



**ET(B) receptor agonist, IRL 1620, does not affect paclitaxel plasma pharmacokinetics in breast tumour bearing rats.**

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*Rai A, Rajeshkumar NV, Shord S, Gulati A.*

Endothelins are potent endogenous vasoactive substances. We have found that intravenous administration of endothelin (ET)B receptor agonist, IRL 1620 (N-suc-[Glu<sup>9</sup>, Ala(11,15)]ET-1 (8-21)) to tumour bearing rats increases blood perfusion and enhances delivery of chemotherapeutic agents to the tumour tissue. This study was conducted to determine whether IRL 1620, an ET(B) receptor selective agonist, alters pharmacokinetics of paclitaxel in breast tumour bearing rats. Breast tumours were induced in female Sprague-Dawley rats by N-methyl-n-nitrosourea (50 mg kg<sup>-1</sup>), i.p). Saline (0.3 mL kg<sup>-1</sup>), i.v.) or IRL 1620 (3 nmol kg<sup>-1</sup>), i.v.), was administered to the tumour bearing rats via the tail vein. Paclitaxel (3 mg kg<sup>-1</sup>), i.v.) was administered 15 min after saline or IRL 1620 injection. Serial plasma samples were collected up to 10 h after paclitaxel administration and analysed using an HPLC-UV assay. In a similar study [3H]-paclitaxel (40 microCi, i.v.) was administered after saline or IRL 1620 injection as described above and serial plasma samples were collected until 24 h. Data was fitted to a three-compartment model and pharmacokinetic parameters were generated using WinNonlin software. The AUC(0-infinity) (9.42 +/- 3.18 microg h mL<sup>-1</sup>), clearance (0.69 +/- 0.17 L h<sup>-1</sup> kg<sup>-1</sup>), volume of distribution (10.31 +/- 4.54 L kg<sup>-1</sup>) and half life (1.00 +/- 0.32 h) of [3H]-paclitaxel in tumour rats were similar in rats treated with IRL 1620 or vehicle. Tumour concentration of [3H]-paclitaxel was determined in rats treated with IRL 1620 or vehicle and there was a significant increase in tumour paclitaxel concentration (308.59 +/- 24.42%) in rats treated with IRL 1620 compared with vehicle. It is concluded that IRL 1620, an ET(B) receptor agonist, does not alter paclitaxel pharmacokinetics and can selectively augment the delivery of paclitaxel to the tumour tissue.