary ligament of the hoof was the stimulus used. In our study 1.41% ISO was used as the value for one MAC. Using a MAC multiple of 1.3 in the calculations of ISO volumes proved to be satisfactory in preliminary trials in our swine nursery. The surgical incision and castration as the determinant of adequate anesthetic depth likely induces more pain than either tail or toe clamp. In our preliminary studies of 14 piglets, an additional unit dose of ISO was injected with the calculated dose to produce an expected overdose. In three of eight of these piglets, respiration slowed, and in two piglets respiratory arrest occurred. Presumably a concentration of ISO equal to the apneic index was attained (Eger 1974; Paulin & Su 1990). Piglets were easily resuscitated by removing the inhaler and administering several breaths. Prior to apnea, the two piglets showed a marked slowing in respiratory rate such as would be associated with deep anesthetic planes in other species. Given this reaction to a deliberate overdose of ISO, it would be advisable to remove the inhaler from the piglet’s nose to cease additional anesthetic administration if marked slowing of ventilation is observed and other signs consistent with excessive anesthetic depth are present. Removing a unit dose from the calculated ISO dose did not provide adequate anesthetic depth for castration.

When the inhaler is in use, rebreathing of carbon dioxide occurs. Although pre-anesthetic end-tidal CO₂ concentrations were not measured, the post-anesthetic CO₂ concentrations were indicative of CO₂ concentrations observed in ISO-anesthetized, spontaneously breathing dogs and cats (Steffey & Howland 1977; Hodgson et al. 1998). More prolonged periods of anesthesia would cause a continued rise in carbon dioxide tension. To minimize the chance of hypoxemia, oxygen was used to fill the inhaler and rebreathing bag. The volume of oxygen in the rebreathing bag exceeded the calculated oxygen consumption of the piglet (Schmidt-Nielsen 1984). Oxygenation was not examined via pulse oximetry or arterial blood gas analysis because of practical constraints, including the herdsman’s desire to process the piglets rapidly and the limited availability of equipment in the swine nursery.

The anesthetic inhaler was designed with adequate cotton wick material to absorb the largest volume of ISO used to anesthetize the piglets in this study. The initial temperature of the inhaler is the same as room temperature (20–21.7 °C). The rate of vaporization of ISO in the inhaler is affected by many factors (Dorsch & Dorsch 1975). After injection of ISO onto the wick, vaporization was initiated by oxygen flushed over the wick as the rebreathing bag was filled. All factors that increase inhaler temperature would increase the rate of vaporization. The hand of the operator holding the inhaler warms the inhaler and increases vaporization. The warmth of the piglet’s respiratory gases passing around the wick also enhances vaporization. An increase in breathing rate and tidal volume increases vaporization rate. The Wick surface area also affects the rate of vaporization. A smaller surface area of inhaler wick could well limit the rate of vaporization. In the design of the inhaler it was hoped that the rate of vaporization would be such to allow rapid induction and then continued vaporization to maintain surgical anesthesia throughout the anesthetic period. The wick design and size selected was fortuitous in that anesthesia was induced and then maintained with a surgical plane of anesthesia for the duration of the procedure. Even though the overall rate of rise of anesthetic concentration is unknown, given the speed of induction, it is expected that vaporization proceeded rapidly.

If vaporization was complete and no anesthetic were removed, the maximum concentration of anesthetic in the inhaler would be dependent on the calculated dose injected onto the wick (Hill 1980). For example, for a piglet weighing 1.5 kg, the calculated dose of 0.137 mL ISO could potentially vaporize to produce a concentration of 11.1 vol.%. Likewise, a 4.0 kg piglet dose could produce a maximal concentration of 21.2% if vaporization were complete within the inhaler without any vapors being removed. However, when the inhaler is used clinically to anesthetize a piglet, vaporization is an ongoing process. As vapors are produced ISO is continually being removed from the inhaler by uptake into the piglet’s tissues. Therefore, at any point of time the inspired concentration of ISO was unknown.

Mathematical calculations are necessary to construct a table for the liquid ISO volumes required for field use (Appendix 1). The ventilatory prime dose is not based on uptake into the tissues. The purpose of
the ventilatory prime dose is to establish the desired concentration of 1.82% ISO in the anesthetic inhaler and the FRC of the lung. Increasing the rebreathing bag size would necessitate a larger ventilatory prime dose. The arterial prime dose establishes a similar concentration in the blood. Unit doses account for the continual uptake of ISO into the various tissue compartments with time. Since the required time for all procedures was brief, only one unit dose was deemed necessary. When Lowe used these principles for doing closed circuit anesthesia in human patients, liquid was injected directly into the anesthetic breathing circuit. He usually recommended injection into the expiratory limb of the breathing circuit. Unit doses were injected at the appropriate time intervals. Alternately an infusion could be used. Unit doses delivered as a bolus caused the concentration to rise rapidly to a peak and then to stabilize at a lower concentration. Use of a syringe pump to deliver a constant infusion for each time period produces a more constant inspired concentration without prominent peaks. In this piglet study it was not desirable for instantaneous vaporization of all the liquid as this could produce a pronounced peak and excessive ISO concentrations. The rate of vaporization with our inhaler produced a rapid induction and consistent surgical plane of anesthesia.

During the study, herdsmen often remarked how quiet and nonstressful it seemed when piglets were castrated with ISO anesthesia. Piglets were held under the arm of the anesthetist and rarely objected to mask application and anesthetic induction. Sows in the adjacent farrowing unit remained quiet and recumbent during processing of anesthetized piglets. When the remaining piglets were castrated without anesthesia, the vocalization of the piglets aroused all of the sows. Many of the sows seemed distressed when hearing the squealing of piglets. When the anesthetized piglets were placed in the box for recovery they usually lay quietly and then abruptly rolled to sternal and stood up. After standing the piglets were mobile and none were injured by the sow in the next 24 hours. When the piglets were placed back with their littermates they usually started nursing immediately.

The technique reported in this pilot study has several positive aspects. Induction of anesthesia was very rapid with little or no struggling. This is markedly different than inductions with CO₂ which elicits violent struggling and vocalization (Kohler et al. 1998). This technique avoids the pain associated with injections and the waiting time required for local anesthetics or analgesics to take effect. The quantity of ISO per piglet is minimal which reduces the cost and waste gas created. The anesthetic delivery equipment is simple, easily portable and inexpensive. Recovery to standing and walking is very rapid and the piglet’s awareness and mobility make it less likely to be injured when returned to the sow.

This study did not examine nociception responses during or after the procedure. It is likely other techniques that included analgesics or local anesthetics might better obtund these responses. Recently, cardiovascular responses and EEG recordings demonstrated a reduction in nociceptive responses when lidocaine injections were used prior to castration in halothane anesthetized piglets (Haga & Ranheim 2005). Analgesics or local anesthetics could affect the mobility of the piglet and could increase the likelihood of injury when piglets are returned to the sow and littermates. Rapid recovery and return to nursing behavior was viewed positively by the herdsmen who observe the animals throughout the day. The applicability of the results of this pilot study to the field situation suggest further investigation would be worthwhile.

At the time of this study, the cost of ISO per piglet was minimal. Liquid ISO for a 1.5 kg piglet is less than $0.02 and for a 4 kg piglet less than $0.03. Inhaler construction was less than $100.00, and each inhaler could be used hundreds of times (Table 2). Cost of equipment and anesthetic would not be prohibitive in the use of this technique.

<table>
<thead>
<tr>
<th>Item</th>
<th>Dollars (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaler</td>
<td></td>
</tr>
<tr>
<td>Acetyl stock</td>
<td>1.25</td>
</tr>
<tr>
<td>Stainless steel round stock</td>
<td>2.50</td>
</tr>
<tr>
<td>Screws</td>
<td>0.15</td>
</tr>
<tr>
<td>Stainless steel wire mesh</td>
<td>0.75</td>
</tr>
<tr>
<td>Cotton wick</td>
<td>0.10</td>
</tr>
<tr>
<td>Machine work</td>
<td>65.00</td>
</tr>
<tr>
<td>Total inhaler cost</td>
<td>69.75</td>
</tr>
<tr>
<td>Mask</td>
<td>32.68</td>
</tr>
<tr>
<td>Microliter syringe</td>
<td>29.10</td>
</tr>
<tr>
<td>Rebreathing bag</td>
<td>1.00</td>
</tr>
<tr>
<td>Isoflurane (100 mL)</td>
<td>10.95</td>
</tr>
<tr>
<td>Oxygen regulator, valve</td>
<td>95.00</td>
</tr>
</tbody>
</table>

Table 2. Equipment and supply costs
As with any sedative or anesthetic technique, it is important that it be conducted or supervised by responsible medical personnel.

Acknowledgement

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References


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Appendix 1
Calculations of isoflurane liquid required to construct Table 1.

Ventilatory prime dose = the amount of isoflurane liquid required to establish the desired anesthetic concentration in the inhaler and the piglet’s pulmonary functional residual capacity (FRC).
Arterial prime dose = the amount of isoflurane liquid required to establish the desired anesthetic concentration in the piglet’s blood.
Unit dose = the amount of isoflurane liquid required to maintain anesthesia for each square-root-of time increment, e.g. (1, 3, 5, 7... minutes).

Ventilatory prime dose = volume of inhaler + piglet FRC (fMAC)
Arterial prime dose = CaQ
Unit dose = 2CaQ

Example calculations for a 3 do. (1.36 kg) piglet

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>1.5 kg0.75</td>
<td>1.26</td>
</tr>
<tr>
<td>MAC isoflurane</td>
<td>1.82%</td>
</tr>
<tr>
<td>Desired MAC multiple</td>
<td>1.3</td>
</tr>
<tr>
<td>fMAC = desired MAC multiple × MAC isoflurane</td>
<td>1.82% = 0.0182</td>
</tr>
<tr>
<td>Ca = fMAC × k</td>
<td>1.82% × 1.5 = 0.0182 × 1.5 = 0.0273</td>
</tr>
<tr>
<td>Q = Cardiac output</td>
<td>2 × kg0.75</td>
</tr>
<tr>
<td>Isoflurane – 1 mL liquid = 206 mL vapor at 37 °C</td>
<td></td>
</tr>
<tr>
<td>ml isoflurane vapor/206 = ml isoflurane liquid</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required isoflurane liquid for a 3 do. (1.36 kg) piglet</td>
<td>0.066 mL</td>
</tr>
</tbody>
</table>

Unit dose = 2CaQ
<table>
<thead>
<tr>
<th>Calculation</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 × 0.0273 × 252 = 13.8 mL isoflurane vapor</td>
<td>13.8/206 = 0.066 mL isoflurane liquid</td>
</tr>
</tbody>
</table>

Total dose = 0.129 mL

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