Kinetics and residues after intraperitoneal procaine penicillin G administration in lactating dairy cows

A. L. CHICOINE*

J. O. BOISON[†]

S. PARKER[‡]

C. CLARK[‡] &

P. M. DOWLING*

Department of Veterinary Biomedical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, SK, Canada; [†]Centre for Veterinary Drug Residues, Canadian Food Inspection Agency, Saskatoon Laboratory, Saskatoon, SK, Canada; [‡]Department of Large Animal Clinical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, SK, Canada

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This paper describes the pharmacokinetic profile of procaine penicillin G after intraperitoneal (IP) administration in eight lactating dairy cows. Procaine pencillin G (PPG, 21 000 IU/kg) was deposited into the abdominal cavity of each cow following an incision in the right paralumbar fossa. Blood and milk samples were taken over the following 10 days, at which point the cows were euthanized. Plasma, milk, muscle, liver, and kidney penicillin concentrations were determined by HPLC, with a limit of quantification of 5 ng/mL for plasma and milk and 40 ng/g for tissue samples. A noncompartmental method was used to analyze plasma kinetics. The mean pharmacokinetic parameters (±SD) were: C_{max}, 5.5 ± 2.6 μg/mL; T_{max}, 0.75 ± 0.27 h; $AUC_{0-\infty}$, 10.8 ± 4.9 μg·h/mL; MRT, 2.2 ± 0.9 h. All milk from treated cows contained detectable penicillin residues for a minimum of three milkings (31 h) and maximum of five milkings (52 h) after administration. Concentrations of penicillin in all muscle, liver, and kidney samples taken 10 days postadministration were below the limit of quantification. Necropsy examinations revealed foci of hemorrhage on the rumenal omentum of most cows but peritonitis was not observed. Systemic inflammation as determined by change in leukogram or plasma fibrinogen was noted in one cow. The results of this study demonstrate that IP PPG is absorbed and eliminated rapidly in lactating dairy cows.

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Alan L. Chicoine, Department of Veterinary Biomedical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, SK, Canada S7N 5B4. E-mail: al.chicoine@usask.ca

INTRODUCTION

Caesarian sections, left or right displaced abomasum corrections, exploratory laparotomies, and umbilical hernia repairs are common abdominal surgeries in bovine practice. The risk of surgical infection is elevated after on-farm surgery due to the nature of abdominal surgery (clean-contaminated, contaminated, or dirty); and the nonsterile operating conditions encountered. In addition to observing proper surgical site preparation, minimal surgery time, and good surgical technique, veterinarians can administer perioperative antimicrobials in an effort to reduce postsurgical infections (Brumbaugh, 1990; Desrochers, 2005). In veterinary teaching hospitals, postsurgical infection rates of 5–15% for bovine abdominal surgeries are reported (de Kruif *et al.*, 1987; Desrochers, 2005). 'On-farm' rates are likely higher. Gram-positive staphylococci (from skin or environment), Gram-negative enteric bacteria (from fecal contamination), and anaerobes (from necrotic tissue) are potential contaminants during bovine surgery. Unfortunately, cultures and susceptibility testing of the bacteria causing postsurgical infections are not routinely performed.

Current guidelines in human and veterinary medicine recommend that if a prophylactic antimicrobial is to be used, it is chosen based on predicted efficacy against probable pathogens with administration *before* microbial contamination occurs (Zelenitsky *et al.*, 2002; Giguere & Walker, 2006; Howe & Boothe, 2006). The benefits of preoperative vs. postoperative administration have also been demonstrated in bovine surgery (Haven *et al.*, 1992), where one preoperative dose of intravenous (i.v.) penicillin was as efficacious as the preoperative dose plus a 7-day postoperative course of intramuscular (i.m.) penicillin in reducing postrumenotomy complications. Both groups had lower rectal temperatures and fewer abscesses than nontreated animals. If an infection becomes established however, a longer course of antimicrobial therapy is warranted. Calves undergoing contaminated umbilical hernia surgery were less likely to have postoperative infections if treated with i.m. penicillin and dihydrostreptomycin for 4 days postoperatively rather than just one (Klein & Firth, 1988).

Rather than using preoperative or postoperative antimicrobials, a third option for practitioners performing bovine abdominal surgery is to administer intraoperative antimicrobials by intraperitoneal (IP) infusion. The IP route can be utilized in human abdominal surgery and peritoneal dialysis, primarily with cephalosporins (cephalothin, cephazolin, ceftazidime) and aminoglycosides (kanamycin, gentamicin) (Ericsson et al., 1978; Sinswat et al., 2000; Sisterhen et al., 2006). Other reports mention IP use of macrolides, vancomycin, metronidazole, and the antifungals amphotericin B and flucytosine (Schwartz et al., 1986; Arthur et al., 2004).

Because the frequency of IP antimicrobial use in cattle has not previously been reported, the authors surveyed bovine veterinarians in Western Canada. Perioperative antimicrobial use was widespread (96/98 respondents), with 54/98 practitioners surveyed using IP antimicrobials occasionally. Of those, 30/98 used IP antimicrobials in ≥75% of their abdominal surgeries (Chicoine et al., 2008). Procaine penicillin G (PPG) and oxytetracycline LP were the most commonly used IP antimicrobials. Veterinarians assumed IP antimicrobial administration is safe and that the drug is absorbed faster than i.m. or s.c. injections, though little PK data in cattle is available to support this assumption. The kinetics of IP antimicrobials in humans are variable, with maximum plasma concentrations occurring from 15 min to 5 h after administration for various antimicrobials (Ericsson et al., 1978; Schwartz et al., 1986).

Bovine experimental trials using IP infusions of oxytetracycline in saline and intramammary (IMM) ampicillin/cloxicillin and kanamycin/penicillin preparations have been performed (Fensterbank, 1976; Gitzel & Grunder, 1994; Klein et al., 1994). One retrospective study showed a lower rate of postsurgical infection after IP antimicrobial administration compared to untreated cows (Klein et al., 1994). Unfortunately, comparisons against preoperative intravenous (i.v.) prophylaxis are not available. IP antimicrobials are also used in other animal species, including rats, rabbits, and fish (Wieriks & Schornagel, 1971; Bruno, 1989; Ablan et al., 1991; Fairgrieve et al., 2006). The data regarding IP antimicrobial efficacy in reducing postoperative infections is not conclusive; some studies demonstrate efficacy while others show no benefit over irrigation with saline alone. One trial in rabbits found that an abdominal lavage containing a cephalosporin was more efficacious than saline alone for treating peritonitis, but only if the bacterial contamination was severe and the antimicrobial was administered promptly after contamination (Ablan et al., 1991).

Because IP antimicrobial administration constitutes extralabel drug use, practitioners have contacted the Canadian global Food Animal Residue Avoidance Databank (CgFARAD) for advice regarding meat and milk withdrawal times. Unfortunately, insufficient data is available in the literature to develop a withdrawal interval estimate. The CgFARAD has anecdotal reports of cows with penicillin-positive milk samples for weeks after IP penicillin administration, though specific details about such cases are lacking (such as the formulation and dose of penicillin administered). Cows given ampicillin by IP infusion had positive milk tests for only 24–96 h, depending on the

formulation (Klein et al., 1989). Tissue residue depletion kinetics in cattle after IP antimicrobial administration are not available, but residues were detected in muscle, kidney, and liver in bulls given IP oxytetracycline 1 h before slaughter (Kersey et al., 1955). Trials using IP injections of oxytetracycline and macrolides in salmon found detectable drug residues in various tissues up to 8 weeks later (Bruno, 1989; Fairgrieve et al., 2006).

The purpose of this study was to determine the plasma pharmacokinetics of penicillin in lactating dairy cows after the administration of 21 000 IU/kg PPG via IP infusion. Milk and meat penicillin residues would also be determined and any adverse reactions evaluated.

MATERIALS AND METHODS

Animals

A total of nine cull, lactating Holstein cows were purchased from a local dairy farm in three groups, with three cows per group. Cows were culled for reproductive failure ($n = 6$), decreased milk production ($n = 2$), or lameness ($n = 1$). Cows were housed in stanchions at the Western College of Veterinary Medicine (WCVM) large animal clinic at the University of Saskatchewan for the duration of the trial and were fed a diet of alfalfa/grass hay and total mixed ration (TMR). Water was freely available. The mean age and days in milk ($n = 8$) were 5.2 ± 1.6 years (range 2.3–7.9 years) and 292 ± 184 days (range 38–642 days). Mean milk production during the current lactation had been 20.5 ± 5.3 kg/day. The cows' estimated weights (using a weight tape measure) ranged from 500 to 700 kg (mean 650 kg). Cows were milked twice daily with a portable vacuum milking machine for the duration of the trial. All cows were free of mastitis for at least 3 months before the trial began. No cows used in the study had undergone prior abdominal surgery. The study protocol was approved by the University of Saskatchewan Animal Care Committee.

Drug administration

Intraperitoneal penicillin administration was designed to mimic a typical dose during bovine abdominal surgery. A paravertebral infusion of lidocaine, 40 mL per site at the cranial border of L1–L3 was used for local anesthesia of the right flank. The right paravertebral fossa was clipped and aseptically prepared for surgery. For cows A, B, and C, a 3 cm incision was made in the skin followed by insertion of a sterile teat canula through the abdominal muscle layers to minimize surgical trauma. The cannula was inserted through the peritoneum, negative air pressure was ascertained audibly, and 21 000 IU/kg (13.1 mg/kg) PPG (Pen Vet 300, Rafter 8 Products, Calgary, AB, Canada) was infused through the cannula. After determining that penicillin concentrations were negligible in milk and plasma of cow A (but easily detectable in cows B and C), it was speculated that the penicillin was infused into the rumen of cow A instead of the abdominal cavity. The blind teat cannula

Fig. 1. Intraperitoneal (IP) administration of penicillin through an incision in the right paralumbar fossa.

approach was replaced in cows D – I by a full surgical incision through the muscle layers and peritoneum, with visualization of the abdomen before penicillin was infused (Fig. 1). Peritoneum, muscle, and skin layers were closed with routine surgical methods.

Blood collection

A jugular catheter was placed in each cow prior to surgery to facilitate blood collection. Blood was drawn into a syringe and transferred into 50 mL polypropylene centrifuge tubes containing 500 IU sodium heparin. Samples were taken at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 h following the IP administration of penicillin. The blood samples were refrigerated for <8 h until centrifuged at 1500 g for 15 min. Plasma was harvested and stored at −20 °C until analysis. Samples were analyzed within 21 days of collection. Blood samples were also submitted for complete blood count and/or chemistry profile before treatment, and multiple (2–4) times between days 1–4 post treatment to document any inflammatory response.

Milk collection

Samples were taken from the total milk collected from each cow after routine morning and evening milkings. Blank milk samples were collected from each cow prior to penicillin administration. Milk was stored at −20 °C until analysis (within 21 days).

Tissue samples

Ten days after treatment, cows were euthanized via captive bolt gun followed by rapid i.v. potassium chloride administration. Necropsies were performed by a pathologist at the Prairie Diagnostic Services at the WCVM. During necropsy, multiple samples of muscle, liver, and kidney were obtained from each cow and stored at −20 °C until analysis (within 10 days).

Drug analysis

Penicillin concentrations were determined in all samples by HPLC with ultraviolet detection at 325 nm using an adapted version of previously published protocols (Boison *et al.*, 1991, 1992, 1994). Penicillin V was used as the internal standard for all assays. Calibration curves were prepared by fortifying blank plasma, milk, muscle, liver, and kidney samples with known concentrations of penicillin G and penicillin V (Sigma-Aldrich Canada Ltd, Oakville, ON, Canada). Two hexane flushes were performed on milk samples to extract fat present in the milk. Protein denaturation on all samples was performed with 5% sodium tungstate and 0.17 M sulfuric acid, followed by washing with 20% sodium chloride and vacuum filtering through a GF/B filter. Samples were cleaned by solid phase extraction using Bond Elut C18 extraction cartridges (Varian Inc, Lake Forest CA, USA) preconditioned with methanol, water, and a 2% sodium chloride solution. After penicillin extraction the cartridges were washed with 2% sodium chloride solution and water. Penicillin was eluted with 1.0 mL elution solution (5% 0.2 M phosphate buffer/35% water/60% acetonitrile) into clean glass tubes. After adding 1.0 mL derivitizing reagent (containing 1,2,4 Triazole and 0.01 M HgCl$_2$) to the eluent, the solution was mixed and placed in a 65 °C water bath for 30 min.

An HP1100 liquid chromatograph was used, consisting of a pump system equipped with an automatic injector (50–100 μL/sample) and a UV variable-wavelength detector at 325 nm. Separation was achieved using a reverse-phase column (Inertsil C8, 5 μm, 150 × 4.6 mm, GL Sciences, Torrance, CA, USA). The mobile phase consisted of a mixture of 28% acetonitrile and 72% 0.05 M phosphate buffer and a flow rate of 1.2 mL/min was used. Calibration curves were linear between 5 and 10 000 ng/mL for plasma, 5–500 ng/mL for milk, and 40–400 ng/g for tissues, with a coefficient of determination (r^2) greater than 0.99 for each curve. The lowest limit of quantification (LOQ) was 5 ng/mL for milk and plasma and 40 ng/g for tissue, based on measured signal:noise ratios of 10. The original tissue method was previously validated at the Centre for Veterinary Drug Residues (Saskatoon, SK).

A milk sample from each cow was qualitatively assayed for penicillin residues immediately following each milking using the IDEXX SNAP beta-lactam test kit with visual inspection (IDEXX Laboratories Inc., Westbrook, ME, USA) with a detection sensitivity of 3.1 ng/mL at the 90% compliance rate with 95% confidence.

Pharmacokinetic analysis

Penicillin concentrations were analyzed using a commercial PK software program (WinNonlin, Version 2.1; Pharsight Corporation, Mountain View, CA, USA). A noncompartmental model was used to analyze the data. Peak concentration in plasma (C_{max}) and time to peak concentration (T_{max}) were determined using observed values. The apparent terminal rate constant, λ, was determined by linear regression of the last 7–8 points on the terminal phase of the logarithmic plasma concentration vs. time

curve. The area under the C-T curve until the final plasma sample (AUC_{0-24h}) was determined using the linear trapezoidal rule. The total area under the curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated by adding the $C_{24h\ obs}/\lambda + AUC_{0-24h}$. The terminal half-life ($t_{1/2\lambda}$) was calculated as $\ln2/\lambda$. Clearance (Cl_B/f) was determined by the dose divided by $AUC_{0-\infty}$. The apparent volume of distribution (V_z/f) was calculated by clearance divided by λ. The mean residence time (MRT) was calculated as the area under the moment curve extrapolated to infinity ($AUMC_{0-\infty}$)/$AUC_{0-\infty}$.

RESULTS

Plasma penicillin kinetics

No adverse effects were observed immediately after IP penicillin administration in any cow. The log mean plasma penicillin concentration vs. time graph is shown in Fig. 2. The pharmacokinetic parameters for each cow are presented in Table 1. The mean (±SD) C_{max} and T_{max} were 5.5 ± 2.6 µg/mL and 0.75 ± 0.27 h, respectively. The mean $AUC_{0-\infty}$ was 10.8 ± 4.9 µg·h/mL. The average $MRT_{0-\infty}$ and $t_{1/2\lambda}$ were 2.2 ± 0.9 h and 1.6 ± 1.0 h respectively.
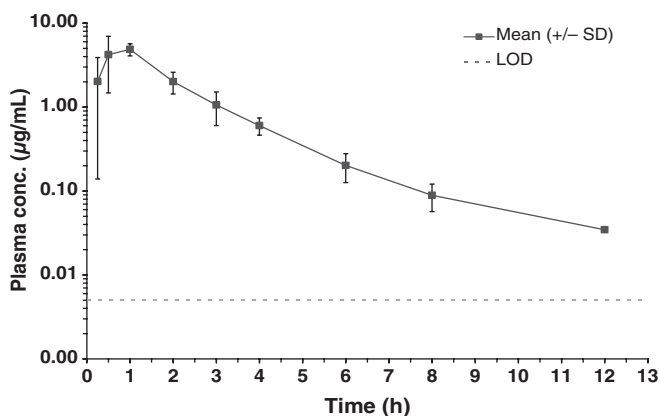

Fig. 2. Mean (±SD) plasma penicillin concentration (µg/mL) vs. time after IP administration of 21 000 IU/kg procaine penicillin G in eight lactating Holstein cows.

Milk penicillin residues

Average milk production per cow over the first 5 days post treatment was 8.5 ± 3.1 kg/day. Each cow's milk tested positive for drug residues using the SNAP ß-lactam test kits for a minimum of three 12-h milking intervals after IP penicillin administration (median, 4; range, 3–5). Quantitative milk penicillin concentrations determined by HPLC are shown in Fig. 3. The maximum milk penicillin concentration for each cow was observed in the first milking after PPG administration (mean 222 ± 100 ng/mL). Milk residues were detectable by HPLC for at least two 12-h milking intervals (median, 3; range, 2–4).

Tissue penicillin residues

No penicillin residues were quantifiable in any muscle, liver, or kidney samples taken at necropsy (10-day post treatment).

Safety and irritation

Ante-mortem evidence of inflammation was determined by abnormal leukograms (neutrophilia) and decreased plasma protein/fibrinogen ratios (≤ 10:1 was used as evidence of inflammation). Only one animal (Cow C) met these criteria at any time post-IP infusion. However, a pretreatment neutrophilia with degenerative left shift and protein/fibriniogen ratio of 9:1 indicated a prior inflammatory process occurring in this cow. Serum chemistry abnormalities included mildly elevated creatine phosphokinase and aspartate aminotransferase enzymes in some cows as the trial progressed. At necropsy, all cows had mild to moderate, focal hemorrhage on the greater omentum overlying the rumen (Fig. 4). Peritonitis or adhesions were not observed in any animal, and no penicillin was grossly visible in the abdomen.

DISCUSSION

Data from only eight out of nine cows were used for kinetic analysis because penicillin was not detected in any tissue, plasma or milk from one animal (cow A). The absorption and elimination of procaine penicillin (PPG) was rapid after IP administration in eight lactating dairy cows. The mean time to

Table 1. Plasma pharmacokinetic parameters determined by noncompartmental analysis after IP administration of 21 000 IU/kg procaine penicillin G in eight lactating dairy cows

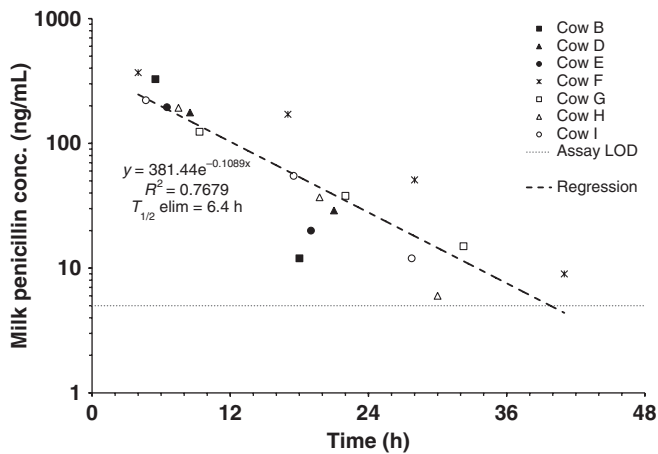| Parameter	Cow B	Cow C	Cow D	Cow E	Cow F	Cow G	Cow H	Cow I	Mean ± SD
C_{max} (µg/mL)	3.1	1.2	3.8	5.6	8.8	7.9	7.1	6.1	5.5 ± 2.6
T_{max} (h)	0.50	1.0	0.50	0.50	1.0	1.0	0.50	1.0	0.75 ± 0.27
λ (1/h)	0.53	0.45	0.49	0.52	1.11	0.18	0.51	0.52	0.54 ± 0.26
$AUC_{0-\infty}$ (µg·h/mL)	5.3	2.89	9.2	9.6	13.5	16.4	15.4	14.0	10.8 ± 4.9
$AUMC_{0-\infty}$ (µg·h²/mL)	9.3	6.1	18.1	17.2	17.9	68.2	30.6	31.3	24.8 ± 19.6
MRT (h)	1.8	2.1	2.0	1.8	1.3	4.2	2.0	2.2	2.2 ± 0.9
$t_{1/2\ \lambda}$ (h)	1.3	1.5	1.4	1.3	0.62	3.9	1.4	1.3	1.6 ± 1.0
Cl_B/f (mL/h/kg)	2.5	4.6	1.4	1.4	0.97	0.80	0.85	0.93	1.7 ± 1.3
V_z/f (L/kg)	4.7	10.2	2.9	2.6	0.87	4.5	1.7	1.8	3.6 ± 2.9

Fig. 3. Milk penicillin residues (ng/mL) vs. time after IP administration of 21 000 IU/kg procaine penicillin G in eight lactating Holstein cows.

Fig. 4. Photograph of typical focal hemorrhage on the greater omentum overlying the rumen 10 days after IP infusion of 21 000 IU/kg PPG.

maximum plasma concentration (T_{max}) of 0.75 ± 0.27 h was quicker than values previously reported in the literature for cattle given PPG by other routes. A T_{max} of 5.3–6.0 h was reported for steers dosed with 24 000–66 000 IU/kg PPG via i.m. or s.c. injections (Papich *et al.*, 1993), compared to 0.5–2.0 h after 20 000 IU/kg i.m. or s.c. injections in cows (Conlon *et al.*, 1993). Other studies reported a mean T_{max} of 1.5 h using 30 000 IU/kg i.m. in calves (Bengtsson *et al.*, 1991) and 2.0–7.1 h after various i.m. doses in lactating cows (Dubreuil *et al.*, 2001). A population pharmacokinetic approach estimated a T_{max} of only 1.14 h after i.m. administration of procaine penicillin (Craigmill *et al.*, 2004).

Intraperitoneal administration also resulted in higher maximum plasma concentrations (C_{max}) than other studies with similar i.m. doses. Mean C_{max} after IP infusion was 5.5 μg/mL vs. mean i.m. values of 0.99 and 1.74 μg/mL (Papich *et al.*, 1993; Dubreuil *et al.*, 2001). The mean elimination half-life ($t_{1/2\lambda}$) of PPG after IP infusion was shorter than that previously reported for i.m. injections (1.6 vs. 7.95 h). The prolonged i.m. half-life is due to procaine-mediated vasoconstriction which slows the absorption rate and thus influences elimination kinetics (Craigmill *et al.*, 2004). Whether or not procaine affects penicillin absorption after IP administration in cows is unclear, though an IP sodium ampicillin $t_{1/2\lambda}$ reported previously (Klein *et al.*, 1989) was similar to the PPG $t_{1/2\lambda}$ in this study. This suggests procaine does not significantly delay IP absorption. The shorter T_{max} after IP infusion may also be due to the large surface area for drug absorption within the abdomen compared to an i.m. injection.

Of interest in this study was the large inter-animal variability in C_{max} (range, 1.2–8.8 μg/mL). One hypothesis is that the exact location of PPG deposition after IP infusion is not uniform, as drug may settle on the greater omentum, small intestines, rumen, uterus, or peritoneum. Each anatomic site has its own local circulation possibly influencing the rate and extent of PPG absorption.

Whether or not intraoperative IP penicillin use in cattle constitutes rational antimicrobial therapy is debatable. Overall, evidence for prophylactic antimicrobials reducing surgical infections in animals is mixed. Some studies have demonstrated efficacy (Haven *et al.*, 1992; Whittem *et al.*, 1999; Eugster *et al.*, 2004) while others have shown no benefit (Vasseur *et al.*, 1985; Brown *et al.*, 1997). The type and duration of surgery, surgical technique, and local conditions are important prognostic factors for the development of infection. Prophylactic antimicrobial efficacy requires high plasma antimicrobial concentrations (including ß-lactams) at the onset of surgery, which prevents infection by keeping intraoperative bacterial counts below a critical threshold. The duration of postsurgical therapy does not influence outcome (Haven *et al.*, 1992; Eugster *et al.*, 2004; Giguere & Walker, 2006). Therefore surgical prophylaxis guidelines recommend plasma drug concentrations greater than the probable pathogen *MIC* before and during the surgery, but not once surgery is completed. This is contrary to the idea of penicillin as a time-dependent antimicrobial when treating established infections, whereby maximum effect occurs when plasma concentrations remain above the pathogen *MIC* for a prolonged period (T > *MIC*) (McKellar *et al.*, 2004). Suitable plasma penicillin concentrations can be achieved at the time of surgery with preoperative i.v. administration, but this route is not commonly used by bovine veterinarians (Chicoine *et al.*, 2008). If preoperative i.v. antimicrobials cannot be administered, the goal of antimicrobial prophylaxis should be to reach suitable systemic drug concentrations as soon as possible after surgery has begun. Therefore, the antimicrobial therapy with the quickest rate of absorption should be most effective in preventing postsurgical infection. Once an infection is established however, a longer course of therapy is required where traditional PK/PD predictors of efficacy (such as T > *MIC*) will apply.

The rapid absorption and elimination after IP infusion of procaine penicillin create a plasma concentration vs. time profile intermediate between those of i.v. and i.m. administration. The swift absorption after IP administration predicts this route will be more efficacious than a single postoperative dose of i.m.

penicillin in preventing postoperative infections. However, IP administration still does not comply with the antimicrobial prophylaxis recommendation of plasma concentrations greater than the *MIC* at the time of incision. Therefore preoperative i.v. administration should be more effective than intraoperative IP infusion. An argument made by some practitioners is that IP antimicrobials have a local effect in the abdomen, working directly at the site of infection. The rapid absorption from the abdominal cavity refutes this theory. If one assumes that the likely pathogens in bovine abdominal surgery are coliforms (especially in unsanitary surgical conditions), then penicillin should be ineffective due to the inherent resistance of coliforms. However, Gram-positive and anaerobic infections could be prevented by penicillin.

The pharmacokinetics of PPG after IP administration determined in this trial cannot be extrapolated to other antimicrobials or doses. As the formulation of each drug differs, rapid absorption and elimination cannot be assumed and therefore IP administration of other antimicrobials cannot be recommended at this time. Other PPG formulations may not produce the same results as this study as PPG formulations (specifically procaine concentrations) are not identical (Chapman *et al.*, 1992).

Although perioperative use of i.m. penicillin could be argued as label therapy (for treatment of wound infections in cattle), IP use is strictly extralabel. AMDUCA specifically states that any extralabel drug in food animals requires extended withdrawal intervals and must not result in residual tissue concentrations exceeding regulatory limits considered safe for human consumption. After administration of 21 000 IU/kg PPG by IP infusion, milk residues were not detectable by HPLC or ELISA for any animal by 72 h. This is similar to the Canadian 96 h milk withdrawal time after on-label i.m. use of the same dose. One difference between the study and general populations was the low milk production of the cull cows used in this trial (8.5 ± 3.1 kg/cow/day). However, low milk production correlates with reduced drug clearance and greater milk residues (Whittem, 1999), therefore the rapid excretion of PPG after IP infusion should be applicable to high producing dairy cows.

No penicillin residues were detected in any tissue at 10-day post treatment. As our small sample size precluded a full tissue residue depletion study, we euthanized at the label withdrawal time after i.m. administration of this same PPG dose. The rapid decline in plasma concentrations and lack of quantifiable tissue residues support a minimum withdrawal interval recommendation of 10 days.

Although no evidence of severe gross or clinical pathological changes was noted after IP administration of PPG in these cows, these findings do not prove that IP infusion is safe. Mildly elevated creatine phosphokinase and aspartate aminotransferase serum concentrations in some cows indicate transient muscle damage, likely from surgery or greater periods of recumbency while housed in stanchions. The cause or clinical significance of the mild-moderate hemorrhage seen on the omentum is not known. Although possibly an incidental finding at necropsy, the consistency of the lesion raises suspicion that penicillin infusion, or possibly general abdominal surgery, may be the cause. Cows with a previous history of abdominal surgery were excluded from the study. Unfortunately, in an effort to maximize the number of penicillin-treated cows, no negative or IP-saline treated control animals were used. Negative controls are required to specifically determine if it is IP penicillin or general abdominal surgery that is responsible for the hemorrhagic omentum. There was evidence of peritonitis in cows after IP infusions of an ampicillin anhydrate formulation, but not sodium ampicillin (Klein *et al.*, 1989). Other antimicrobials and formulations have not been evaluated for irritability or safety in cattle. Although the IP route is generally considered nonirritating and safe in human medicine, peritoneal reactions may depend on the formulation of the antimicrobial. When IP infusions are performed in people an i.v. antimicrobial formulation thoroughly diluted in a lavage/dialysis solution is used. The procaine component of PPG may not be innocuous, as procaine can retard wound healing (Morris & Appbly, 1980) and procaine-mediated vasoconstriction of the omental vasculature is a possible explanation for the omental hemorrhage. Other antimicrobials such as tetracycline, neomycin, and streptomycin can cause chemical peritonitis or adhesions in animals when administered IP (Withrow & Black, 1979).

This study found rapid absorption and elimination of PPG after IP administration of 21 000 IU/kg in lactating dairy cows, with no evidence of prolonged meat or milk drug residues or serious adverse reactions. Prospective clinical trials are required to validate whether this practice minimizes postsurgical abdominal infections in cattle and is a rational therapeutic choice.

ACKNOWLEDGMENTS

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