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Unrelieved Pain/Distress

Title: Evaluation of Toxicity of New Imaging Agents
Protocol Number: PMY22074N
Approved Animal Use: Rabbits and Rats

Description of procedures: Rabbits

Per test article
Acute study: control group 4 animals
experimental groups - 3 groups @ different dose concentrations, 4 animals per group = 12 animals

Subchronic study: control group = 7 animals
experimental group = 7 animals

Animals are injected IV with a test article or control article in the same vehicle. maximum dose used is 2 ml/kg.

Acute study - animals are dosed individually with a single injection, dose calculated from their weight and according to group in an up/down fashion. This allows for a lower concentration to be administered if the higher concentration is toxic. This approach focuses in on the LD50 with the minimum use of animals.

Subchronic study - animals are dosed at approximately 1,000X the expected human dose of the drug. The animals are dosed Monday-Friday for two weeks. Each animal is dosed individually with a single daily injection calculated from the animal's weight.

The acute study allows for at least a week of conditioning before any injections are given. The animal weights are recorded during this time to monitor weight gain before injections. The single injection is given on day 0. Only one group of four animals is injected at a time, which allows for the adjustment, in an up/down fashion, of the dosage of the next group. The animals are monitored for acute signs of toxicity, with all observations recorded. Animal weights are monitored for 2 weeks to note any weight loss or food consumption changes. Clinical observations are made regarding behavioral changes or tissue changes at the injection site. Fourteen days after injection, the surviving animals are euthanized. (Actual study time = 14 days).

The subchronic study allows for a week of conditioning before any injections are given. Animal weights are recorded. Injections are given Monday-Friday for two weeks. Animal weights are monitored for two weeks during the injection period and for the following two weeks to note any weight loss or food consumption changes. Clinical observations are made regarding behavioral changes or tissue changes at injection site. two after final injection animals are euthanized. (Actual study time = 25 days).

Justification

Toxicity studies are requirements for FDA approval for the administration of newly developed drugs in humans. The purpose of the studies is to elicit potential toxic effects of candidate drugs which will ultimately be used in humans. Both production of toxicity and relative reversibility of those signs need to be demonstrated and observed. If adverse events occur it is necessary not to interfere as recovery is often possible. This is critical in the testing of new drugs to estimate the permanence or reversibility of adverse effects. In seriously affected animals, death usually occurs within minutes of dosing, thus limiting the period of discomfort. Two species have been selected (rabbits and rats), since they usually respond at different dose levels and can elicit different effects than the other and allows for the maximum information with a minimum number of animals used. This provides added assurance of picking up possible drug side effects which could result upon the administration of the drug in humans.