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COMMUNICATIONS

Bupivacaine kinetic changes during the oestrous cycle in rats

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Abstract—After a single 20 mg kg^{-1} i.p. dose during pro-oestrus, oestrus or dioestrus, bupivacaine kinetics in rats were not significantly different except for C_{max} which was significantly higher during dioestrus.

Bupivacaine is a local anaesthetic agent widely used in local or regional anaesthesia and in the control of postoperative or chronic pain. Its central nervous or cardiovascular side effects justify the need of a better understanding of its pharmacokinetics (Tucker & Mather 1979). Many factors may modify the kinetics of bupivacaine and thus must be investigated; among these, kinetic changes related to the phase of the menstrual cycle, demonstrated for other drugs such as antipyrine, ethanol, methaqualone and salicylates (reviewed by Bruguerolle 1986), may be of importance. As for other widely used drugs it was of interest to investigate whether or not the kinetics of bupivacaine was modified throughout the cycle since we are concerned at present by factors which may affect bupivacaine kinetics: thus the aim of this study was to document the possible changes in bupivacaine kinetics in rats according to the stage of the oestrous cycle.

Materials and methods

Adult female Wistar AF IOPS rats (n = 15, mean weight = 225 g) were housed five to a cage for a minimum of 3 weeks before use with controlled relative humidity (50–55%), temperature 25 ± 1°C and synchronization by a 12 h light-dark cycle (lights on 0600 h) with free access to food and water. The oestrus cycle was monitored by daily vaginal smears, taken between 0800–0900 h, during two weeks before the experiment; thus only animals presenting a four-day regular cycle were retained for this study. According to the stage of the oestrous cycle (i.e. group 1 = pro-oestrus, group 2 = oestrus, group 3 = dioestrus) 2 animals in three different groups of 5 animals each received a single 20 mg kg^{-1} intraperitoneal dose of bupivacaine (5 mg mL^{-1} in 0·9% NaCl (saline)) at 0800 h to avoid possible circadian variations. Blood (0·5 mL) was collected for each animal by puncture at the retro-orbital sinus at 0·25, 0·5, 1, 2, 4, and 8 h after administration. After each sample, 0·5 mL of saline was injected intraperitoneally in order to correct the blood loss. Blood was centrifuged and plasma was immediately frozen at −20°C until assayed.

Concentrations of bupivacaine in plasma were determined according to the modified GLC method of Prat & Bruguerolle (1987). Plasma bupivacaine concentrations were plotted against time and pharmacokinetic parameters were determined assuming a two-compartment open model. The parameters assessed were: maximal concentration (C_{max}), α and β phase elimination half-lives ($t_{\frac{1}{2}\alpha}$, $t_{\frac{1}{2}\beta}$) and the area under the serum concentration curve extrapolated to infinity (AUC_{∞}). These values were assessed according to conventional methods by a personal computer program. The curve fitting of the data was done by the method of residuals according to Wagner (1978); the α and β phases were assessed by linear regression (2 to 4 points for α and 2 to 4 for β phase). All data were quantified (means ± s.e.m.) and compared by analysis of variance and Fisher *t*-test.

Results

Fig. 1 illustrates the different plasma bupivacaine concentrations vs time according to the stage of the oestrous cycle. Table 1 shows mean ± s.e.m. values of the pharmacokinetic parameters determined at the different phases of the cycle and the statistical significance of the differences between the different groups. It seems from this table that $t_{\frac{1}{2}\beta}$ and AUC vary during the cycle with higher values during dioestrus but these differences are not statistically significant. Thus bupivacaine kinetics did not significantly vary according to the stage of the oestrous cycle, except for C_{max}; only this parameter was significantly higher during dioestrus.

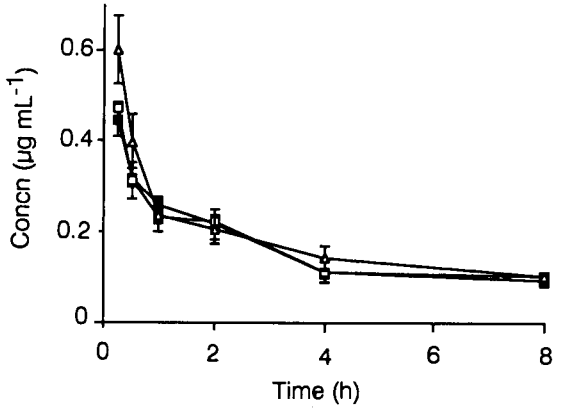

FIG. 1. Plasma bupivacaine concentrations vs time according to the stage of the oestrous cycle. Group 1, ■; group 2, □; group 3, △.

Discussion

Many physiopathological or pharmacological factors may modify the kinetics of bupivacaine and must be investigated. Bupivacaine is known to be highly bound (90%) to plasma proteins, mainly metabolized to pipecolylxylidine by *N*-dealkylation in the liver and excreted in urine (10%) as small amounts of pipecolylxylidine, unchanged drug (5%) and other metabolites (Tucker & Mather 1979). Thus distribution, metabolism and elimination of bupivacaine may be modified according to the phase of the oestrous cycle. In the present study, we could only demonstrate a statistically significant difference in C_{max}

Table 1. Bupivacaine pharmacokinetic parameters in plasma according to oestrous cycle; C_{max}: maximal concentration in serum, $t_{\frac{1}{2}\alpha}$: α elimination half-life, $t_{\frac{1}{2}\beta}$: β elimination half-life, AUC: area under concentration curve.

	C_{max} ($\mu g\ mL^{-1}$)	$t_{\frac{1}{2}\alpha}$ (h)	$t_{\frac{1}{2}\beta}$ (h)	AUC_0^{∞} ($\mu g\ mL^{-1}\ h$)
Group 1 (pro-oestrus)	0·447 ± 0·030	0·295 ± 0·120	5·80 ± 1·10	2·03 ± 0·14
Group 2 (oestrus)	0·474 ± 0·006	0·430 ± 0·180	8·20 ± 1·70	2·50 ± 0·32
Group 3 (dioestrus)	0·614 ± 0·035[a,b]	0·160 ± 0·040	9·20 ± 3·30	2·81 ± 0·33
ANOVA				
F value	F = 11·24	F = 0·96	F = 0·73	F = 2·03
P value	*P* = 0·002	*P* = 0·41	*P* = 0·50	*P* = 0·18

Statistical comparison: analysis of variance amongst the three groups and Fisher test two by two. [a] Significant statistical difference between groups 1 and 3. [b] Significant statistical difference between groups 2 and 3.

according to the stage of the cycle with a significantly higher value during dioestrus. Since bupivacaine was administered intraperitoneally, cyclic changes in the distribution process may be evoked as suggested for theophylline whose bioavailability has been shown to be significantly higher during dioestrus in the rat (Bruguerolle 1987). Also, alcohol (Jones & Jones 1976) and salicylate (Miaskewicz et al 1982) absorption has been shown to be modified in women, with a slower absorption in the midcycle.

The metabolic pattern of bupivacaine was also suggested to vary during the oestrous cycle; indeed, Iwasaki et al (1986) have reported on the influence of sex on the metabolism of tiaramide: there is a sex difference in the *N*-dealkylation of tiaramide (decreased in the female). Also methaqualone metabolism (Wilson et al 1982) has been reported to be two times higher at the moment of ovulation and phenytoin is more rapidly eliminated in epileptic women at the end of the cycle (Shavit et al 1984). Nevertheless, we could not demonstrate any significant difference of bupivacaine metabolism and elimination during the oestrous cycle.

Thus, as for some other drugs such as antipyrine (Kellerman et al 1976), carbamazepine (Backstrom & Jorpes 1979), D-xylose (Fiset & LeBel 1990), nitrazepam (Jochemsen et al 1982), paracetamol (Wojcicki et al 1979) and phenobarbitone (Backstrom & Jorpes 1979), the kinetics of bupivacaine are not greatly modified during the oestrous cycle in the rat.

If such data are confirmed in man, they will indicate that the phase of the menstrual cycle is not, under clinical practical conditions, a significant factor of modification of bupivacaine kinetics and need not be taken into account as a factor of exclusion in kinetic studies.

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