Characterization of microminipig as an experimental model for evaluating the cardiac safety of pharmaceutical products

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We characterized microminipig as an experimental model for evaluating cardiac safety of drugs in comparison with a dog. Microminipig was anesthetized with ketamine (16 mg/kg, i.m.) and xylazine (1.6 mg/kg, i.m.) followed by 1% halothane inhalation. Pilsicainide (1 mg/kg), verapamil (0.1 mg/kg), E-4031 (0.01 and 0.1 mg/kg), moxifloxacin (0.03, 0.3 and 3 mg/kg), terfenadine (0.03, 0.3 and 3 mg/kg), dipyrindamole (0.056 and 0.56 mg/kg), azithromycin (0.3, 3 and 30 mg/kg), oseltamivir (0.3, 3 and 30 mg/kg) and fluvoxamine (0.1, 1 and 10 mg/kg) were intravenously administered over 10 min (n=4 for each treatment). Pilsicainide, E-4031, moxifloxacin and terfenadine prolonged QTc, but its reverse was true for verapamil, azithromycin, oseltamivir and fluvoxamine, whereas no significant change was detected by dipyrindamole. Changes in QTc were in good accordance with those in our previous canine studies except for those by verapamil, azithromycin, oseltamivir and fluvoxamine. Moreover, the high dose of fluvoxamine increased the heart rate and mean blood pressure together with skin flush and myoclonus, which was not observed in dogs. The discrepancy in the responses between the Microminipig and dog can be partly explained by the smaller volume of distribution of a drug in Microminipig; thus, the high dose of fluvoxamine may have induced serotonin syndrome. These observations may help apply this new animal for safety pharmacology study.