Title : **PHARMACOKINETIC ANALYSIS OF BUPIVACAINE AFTER SHORT AND LONG TERM INFUSIONS IN CONSCIOUS DOGS**

Authors : J.X. Mazoit, MD, C. Lambert, PhD, R. Froidevaux, MD, J.L. Gerard, MD, A. Berdeaux, MD, PhD

Affiliation : Departments of Anesthesiology and Pharmacology, Université Paris-Sud, Hôpital Bicêtre. 94275 Le Kremlin-Bicêtre FRANCE

INTRODUCTION. Lidocaine (L) clearance (CL) is markedly decreased after prolonged infusion as compared with CL calculated after iv bolus injection. This time dependence of CL have been demonstrated either in dogs (1) and in humans (2). In contrast, bupivacaine (B) CL is considered constant in human even after several days of administration for cancer pain relief (3). Thus, the aim of our study was to compare pharmacokinetics of B in dogs after short iv infusion (SI) and prolonged infusion (PI).

METHODS. Six mongrel dogs wheighing 21 ± 5 kg (mean ± SD) were implanted with femoral artery and venous catheters under ketamine anesthesia. After at least ten days recovery period, they received in a random, crossover manner SI or PI at one week interval . SI consisted of infusion of B 1.5 mg/kg in 15 min. PI consisted of two successive infusions of B 0.5 mg/kg in 15 min followed by 0.3 mg/kg/h during 24 hours. Blood samples were drawn at frequent intervals during SI or during the last hour of PI and after cessation of infusion until 480 min. B concentration was measured in serum using gas chromatography. Concentration-time data were fitted to a two-compartments model. Following parameters were derived: terminal half-life (T1/2),total body clearance (CL), steady-state volume of distribution (VSS). Indocyanin green (ICG) CL was measured during the last hour of PI and 90 min after cessation of infusion for both treatments. Statistical analysis was performed using Wilcoxon test for paired data for kinetics and using ANOVA for ICG CL.

RESULTS. Fig 1 shows the concentration-time data of a representative dog.T1/2 was increased ($p<0.05$) and CL was decreased ($p<0.05$) during PI as compared with SI, whereas VSS remained unchanged (Table 1). ICG CL did not differ significantly during the three sets of measurement (28.6 ± 10.0 ml/min/kg (mean ± SD) 90 min after cessation of SI,30.4 ± 7.5 ml/min/kg during the last hour of PI and 28.0 ± 2.9 ml/min/kg 90 min after cessation of PI).

DISCUSSION. This random crossover study done on conscious dogs demonstrates that 24 hours of B infusion induces an important increase in T1/2 which is only due to a decrease in CL when compared with the corresponding parameters obtained after SI of B. A non linear kinetic process appears unlikely since concentrations of B were in the same order of magnitude in the declining phase for both SI and PI. Moreover,B is of low hepatic extraction and a decrease in hepatic blood flow is also unlikely since ICG CL does not change significantly regardless duration of B infusion. These results demonstrate that B CL is time dependent in contrast with a previous study (3). Thus, we conclude that the time dependent decrease of B CL is due, as with L (2),to the decrease in intrinsic CL but not to the decrease in hepatic blood flow which remains constant even after 24 hours infusion.

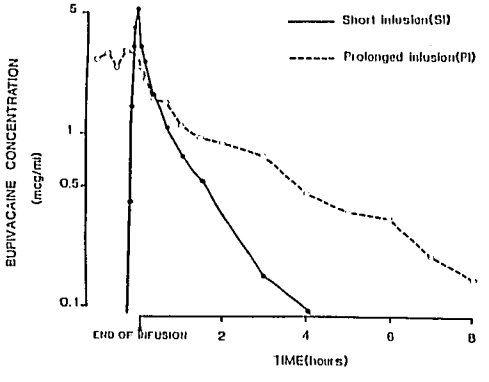

Figure 1. Plot of concentration vs time for one dog

	T1/2 (min)		CL (ml/min/kg)		VSS (ml/kg)		Cmax* (mcg/kg)	Css+ (mcg/kg)
	SI	PI	SI	PI	SI	PI	SI	PI
mean	53	167	9.5	5.1	512	424	3.8	1.7
SD	13	86	4.6	4.6	188	203	1.7	0.5
	$p<0.05$		$p<0.05$		NS			

Table 1. Pharmacokinetic parameters in the six dogs
* Observed maximum peak concentration.
\+ Mean of observed concentrations during the last hour of PI.

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