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ABSORPTION, METABOLISM AND EXCRETION OF A SINGLE ORAL DOSE OF ^{14}C-PALIPERIDONE 1 MG IN FIVE HEALTHY MALE SUBJECTS. M. Vermeir, PhD, S. Boom, I. Naessens, K. Talluri, M. Eerdekens, Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium.

OBJECTIVES: To establish the absorption, metabolism and excretion of paliperidone, a potentially new psychotropic.

METHODS: Male subjects (n=5) received oral ^{14}C-paliperidone 1mg. Urine, feces and blood and plasma samples were collected pre-dose and ≤1 week post-dose, and levels of radioactive paliperidone and its metabolites were analysed.

RESULTS: One week post-dose, 88.4-93.8% of the administered radioactivity was excreted: 77.1-87.1% in urine; 6.8-14.4% in feces. Unchanged drug (UD) accounted for most of the total radioactivity (TR) in plasma ≤24h post-dose (UD vs TD=97%). Total body clearance of TR and UD averaged 97.9 and 91.0mL/min, respectively. In urine, UD accounted for 51.4-67.5% of the dose, representing 65.5-82.1% of TR excreted into urine. Besides parent drug, four metabolites were identified in urine (Table), each accounting for ≤6.5% of the dose. Two metabolites were identified in feces extracts (metabolite #16 and #9). Given the total excretion of radioactivity in feces (11.4% of the dose), fecal metabolites represented a minor fraction of the dose, each between 0.4-0.9%. No UD was found in fecal extracts.

CONCLUSIONS: Paliperidone was metabolized to a limited extent. No important metabolic interactions are expected for paliperidone.

Code	Biotransformation route	Metabolite	Mean ± SD (Expressed as % of dose)
#1	Oxidative *N*-dealkylation	Acid metabolite R093725	4.6 ± 1.4
#16	Benzisoxazole scission & glucuronidation	R084852-glucuronide	4.1 ± 1.0
#9	Alicyclic mono-hydroxylation	Monohydroxy-paliperidone	3.8 ± 1.4
UD	Unchanged drug	Paliperidone	59.4 ± 7.1
#12	Alcohol dehydrogenation	Ketone metabolite R125239	2.7 ± 1.7

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EFFECTS OF VERAPAMIL PRE-TREATMENT ON THE DISTRIBUTION OF A P-GLYCOPROTEIN SUBSTRATE, ^{3}H-DOMPERIDONE, IN HEART AND WHOLE-BODY TISSUES OF HARTLEY GUINEA PIGS. L. Couture, MSc, J. A. Nash, PhD, L. Nguyen, PhD, J. Turgeon, PhD, Faculté de pharmacie, Université de Montreal, Charles River Laboratories, Preclinical Services - CTBR, Montreal, PQ, Canada.

BACKGROUND: P-glycoprotein (P-gp), an ABC transporter, is expressed in normal tissues such as the heart. Domperidone, a P-gp substrate, is associated with a block of voltage-gated cardiac K^+ channels and drug-induced Long QT syndrome. The aim of our study was to determine effects of verapamil (also a P-gp substrate) pre-treatment on distribution of ^{3}H-domperidone to the heart and other tissues.

METHODS: Male Hartley guinea pigs were pre-treated or not with a single intraperitoneal injection of verapamil (11.6 mg/kg) 2 h prior the intraperitoneal injection of ^{3}H-domperidone (2.5 mg/kg). Animals were sacrificed at 9 different timepoints up to 7 h after the administration of ^{3}H-domperidone. Tissues were excised and processed by liquid scintillation spectroscopy to determine radioactivity levels.

RESULTS: Higher AUC values were generally observed in heart structures (11 to 15%) and other tissues (up to 19%) of animals pre-treated with verapamil compared to control animals. The highest differences were observed in prostate gland, testes, heart and liver, tissues known to express P-gp.

CONCLUSIONS: The higher levels of ^{3}H-domperidone in heart from verapamil pre-treated guinea pigs would suggest a higher incidence of cardiotoxicities such as drug-induced Long QT syndrome when domperidone is co-administered with another P-gp substrate. The impairment of P-gp activities by verapamil pre-treatment suggests that caution is advisable when prescribing domperidone with another P-gp substrate.