Physical dependence on morphine and cocaine in rats

S. Jarmouni-Idrissi, S. Biosa, Ph. Delataille, V. Ricou, F. Besse, R.M. Streff, L. Lecompte, A. Balondrade, K. Nahas, S. Ferry.

Pfizer PGRD Z.I Pocé sur Cisse 37401 AMBOISE

According to the new guideline on the non-clinical investigation of the dependence potential of medicinal products from the EMEA, the potential of the compounds that bind to molecular targets in the central nervous system to induce drug abuse must be assessed in appropriate preclinical models. In this context, we validated in house a paradigm to evaluate physical dependence in rats in order to include this assessment in the reversibility phase of our toxicological studies. For this purpose, we evaluated withdrawal symptoms in the rat after the administration of two reference compounds, morphine and cocaine. Sprague-Dawley rats received either 7-day continuous subcutaneous infusion of morphine at daily dose levels of 0, 10, 20 and 40 mg/kg via osmotic minipumps or intraperitoneal cocaine administrations at daily dose levels of 0, 10, 20 and 30 mg/kg for 14 days. The physical dependence symptoms were assessed during a 30-min observation session each day for the 10 days following the removal of the pumps (morphine) or cessation of the treatment (cocaine). The observers counted occurrences and incidences of signs using a standard checklist of abstinence signs. The results showed that withdrawal from morphine induced a significant dose-related loss of body weight and increased the occurrence of wet-dog shakes and stretching. Withdrawal from morphine also increased the incidence of genital grooming, abnormal posture and to a lesser extent diarrhea and jumping. The results also showed that withdrawal from cocaine failed to induce significant physical dependence symptoms. Therefore, the results obtained confirm literature data concerning the ability and inability of opiates and psychostimulants to induce physical dependence in rats, respectively.