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Pharmacokinetics of ketamine and norketamine following intramuscular administration combined with dexmedetomidine in tigers (*Panthera tigris*).

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In zoo practice, for physical examination or medical procedure in captive tigers, chemical immobilization is needed and ketamine (KET) in association with sedatives is an option frequently used (Clark-Price et al., 2015). Aims of the study is the assessment of the pharmacokinetics of KET and its main metabolite, norketamine (NORKET), after its intramuscular administration in combination with dexmedetomidine in tigers.

Nineteen adult captive tigers, from different zoos, were scheduled for periodic physical examination or diagnostic procedures at the Milan University facilities. All animals were administered with a combination of KET at 2 mg/kg and dexmedetomidine at 10 µg/kg, given intramuscularly through blowpipe darts. If necessary, tigers where re-administered with variable doses of KET and dexmedetomidine or other drugs. When animals were sufficiently sedated, blood samples were collected every 5-10 min for the time tigers were safely approachable. Nine animals were assigned to standard protocol group (KET 2 mg/kg and dexmedetomidine 10 µg/kg) and ten animals to non-standard protocol group (tigers administered with different doses of KET, 2 – 2.5 mg/kg, and dexmedetomidine 10 – 30 µg/kg or with any other necessary drug, such as titrate-to-effect propofol and isoflurane, respectively for anaesthesia induction and maintenance). Ketamine and NORKET were extracted from plasma according to a validated HPLC-UV method (Zonca et al., 2012). For pharmacokinetic assessment, KET and NORKET concentrations were analysed with a noncompartmental approach (Phoenix® 7.0, Pharsight).

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Differences in the pharmacokinetic parameters between groups were statistically analysed (SPSS 25.0, SPSS Inc.). Results are reported in Table 1.

This is the first study that evaluates the pharmacokinetics of KET and NORKET in tigers. Due to the harmful attitude of these animals, samples collection was limited to the period of sedation, a short time for a complete pharmacokinetic evaluation. Nevertheless, we observed a favorable kinetic profile of KET and NORKET and, from a clinical point of view, all animals showed a good recovery, no adverse effects and a good level of sedation.

Table 1: Pharmacokinetic parameters of ketamine and norketamine in nineteen adult captive tigers after intramuscular administration of 2 mg/kg of ketamine, with or without variation from the standard protocol, in combination with dexmedetomidine (with * are indicated results with $p < 0.05$).

			Standard Protocol (mean ± s.d.)	**Non-Standard protocol (mean ± s.d.)**
Ketamine	*HL_Lambda_z*	*min*	*77.62 ± 54.50*	*76.14 ± 67.32*
	Tmax	*min*	*27.78 ± 7.90*	*49.70 ± 29.64*
	Cmax	*ug/mL*	*0.63 ± 0.17*	*0.67 ± 0.19*
	AUClast	*min*ug/mL*	*23.84 ±6.40**	*35.97 ± 12.84**
	AUMClast	*min*min*ug/mL*	*802.24 ± 331.03**	*2054.97 ± 1018.88**
	MRTlast	*min*	*32.88 ± 5.71**	*54.38 ± 19.71**
Norketamine	*Tmax*	*min*	*51.89 ± 8.95**	*77.10 ± 24.41**
	Cmax	*ug/mL*	*0.24 ± 0.07*	*0.23 ± 0.09*
	AUClast	*min*ug/mL*	*7.30 ± 3.98*	*11.07 ± 5.46*
	AUMClast	*min*min*ug/mL*	*291.94 ± 227.01**	*701.87 ± 424.80**
	MRTlast	*min*	*36.95 ± 7.32**	*58.65 ± 19.58**

HL_Lambda_z = Elimination Half-Life; Tmax = Time to Maximum concentration; Cmax = Maximum Concentration; AUClast = Area Under the Curve to the last concentration; AUMClast = Area under the first Moment Curve to the last concentration ;MRTlast = Mean Residence Time to the last concentration.

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