

International Conference & Exhibition on Pharmaceutical Regulatory Affairs

6-7 September 2011 Baltimore, USA

A comparative safety risk assessment study for alkaloid extract of Malaysian *Mitragyna speciosa* and its main alkaloid compound, mitragynine, in experimental animal model

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Mitragyna speciosa is a local plant originated from Thailand and Malaysia that has been used in the folk medicine for its morphine-like effect mainly to ameliorate the abstinence period following weaning the morphine-addicted off as well as to relieve pain. Scientifically proven for possessing analgesic effect, there is lacking of data on the therapeutic index for the extract of the plant as well as mitragynine as the main alkaloid compound for further clinical use as a safe alternative of morphine substitute in addiction treatment. Therefore, the aim of this study is to evaluate the therapeutic index of Malaysian *M. speciosa* and mitragynine and comparing with that of morphine. Five doses of alkaloid extract (20, 50, 160, 320, and 400 mg/kg, p.o) and five equivalent doses of mitragynine (4.2, 10.5, 33.6, 67.2, and 84 mg/kg, p.o.) were evaluated for analgesic activity using hot plate test and the ED_{50} s as well as relative potency for the extract and mitragynine were compared with morphine (2.5-10 mg/kg, s.c.). LD_{50} s of the extract and mitragynine were also estimated by acute toxicity up-and-down- procedure and further therapeutic indices of both test substances were calculated and compared with morphine. Both alkaloid extract (ED_{50} =194.4 mg/kg) and mitragynine (ED_{50} = 21.96 mg/kg) significantly and dose-dependently showed analgesic effect compared to morphine (ED_{50} =3.69 mg/kg). In addition, based on the acute toxicity study the LD_{50} for alkaloid extract and mitragynine was estimated 591.6 mg/kg and 477mg/kg. The calculated therapeutic index for mitragynine was 7 times more than that of alkaloid extract and 7 times less than that of morphine. Although the alkaloid extract of *M. speciosa* was found far more toxic than morphine, the pure major compound of this plant, mitragynine, was relatively safe compared to morphine and can be a suitable alternative for further clinical studies on morphine addiction treatment.