SUPPLEMENTARY MATERIAL

Distribution of Synthetic Cannabinoids JWH-210, RCS-4 and Δ 9-Tetrahydrocannabinol After Intravenous Administration to Pigs

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S1 SURGICAL PROCEDURES

Premedication consisted of an intramuscular injection of ketamine hydrochloride (30 mg/kg, Ursotamin; Serumwerk Bernburg, Bernburg, Germany), xylazine hydrochloride (2.5 mg/kg, Rompun; Bayer, Leverkusen, Germany), and 1 mg atropine (Braun, Melsungen, Germany). Analgosedation was maintained by isoflurane (2-4 %, Forene, AbbVie, Ludwigshafen, Germany). Oral intubation was performed (7.5 ET tube; Portex, Hythe, UK), and the animals were mechanically ventilated with a mixture of oxygen and air (1:2 vol/vol; FiO_2 of 0.30; Respirator ABV-U; F. Stephan GmbH, Gackenbach, Germany) and volume cycled with a tidal volume of 10-12 mL/kg. The respiratory rate was adapted between 10 and 15 breaths/min according to arterial blood gas analysis to keep $PaCO_2$ constant between 30 and 45 mmHg. O_2 saturation was monitored by pulse oximetry. The left ear vein was catheterized for fluid replacement (sodium chloride 0.9 % [8 mL $kg^{-1} \cdot h^{-1}$], Braun, Melsungen, Germany). A triple-lumen 7F (Certofix Trio, Braun, Melsungen, Germany) central venous catheter was placed into the jugular vein for i.v. drug administration. After surgical preparation, the animals were allowed to stabilize for 10-15 min.

S2 SOLID PHASE EXTRACTION

Strata C_{18} endcapped cartridges (200 mg/3 mL; Phenomenex LTD, Aschaffenburg, Germany) were conditioned with 2x3 mL methanol and 3 mL phosphate buffer. The samples were loaded to the cartridges. Subsequently, three washing steps with 3 mL phosphate buffer, 3 mL acetic acid, and 3 mL water were applied, 60 µL acetone was added, and the columns were dried for 10 min under vacuum. Analyte elution was then performed with 1.5 mL methanol-acetone (1:1, v/v). The eluates were evaporated under a stream of nitrogen at 60°C and the dry residues were dissolved in 100 µL of a mixture of mobile phases A and B (50:50, v/v). Mobile phase A consisted of 0.1% aqueous formic acid and B was 0.1 % formic acid in acetonitrile. Twenty microliters were then injected onto LC-MS/MS system.

S3 LC-MS/MS

A Thermo Fisher (TF, Dreieich, Germany) HPLC consisting of one Allegro pump, an HTC PAL autosampler and a valve module with several switching valves was used. Detection was achieved using a TF TSQ Quantum Ultra Accurate Mass triple stage mass spectrometer with an atmospheric pressure chemical ionization (APCI) interface run in the positive mode. A Waters (Wexford, Ireland) Sunfire C_{18} column (150 x 2.1 mm, 3.5 µm) with a gradient elution was applied using mobile phase A and B. The gradient started with 25 % solvent B at a flow rate of 0.5 mL/min and increased within 4 min to 100 % of solvent B, which was kept for 4 min. Starting conditions were restored and kept for 1 min. The runtime was about 10 min. Ionization was achieved using an APCI source in positive mode and following parameter settings: discharge current 5.0 µA; vaporizer temperature 400°C; sheath gas 40 arbitrary units; auxiliary gas 15 arbitrary units; capillary temperature 270°C. Detection and quantification of the compounds were carried out in multiple-reaction monitoring mode detecting three transitions per precursor ion.