Depletion and Metabolism study in neonatal pigs. Sponsor = Bayer, Leverkusen

Tissue Distribution of Radioactivity

Following a single oral administration of [^{14}C]-ponazuril, tissue samples were taken at various times up to 150 days after dosing. Radioactivity was well distributed throughout the tissues with the highest residues generally seen in the liver, and the lowest in the muscle. The residues were slowly cleared from the tissues, but had fallen to <1% of their levels between day 7 and 49, and to <0.1% between day 7 and 150. In order to analyse the tissues at the later timepoints (day 70 and after) they were reanalysed to lower the limit of detection, but the methodology could not be adapted for the skin. This meant that the results obtained for the skin remained close to the limit of detection and the concentration of residues in this tissue may have been overestimated at the later timepoints. There were no consistent differences in the concentrations of residues between males and females. Residues were slightly higher in females than males on day 7, and 49, and were slightly higher in males than females on day 21, 28, and 70.

Tissue	Concentration of radioactivity in tissues (as µg equivalents ponazuril/g tissue) after:-						
	7 days	21 days	28 days	49 days	70 days	119 days	150 days
Liver	12.10	3.956	2.724	0.208	0.01503	0.01206	0.00479
Kidney	8.460	3.221	1.789	0.083	0.00711	0.00607	0.00259
Muscle	4.959	1.599	0.677	0.030	0.00226	0.00131	0.00103
Skin	6.738	1.943	1.045	0.065	0.02769	0.00837	BLD
Fat	8.699	2.822	1.272	0.068	0.00684	0.00381	0.00255

BLD - Concentration in the sample is below limit of detection (i.e. DPM in aliquot analysed < background DPM). The calculated value for the residue concentration has been used in statistics.

Excretion/Balance

Over a 21-day period, 42% of the dosed radioactivity was found in the excreta of male and female pigs given a single oral dose of [^{14}C]-ponazuril. The major route of elimination was via the urine in males (27.11% of dose) and faeces in females (19.71% of dose). Overall, the mean urinary excretion accounted for 21.5% of dose. The elimination of the dose was slow, with the daily elimination in urine peaking at 1.58% of the dose on Day 7.

Sample	Per cent of administered dose		
	Males	Females	Mean
Urine	27.11	15.84	21.48
Faeces	14.24	19.71	16.98
Cage Wash	2.217	0.966	1.591
Final Cage Wash	0.060	0.027	0.043
Cage Debris	2.308	2.385	2.347
Total	45.94	38.93	42.43

Metabolism

Examination of the urine, faecal and tissue extracts by radio-HPLC showed that ponazuril was the major component present at virtually all timepoints. There were also small amounts of desmethyl ponazuril, ponazuril alcohol and ponazuril acid present in some extracts of tissues and faeces, and in the urine. The presence of desmethyl ponazuril was confirmed by HPLC/MS analysis of extracts of kidney.

Overall, ponazuril accounted for 85 to 100% of the residues in the tissues of the piglets at the early timepoints (up to Day 49 in all tissues except skin) and for greater than 61% at the other timepoints analysed. Ponazuril also accounted for 76-100% of the radioactivity in the faeces.