REPURPOSING TO SPEED CHEMICAL AND BIOLOGICAL MEDICAL COUNTERMEASURE DISCOVERY AND DEVELOPMENT

The Göttingen Minipig As A Large Animal Model For Medical Countermeasure Development: Overview Of Benefits And Recent Strides Forward

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The Göttingen minipig is fast becoming the standard for assessing dermal chemical hazards because its skin is predictive of human skin response and this strain's smaller size makes laboratory manipulations and husbandry easier. Much prior work has relied upon non-human primate (NHP) models, but concerns arise over their continued use. Models such as the rhesus macaque are excellent for many research questions but of limited use for dermal toxicity studies. Reduced availability and increased cost of NHP species makes this problem particularly poignant.

The Gottingen minipig could be advanced as a near-term and long-term replacement for NHPs, capable of providing comparable or even superior attributes for most research questions related to medical chemical defense, but studies must be designed, funded, and completed to meet this goal.

Targeted development of the Gottingen minipig as a large animal model for medical chemical defense will likely confer multiple advantages, including improved study design, adequate statistical power, reduced cost, and increased throughput in support of advancing medical countermeasures for FDA approval and fielding.

However, few studies have examined the pharmacokinetics of standard medical countermeasures against nerve agent exposure in unanaesthetized swine, and no known studies have evaluated the physiological safety of those countermeasures in swine. The present research addressed both research gaps. Göttingen minipigs were surgically implanted with vascular access ports and telemetric devices to monitor cardiovascular, respiratory, arterial pressure, and temperature signals. Unanaesthetized minipigs were intramuscularly administered atropine sulfate, pralidoxime chloride (2-PAM), diazepam, or pyridostigmine bromide, and physiological signals were recorded for up to 6 hours following injection. At the highest doses administered, 2-PAM, diazepam, and pyridostigmine were devoid of significant effects on cardiovascular, respiratory, arterial pressure, and temperature parameters in the Göttingen minipig. Atropine, however, produced a dose-dependent increase in the magnitude ($p < .001$) and duration ($p < .001$) of tachycardia. The two highest doses of atropine significantly decreased the PR ($p < .001$) and ST ($p < .001$) intervals. The magnitude and duration of the decreased PR and ST intervals were dose-dependent. These findings are consistent with those obtained from other species and provide further validation of the Göttingen minipig model being developed to evaluate countermeasure safety and efficacy as well as chemical agent toxicity.

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The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011) and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.

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