The Judicious Use of Antibiotics in Large Laboratory Animals

INTRODUCTION

The increasing incidence of antibiotic resistant bacteria has caused major revisions in the way antimicrobials are used in both human and veterinary medicine. Because the emergence of resistance has important clinical implications and resistance patterns are directly affected by antibiotic exposure, the rational use of antimicrobials in laboratory animals is critical.

Given that the field of medicine is constantly evolving as new information is published, periodic review, updating and revision of antimicrobial guidelines are to be expected. The guidelines may not be appropriate for all clinical situations. Veterinarians must exercise professional judgment and consider individual circumstances and available resources when determining the appropriateness of prophylactic antibiotics and the best selection when indicated.

IMPORTANCE OF ASEPSIS IN SURGERY

When considering the use of antimicrobials for prophylaxis, the risks contributing to the development of post-operative infections must be considered. **Antimicrobial use is not a substitute for proper aseptic technique, and all recovery surgery must be performed aseptically.** The surgeon's experience and the length of the procedure have a strong impact on wound infection rates.

GOALS OF SURGICAL PROPHYLAXIS

Prophylaxis refers to the prevention of an infection through the preemptive use of antibiotics. Ideally, an anti-infective drug for surgical prophylaxis should achieve the following goals:

1. Prevent post-operative infection of the surgical site, morbidity and mortality
2. Reduce the duration and intensity of post-operative care required
3. Produce no adverse effects

To achieve these goals, an antimicrobial drug should be:

1. Active against the pathogens most likely to contaminate the wound
2. Given in an appropriate dosage and at a time that ensure adequate concentrations at the incision site during the period of potential contamination
3. Safe
4. Administered for the shortest effective period to minimize adverse effects and development of resistance

Typically, prophylactic antimicrobials are not indicated for clean surgical procedures when aseptic technique is properly followed. Prophylactic antimicrobials for procedures involving prosthetic placement is justified because of the potential for severe complications. Timing of antibiotic administration and rational selection of appropriate antibiotics must be considered. Effective antimicrobial use is based on two criteria: (1) which microoranisms are most likely to cause wound infections and (2) which antibiotics are most likely to be effective

against potential offending microorganisms. Coagulase-positive *Staphylococcus* species and *Escherichia coli* are the preponderant aerobic bacteria isolated from veterinary surgical patients.

PROPHYLAXIS IN VETERINARY PATIENTS

At present, cefazolin, a first generation cephalosporin, at 22mg/kg IV is the antibiotic of choice for prophylaxis in veterinary orthopedic surgery. Antibiotics should be administered at the time of anesthetic induction, repeated every 2 hours, and discontinued at the completion of surgery (Johnson 2007).

Surgical microbial prophylaxis in animals is largely based on human studies due to the lack of controlled clinical trials in veterinary patients. The optimal duration of antimicrobial prophylaxis in veterinary medicine is unknown. However, the vast majority of published evidence in human medicine demonstrates that antimicrobial prophylaxis after wound closure is unnecessary (Giguere 2006). Prolonged use of prophylactic antimicrobial agents is associated with the emergence of resistant bacteria and is more likely to result in adverse effects.

PROPHYLAXIS IN HUMAN PATIENTS

The use of prophylactic antibiotics in human neurosurgery remains controversial (AHSP 1999, Cacciola 2001, Jones 2005, Savitz 2002). However, meta-analysis of randomized studies have demonstrated the efficacy of prophylactic antibiotics in patients experiencing craniotomies (Barker 1994). Importantly, clean surgical procedures carry a risk of less than 5% for post-operative wound infections. In humans, *S. epidermidis* and *S. aureus* are the predominant isolates from post-surgical infections (AHSP 1999), similar to that found in veterinary patients. According to the American Society of Health-System Pharmacists, cefazolin continues to be the drug of choice for antimicrobial prophylaxis in humans due to the low overall frequency of cefazolin failure as a result of resistance including for elective craniotomies and orthopedic surgeries with implantation of internal devices (AHSP 1999).

Current recommendations in neurosurgery include the prophylactic use of antibiotics for up to 24 hours (Iacob 2010). The antibiotic selected should have a narrow spectrum of activity based on microbes likely to infect the surgical site and the prophylactic use of broad spectrum antibiotics for long durations is to be avoided (Iacob 2010). Cefazolin is commonly used in human craniotomies (Klekner 2003) and shown to be efficacious when repeated at 2-4 hour intervals during surgery. Because of the preponderance of Gram positive pathogens, cefazolin has been used perioperatively to prevent infection and has been efficacious when administered as a single dose prior to surgery (Dempsey 1988). Cefazolin remains above the MIC for most bacteria in the serum for approximately 6 hours and in wound excretion for 12 hours following the last dose (Klekner 2003).

For patients in which MRSA is a significant concern, human neurosurgeons choose cefuroxime (a cephalosporin similar to cefazolin) combined with gentamicin (Hammond 2002) at induction. In this report, only one MRSA infection was prevented per 421 patients treated compared with cefuroxime alone with an assumed 15% prevalence of MRSA. Singe dose administration an antibiotic (usually a cephalosporin) with cleansing of the surgical site with

rifamycin or a similar drug also has demonstrated efficacy in preventing post-operative infections in clean neurosurgery (Cacciola 2001).

Some reports describe the use of prophylactic antibiotics for seven days following neurosurgery with second-generation cephalosporins being the most efficacious in preventing post-operative infection (Yamamoto 1992). However, single doses of ampicillin/sulbactam at induction of anesthesia and continued at 5 hour intervals during surgery were as efficacious in preventing post-operative infections in clean neurosurgery patients as seven day courses of antibiotics following surgery in another report (Fujiwara 2000).

Based on published data, the current recommendation from the National Surgical Infection Prevention Project is that prophylactic antimicrobial agents be discontinued within 24hrs of the end of surgery (Bratzler 2005).

Interestingly, one report found that intra-operative lavage with povidine-iodine diluted with sterile saline (1:1) was more efficacious than prophylactic antibiotics (even when continued 10 days post-operatively) at preventing post-operative wound infection in neurosurgical patients (Strohecker 1985). Following this study, the authors limited the practice of antimicrobial prophylaxis to cases that were known to be contaminated and kept a post-operative infection rate at 0.8%. This report indicates the importance of surgical asepsis in preventing post-operative infections and highlights the limited role of prophylactic antibiotics in compensating for poor aseptic technique. These findings have been reported in other randomized clinical trials for neurosurgery and other procedures without compromising wound healing (Cheng 2005, Fournel 2010).

DLAM POLICY ON PERIOPERATIVE ANTIBIOTIC USE

1. Aseptic technique is the most important prevention for post-operative infection. Careful attention to proper aseptic technique is required for all recovery surgeries.

2. Cefazolin 22mg/kg IV, administered at time of anesthetic induction and repeated at 2hr intervals throughout the surgery, is the antibiotic of choice for procedures involving implantation of devices or opening a major cavity.

3. DLAM encourages intra-operative lavage with 10% povidine-iodine solution diluted with sterile saline (1:1) prior to closure for procedures involving implantation of devices.

4. The routine use of post-operative antibiotics is generally not indicated. For cases where post-operative infection would be catastrophic, investigators should consult with DLAM veterinarians to determine the most appropriate post-operative antibiotic regimen.

References

1. American Society of Health-System Pharmacists. 1999. Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery. Available at: http://www.ashp.org/DocLibrary/BestPractices/TGSurgery.aspx. [Accessed 11 Dec 11].
2. Barker FG. 1994. Efficacy of Prophylactic Antibiotics for Craniotomy: A Meta-Analysis. Neurosurg 35(3):484-490.
3. Bratzler DW, Houck PM. 2005. Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project. Am J Surg 189:395.
4. Cacciola F, Cioffi F, Anichini P, DiLorenzo N. 2001. Antibiotic Prophylaxis in Clean Neurosurgery. J Chemother 13 Spec No 1(1):119-122.
5. Cheng MT, Chang MC, Wang ST, Yu WK, Liu CL, Chen TH. 2005. Efficacy of Dilute Betadine Solution Irrigation in the Prevention of Postoperative Infection of Spinal Surgery. Spine 30(15):1689-1693.
6. Dempsey R, Rapp RP, Young B, Johnston S, Tibbs P. 1988. Prophylactic Parenteral Antibiotics in Clean Neurosurgical Procedures: A Review. J Neurosurg 69(1):52-57.
7. Federation of Veterinarians of Europe. Antibiotic Resistance & Prudent Use of Antibiotics in Veterinary Medicine. Available at: http://www.fve.org/news/publications/pdf/antibioen.pdf. [Accessed 11 Dec 11].
8. Fournel I, Tiv M, Soulias M, Hua C, Astruc K, Aho Glele LS. 2010. Meta-Analysis of Intraoperative Povidone-Iodine Application to Prevent Surgical-Site Infection. Brit J Surg 97(11):1603-1613.
9. Fujiwara K, Suda S, Ebina T. 2000. Efficacy of Antibiotic Prophylaxis in Clean Neurosurgical Operations: A Comparison of Seven-Day versus One-Day Administration. No Shinkei Geka 28(5):423-427.
10. Giguere S, Walker RD. 2006. Antimicrobial Prophylaxis for Surgery. In: Antimicrobial Therapy in Veterinary Medicine. 4th ed. Blackwell Press.
11. Hammond CJ, Gill J, Peto TE, Cadoux-Hudson TA, Bowler IC. 2002. Investigation of Prevalence of MRSA in Referrals to Neurosurgery: Implications for Antibiotic Prophylaxis. Br J Neurosurg 16(6):550-4.
12. Iacob G, Iacob S. 2010. Prophylactic Antibiotherapy in Neurosurgery. Roman Neuro XVII 3:321-326.
13. Johnson AL. 2007. Fundamentals of Orthopedic Surgery and Fracture Management. In: Small Animal Surgery. 3rd ed. Ed. TW Fossum. Mosby: St. Louis, MO.
14. Jones J. 2005. Prophylactic Antibiotic use in Clean Neurosurgery: Of Potential Benefit or Harm to the Patient? J Wound Care 14(1):39-41.
15. Klekner A, Ga'spa'r A, Kardos S, Szabo J, Cse'csei G. 2003. Cefazolin Prophylaxis in Neurosurgery Monitored by Capillary Electrophoresis. J Neurosurg Anes 15(3):249-254.
16. Savitz SI, Rivlin MM, Savitz MH. 2002. The Ethics of Prophylactic Antibiotics for Neurosurgical Procedures. 28(6):358-363.
17. Strohecker J, Piotrowski WP, Lametchwandtner A. 1985. The Intra-Operative Application of Povidone-Iodine in Neurosurgery. J Hosp Infect 6 Suppl A:123-125.
18. Yamamoto M, Jimbo M, Tanaka N, Umebara Y, Hagiwara S. 1992. Postoperative Neurosurgical Infection and Antibiotic Prophylaxis. Neurol Med Chir (Tokyo) 32(2):72-79.