

DESCRIPTION

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Explanation of Category E Animal

Protocol # 2009/10-22 “Experimental *Clostridium difficile* Infection in Hamsters”

Antibiotics are prescribed drugs used to combat bacterial infections in humans and animals. Because several bacteria have become resistant (can not be killed) to many commonly used antibiotics, the discovery of new and improved antibiotics could be used to effectively treat resistant bacterial infections. The purpose of this project is to focus on the preclinical (before human) development and testing of new (test) antibiotics that can effectively treat intestinal infections caused by the bacterium, *Clostridium difficile*. This protocol will examine the effectiveness of antibiotic treatment in a hamster intestinal infection model with *C. difficile*. Ironically, antibiotic treatment for other bacterial infections often leads to *C. difficile* infections in humans. Clindamycin is an antibiotic frequently associated with *C. difficile* intestinal infections and will be used in this model to subcutaneously (beneath the skin) treat hamsters 24 to 48 hours prior to infection. Clindamycin treated hamsters will be orally infected with *C. difficile*, and oral treatment with a test antibiotic will be initiated 6 to 24 hours after infection. The test antibiotic can be given up to 3 times per day for up to 7 days of total treatment. Each study will incorporate up to 4 treatment groups (10 animals per group) and one control group (10 animals per group) for the duration of the study. At the end of a study, animals will be euthanized and sections of their intestines (cecum) will be removed. Antibiotic effectiveness (how well it works) in this model will be determined by the amount of bacteria recovered from the large intestine (cecum) of treated/infected animals after approximately 10 days. Also, to determine if the infection has spread to the blood, whole blood from treated/infected animals will be processed for bacterial recovery. Infected animals will be monitored daily for signs of an advanced disease state, which includes prolonged weight loss, an enlarged gut, and slow movement. If an animal exhibits these signs, animal facilities personnel will be notified and the animal will be euthanized. This model is critical in determining an antibiotic's utility in treating this type of infection.

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JUSTIFICATION

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Explanation of Category E Animal

Protocol # 2009/10-22 "Experimental *Clostridium difficile* Infection in Hamsters"

The objective of this study is the pre-clinical evaluation of novel antibiotic classes in an intestinal infection model. Medicine used to relieve pain may interfere with the potential therapeutic effects a novel antibiotic may have in this model. Therefore, it is imperative that animals used in this model will not be given pain relief in order to correctly assess the effectiveness of a test antibiotic.

The references are as follows:

- Anton, P.M., O'Brien, M., Kokkotou, E., Eisenstein, B., Michaelis, A., Rothstein, D., Paraschos, S., Kelly, C. P., Pothoulakis, C. (2004). Rifalazil Treats and Prevents Relapse of *Clostridium difficile*- Associated Diarrhea in Hamsters. *Antimicrob. Agents Chemother.* 48: 3975-3979
- Bailey, J.M., Erramousepe, J. (2004). Nitazoxanide Treatment for Giardiasis and Cryptosporidiosis in Childre. *Ann Pharmacother* 38: 634-640
- Guttner, Y., Windsor, H.M., Viiala, C. H., Dusci, L., Marshall, B. J. (2003). -itazoxanide in Treatment of *Helicobacter pylori*: a Clinical and In Vitro Study. *Antimicrob. Agents Chemother.* 47: 3780-3783
- Stettler, M., Fink, R., Walker, M., Gottstein, B., Geary, T. G., Rossignol, J. F., Hemphill, A. (2003). In Vitro Parasiticidal Effect of Nitazoxanide against *Echinococcus multilocularis* Metacestodes. *Antimicrob. Agents Chemother.* 47: 467-474
- Sisson, G., Goodwin, A., Raudonikiene, A., Hughes, N.J., Mukhopadhyay, A. K., Berg, D. E., Hoffman, P.S. (2002). Enzymes Associated with Reductive Activation and Action of Nitazoxanide, Nitrofurans, and Metronidazole in *Helicobacter pylori*. *Antimicrob. Agents Chemother.* 46:2116-212
- Pelaez, T., Alonso, R., Perez, C., Alcala., L., Cuevas, O., Bouza, E. (2002). In Vitro Activity of Linezolid against *Clostridium difficile*. *Antimicrob. Agents Chemother.* 46:1617-1618

INTERVENTION

Animals are observed two-three times a day for the duration of the experiment for mortality and morbidity and for the presence of diarrhea. Criteria used to assign a moribund state are extended periods (6 days) of weight loss, progression to an emaciated state, prolonged lethargy (more than 3 days), signs of paralysis, skin erosions or trauma, hunched posture, and a distended abdomen. These moribund state effects can be a result of the infection and/or test antibiotic treatment. If a moribund state is detected for an animal, animal facilities personnel will be notified and a course of action (euthanasia) will be determined at that time.

Column E Explanation

#1. Registration Number: 74-R-0081

#2. Protocol # 2009/10-22

#3. Species (common name) Hamsters of animals used in this study.

#4. Explanation and Description is Attached.

#5. Scientific justification is Attached.

#6. Intervention is Attached.

APHIS Form 7023 Site Addendum for FY: 2012

Registration Number: 74-R-0081

Customer ID Number: 1502

Facility Business Address Information :

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(b) (6), (b) (7)(C)

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