Toxicity testing using the Göttingen Minipig and the effect of a major surgical procedure on survival

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Introduction

Fentanyl is a synthetic opioid that the federal Centers for Disease Control and Prevention estimates to be about 80 times stronger than morphine and hundreds of times stronger than heroin (DHMH, 2014). Fentanyl is a highly effective analgesic when administration is limited and controlled. However, since fentanyl is such a powerful narcotic, it can be extremely dangerous with a high potential for overdose. It is only injected in small volumes for therapeutic use, so little data on fentanyl toxicity exists for dosages exceeding those that are recommended. The LD₅₀ is the dosage which is lethal to 50 percent of the exposed population when the drug is administered intravenously. To date, no data exists on the LD₅₀ value of fentanyl for pigs. Pigs are often used as laboratory animals because they are very similar to humans in both anatomy and physiology.

This research project had three objectives: 1. To determine the intravenous LD₅₀ for a single bolus injection of fentanyl in Göttingen minipigs 2. To determine if surgical implantation of radiotelemetry units statistically alters the lethal dose and 3. To use physiological data collected radio-telemetrically from the dosed animals to develop a better understanding of the sequence of events resulting from a fatal overdose of fentanyl.

Materials and Methods

Conscious, freely moving, male Göttingen Minipigs were divided into two groups after arriving at the lab. All pigs had minor surgeries to implant a dual lumen jugular cannula which was used to administer the fentanyl and collect blood samples. The second group of pigs also had a much more extensive surgical procedure where a D70-CCTP transmitter was implanted under the skin. This sensor measured heart rate (ECG), brain waves (EEG), blood pressure, and temperature.

One pig from each group was given the same dosage of fentanyl at or slower than what it was at baseline, as seen in Graph 3. From this experiment, it can be concluded that Göttingen minipigs are not the ideal animal for testing fentanyl because they have such a high LD₅₀ value and they do not respond in the same way that humans do after exposure. This is most likely because fentanyl disperses quickly to peripheral tissues, thereby reducing the concentration in the central blood compartment. Further studies of fentanyl could be completed with the use of other test subjects to better determine the effects of the drug as they would be in humans and to see if any other animals react to fentanyl with excitability like pigs do.

Results

Cardiac troponin levels increased in all pigs following exposure, including those with and without a transmitter.

In most pigs, there was a significant increase in heart rate (tachycardia) following exposure, then a decrease over the next seven days. Since there was no significant difference in the life or death outcomes in each set of pigs and, as seen in Graph 1, cardiac troponin levels increased following exposure for all animals, it is evident that the major surgical procedure had no effect on the lethal dose.

Graph 2 displays how Pig 16 showed excitability and restlessness after exposure to low dosages. Blue markers represent activity at baseline and red markers represent activity following exposure.

Change in heart rate over one week

Conclusions

Due to the high cost of fentanyl and Göttingen minipigs, research was unable to be continued and the LD₅₀ was unable to be determined. Since experimentation was completed up to a dosage of 8.013 mg/kg and the pig lived, it is safe to assume that the LD₅₀ is greater than that amount. Research could be continued from this point in the future to determine the true LD₅₀ of a Göttingen minipig. The D70-CCTP transmitter may be used in further studies with confidence that it will not alter the results because of the outcomes shown in Graph 1.

When small amounts of fentanyl are exposed to them intravenously, Göttingen minipigs show unexpectedly high levels of excitability and salivation, as displayed in Graph 2. At higher doses, the pigs are very calm and may lie down or fall asleep. At all doses, pigs’ heart rates increased following exposure, but this effect was not permanent, as Graph 3 exhibits. The increase in cardiac troponin after exposure suggests that fentanyl may cause cardiac damage even at the lowest doses, so the veterinary use of fentanyl should be researched further.

I would like to thank Dr. Stanley Hulet and everyone else at ECBC for giving me the opportunity to work in such a great environment and for teaching me a lot throughout the year. Without their laboratory work, the completion of my part of the project would not have been possible. I would also like to thank Mr. Davis for the constant guidance and support.

Acknowledgements

References