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A review of pain assessment techniques and pharmacological approaches to pain relief after bovine castration: Practical implications for cattle production within the United States

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ABSTRACT

Castration of male calves destined for beef production is a common livestock management practice in the United States amounting to approximately 7 million procedures per year. Recently there has been renewed interest in identifying methods to reduce pain associated with dehorning and castration. Although several studies have reported that analgesic drug administration prior to castration attenuates plasma cortisol response, there are currently no compounds specifically approved for pain relief in livestock in the U.S. Validated pain assessment tools are needed to support regulatory approval of analgesic compounds. This may include use of accelerometers, videography, heart rate variability determination, electroencephalography, thermography and plasma neuropeptide measurement to assess behavioral, physiological and neuroendocrine changes associated with a pain response. Extra-label drug use (ELDU) for pain relief is regulated under the Animal Medicinal Drug Use Clarification Act (AMDUCA) and requires that drugs be administered by or under the supervision of a veterinarian. Agents that may provide preemptive analgesia include local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, α2-agonists, and *N*-methyl D-aspartate (NMDA) receptor antagonists. A review of the published literature suggests that a significant decrease in plasma cortisol concentration after castration was associated with preemptive administration of a NSAID and local anesthesia. Local anesthesia alone tended to decrease peak plasma cortisol concentrations more than NSAIDs. However NSAIDs alone tended to decrease the area under the plasma cortisol–time curve more than local anesthesia alone. These findings suggest that multimodal analgesic regimens that extend into the post-operative period are more effective at mitigating pain and distress associated with castration than a single drug modality. Regulatory approval of safe and cost effective analgesic compounds with convenient routes of administration is needed for routine use of pain relieving drugs to be considered as standard practice at the time of castration.

1. Introduction

Castration of male calves destined for beef production is one of the most common livestock management practices performed in the United States amounting to approximately 7 million procedures per year (USDA, 2009). Methods of castration are typically associated with physical, chemical or hormonal damage to the testicles (Stafford and Mellor, 2005). In most production settings, physical castration methods are the most common. These can be subdivided into procedures involving surgical removal of the testes, or methods that irreparably damage the testicles

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by interruption of the blood supply using a castration clamp (Burdizzo castration), rubber ring or latex band (AVMA, 2009).

Benefits of castration include a reduction in aggression and mounting behavior of males resulting in fewer injuries in confinement operations and reduced dark-cutting beef (Tarrant, 1981). Steers also have higher meat quality with increased tenderness and marbling. Carcasses from steers therefore command higher prices at market when compared with bulls (AVMA, 2009). Castration also prevents physically or genetically inferior males from reproducing and prevents pregnancy in commingled pubescent groups (Stafford and Mellor, 2005). Although the benefits of castration are widely accepted in most countries, all castration methods have been demonstrated to produce physiological, neuroendocrine, and behavioral changes indicative of pain and distress (Fisher et al., 1996; Stafford and Mellor, 2005; Pang et al., 2006, 2008; Stilwell et al., 2008; Currah et al., 2009; González et al., 2010).

Societal concern about the moral and ethical treatment of animals is becoming more prevalent (Rollin, 2004). In particular, negative public perception of pain associated with castration procedures is mounting, with increasing call for the development of practices to relieve pain and suffering in livestock (Weary and Fraser, 2004). Preemptive analgesia can be applied in advance of the painful stimulus thereby reducing sensitization of the nervous system to subsequent stimuli that could amplify pain. Agents that could be used to provide preemptive analgesia include local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, α2-agonists, and *N*-methyl D-aspartate (NMDA) receptor antagonists (Thurmon et al., 1996). The AVMA "supports the use of procedures that reduce or eliminate the pain of dehorning and castrating of cattle" and proposes that "available methods of minimizing pain and stress include application of local anesthesia and the administration of analgesics" (AVMA, 2009). In spite of this, a recent survey of bovine veterinarians conducted by our research group found that only 1 in 5 survey respondents use anesthesia or analgesics at the time of castration (Coetzee et al., 2010a). Furthermore, 90% of respondent indicate that they castrate and dehorn cattle at the same time yet studies examining the effect of this on the animal are deficient in the literature.

It is remarkable that although administration of local anesthesia prior to castration and dehorning is legislated in several European countries (DEFRA, 2003) there are currently no analgesic drugs specifically approved for pain relief in livestock by the U.S. Food and Drug Administration (FDA) (Compendium of Veterinary Products, 2010). FDA Guidance Document 123 for the development of effectiveness data for non-steroidal anti-inflammatory drugs states that "validated methods of pain assessment must be used in order for a drug to be indicated for pain relief in the target species" (FDA-CVM, 2009). The identification and validation of robust, repeatable pain measurements is therefore fundamental for the development and approval of effective analgesic drug regimens for use in livestock.

The development of robust biomarkers for the objective measurement of pain is necessary for evaluating the efficacy of analgesic treatment regimens during routine animal husbandry procedures such as castration and dehorning. This process is especially complex in a prey species, such as cattle, that inherently conceal pain (Underwood, 2002). Pain is defined as "An aversive feeling or sensation associated with actual or potential tissue damage resulting in physiological, neuroendocrine, and behavioral changes that indicate a stress response" (Molony and Kent, 1997). In previous research, markers for the evaluation of pain and distress associated with noxious animal husbandry procedures have focused on assessing behavioral, physiological and neuroendocrine changes. A change in animal behavior has been assessed using visual pen scoring (McMeekan et al., 1999), videography (Currah et al., 2009), vocalization (Currah et al., 2009; Coetzee et al., 2008), chute exit speed measurement (Burrows and Dillon, 1997; Fell et al., 1999; Baldridge et al., 2011], pedometers (Currah et al., 2009) and accelerometers (White et al., 2008). Physiological changes have been assessed using serum cortisol measurement (Stafford and Mellor, 2005), heart rate determination (Schwartzkopf-Genswein et al., 2005), feed intake and average daily gain (Lents et al., 2001; Berry et al., 2001). Neuroendocrine changes have been assessed through measurement of the neuropeptide substance P (Coetzee et al., 2008), infrared thermography (Stewart et al., 2009, 2010), heart rate variability (HRV) (von Borell et al., 2007; Stewart et al., 2009, 2010), skin electrical impedence (electrodermal activity) (Kotschwar et al., 2009; Baldridge et al., 2011) and electroencephalography (EEG) (Gibson et al., 2007; Bergamasco et al., 2011). Several of these tools have also been used to assess the efficacy of analgesic compounds.

This review will discuss the challenges associated with pain assessment and the provision of analgesia to calves prior to castration and the tools that have been used to assess analgesic drug efficacy. Published evidence to support the effect of analgesic compounds on physiological, neuroendocrine, and behavioral changes associated with castration will also be reviewed. Publications were identified on *PubMed* using the search terms "Castration" and "Bovine" and "Analgesia". Studies that compared pain biomarkers in castrated control calves with calves treated with an analgesic prior to castration were used to determine a percent change associated with drug treatment (Tables 1 and 2).

2. Challenges associated with providing analgesia in food animals

There are several challenges associated with providing effective analgesia in food animals in the United States. Firstly, there are currently no analgesic drugs specifically approved for the alleviation of pain in livestock (Compendium of Veterinary Products, 2010). Therefore, use of any drug for pain relief constitutes extra-label drug use (ELDU) (Smith et al., 2008). Under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) (AMDUCA, 1994), ELDU is permitted for relief of suffering in cattle provided specific conditions are met. These conditions include that (1) ELDU is allowed only by or under the supervision of a veterinarian, (2) ELDU is allowed only for FDA approved animal and human drugs; (3) ELDU is

Table 1
Summary of the scientific literature examining the effect of analgesic drug administration on plasma cortisol response in castrated calves.

Reference	Procedure	Study population	Analgesic regimen	Outcome parameter	Percent change in cortisol (%)	Significance (*P*-value)
Faulkner et al. (1992)	Surgical castration	6–9 months Beef	Xylazine 0.02 mg/kg and butorphanol 0.07 mg/kg IV 90 s prior to castration	Cortisol (day 3)	−10.03	NS
Fisher et al. (1996)	Burdizzo clamp castration	5.5 months Dairy	Lidocaine local anesthesia, 8 mL/testicle, 15 min prior to castration	Cortisol (C_{max})	−15.61	NS
				Cortisol AUEC	−13.15	NS
	Surgical castration		Lidocaine local anesthesia, 8 mL/testicle, 15 min prior to castration	Cortisol (C_{max})	−23.04	<0.05
				Cortisol AUEC	−21.97	<0.05
Earley and Crowe (2002)	Surgical castration	5.5 months	Ketoprofen 3 mg/kg IV, 20 min prior to castration	Cortisol (C_{max})	−46.07	<0.05
		Dairy		Cortisol AUEC	−55.65	<0.05
			Lidocaine local anesthesia, 6 mL/testicle, 20 min prior to castration	Cortisol (C_{max})	−51.75	<0.05
				Cortisol AUEC	−25.72	NS
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 6 mL/testicle administered 20 min prior to castration	Cortisol (C_{max})	−37.12	<0.05
				Cortisol AUEC	−33.22	<0.05
Stafford et al. (2002)	Rubber ring castration	2–4 month Dairy	Lidocaine local anesthesia, 3 mL/testicle, 20 min prior to castration	Cortisol (C_{max})	−68.42	<0.05
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min prior to castration	Cortisol (C_{max})	−55.26	<0.05
	Band castration		Lidocaine local anesthesia, 3 mL/testicle, 20 min prior to castration	Cortisol (C_{max})	−72.28	<0.05
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min prior to castration	Cortisol (C_{max})	−74.26	<0.05
Stafford et al. (2002)	Surgical castration (pull)	2–4 month Dairy	Lidocaine, 3 mL/testicle, 20 min prior to castration	Cortisol (C_{max})	−2.94	NS
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min prior to castration	Cortisol (C_{max})	−55.88	<0.05
	Surgical castration (cut)		Lidocaine, 3 mL/testicle, 20 min prior to castration	Cortisol (C_{max})	52.73	<0.05
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min prior to castration	Cortisol (C_{max})	−43.64	<0.05
	Burdizzo clamp castration		Lidocaine local anesthesia, 3 mL/testicle, 20 min prior to castration	Cortisol (C_{max})	−17.19	NS
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min prior to castration	Cortisol (C_{max})	−67.19	<0.05
Ting et al. (2003a)	Burdizzo clamp castration	13 months Dairy	Ketoprofen 3 mg/kg IV, 20 min prior to castration	Cortisol (C_{max})	−33.76	<0.001
				Cortisol AUEC	−52.47	<0.001
			Lidocaine, 8 mL/testicle, 20 min prior to castration	Cortisol (C_{max})	−34.55	<0.001
				Cortisol AUEC	1.14	NS
			Xylazine 0.05 mg/kg and lidocaine 0.4 mg/kg epidural, 10 min prior to castration	Cortisol (C_{max})	−24.65	<0.001

Table 1 (*Continued*)

Reference	Procedure	Study population	Analgesic regimen	Outcome parameter	Percent change in cortisol (%)	Significance (*P*-value)
				Cortisol AUEC	14.07	NS
Ting et al. (2003b)	Surgical castration	11 months Dairy	Ketoprofen 3 mg/kg IV, 20 min prior to castration	Cortisol (C_{max})	11.82	NS
				Cortisol AUEC	−41.67	<0.05
			Ketoprofen 1.5 mg/kg IV twice; 20 min prior to castration and repeated at castration	Cortisol (C_{max})	−2.95	NS
				Cortisol AUEC	−42.59	<0.05
			Ketoprofen 1.5 mg/kg IV, 20 min prior to castration, repeated at castration and 3 mg/kg at 24 h post-castration	Cortisol (C_{max})	0.00	NS
				Cortisol AUEC	−26.54	<0.05
Pang et al. (2006)	Band castration	5.5 months Dairy	Carprofen 1.4 mg/kg IV, 20 min prior to castration	Cortisol (C_{max})	−18.74	NS
				Cortisol AUEC	−22.99	NS
	Burdizzo clamp castration		Carprofen 1.4 mg/kg IV, 20 min prior to castration	Cortisol (C_{max})	−4.07	NS
				Cortisol AUEC	−25.85	NS
Coetzee et al. (2007)	Surgical castration–Henderson castration tool	4–6 months Beef	Sodium Salicylate 50 mg/kg IV < 30 s prior to castration	Cortisol (C_{max})	−11.44	NS
				Cortisol AUEC	−6.33	NS
			Acetylsalicylic Acid 100 mg/kg PO < 30 s prior to castration	Cortisol (C_{max})	23.29	NS
				Cortisol AUEC	17.72	NS
Thüer et al. (2007)	Burdizzo clamp castration	<1 month Dairy	Lidocaine, 10 mL local anesthesia 5 min prior to castration	Cortisol (C_{max}) estimated	−35.38	P = 0.014
	Band castration		Lidocaine, 10 mL local anesthesia 5 min prior to castration	Cortisol (C_{max}) estimated	−25.00	NS
Stilwell et al. (2008)	Burdizzo clamp castration	6 month old Dairy	Lidocaine, 4 mL epidural administered 5 min prior to castration	Cortisol (6 h)	−41.38	NS
				Cortisol (24 h)	−22.41	NS
				Cortisol (48 h)	45.76	NS
			Flunixin meglumine 2.2 mg/kg SC and lidocaine, 4 mL epidural administered 5 min prior to castration	Cortisol (6 h)	−51.90	<0.05
				Cortisol (24 h)	−30.69	NS
				Cortisol (48 h)	30.37	NS
			Carprofen 1.4 mg/kg SC and lidocaine, 4 mL epidural administered 5 min prior to castration	Cortisol (6 h)	−58.89	<0.05
				Cortisol (24 h)	−47.52	<0.05
				Cortisol (48 h)	−36.48	<0.05
Boesch et al. (2008)	Burdizzo clamp castration	1 week Dairy	Lidocaine, 10 mL local anesthesia 20 min prior to castration	Cortisol (C_{max}) estimated	−35.00	p = 0.061
			Bupivacaine, 10 mL local anesthesia 20 min prior to castration	Cortisol (C_{max}) estimated	−29.17	NS
González et al. (2010)	Band castration	210 days Beef	Xylazine 0.07 mg/kg epidural and IV flunixin meglumine at 1.1 mg/kg	Salivary cortisol (4 h)	−59.84	0.03
				Salivary cortisol (24 h)	−26.04	0.31
				Salivary cortisol (14 days)	0.00	0.77

Table 1 (*Continued*)

Reference	Procedure	Study population	Analgesic regimen	Outcome parameter	Percent change in cortisol (%)	Significance (*P*-value)
Coetzee et al. (2010a,b)	Surgical castration–Henderson castration tool	4–6 months Beef	Xylazine 0.05 mg/kg IV < 30 s prior to castration	Cortisol (C_{max})	−8.21	NS
				Cortisol AUEC	28.70	NS
			0.05 mg/kg xylazine and 0.1 mg/kg Ketamine IV < 30 s prior to castration	Cortisol (C_{max})	−8.69	NS
				Cortisol AUEC	22.50	NS
Stewart et al. (2010)	Surgical castration	4 month Dairy	Lidocaine, 5 mL into the scrotum followed by 7 mL at the neck of the scrotum	Cortisol (C_{max})	−39.67	p < 0.05
Webster et al. (2010)	Surgical castration–Henderson castration tool	2–3 month Dairy	Flunixin meglumine, 1.1 mg/kg IV, 20 min pre-castration	Cortisol (C_{max})	−26.37	NS
				Cortisol AUEC	−33.55	NS
			2% Lidocaine ring block (20 cc) and intratesticular (5 mL/testes), 20 min pre-castration	Cortisol (C_{max})	−10.56	NS
				Cortisol AUEC	−21.94	NS
			2% Lidocaine ring block (20 cc) and intra-testicular (5 mL/testes) and flunixin meglumine 1.1 mg/kg IV, 20 min pre-castration	Cortisol (C_{max})	−48.16	NS
				Cortisol AUEC	−48.26	NS
Baldridge et al. (2011)	Surgical castration followed by surgical dehorning (Barnes)	2–4 month Dairy	Sodium salicylate at 2.5–5 mg/mL in the drinking water (13.62–151.99 mg of salicylate/kg bodyweight)	Cortisol (C_{max})	1.60	NS
				Cortisol AUEC (0–1 h)	−9.27	NS
				Cortisol AUEC (1–6 h)	−36.90	p < 0.05
				Cortisol AUEC (6–24 h)	−22.83	NS
			0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine co-administered IM immediately prior to castration	Cortisol (C_{max})	−12.00	NS
				Cortisol AUEC (0–1 h)	−28.90	p < 0.05
				Cortisol AUEC (1–6 h)	−5.82	NS
				Cortisol AUEC (6–24 h)	−0.01	NS
			Sodium salicylate at 2.5–5 mg/mL in the drinking water (13.62–151.99 mg of salicylate/kg bodyweight) and 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine co-administered IM immediately prior to castration	Cortisol (C_{max})	−3.46	NS
				Cortisol AUEC (0–1 h)	−20.89	NS
				Cortisol AUEC (1–6 h)	−24.19	NS
				Cortisol AUEC (6–24 h)	−15.69	NS

Percent change in cortisol was calculated using the formula [(mean of analgesic group/mean of castrated control group) − 1] × 100. AUEC: area under the effect curve for cortisol. C_{max}: maximum plasma concentration.

Table 2
Summary of scientific literature examining the effect of analgesic drug administration on other outcomes in castrated calves.

Reference	Procedure	Study population	Analgesic regimen	Outcome parameter	Percent change (%)	Significance (*P*-value)
Faulkner et al. (1992)	Surgical castration	6–9 months Beef	Xylazine 0.02 mg/kg and butorphanol 0.07 mg/kg IV 90 s prior to castration	ADG (0–27 d)	−11.11	NS
				Feed intake (0–27 d)	−5.00	NS
				Gain/feed	−11.11	NS
				Morbidity (0–27 d)	−4.17	NS
				Mortality (0–27 d)	0.00	NS
Fisher et al. (1996)	Burdizzo clamp castration	5.5 months Dairy	Lidocaine local anesthesia, 8 mL/testicle, 15 min prior to castration	Feed intake (d 1–20)	0.49	NS
				ADG (d 0–35)	−1.15	NS
	Surgical castration		Lidocaine local anesthesia, 8 mL/testicle, 15 min prior to castration	Feed intake (kg) (d 1–20)	0.96	NS
				ADG (d 0–35)	32.79	$p < 0.05$
Earley and Crowe (2002)	Surgical castration	5.5 months Dairy	Ketoprofen 3 mg/kg IV, 20 min prior to castration	Fibrinogen (d 35)	−8.43	$p < 0.05$
				Haptoglobin (d 35)	50.00	NS
				Feed intake (d 1–35)	−4.64	NS
				ADG (d 0–35)	71.43	NS
			Lidocaine local anesthesia, 6 mL/testicle, 20 min prior to castration	Fibrinogen (d 35)	−13.79	$p < 0.05$
				Haptoglobin (d 35)	50.00	NS
				Feed intake (d 1–35)	−2.79	NS
				ADG (d 0–35)	17.86	NS
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 6 mL/testicle administered 20 min prior to castration	Fibrinogen (d 35)	−28.93	$p < 0.05$
				Haptoglobin (d 35)	0.00	NS
				Feed intake (d 1–35)	−2.48	NS
				ADG (d 0–35)	96.43	$p < 0.05$
Ting et al. (2003a)	Burdizzo clamp castration	13 months Dairy	Ketoprofen 3 mg/kg IV, 20 min prior to castration	Feed intake (d −1 to 33 d)	4.66	NS
				ADG (d −1 to 35 d)	46.51	NS
			Lidocaine, 8 mL/testicle, 20 min prior to castration	Feed intake (d −1 to 33 d)	−0.26	NS
				ADG (d −1 to 35 d)	0.00	NS
			Xylazine 0.05 mg/kg and lidocaine 0.4 mg/kg epidural, 10 min prior to castration	Feed intake (d −1 to 33 d)	−0.26	NS
				ADG (d −1 to 35 d)	20.93	NS
Ting et al. (2003b)	Surgical castration	11 months Dairy	Ketoprofen 3 mg/kg IV, 20 min prior to castration	Feed intake (d −1 to 33 d)	−0.82	NS
				ADG (d −1 to 35 d)	7.69	NS
			Ketoprofen 1.5 mg/kg IV twice; 20 min prior to castration and repeated at castration	Feed intake (d −1 to 33 d)	6.28	NS
				ADG (d −1 to 35 d)	−9.23	NS
			Ketoprofen 1.5 mg/kg IV, 20 min prior to castration, repeated at castration and 3 mg/kg at 24 h post-castration	Feed intake (d −1 to 33 d)	2.73	NS
				ADG (d −1 to 35 d)	−18.46	NS

Table 2 (*Continued*)

Reference	Procedure	Study population	Analgesic regimen	Outcome parameter	Percent change (%)	Significance (*P*-value)
Pang et al. (2006)	Band castration	5.5 months Dairy	Carprofen 1.4 mg/kg IV, 20 min prior to castration	Fibrinogen (d 35)	−19.25	NS
				Haptoglobin (d 35)	−76.19	$p < 0.05$
				Rectal temperature	0.00	NS
	Burdizzo clamp castration		Carprofen 1.4 mg/kg IV, 20 min prior to castration	Fibrinogen (d 35)	−2.13	NS
				Haptoglobin (d 35)	0.00	NS
				Rectal temperature	0.26	NS
González et al. (2010)	Band castration	210 days Beef	Xylazine 0.07 mg/kg epidural and IV flunixin meglumine at 1.1 mg/kg	ADG (0–42 d)	0.00	0.21
				Feed intake (0–42 d)	−1.54	0.02
				Fecal *E. coli*, log (cfu)	−10.16	0.9
				Lying time, %	29.65	0.1
				Step length (back)	−3.83	0.04
				Step length (front)	−1.03	0.38
Stewart et al. (2010)	Surgical castration	4 month Dairy	Lidocaine, 5 ml into the scrotum followed by 7 ml at the neck of the scrotum	Heart rate (0–2 min)	−58.82	<0.05
				Eye temperature (5–20 min post-castration)	−40.43	<0.05
				HRV: LF power	−7.34	NS
				HRV: HF power	−7.34	NS
				HRV: LF:HF ratio	−76.19	NS
Baldridge et al. (2011)	Surgical castration followed by surgical dehorning (Barnes)	2–4 month Dairy	Sodium salicylate at 2.5–5 mg/mL in the drinking water (13.62 to 151.99 mg of salicylate/kg bodyweight)	ADG (0–13 d)	1101.12	<0.05
				Chute exit speed	−0.97	NS
			0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine co-administered IM immediately prior to castration	ADG (0–13 d)	729.98	NS
				Chute exit speed	77.81	<0.05
			Sodium salicylate at 2.5 to 5 mg/mL in the drinking water (13.62 to 151.99 mg of salicylate/kg bodyweight) and 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine co-administered IM immediately prior to castration	ADG (0–13 d)	1095.92	<0.05
				Chute exit speed	94.97	<0.05
Coetzee et al. (2011)	Surgical Castration	8–10 months (193–285 kg)	Meloxicam tablets at 1 mg/kg suspended in 50 mL of water in a dosing syringe and administered orally, 24 h prior to castration	ADG (1–14 d)	21.79	NS
				DMI (1–14 d)	2.13	NS
				G:F Ratio (1–14 d)	18.75	NS
				ADG (15–28 d)	−2.60	NS
				DMI (15–28 d)	0.86	NS
				G:F Ratio (15–28 d)	−4.55	NS
				Pull Rate	−42.92	<0.05

Table 2 (*Continued*)

Reference	Procedure	Study population	Analgesic regimen	Outcome parameter	Percent change (%)	Significance (*P*-value)
				Bovine respiratory disease treatment rate	−49.11	<0.05

Percent change in cortisol was calculated using the formula [(mean of analgesic group/mean of castrated control group) − 1] × 100. ADG: average daily gain in bodyweight; cfu: colony forming units; HRV: heart rate variability; LF: low frequency; HF: high frequency; DMI: dry matter intake; G:F ratio: gain to feed ratio.

only permitted when the health of the animal is threatened and not for production purposes; (4) ELDU in feed is prohibited and (5) ELDU is not permitted if it results in a violative drug residue in food intended for human consumption. Therefore, use of an analgesic to alleviate pain associated with castration in calves in the United States would be required by law to comply with these regulations.

A second challenge to providing effective analgesia in cattle is that there is often a delay between the time of drug administration and the onset of analgesic activity. For example, local anesthetics require 2–5 min before a maximal effect is achieved (Spoormakers et al., 2004; Lemke and Dawson, 2000). This may slow animal processing and that may serve as a disincentive to producers to provide routine preemptive analgesia. Furthermore, this may result in procedures being initiated before optimal analgesia is achieved. A third challenge is that the route or method of analgesic drug administration may require specialized training and expertise or may be hazardous to the operator. For example, the NSAID flunixin meglumine is only approved for IV administration in the United States (Smith et al., 2008). Therefore, administration requires the animal to be adequately restrained and the operator to be proficient in IV administration. Similar issues are encountered with epidural analgesic drug administration and administration of local anesthesia into the scrotum. The latter procedure is also considered especially hazardous by many livestock handlers. In addition, the majority of analgesic drugs that are available in the U.S. have a short elimination half-life necessitating frequent administration in order to be effective (Smith et al., 2008). This increases the stress on the individual animal and increases labor and drug costs.

In addition to the regulatory considerations discussed previously, certain drug classes such as the opioid and NMDA receptor antagonists are designated as Schedule 3 drugs and are subject to regulation by the U.S. Drug Enforcement Administration (DEA) (DEA, 2010). Therefore application of these compounds to provide pre-emptive analgesia is restricted to use by licensed veterinarians. Finally, the cost associated with providing preemptive analgesia contributes to the reluctance of producers to adopt these measures especially since there is no perceived economic benefit for doing so. It may also be difficult for producers and veterinarians to determine if analgesic compounds are effective because cattle may not show overt signs of pain and distress. Thus determining the need for analgesia and the dose, route, duration and frequency of drug administration in cattle can be especially challenging.

3. Assessment tools used to determine the efficacy of analgesic drugs in cattle following castration

3.1. Assessment of behavioral changes after castration

Assessment tools that have been used to quantify changes in animal behavior following castration include visual scoring systems (Schwartzkopf-Genswein et al., 2005) videography (Currah et al., 2009; González et al., 2010), vocalization assessment (Currah et al., 2009), chute behavior (Currah et al., 2009), pedometers (Currah et al., 2009) and accelerometers (White et al., 2008).

The literature pertaining to behavioral responses associated with castration has been summarized in an excellent review by Stafford and Mellor (2005). The authors conclude that assessments of individual animal behavioral changes in response to pain are highly subjective. Escape behaviors demonstrated at castration but not seen afterwards may reflect a pain response (Mellor et al., 2000) or a desire to escape confinement (Fell et al., 1986). Fell et al. (1986) reported that surgically castrated calves struggle and kick during the procedure but calves castrated with rubber rings are quieter. Macauley et al. (1986) found that calves castrated surgically were less active than control calves or calves castrated using a Burdizzo. Robertson et al. (1994) found that rubber-ring, Burdizzo and surgical castration caused significant behavioral responses indicative of pain during the first 3 h after castration. Fisher et al. (2001) found that 14-month-old bulls castrated surgically stamped their hind feet, swished their tails and grazed less following castration than control bulls and bulls castrated using bands. Behaviors indicative of a painful sensation such as turning the head towards the hindquarters, alternate lifting of the hindlegs, abnormal postures and slow movement of the tail has been reported weeks after rubber-ring castration (Fisher et al., 1997).

Currah et al. (2009) and González et al. (2010) used videography to determine stride length of calves before and after surgical and band castration respectively. Both studies report that stride length was significantly shortened after castration. Furthermore, Currah et al. (2009) concluded that calves took significantly fewer steps after surgical castration in a study that used pedometers to compare step count before and after the procedure. In the same study only 10 out of 71 calves (14%) vocalized during castration and did not report a difference in chute behavior assessed using load cells. White et al. (2008) used accelerometers to evaluate standing and laying behavior in calves before and after surgical castration. The study concluded that calves spent significantly more time standing after castration.

3.2. Assessment of physiological changes after castration

Physiological changes after castration has been assessed using serum cortisol, heart rate; feed intake and average daily gain measurements.

Several studies have evaluated acute cortisol response as a method of determining the extent and duration of distress associated with castration in cattle (Chase et al., 1995; Molony and Kent, 1997; Fisher et al., 1997; Earley and Crowe, 2002; Stafford et al., 2002). Studies reviewed by Stafford and Mellor (2005) indicate that surgical and latex band castrations, especially when performed in older cattle, appear to elicit higher plasma cortisol responses that remain above pre-treatment levels for longer. Peak cortisol concentration following surgical castration occurs within the first 30 min after castration and range from 45 nmol/L following rubber ring castration to 129 nmol/L following surgical castration. The duration of plasma cortisol response above pre-treatment levels typically ranges from 60 min following Burdizzo castration to 180 min following surgical castration.

Cortisol has been widely used as a measurement of distress since its response magnitude, as indicated by peak height, response duration and/or integrated response usually accords with the predicted noxiousness of different procedures (Mellor et al., 2000; Broom, 2000). At each end of the cortisol response range, however, interpretation is less straightforward. At the lower end, for example, studies have shown that tail docking with a ring and tail docking with a docking iron cause similar cortisol responses to control handling in older lambs (Molony and Kent, 1997). At the upper end of the range, there are several examples where cortisol responses do not increase proportionally to the severity of different treatments as might be expected. This may suggest a "ceiling effect" on plasma cortisol responses (Molony and Kent, 1997; Coetzee et al., 2007). Other studies have shown that plasma cortisol concentrations following surgical castrations vary greatly between animals (Stafford et al., 2002). Based on these data, it has been hypothesized that low responses may be due to individuals having high pain thresholds (Stafford and Mellor, 2005). Variations may also come about due to differences in the way in which a particular castration method is performed by different operators. These data suggest that plasma cortisol levels may not always accurately reflect the extent of the pain response in animals.

Schwartzkopf-Genswein et al. (2005) evaluated the heart rate in 15 calves before and after surgical castration. It is noteworthy that heart rates were significantly lower at 15 and 30 min after castration compared with pre-castration rates. However there was a significant increase in heart rate at 120 min after castration. The authors concluded that castration had little effect on heart rate. However these results may have been confounded because calves had been dehorned 21 days previously and the overall heart rates were higher before and after castration than they were prior to the dehorning period.

Production parameters are often too imprecise to reflect the pain experienced by animals following castration (Stafford and Mellor, 2005). Furthermore, weight gain following castration may be negatively influenced by a decrease in testosterone following removal of the testes (King et al., 1991). However, assessment of production parameters is critical if animal well-being research is to have relevance to livestock producers. In studies reviewed by Stafford and Mellor (2005), Burdizzo or surgical castration were found to have no effect on average daily gain (ADG) over a 3-month period following castration (Knight et al., 1999; King et al., 1991). However, the ADG of 7-week-old calves during the 5 weeks following castration using rubber rings, clamp or surgery was found to be lower than non-castrated calves but similar between the different castration methods (King et al., 1991). Rubber ring and surgical castration were reported to cause a decrease in ADG of 50% and 70%, respectively in cattle aged 8–9 months (ZoBell et al., 1993). When 8, 9 and 14-month-old cattle were castrated surgically or using latex bands, cattle castrated later had poorer growth rates than those castrated at weaning. Cattle castrated with latex bands also had lower growth rates than those castrated surgically during the following 4–8 weeks (Fisher et al., 2001; Knight et al., 1999).

In a study conducted by Oklahoma State University, 162 bull calves were used to determine the effects of latex banding of the scrotum or surgical castration on growth rate. Bulls that were banded at weaning gained less weight than bulls that were banded or surgically castrated at 2–3 months of age (Lents et al., 2001). In a second study, 368 bull calves were used in two separate experiments to examine the effect of method of castration on receiving health and performance. In the first experiment latex banding intact males shortly after arrival was found to decrease daily gain by 19% compared with purchasing steers, and by 14.9% compared with surgically castrating intact males shortly after arrival. In the second experiment purchased, castrated males gained 0.58 lbs more and consumed 1.26 lbs more feed per day than intact males surgically castrated shortly after arrival (Berry et al., 2001).

3.3. Assessment of neuroendocrine changes after castration

Neuroendocrine changes have been assessed through measurement of the neuropeptide substance P (Coetzee et al., 2008), infrared thermography (Stewart et al., 2009, 2010), heart rate variability (HRV) (von Borell et al., 2007; Stewart et al., 2009, 2010), electrodermal activity (Kotschwar et al., 2009; Baldridge et al., 2011) and electroencephalography (EEG) (Gibson et al., 2007; Bergamasco et al., 2011).

Substance P is an 11-amino acid prototypic neuropeptide that regulates the excitability of dorsal horn nociceptive neurons and is present in areas of the neuroaxis involved in the integration of pain, stress, and anxiety. One study found that plasma SP concentrations are up to 27-fold greater in human patients with soft tissue injury than healthy controls (Onuoha and Alpar, 1999). In a recent study to evaluate plasma substance P (SP) and cortisol response following castration, no significant difference in plasma cortisol response between castrated and uncastrated calves was observed over time ($p = 0.644$) (Coetzee et al., 2008). In contrast, mean plasma

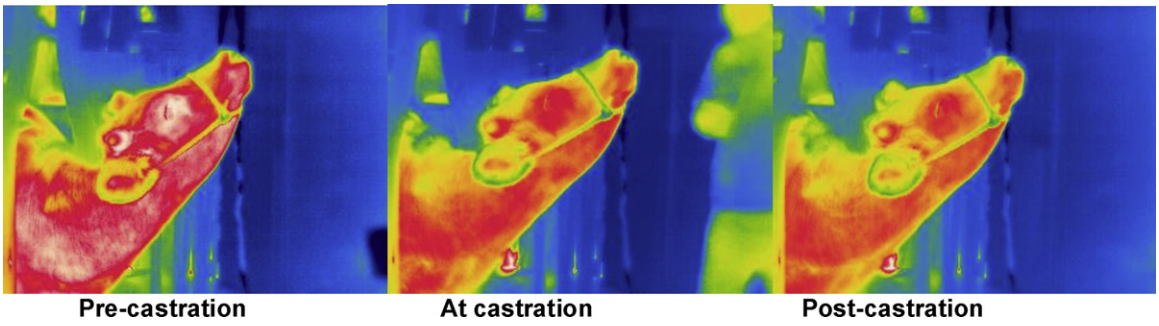

Fig. 1. Time sequence thermography images taken before castration, at the time of castration and immediately after castration in a Holstein calf. Color changes likely indicate changes in peripheral perfusion associated with catecholamine release following castration.

SP concentrations were significantly higher in castrated calves compared to uncastrated controls over the course of the study ($p = 0.042$). Significant increases in plasma SP concentration post-castration suggest that this measurement may be associated with nociception although further investigation is necessary.

Infrared thermography evaluates changes in surface temperature (Stewart et al., 2009). Epinephrine release associated with castration causes changes in sympathetic tone. The adrenergic effects on cutaneous blood flow cause changes in skin temperature that can be quantified with a thermography camera (Fig. 1). A decrease in eye temperature observed following castration of calves without local anesthetic has been attributed to sympathetically mediated alterations in blood flow in capillary beds (Stewart et al., 2010).

Heart rate variability (HRV) measurement assesses variation in the intervals separating consecutive heart beats (von Borell et al., 2007). HRV is used to investigate the functioning of the autonomic nervous system, especially the balance between sympathetic and vagal activity (von Borell et al., 2007). It has been hypothesized that HRV measurement provides a more detailed measure of a stress response than heart rate alone (Stewart et al., 2009). This is because HRV makes it possible to measure the balance between sympathetic and parasympathetic tone, therefore providing a more detailed interpretation of autonomic activity (von Borell et al., 2007). HRV data are analyzed using frequency domain measures including high frequency power (HF; 0.30–0.80 Hz), low frequency power (LF; 0.04–0.30 Hz), and the LF:HF ratio. These outcomes are calculated by fast Fourier transformation (Stewart et al., 2009, 2010).

Recently, Stewart et al. observed a significant increase in high frequency power from baseline in calves castrated surgically without local anesthesia (Stewart et al., 2010). In contrast, a significant decrease in low frequency power compared to baseline was observed in calves castrated surgically with local anesthesia. The authors conclude that an increase in HF power indicates an increase in parasympathetic activity that may be associated with deep visceral pain as might occur when the spermatic cords are torn.

Electrodermal activity (EDA) is the measurement of the electrical resistance between 2 electrodes applied to the skin (Benford and Dannemiller, 2004). EDA can be influenced by changes in resistance as a result of changes in sympathetic outflow. The Pain Gauge® (Public Health Information Systems, Inc., Dublin, OH) is purported to be a device capable of measuring EDA although there is a paucity of data to support this use in livestock species. A study that used the Pain Gauge® in rats found it ineffective for accurately assessing postoperative pain because pain scores did not decrease with increasing dosages of analgesic regimens (Richardson et al., 2007). Similar results were reported by Kotschwar et al. (2009) in calves subjected to an amphoterecin B lameness model. Baldridge et al. (2011) observed a significant decrease in EDA measurement coinciding with the presence of quantifiable plasma xylazine, ketamine and butorphanol concentrations. After 90 min, EDA increased and was not significantly different from other treatment groups. It is noteworthy that a difference in EDA between a sham and actual castration and dehorning period both with analgesia was not observed. Therefore, it was concluded that EDA measurement was not a reliable indicator of pain associated with dehorning and castration in calves and that EDA effects were likely associated with other physiological changes associated with drug exposure.

EEG responses of calves to noxious stimulus associated with scoop dehorning using a minimal anesthesia model have been studied (Gibson et al., 2007). However, the use of general anesthesia may have confounded these results. Further studies are needed to determine the relevance of this research to understanding pain in the conscious calves. Our research group is currently investigating the effect of age and method of castration on EEG response in conscious calves (Bergamasco et al., 2011). Fig. 2 represents the EEG taken from a fully conscious, 12-week-old Holstein calf before and after surgical castration. Prior to castration, a distinct, low frequency wave pattern predominates. Immediately following castration there is a significant shift towards high-frequency, low-amplitude brain activity (beta frequency). Relative power of the low and high frequency waves decreased and increased respectively between baseline and castration periods. This activity is known as desynchronization of waves and is associated with nociception (Gibson et al., 2007). Delta bands showed a tendency towards an increase during the first recovery period suggesting attempted synchronization within 5–10 min after castration. The results of this study suggest that EEG may be a sensitive and specific measure of changes in brain electrical activity associated with castration.

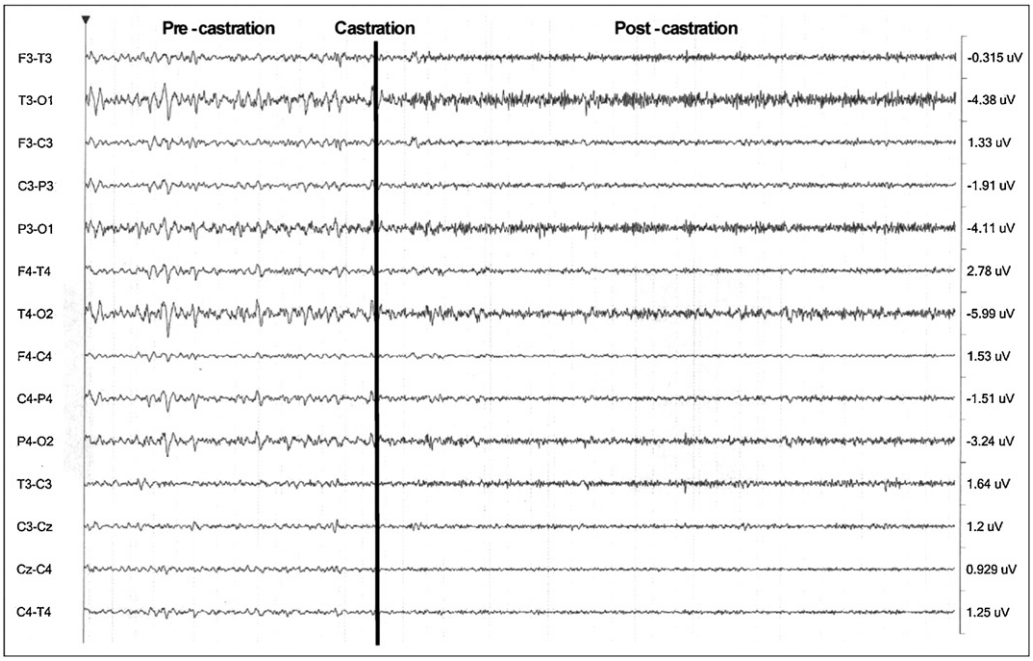

Fig. 2. Example of an electroencephalography (EEG) trace (30 s duration) illustrating brain electrical activity in a 6-week-old calf at castration. Note the transition in wave activity between the pre-castration period (calf restrained into the chute), Castration (beginning of the procedure) and the post-castration period. There is a shift from a medium high amplitude-slow frequency wave activity to low amplitude-fast frequency EEG wave pattern (Bipolar montage; time constant = 0.3 s; high frequencies filter = 70 Hz; notch filter inserted, aEEG 2–30). Figure provided courtesy of Dr Luciana Bergamasco, Kansas State University.

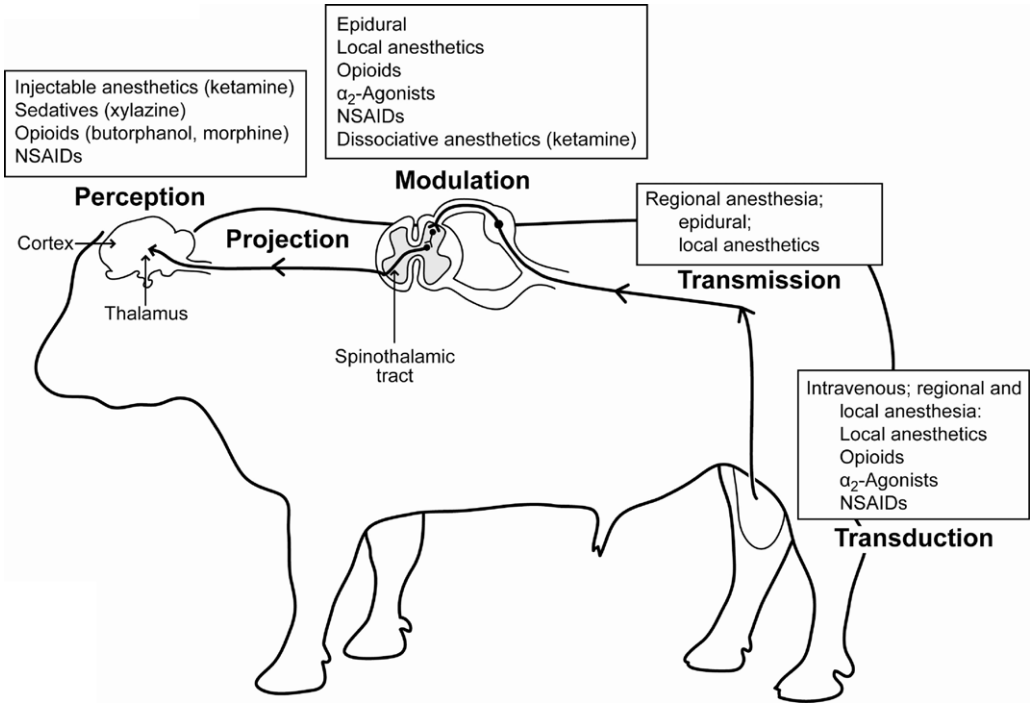

Fig. 3. A schematic representation of the nociceptive pathway in cattle indicating the anatomic location of target receptors for analgesic drug activity. *Source*: Figure provided courtesy of Mal Hoover, Kansas State University.

4. Analgesic strategies and their effects on pain biomarkers

Pain perception involves the transduction of chemical signals at the site of injury into electrical energy (Fig. 3). This is followed by transmission of the electrical signal via nerve fibers up the spinothalamic tracts where modulation may occur in the dorsal horn (Muir and Woolf, 2001). Finally the impulse is projected to the brain where pain perception occurs (Gottschalk and Smith, 2001). The initial response to a noxious stimulus is typically brief, well-localized and somewhat proportional to the intensity of the insult. The second phase of the response is prolonged, diffuse and often associated with hypersensitivity around the point where the initial stimulus was applied (Gottschalk and Smith, 2001). This effect may lead to persistent post-injury changes in the central nervous system resulting in pain hypersensitivity or central sensitization ("wind-up") (Kissin, 2000; Gottschalk and Smith, 2001). These effects lead to hyperalgesia (increased pain from previously painful stimuli) and allodynia (a previously non-painful stimulus now produces pain) (Ochroch et al., 2003).

Surgery-induced pain and central sensitization consist of two phases: an immediate incisional phase and a prolonged inflammatory phase that arises primarily due to tissue damage (Kissin, 2000). The goal of administering analgesic compounds prior to castration is to mitigate both the incisional and inflammatory phase of the pain response. Effective analgesia therefore requires a multimodal approach using compounds that act on different receptor targets along the nociceptive pathway (Muir and Woolf, 2001) (Fig. 3). This can be achieved through a combination of local anesthesia, NSAIDs and sedative-analgesic combinations of opioids, α2-agonists, and *N*-methyl D-aspartate receptor antagonists.

4.1. Local anesthesia

Local anesthetics are the most commonly prescribed pre-emptive analgesic drugs used in food animal practice (Muir et al., 1995). These compounds produce reversible loss of sensation in a localized area without causing loss of consciousness. Local anesthetics enter and block open sodium channels of nerve cells and prevent generation and propagation of nerve impulses (Webb and Pablo, 2009). Repeatedly stimulated nerve cells are therefore more susceptible to the effects of local anesthetics. Furthermore, unmyelinated nerve fibers that transmit pain signals are preferentially blocked by local anesthetics compared with myelinated fibers that are responsible for pressure sensation and motor activity. The quality of local anesthesia in an acidic environment, such as infected tissues, is often poor because these compounds are weak bases that must dissociate in an alkaline environment to exert their effect. Local anesthetic administration into the epidural space has also been shown to provide regional analgesia of the perineal region commencing 5 min after administration of 0.2 mg/kg lidocaine and lasting 10–115 min (Muir et al., 1995).

Lidocaine and bupivacaine have been examined as potential local anesthetics for use prior to bovine castration (Table 1). Lidocaine has a fairly rapid onset of activity (2–5 min), an intermediate duration of action (90 min) and a lower toxicity than bupivacaine (Webb and Pablo, 2009). Bupivacaine is the most potent long acting amide local anesthetic with a slower onset of activity (20–30 min) but a longer duration of action (5–8 h) (Webb and Pablo, 2009). Boesch et al. (2008) reported a similar reduction in plasma cortisol concentrations in 1-week-old dairy calves treated with lidocaine and bupivacaine prior to burdizzo clamp castration. This suggests that bupivacaine may not offer significant clinical advantages over lidocaine possibly due to the slower onset of activity.

Surveys report that 10% of New Zealand producers (Stafford et al., 2000), 43% of British veterinarians (Kent et al., 1996) and 22% of U.S. veterinarians (Coetzee et al., 2010a) administer local anesthetics prior to castration. A review of the literature identified 8 studies evaluating the effect of local anesthesia on plasma cortisol concentration after surgical and non-surgical castration (Table 1). The average percent reduction in peak plasma cortisol concentration (C_{max}) in calves receiving local anesthesia alone prior to castration when compared with castrated controls was 25.8% (95% CI: 2.46–49.1%). However, the average area under the effect curve (AUEC) for cortisol was only reduced by 16. 3% (95% CI: 2.91–29.7%) (Fig. 4). This suggests that local anesthetics alone are effective in reducing acute distress associated with castration. However, the overall AUEC is only modestly reduced in calves receiving local anesthesia prior to castration likely due to the absence of analgesic and anti-inflammatory effects extending into the post-operative period (Fig. 5).

Several studies have evaluated the effect of local anesthetic administration prior to castration on feed intake, average daily weight gain and inflammatory mediators (Table 2). In most cases the results of these studies have not shown a significant difference in performance between treated and control calves (Fisher et al., 1996; Ting et al., 2003a,b). Recently, Stewart et al. (2010) observed significant differences in heart rate and eye temperature in calves castrated with local anesthesia compared with untreated castrated controls. Changes were also observed in heart rate variability however the extent of this change from baseline levels in the castrated groups was not statistically significant.

4.2. Nonsteroidal anti-inflammatory drugs

NSAIDs produce analgesia and anti-inflammatory effects by reducing prostaglandin (PG) synthesis through inhibition of the enzyme cyclo-oxygenase (COX) in the peripheral tissues and central nervous system (Ochroch et al., 2003). COX exists in two isoforms. COX-1 is constitutively expressed in both peripheral and central nervous systems although expression is enhanced by pain and inflammatory mediators. COX-2 is ubiquitous in the CNS but only becomes the major enzyme for PG synthesis after induction by factors released during cell damage and death (Smith and Langenbach, 2001). It takes 2–8 h for maximal COX-2 mRNA expression to occur in the peripheral

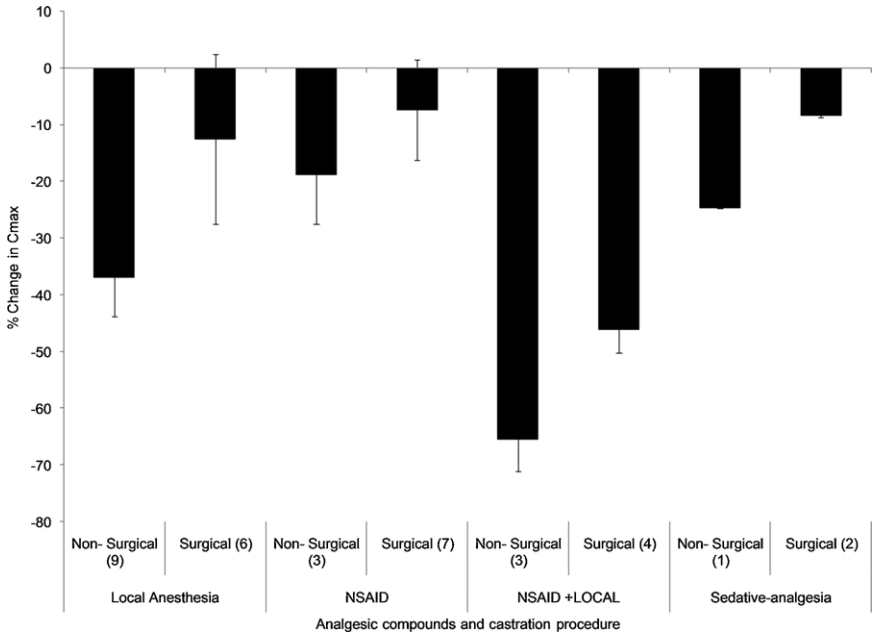

Fig. 4. Summary of the mean (±SEM) percent change in peak plasma cortisol concentrations (C_{max}) in analgesic treated calves compared with untreated castrated control calves in the published literature. The number of treatment groups evaluated is indicated in parentheses. Percent change in cortisol was calculated using the formula [(mean of analgesic group/mean of castrated control group) − 1] × 100.

tissues therefore initial release of PG is primarily due to COX-1 (Svensson and Yaksh, 2002). PG in the peripheral tissues lowers the activation threshold of sensory neurons and may initiate nociceptive activity. PG also works in concert with substance P, histamine, calcitonin gene-related peptide (CGRP) and bradykinin to lower the firing threshold of sensory nerves and produce inflammation. Therefore NSAIDs that inhibit COX-1 may have a more immediate impact on pain by inhibiting PG production in the periphery than COX-2 selective compounds (Ochroch et al., 2003).

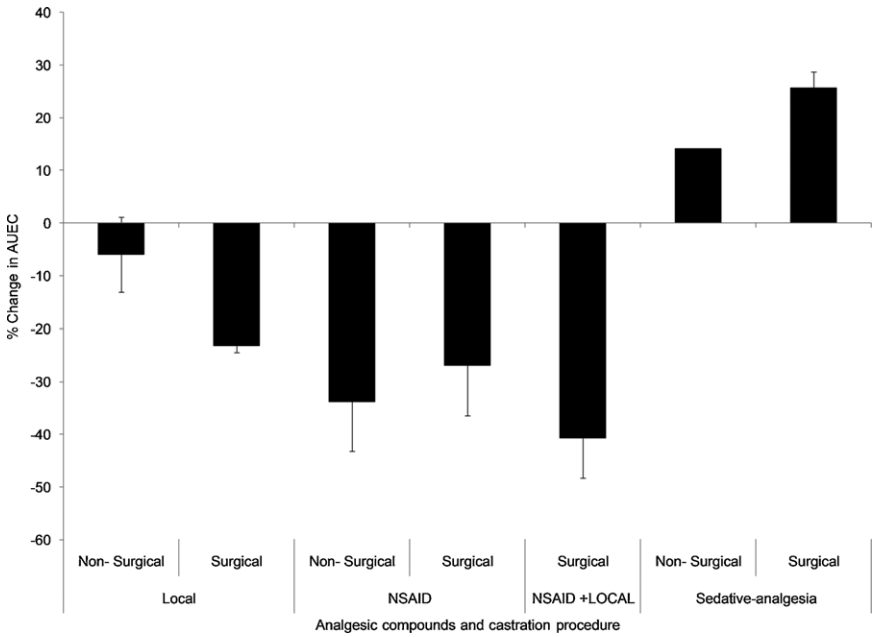

Fig. 5. Summary of the mean (±SEM) percent change in area under the plasma cortisol concentration over time curve (AUEC) in analgesic treated calves compared with untreated castrated control calves in the published literature. The number of treatment groups evaluated is indicated in parentheses. Percent change in cortisol was calculated using the formula [(mean of analgesic group/mean of castrated control group) − 1] × 100.

Table 3
Non-steroidal anti-inflammatory compounds available for use in cattle in the United States.

Drug	Approved species	Indications	Dose (Cattle)	*T½*	Withhold period
Flunixin meglumine	Cattle, horses and pigs	Antipyretic, anti-inflammatory	2.2 mg/kg IV	3–8 h	Meat – 4 days Milk – 36 h
Phenylbutazone	Horses and dogs	Anti-inflammatory	4 mg/kg IV	40–55 h	Not approved in cattle in the USA
Ketoprofen	Horses and dogs	Anti-inflammatory	1.5 mg/kg IV, IM	0.42 h	Not approved in cattle in the USA
Aspirin	No FDA approval Horses and Cattle	Reduction of fever relief of minor muscle aches and joint pain	50–100 mg/kg PO oral F < 20%	0.5 h (IV salicylate)	No formal FDA approval Not approved for use in lactating cattle
Carprofen	EU approval in cattle and dogs	Adjunctive therapy of acute respiratory disease and mastitis	1.4 mg/kg bodyweight IV or SC	Age dependent <10 weeks: 49.7 ± 3.9 h (R−) and 37.4 ± 2.4 h (S+) Adult cows; 30.7 ± 2.3 h	Not approved for use in cattle in the USA
Meloxicam	EU and Canadian approval in cattle Dogs and cats	Adjunctive therapy of acute respiratory disease; diarrhea and acute mastitis (Europe)	0.5 IV, SC 0.5–1 mg/kg PO	27 h (Range: 19.97–43.29 h)	Not approved in cattle in the USA

IV: intravenous; SC: subcutaneous; PO: Per Os (oral); F: Bioavailability.

However, NSAIDs that inhibit COX-1 may be associated with increased risk for adverse gastrointestinal and renal effects.

Spinal PG, notably PGE_2, is responsible for increased excitability of the dorsal root ganglia leading to centrally mediated hyperalgesia. Given that COX-2 is constitutively expressed in the CNS, inhibition of spinal PGE_2 production by NSAIDs that inhibit COX-2 may be an important mechanism in preventing the establishment of hyperalgesia (Svensson and Yaksh, 2002; Ochroch et al., 2003). The effect of NSAIDs on both central and peripheral PG synthesis suggests that these compounds have an important role in multimodal analgesic protocols.

The dose and pharmacokinetic parameters of the commonly used analgesic compounds in the United States are summarized in Table 3. A review of the literature identified 8 studies evaluating the effect of NSAIDs alone on plasma cortisol concentration after surgical and non-surgical castration (Fig. 4). The average percent reduction in peak plasma cortisol concentration (C_{max}) in calves receiving only an NSAID prior to castration when compared with castrated control calves was 10.8% (95% CI: 4.2% increase – 25.9% decrease in cortisol). However, the area under the effect curve (AUEC) for cortisol was reduced by an average of 29% (95% CI: 13.2–44.8% reduction). This suggests that NSAIDs alone are not effective in reducing acute distress associated with castration. However, the reduction in overall AUEC was greater in calves receiving an NSAID compared with calves administered only local anesthesia prior to castration. This is likely due to the analgesic and anti-inflammatory effects of NSAIDs extending into the post-operative period.

It is noteworthy that the majority of studies examining the effect of NSAIDs on pain biomarkers after bovine castration involved administration of the analgesic 20 min prior to the start of the procedure. This was presumably conducted to ensure adequate analgesic drug concentrations in the tissues at the time of castration. However, this significantly diminishes the external validity of these studies since such a delay is impractical in field situations. Future studies should examine the effect of drug administration at the time of the procedure so that the results will be relevant to typical livestock production settings.

Earley and Crowe (2002) and Stafford et al. (2002) demonstrated a significant reduction in peak plasma cortisol concentrations in calves that were administered a combination of local anesthesia and an NSAID prior to castration compared with calves receiving either drug alone (Table 1). The average percent reduction in peak plasma cortisol concentration (C_{max}) in calves receiving local anesthesia and an NSAID prior to castration when compared with castrated control calves was 54.5% (95% CI: 42.5–66.53% decrease in cortisol) compared with 25.8% (95% CI: 2.46–49.1%) for local anesthesia alone and 10.8% (95% CI: 4.2% increase – 25.9% decrease in cortisol) for NSAID alone (Fig. 4). These results indicate that a multimodal analgesic approach using drugs that act on different receptors in the nociceptive pathway is more effective in mitigating pain associated with castration than a single analgesic agent.

4.3. Flunixin meglumine

Flunixin is a highly substituted derivative of nicotinic acid. Currently flunixin meglumine is the only NSAID approved for use in cattle in the United States (Smith et al., 2008). The plasma elimination half-life of flunixin is reported to be 3–8 h (Anderson et al., 1990). Following a single intravenous dose of 2.2 mg per kg of body weight (mg/kg), plasma concentrations decreased from 16.16 ± 5.28 to 1.22 ± 0.16 μg/mL in 2 h, and reached 0.5 ± 0.02 μg/mL by 30 h (USP Monographs, 2004a). A

peak concentration (C_{max}) of 0.9 ± 0.05 mcg/mL occurred at 3.5 ± 1.0 h (T_{max}) after a single oral dose of 2.2 mg/kg with an estimated half life of 6.2 h and bioavailability of 60% (Odensvik, 1995; USP Monographs, 2004a). Therefore, once daily administration is required to maintain effective plasma drug concentrations. Although this drug class is recognized as having analgesic properties, flunixin is only indicated for control of fever associated with respiratory disease or mastitis, and fever and inflammation associated with endotoxemia, rather than for control of pain. Studies demonstrating the analgesic effects of flunixin administered alone at the approved dose of 2.2 mg/kg are deficient in the published literature. Use of flunixin meglumine is further complicated by the requirement for intravenous administration which is more stressful on the animal and involves more skill and training on the part of the operator. Several reports have suggested that the IM administration of flunixin may result in significant myonecrosis and tissue residues (Smith et al., 2008).

Stilwell et al. (2008) reported that flunixin meglumine (2.2 mg/kg) combined with lidocaine epidural administration 5 min prior to burdizzo clamp castration decreased plasma cortisol concentration at 6 h post-castration by 50% compared with castrated control calves (Table 1). However at 48 h after castration plasma cortisol concentration was 30% higher in flunixin-treated compared with control calves although this difference was not statistically significant. Currah et al. (2009) observed that beef calves receiving 2.2 mg/kg flunixin meglumine combined with a lidocaine epidural took significantly more steps after surgical castration than castrated control calves. Furthermore stride length was significantly greater in calves receiving flunixin than untreated calves at 4 and 8 h after castration however at 12 h there was no difference in treatment groups.

González et al. (2010) observed that salivary cortisol concentrations were 60% lower at 4 h after band castration in calves receiving xylazine epidural and flunixin meglumine (1.1 mg/kg) compared with castrated controls. However, this difference was less evident at 24 h and 14 days after castration. Stride length and feed intake was also significantly less in flunixin-treated calves compared with castrated controls. Webster et al. (2010) found that peak plasma cortisol concentrations were 26% lower in calves receiving 2.2 mg/kg flunixin IV at 20 min prior to surgical castration compared with untreated calves. Calves that were administered a combination of lidocaine local anesthesia and flunixin meglumine IV had 48% lower peak plasma cortisol concentrations compared with castrated control calves. Neither of these differences was statistically significant.

4.4. Phenylbutazone

Phenylbutazone is not approved for use in cattle in the U.S although it has been used in veterinary medicine for more than 50 years (Arifah and Lees, 2002; USP Monographs, 2004b). The pharmacokinetics of phenylbutazone is characterized by a slow clearance and longer terminal half-life compared with other NSAIDs (Lees et al., 1988). The oral bioavailability of phenylbutazone ranges from 54% to 69% with peak plasma concentrations achieved in 8.9–10.5 h. Phenylbutazone has been associated with rare but fatal blood dyscrasias, including aplastic anemia, leukopenia, agranulocytosis, thrombocytopenia and deaths in humans (FDA-CVM, 2010). Hypersensitivity reactions of the serum-sickness type have also been reported. In addition, phenylbutazone is recognized as a carcinogen. Therefore, the FDA has issued an order prohibiting the extralabel use of phenylbutazone animal and human drugs in female dairy cattle 20 months of age or older. There is also a zero tolerance for phenylbutazone residues in edible tissues from any class of animal. Use of phenylbutazone as an analgesic in food animals is therefore discouraged. Studies demonstrating the analgesic effects of phenylbutazone administered prior to castration are deficient in the published literature.

4.5. Ketoprofen

Ketoprofen is a member of the propionic acid class of NSAIDs (USP Monographs, 2004c). Ketoprofen has a very short elimination half-life of 0.42 h in cattle making it less attractive for use as a preemptive analgesic (Landoni et al., 1995). Eighty percent of a parenteral dose is reportedly eliminated in the urine within 24 h of administration. Therefore multiple doses of ketoprofen will likely be required to maintain adequate analgesic concentrations. If ketoprofen is administered to cattle in the United States at 3.3 mg per kg q24 h for up to 3 days, the Food Animal Residue Avoidance Databank (FARAD) suggests that a meat withdrawal time of 7 days and a milk withholding time of 24 h would be sufficient to avoid residues.

Single or multiple doses of ketoprofen administered alone or in combination with local anesthesia prior to castration in cattle have been studied (Earley and Crowe, 2002; Ting et al., 2003a,b) (Tables 1 and 2). Administration of ketoprofen without local anesthesia prior to castration reduced plasma cortisol concentrations by an average of 14% (95% CI: 16.2% increase – 44.63% decrease in cortisol). However, the combination of local anesthesia and ketoprofen markedly reduced plasma cortisol concentrations by an average of 56% (95% CI: 41–70% decrease) compared with castrated controls. These studies suggest that ketoprofen is more effective if combined with local anesthesia as part of a multimodal analgesic protocol.

4.6. Salicylic acid derivatives

Salicylic acid derivatives, including aspirin (acetylsalicylic acid) and sodium salicylate, were the first NSAIDs to be used in modern medicine and are still widely used for their analgesic, antipyretic, and anti-inflammatory properties (Langston, 2003). Although the veterinary forms of aspirin are extensively marketed with label indications for the treatment of fever, inflammation, and pain relief, these have never been approved by the FDA Center for Veterinary Medicine for these indications (USP Monographs, 2004d). Therefore the legality of using salicylic acid derivatives in cattle is questionable because these are technically compounded products.

Aspirin is a weak acid with a pK_a of 3.5. In the relatively alkaline environment of the rumen (pH ranging from 5.5 to 7.0) approximately 1,000 times as much aspirin is in the ionized form compared to the more diffusable nonionized form. This results in a slow absorption rate in cattle. Aspirin is also highly protein bound (70–90%), a characteristic shared by all NSAIDs discussed in this review. Administration of two NSAIDs at one time, or a NSAID in conjunction with another highly protein bound drug may result in higher concentrations of free drug in the plasma due to competition for binding sites.

Aspirin elimination half-times after oral administration range from approximately 4.0 h after oral administration in cattle to approximately 38 h in cats. The slow absorption rate after oral administration demonstrated in adult dairy cows is evident in the difference between elimination half-times for IV sodium salicylate (0.54 ± 0.04 h) and oral acetylsalicylic acid (3.70 ± 0.44 h). The elimination half-life is longer after oral administration of aspirin because the rumen acts as a slow release reservoir for aspirin absorption. The low volume of distribution (0.24 ± 0.02 L/kg) is indicative of limited distribution to tissues. It is noteworthy that salicylic acid derivatives are not associated with clotting deficits in cattle (Langston, 2003).

In previous bovine castration studies, plasma concentrations of sodium salicylate above 25 μg/mL have coincided with decreased peak cortisol concentrations as compared to castration with no analgesia (Coetzee et al., 2007). In one study, an oral dose of 100 mg/kg (70 grains/100 lbs) maintained serum concentrations in excess of 30 g/mL between approximately 1 h and 5 h after administration (Gingerich et al., 1975). The mean peak serum concentration was close to 50 g/mL. An oral dose of 50 mg/kg failed to reach serum concentrations of 30 g/mL. Gingerich et al. (1975) used 30 g/mL as the minimum concentration for pain relief based on human serum concentrations required for relief of headaches, aches, and pains. Serum concentrations near 100 g/ml are necessary in man to relieve severe arthritis pain. The authors noted clinical improvement in two cows with nonsuppurative tarsitis at 100 mg/kg orally, but noted no improvement at this dose in a bull with suppurative tarsitis. They recommended 100 mg/kg every 12 h to maintain serum concentrations above 30 μg/ml.

Salicylate is more soluble than aspirin and may offer a convenient and cost-effective means of providing free-choice access to a NSAID in drinking water. Baldridge et al. (2011) found that calves receiving 2.5–5 mg sodium salicylate/mL of water beginning 72 h prior to concurrent surgical castration and dehorning and continuing for 48 h after surgery had a higher average daily weight gain for 13 days after castration-dehorning than untreated calves. However, water consumption decreased over the course of treatment suggesting that the inclusion of sodium salicylate had a negative effect on water palatability. Calves receiving sodium salicylate also has a significantly lower AUEC for cortisol in the period 1–6 h after dehorning-castration.

The use of sodium salicylate is only permitted using an approved animal or human formulation under the supervision of a veterinarian to alleviate suffering provided use does not result in a violative tissue residue (Smith et al., 2008). If aspirin is administered to cattle at a dose of 100 mg/kg every 12 h, the Food Animal Residue Avoidance Databank (FARAD) suggests that a meat and milk withdrawal time of 1 day (24 h) would be sufficient to avoid residues.

4.7. Carprofen

Carprofen is a member of the propionic acid class of NSAIDs (USP Monographs, 2004e). The relative anti-inflammatory, analgesic and antipyretic activity of carprofen is reported to be greater than phenylbutazone or aspirin (Delatour et al., 1996). Carprofen exists in 2 enantiomeric forms, R(−) and S(+). *In vitro* studies in canine plasma suggesting that the S(+) enantiomer is 100 times more active against COX-2 than the R(−) enantiomer (Ricketts et al., 1998). Carprofen also demonstrates age-dependent pharmacokinetics. The reported half-life of the R(−) and S(+) enantiomer in calves less than 10 weeks of age is 49.7 ± 3.9 h and 37.4 ± 2.4 h, respectively. In adult cows after SC administration the half-life of the racemic mixture is 30.7 ± 2.3 h. Carprofen is approved in the European Union as an adjunct to antimicrobial therapy to reduce clinical signs in acute infectious respiratory disease and acute mastitis in cattle. The recommended dose for subcutaneous or intravenous administration is 1.4 mg/kg bodyweight. Carprofen is commonly used in small animal medicine in the United States (Smith et al., 2008) however; there are currently no approved formulations for use in livestock.

Pang et al. (2006) observed that carprofen administered at 1.4 mg/kg IV, 20 min prior to band castration reduced peak plasma cortisol concentrations by 19% compared with castrated control calves (Table 1). However, this difference was not statistically significant. Carprofen treated calves demonstrated a significant reduction in plasma haptoglobin concentrations (Table 2). These effects were less in calves castrated with a burdizzo clamp. Stilwell et al. (2008) report a 59% reduction in plasma cortisol concentrations at 6 h and a 36% reduction at 48 h after burdizzo clamp castration in calves receiving 1.4 mg/kg carprofen combined with a lidocaine epidural compared with castrated controls.

4.8. Meloxicam

Meloxicam is a NSAID of the oxicam class that is approved in the European Union for adjunctive therapy of acute respiratory disease; diarrhea and acute mastitis when administered at 0.5 mg/kg IM or SC (EMEA, 2009). Heinrich et al. (2009) demonstrated that 0.5 mg/kg meloxicam IM combined with a cornual nerve block reduced serum cortisol response for longer compared with calves receiving only local anesthesia prior to cautery dehorning. Furthermore, calves receiving meloxicam had lower heart rates and respiratory rates than placebo treated control calves over 24 h post-dehorning. Stewart et al. (2009) found that meloxicam administered IV at 0.5 mg/kg mitigated the onset of pain responses as measured by heart rate variability and eye temperature, compared with administration of a cornual nerve block alone. These reports demonstrate

that administration of meloxicam prior to dehorning at 0.5 mg/kg IV or IM may be effective at alleviating pain and distress associated with painful procedures in cattle.

The pharmacokinetic–pharmacodynamic relationship and dose response to meloxicam in horses with induced carpal arthritis has been reported (Toutain and Cester, 2004). Based on this work, the reported EC50 for meloxicam in the plasma of lame horses is approximately 0.2 μg/mL. The pharmacokinetics of meloxicam after oral and IV administration have recently been described (Coetzee et al., 2009). A mean peak plasma concentration (C_{max}) of 3.10 μg/mL (range: 2.64–3.79 μg/mL) was recorded at 11.64 h (range: 10–12 h) with a half-life ($T½\ \lambda z$) of 27.54 h (range: 19.97–43.29 h) after oral meloxicam administration. The bioavailability (F) of oral meloxicam corrected for dose was 1.00 (range: 0.64–1.66). These findings indicate that oral meloxicam administration could be an effective and convenient means of providing long-lasting analgesia to ruminant calves.

Meloxicam (20 mg/ml) is approved for use in cattle in several European countries with a 15 day meat withdrawal time and a 5 day milk withdrawal time following administration of 0.5 mg/kg IM or SC. An oral meloxicam suspension (1.5 mg/mL) and injectable formulation (5 mg/mL) are approved in the United States for the control of pain and inflammation associated with osteoarthritis in dogs. Furthermore, an injectable formulation (5 mg/ml) is approved for the control of post-operative pain and inflammation in cats. Several inexpensive generic tablet formulations containing meloxicam (7.5 and 15 mg) have recently been approved for relief of signs and symptoms of osteoarthritis in human medicine. In the absence of FDA approved analgesic compounds in food animals, use of oral meloxicam tablets for alleviation of pain in cattle could be considered under AMDUCA. In a recent study our group reported that meloxicam administration prior to castration in post-weaning calves reduced the incidence of respiratory disease at the feedlot (Coetzee et al., 2011). These findings have implications for developing NSAID protocols for use in calves at castration with respect to addressing both animal health and welfare concerns.

4.9. Sedative-analgesic drugs

Opioids, α2-agonists, and *N*-methyl D-aspartate receptor antagonists are the most commonly used sedative analgesic compounds in veterinary medicine. These compounds may act synergistically and are therefore increasingly co-administered. A recent survey of Canadian veterinarians revealed that respondents that did use an analgesic at the time of castration used xylazine (>50% of respondents) more frequently than lidocaine (<30% of respondents) (Hewson et al., 2007). Administration of local anesthetics into the testicles is considered by some to be dangerous and time consuming with unpredictable efficacy, especially when circumstances do not allow sufficient time for maximal anesthesia to take effect (Hewson et al., 2007). Sedative-analgesic compounds may replace the need for intra-testicular anesthetic injection and thus enhance animal well-being and operator safety. A sub-anesthetic combination of xylazine, administered at 0.02–0.05 mg/kg and ketamine at 0.04–0.1 mg/kg given IV or IM ("Ketamine Stun") is reported to provide mild sedation without recumbency in cattle (Abrahamsen, 2009). Butorphanol (0.01 mg/kg) or morphine (0.05 mg/kg) may be included for enhanced analgesic effects.

4.10. Opioid analgesics

The analgesic effect of opioids are associated with binding to spinal and supraspinal mu (μ), kappa (κ) and sigma (δ) receptors (KuKanich and Papich, 2009). Drug binding decreases propagation of the nociceptive signal by activating receptor linked potassium channels and inhibiting voltage-gated calcium channels. In addition to producing analgesia, μ receptor activation is associated with respiratory depression, decreased gastrointestinal motility, increased appetite, sedation, euphoria and nausea. Therefore partial and mixed receptor opioids have been developed with fewer adverse effects and in some cases, a lower abuse potential than pure μ agonists. There are currently no narcotic analgesics approved for use in cattle in the United States. Opiods are designated as Schedule 3 drugs in the United States and are subject to regulation by the U.S. Drug Enforcement Agency.

Butorphanol is a κ-opioid receptor agonist and either a partial μ agonist or antagonist. The potency of butorphanol is reported to be 5–7 times that of morphine although some authors dispute this (KuKanich and Papich, 2009). The efficacy of butorphanol is limited to mild and moderate pain but it is one of the most common narcotic analgesics used in veterinary medicine. The half-life of butorphanol in dairy cows administered 0.25 mg/kg IV was 82 min (Court et al., 1992). Baldridge et al. (2011) reported a peak plasma concentration for butorphanol of 7.07 ± 0.55 ng/mL at 9.5 ± 0.50 min after co-administration of 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine IM immediately prior to dehorning and castration with a plasma elimination half-life of 71.28 ± 7.64 min. In dogs a plasma concentration of 45 ng/mL is considered an effective analgesic concentration but this has not been confirmed in cattle (KuKanich and Papich, 2009).

Faulkner et al. (1992) investigated the health and performance effects of intravenous butorphanol (0.07 mg/kg) and xylazine (0.02 mg/kg) co-administration to weanling bulls at the time of castration. Co-administration of xylazine and butorphanol resulted in reduced chute activity and clinical sedation characterized by muscle relaxation and occasional (<15–20%) difficulty in exiting the chute. It is noteworthy that cortisol concentrations immediately post-castration were not evaluated in this study. However, treated calves were found to have significantly higher cortisol concentrations at 3 days post-castration compared with castrated controls. The authors conclude that butorphanol and xylazine did not reduce stress or improve performance.

4.11. Alpha-2 adrenergic agonists

Alpha-2-adrenergic agonists produce profound sedation, chemical restraint and analgesia in cattle. Activation of α2-adrenergic receptors inhibits the positive feedback mechanism for the release of norepinephrine from

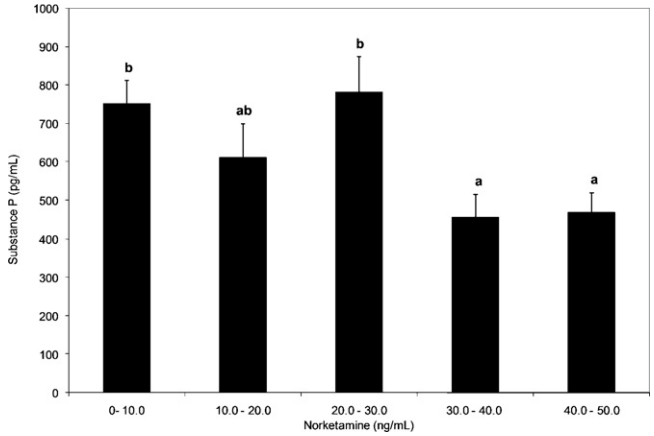

Fig. 6. Comparison between plasma substance P concentrations (pg/mL) and plasma norketamine concentrations (ng/mL) in calves receiving 0.1 mg/kg of ketamine prior to surgical castration. Columns with different letters are significantly different ($p < 0.05$).

the presynaptic nerve endings by reducing calcium conductance (Postner and Burns, 2009). Attenuation of norepinephrine release causes dose-dependent sedation and inhibits the afferent pain pathway (Postner and Burns, 2009). In addition, alpha-2-adrenergic agonists decrease cardiac output, cause a centrally mediated reduction in respiratory rate, produce muscle relaxation and depress gastrointestinal motility. Epidural administration of α2-agonists can produce analgesia with minimal sedative and cardiovascular effects compared with IV administration.

Xylazine is the most commonly used α2-adrenergic agonist used in cattle and is approved in the European Union for IM administration at 0.05–0.3 mg/kg. Administration of the lower dose is characterized by a slight decrease in muscle tone but the ability to stand is maintained. Higher doses cause recumbency, very deep sedation and a degree of analgesia. It is recommended that cattle are fasted prior to systemic administration of higher doses of xylazine to reduce the risk of rumen tympany and aspiration of rumen contents.

Xylazine epidural has been shown to produce greater perineal analgesia than xylazine given intramuscularly (Caron and LeBlanc, 1989). Xylazine epidural has been proposed as a method of providing sedation and analgesia to facilitate castration in mature bulls (Caulkett et al., 1993). Grubb et al. (2002) compared the time of onset and duration of analgesia produced by lidocaine and xylazine alone and in combination. The onset of analgesia following administration of xylazine alone was significantly longer (11.7 ± 1 min) than the combination of xylazine and lidocaine (5.1 ± 0.9 min) and lidocaine alone (4.8 ± 1.0 min). The combination of lidocaine and xylazine produced analgesia of significantly longer duration (302.8 ± 11.0 min) than xylazine alone (252.9 ± 18.9 min) or lidocaine alone (81.8 ± 11.8 min). Xylazine induced mild to moderate sedation and ataxia. Ataxia was also noted in cattle receiving lidocaine alone.

Previously Grant and Upton (2004) reported that 0.05 mg/kg xylazine IV in sheep produced analgesia lasting 25 min with only 3/7 animals showing signs of mild sedation. Garcia-Villar et al. (1981) reported that an IV dose of 0.2 mg/kg xylazine in cattle was associated with a peak plasma concentration of 1.050 μg/mL, a plasma elimination half-life of 36 min, and a total body clearance of 42 mL/min/kg. Baldridge et al. (2011) reported a peak plasma concentration for xylazine of 20.95 ± 1.68 ng/mL at 9.5 ± 0.50 min after co-administration of 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine IM immediately prior to dehorning and castration in calves. In this study the plasma elimination half-life of xylazine was 96.40 ± 20.33 min. Xylazine given at a dose of 0.05–30 mg/kg IM has a FARAD recommended withdrawal time of 4 days in meat and 24 h in milk (Haskell et al., 2003).

Ting et al. (2003a) found that peak plasma cortisol concentrations were not significantly attenuated in calves administered a combination of 0.05 mg/kg xylazine and 0.4 mg/kg lidocaine epidural prior to burdizzo clamp castration. However, the integrated cortisol response (AUEC) was 26.5% less than untreated calves ($p < 0.05$) (Table 1). González et al. (2010) observed that salivary cortisol concentrations were 60% lower at 4 h after band castration in calves receiving xylazine epidural and flunixin meglumine (1.1 mg/kg) compared with castrated controls. Coetzee et al. (2010b) found that xylazine alone at 0.05 mg/kg IV or in combination with ketamine at 0.1 mg/kg reduced peak plasma cortisol concentrations by 8% compared with surgically castrated control calves. However, the integrated cortisol response was higher in treated calves compared with untreated controls. These data suggest a rebound in plasma cortisol concentrations once the effect of the drug wears off. Similar findings were reported in calves receiving a combination of xylazine, ketamine and butorphanol prior to concurrent dehorning and castration in calves (Baldridge et al., 2011).

5. *N*-methyl D-aspartate receptor antagonists

Ketamine is an NMDA-receptor antagonist that produces analgesia and dissociative anesthetic effects when administered at a dose of 2–4 mg/kg IV to calves (Postner and Burns, 2009). Ketamine and its active metabolite, norketamine also bind mu and kappa opioid receptors producing analgesia (Annetta et al., 2005). Data from rats

suggest that norketamine contributes to the analgesic effect of ketamine, with a potency that is one-third of the parent drug (Leung & Baillie, 1986).

Sub-anesthetic ketamine administered at 0.1–1 mg/kg as an IV bolus is effective in managing acute post-operative pain in human medicine (Schmid et al., 1999). In humans plasma ketamine concentrations above 4–5 μmol/L (1,000 ng/mL) are required to produce anesthetic effects while analgesic effects are associated with plasma concentrations below 1 μmol/L (275 ng/mL) or 1/10th–1/5th of the anesthetic dose (Eide, 1999). Grant et al. (1981) reported that plasma ketamine concentrations ranging from 40 to 150 ng/mL were associated with analgesia in humans. Our group previously demonstrated that mean plasma ketamine and norketamine concentrations in cattle decreased to below 40 ng/mL and 10 ng/mL after 30 and 60 min, respectively, after administration of a sub-anesthetic combination of xylazine (0.05 mg/kg) and ketamine (0.1 mg/kg) (Gehring et al., 2009). NMDA receptor antagonists are designated as Schedule 3 drugs and are subject to regulation by the U.S. Drug Enforcement Agency.

Coetzee et al. (2010b) found that ketamine administered at 0.1 mg/kg in combination with xylazine at 0.05 mg/kg IV reduced peak plasma cortisol concentrations by 8% compared with surgically castrated control calves. However, the integrated cortisol response (AUEC) tended to be higher in treated calves compared with untreated controls. In this study the half-life of xylazine and ketamine after IV administration was approximately 11 min. This suggests that plasma cortisol concentrations likely rebounded in treated calves after the sedative-analgesic effect of the drug diminish. In this study higher plasma norketamine concentrations were associated with lower plasma substance P concentrations compared with lower norketamine concentrations (Fig. 6).

6. Future prospects for treating chronic pain and central sensitization in cattle

Gabapentin (1-(aminomethyl) cyclohexane acetic acid) is a γ-aminobutyric acid (GABA) analogue originally developed for the treatment of spastic disorders and epilepsy (Cheng and Chiou, 2006). Studies have reported that gabapentin is also effective for the management of chronic pain of inflammatory of neuropathic origin (Hurley et al., 2002). Although the mechanism of action of gabapentin is poorly understood, it is thought to bind to the α2-δ subunit of voltage gated calcium channels acting pre-synaptically to decrease the release of excitatory neurotransmitters (Taylor, 2009). Efficacy of gabapentin in humans is associated with 2 μg/mL plasma drug concentrations (Sivenius et al., 1991). It has also been reported that gabapentin can interact synergistically with NSAIDs to produce antihyperalgesic effects (Hurley et al., 2002; Picazo et al., 2006). In a recent study we report a mean peak plasma gabapentin concentration (C_{max}) of 3.40 μg/mL (range: 1.70–4.60 μg/mL) at 7.20 h (range: 6–10 h) after oral gabapentin administration at 15 mg/kg. An elimination half-life ($T½\ \lambda z$) of 7.9 h (Range: 6.9–12.4 h) was recorded (Coetzee et al., 2010c). Oral administration of gabapentin at 15 mg/kg may be associated with plasma concentrations of >2 μg/mL for up to 15 h. The pharmacokinetics of gabapentin suggests that this compound may be useful in mitigating chronic neuropathic and inflammatory pain in ruminant cattle.

7. Conclusions

Castration of cattle is considered necessary to reduce aggression, prevent injuries in confinement operations and to improve meat quality. However, all methods of castration have been shown to produce physiological, neuroendocrine, and behavioral changes indicative of pain and distress. Direct and indirect measurement of these changes using accelerometers, videography, heart rate variability determination, electroencephalography, thermography and plasma neuropeptide assessment may provide information that would lead to regulatory approval of analgesic drugs in livestock.

Administration of a local anesthetic alone effectively mitigates acute distress associated with castration but the integrated cortisol response is only modestly reduced. NSAID administration alone is not effective in reducing acute distress associated with castration however, the reduction in overall AUEC reported is greater in NSAID-treated calves compared with calves receiving only local anesthesia. The combination of local anesthesia and an NSAID achieved the greatest reduction in cortisol response in published reports suggesting that a multimodal analgesic approach is more effective in mitigating pain associated with castration than use of a single analgesic agent. Lidocaine and flunixin meglumine are the only compounds with analgesic properties that are approved by U.S. FDA for use in cattle. However flunixin requires IV administration and at least once daily dosing to be effective. In the absence of compounds specifically licensed for pain relief in cattle, ELDU regulations allow for unapproved analgesic drugs to be administered by or under the supervision of a veterinarian provided such use does not result in a violative tissue residue. Accordingly, a combination of local anesthesia with oral administration of a long-acting NSAID like meloxicam, may provide the optimum balance of convenience and analgesic efficacy at the time of castration.

Regulatory concerns combined with unease about the cost and convenience of drug administration at the time of castration is an impediment to the routine adoption of analgesic protocols in production systems. Although administration of multimodal analgesic protocols is associated with a significant decrease in plasma cortisol concentration after castration, most studies have not addressed the practical or production implications of these interventions in a commercial livestock environment especially in beef cattle. Studies examining the health and performance effects of newer drugs with extended durations of activity are also needed. Regulatory approval of safe, cost effective and convenient analgesic compounds will support the implementation of practical pain management strategies as a part of standard industry practice at the time of castration.

Conflict of interest

Dr Coetzee has been a consultant for Intervet-Schering Plough Animal Health, Norbrook Laboratories Ltd and Boehringer Ingelheim Vetmedica.

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