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Interagency Report Control No. 0180-DOA-AN

Fiscal year: 2022

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

Annual Report of Research Facility
Column E Explanation

(TYPE OR PRINT)

This information is required by law (7 U.S.C. 2143 and 9 C.F.R. §2.36). Failure to report according to the regulations can result in an order to cease and desist.

1. REGISTRATION NUMBER

74-R-0081

2. Research Facility Headquarters address

3500 Camp Bowie Blvd
Fort Worth,Texas 76107

3. Number of animals used in the study.

27

4. Species (common name) of animals used in the study. Hamster

5. Explain the procedure producing pain and distress.

Animals associated with this model may experience pain or distress as a result of infection and/or treatment with a compound. Historically, animals often do not manifest any signs of pain or distress prior to death, and 75% of the animals in those studies have either remained healthy and normal or have been euthanized to prevent prolonged suffering. Signs that indicate a severe disease state as a result of Clostridioides difficile infection include lethargy, acute/chronic diarrhea, hypothermia, >15% decrease in body weight, reduced water/food intake, and swollen peritoneum. In addition to the possible effects related to the infection, treatment with test articles (compounds) could also induce negative effects in an animal as well. Signs of test article related effects include acute paralysis, increased respiratory/heart rates, and a rough coat. To prevent treatment related effects, all compounds evaluated in this model are pre-screened for potential toxicity by the sponsors and selected dosing regimens will be based on what has been safely used for evaluating other test articles in this model.

All animals associated with this protocol will be monitored for severe disease every 6 to 8 hours throughout the duration of a study (up to 37 days). A clinical observation sheet for each day of a study will be maintained that will include recording observations and animal disposition, including the date (day and time) and personnel initials. Using the guidelines associated with the IACUC 'Pain and Discomfort' (document 013) and 'Humane Endpoints' (document 008) protocols, any animal that appears to be moribund will be immediately removed from the study and euthanized.

6. Provide the scientific justification for not providing the appropriate anesthetics, analgesics, or tranquilizing drugs during procedures where the animal experienced accompanying pain or distress greater than momentary or slight.

Most of the test articles that will be evaluated in this model are new investigational compounds and possible drug interactions have not been fully determined. If another drug is used to relieve pain and/or distress, this may interfere with the possible therapeutic/prophylactic efficacy a test article may have in this model. For example, buprenorphine (analgesic) is metabolized by the cytochrome 450-3A4 (CYP450-3A4) pathway. This same metabolic pathway interacts with 3 different antibiotic classes that include macrolides (clarithromycin), rifamycins (rifampin), and fluoroquinolones (ciprofloxacin). Interactions of these drugs in this pathway have been shown to alter the pharmacokinetics of each drug, which can directly impact their efficacy within the host (animal or human). Additionally, several nonsteroidal anti-inflammatory drugs (NSAIDS) are metabolized by the cytochrome 450-2C9 (CYP450-2C9) pathway, which also metabolically interacts with the antibiotics metronidazole and rifampin. As is the case with buprenorphine, the interaction of NSAIDS and other drugs in the CYP450-2C9 pathway can impact the efficacy of each drug by altering their metabolism and pharmacokinetics in the host. In addition to metabolic interference, NSAID use has been shown to clinically aggravate colitis caused by intestinal infections. Given these facts about documented drug interactions within critical metabolic pathways and how these interactions can interfere with drug efficacy or disease outcome in the host (Gudin J et al., 2012; Preissner S et al. 2012), it is imperative that non-study associated drugs used to relieve pain and/or distress not be administered in animals associated with this model so that the therapeutic and/or prophylactic efficacy of a new investigational compound can be accurately evaluated. If a new compound is efficacious in this animal model, then these results would be critical to its development for treating life-threatening Clostridioides difficile-associated diarrhea (CDAD) in humans. References:

References:
Gudin J. Opiod Therapies and Cytochrome P450 Interactions. J of Pain and Symp Management, 2012 Dec 1; 44(6): S4-S14.
Preissner S, Kuzman D, Pischon N. Drug Interactions Involving the Cytochrome P450 Enzymes: Analysis of Common Combinations of Antibiotics and Pain Relieving Drugs. J Drug Metab Toxicol 2012, 3:5.

7. What, if any, Federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number, and the specific section number (e.g., APHIS, 9 CFR 113, 102):

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Agency	CFR

Column E Explanation
Registration Number: 74-R-0081 Fiscal Year 2022

1. Study One:
Number of animals used in this study: 27
Species used in this study: Hamster
Explanation of procedure producing pain and/or distress:
Animals associated with this model may experience pain or distress as a result of infection and/or treatment with a compound. Historically, animals often do not manifest any signs of pain or distress prior to death, and 75% of the animals in those studies have either remained healthy and normal or have been euthanized to prevent prolonged suffering. Signs that indicate a severe disease state as a result of Clostridioides difficile infection include lethargy, acute/chronic diarrhea, hypothermia, >15% decrease in body weight, reduced water/food intake, and swollen peritoneum. In addition to the possible effects related to the infection, treatment with test articles (compounds) could also induce negative effects in an animal as well. Signs of test article related effects include acute paralysis, increased respiratory/heart rates, and a rough coat. To prevent treatment related effects, all compounds evaluated in this model are pre-screened for potential toxicity by the sponsors and selected dosing regimens will be based on what has been safely used for evaluating other test articles in this model.
All animals associated with this protocol will be monitored for severe disease every 6 to 8 hours throughout the duration of a study (up to 37 days). A clinical observation sheet for each day of a study will be maintained that will include recording observations and animal disposition, including the date (day and time) and personnel initials. Using the guidelines associated with the IACUC 'Pain and Discomfort' (document 013) and 'Humane Endpoints' (document 008) protocols, any animal that appears to be moribund will be immediately removed from the study and euthanized.
Explanation with reason(s) for why anesthetics, analgesics and tranquilizers could not be used:
Most of the test articles that will be evaluated in this model are new investigational compounds and possible drug interactions have not been fully determined. If another drug is used to relieve pain and/or distress, this may interfere with the possible therapeutic/prophylactic efficacy a test article may have in this model. For example, buprenorphine (analgesic) is metabolized by the cytochrome 450-3A4 (CYP450-3A4) pathway. This same metabolic pathway interacts with 3 different antibiotic classes that include macrolides (clarithromycin), rifamycins (rifampin), and fluoroquinolones (ciprofloxacin). Interactions of these drugs in this pathway have been shown to alter the pharmacokinetics of each drug, which can directly impact their efficacy within the host (animal or human). Additionally, several nonsteroidal anti-inflammatory drugs (NSAIDS) are metabolized by the cytochrome 450-2C9 (CYP450-2C9) pathway, which also metabolically interacts with the antibiotics metronidazole and rifampin. As is the case with buprenorphine, the interaction of NSAIDS and other drugs in the CYP450-2C9 pathway can impact the efficacy of each drug by altering their metabolism and pharmacokinetics in the host. In addition to metabolic interference, NSAID use has been shown to clinically aggravate colitis caused by intestinal infections. Given these facts about documented drug interactions within critical metabolic pathways and how these interactions can interfere with drug efficacy or disease outcome in the host (Gudin J et al., 2012; Preissner S et al. 2012) it is imperative that non-study associated drugs used to

relieve pain and/or distress not be administered in animals associated with this model so that the therapeutic and/or prophylactic efficacy of a new investigational compound can be accurately evaluated. If a new compound is efficacious in this animal model, then these results would be critical to its development for treating life-threatening Clostridioides difficile-associated diarrhea (CDAD) in humans.

References:

Gudin J. Opiod Therapies and Cytochrome P450 Interactions. J of Pain and Symp Management, 2012 Dec 1; 44(6): S4-S14.

Preissner S, Kuzman D, Pischon N. Drug Interactions Involving the Cytochrome P450 Enzymes: Analysis of Common Combinations of Antibiotics and Pain Relieving Drugs. J Drug Metab Toxicol 2012, 3:5.

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1. REGISTRATION NUMBER
74-R-0081

2. Research Facility Headquarters address
3500 Camp Bowie Blvd
Fort Worth, Texas 76107

3. Number of animals used in the study.
6

4. Species (common name) of animals used in the study. Rabbit

5. Explain the procedure producing pain and distress.

Animals associated with this model may experience pain or distress as a result of infection and/or treatment with a compound. Historically, animals often do not manifest any signs of pain or distress prior to death, and 99% of the animals in those studies have either remained healthy and normal or have been euthanized to prevent prolonged suffering. Signs that indicate a severe disease state as a result of a bacterial pneumonia infection include lethargy, hypothermia, hunched posture, emaciated state, and labored breathing. In addition to the possible effects related to the infection, treatment with test articles (compounds) could also induce negative effects in an animal as well. Signs of test article related effects include acute paralysis, increased respiratory/heart rates, and a rough coat. To prevent treatment related effects, all compounds evaluated in this model are pre-screened for potential toxicity by the sponsors and selected dosing regimens will be based on what has been safely used for evaluating other test articles in this model.

All animals associated with this protocol will be monitored for severe disease every 6 to 8 hours throughout the duration of a study (up to 21 days). A clinical observation sheet for each day of a study will be maintained that will include recording observations and animal disposition, including the date (day and time) and personnel initials. Using the guidelines associated with the IACUC 'Pain and Discomfort' (document 013) and 'Humane Endpoints' (document 008) protocols, any animal that appears to be moribund will be immediately removed from the study and euthanized.

6. Provide the scientific justification for not providing the appropriate anesthetics, analgesics, or tranquilizing drugs during procedures where the animal experienced accompanying pain or distress greater than momentary or slight.

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References:

Gudin J. Opiod Therapies and Cytochrome P450 Interactions. J of Pain and Symp Management, 2012 Dec 1; 44(6): S4-S14.

Preissner S, Kuzman D, Pischon N. Drug Interactions Involving the Cytochrome P450 Enzymes: Analysis of Common Combinations of Antibiotics and Pain Relieving Drugs. J Drug Metab Toxicol 2012, 3:5.

7. What, if any, Federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number, and the specific section number (e.g., APHIS, 9 CFR 113, 102):

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Agency	CFR

Column E Explanation
Registration Number: 74-R-0081 Fiscal Year 2022

1. Study One:
Number of animals used in this study: 6
Species used in this study: Rabbit
Explanation of procedure producing pain and/or distress:
Animals associated with this model may experience pain or distress as a result of infection and/or treatment with a compound. Historically, animals often do not manifest any signs of pain or distress prior to death, and ~99% of the animals in those studies have either remained healthy and normal or have been euthanized to prevent prolonged suffering. Signs that indicate a severe disease state as a result of bacterial pneumonia infection include lethargy, hypothermia, hunched posture, emaciated state, and labored breathing. In addition to the possible effects related to the infection, treatment with test articles (compounds) could also induce negative effects in an animal as well. Signs of test article related effects include acute paralysis, increased respiratory/heart rates, and a rough coat. To prevent treatment related effects, all compounds evaluated in this model are pre-screened for potential toxicity by the sponsors and selected dosing regimens will be based on what has been safely used for evaluating other test articles in this model.
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therapeutic and/or prophylactic efficacy of a new investigational compound can be accurately evaluated. If a new compound is efficacious in this animal model, then these results would be critical to its development for treating life-threatening respiratory infections in humans.

References:

Gudin J. Opiod Therapies and Cytochrome P450 Interactions. J of Pain and Symp Management, 2012 Dec 1; 44(6): S4-S14.

Preissner S, Kuzman D, Pischon N. Drug Interactions Involving the Cytochrome P450 Enzymes: Analysis of Common Combinations of Antibiotics and Pain Relieving Drugs. J Drug Metab Toxicol 2012, 3:5.