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Circadian phase dependent acute toxicity and pharmacokinetics of etidocaine in serum and brain of mice

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Abstract—The aim of this study was to investigate the possible influence of the time of administration on etidocaine acute toxicity and kinetics in mice. Different groups of adult male NMRI mice maintained under controlled environmental conditions (lights on 06·00–18·00) were injected at one of the following times: 10·00, 16·00, 19·00, 22·00, 01·00 and 04·00 h with four doses of etidocaine at each time point to establish the acute toxicity (LD 50). To assess chronokinetics, a single 40 mg kg^{-1} i.p. dose of etidocaine was given to adult male NMRI mice at four fixed times: 10·00, 16·00, 22·00 and 04·00 h. Etidocaine serum levels were determined by GLC. The data showed significant 24 h variations of the C_{max} only (highest value = 9·64 ± 1·31 μg mL^{-1} at 10·00 $P < 0·05$; amplitude, (maximum-minimum) mean × 100 = 84%) Vd, (amplitude = 59·7%), α and β phase elimination half-lives (amplitude = 52 and 35%, respectively), clearance (amplitude = 23%) and AUC% (amplitude = 22%) were not found to be significantly time dependent. Etidocaine kinetics in brain were determined similarly; a significant temporal variation was found for the elimination half life (amplitude, 161·9%) and AUC (amplitude, 133·2%) but not for C_{max}. These data demonstrate a temporal pattern of etidocaine kinetics similar to those reported previously for other local anaesthetic agents, bupivacaine and mepivacaine. The temporal changes in etidocaine induced acute toxicity may result in part from its chronokinetic changes.

We have previously reported data on the chronokinetics of lignocaine (Bruguerolle et al 1982), bupivacaine (Bruguerolle & Prat 1987) and mepivacaine (Bruguerolle & Prat 1988) in rodents. The present report examines the pharmacokinetic changes of etidocaine, another amide type anaesthetic agent, in serum and brain related to the hour of its administration, by assessment of temporal changes in its pharmacokinetic parameters after a single i.p. dose in the mouse. Possible temporal changes in chronotoxicity of etidocaine and its relationship with its chronokinetics have been examined.

Materials and methods

Methods used were those in the reports on bupivacaine (Bruguerolle & Prat 1987) and mepivacaine (Bruguerolle & Prat 1988) in mice. Thus groups of adult male NMRI mice maintained under controlled environmental conditions (light period = 06·00–18·00 h) were injected at one of the following times: 10·00, 16·00, 19·00, 22·00, 01·00 and 04·00 h with four doses of etidocaine at each time to establish the acute toxicity (LD 50). To assess chronokinetics, a single 40 mg kg^{-1} i.p. dose of etidocaine was given to adult male NMRI mice at four fixed times: 10·00, 16·00, 22·00 and 04·00 h. Etidocaine serum levels at 5, 10, 30, 45, 60, 120, 180 and 360 min after treatment (5 animals per time point) were determined by GLC. For brain etidocaine determination, the extraction procedure used previously was applied after homogenization of tissues in 2 to 5 volumes of saline. Pharmacokinetics in brain tissue were calculated as for pharmacokinetics. All data were quantified (mean ± s.e.m.) and compared by statistical analysis (analysis of variance, ANOVA). For each kinetic parameter, the amplitude of the temporal change was calculated as (maximum-minimum)/mean × 100.

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Results

Acute toxicity. The results presented in Fig. 1 and Table 1 indicated a circadian variation in the acute toxicity of mepivacaine. Single cosinor data validated a statistically significant circadian rhythm ($P = 0·05$, R = 82·8).

Kinetics. Table 2 shows the different pharmacokinetic parameters (mean ± s.e.m.) of etidocaine in serum after a single 40 mg kg^{-1} i.p. dose at 10·00, 16·00, 22·00 and 04·00 h and statistical analysis (ANOVA) of the comparison. Table 3 shows the different pharmacokinetic parameters (mean ± s.e.m.) of etidocaine in brain at 10·00, 16·00, 22·00 and 04·00 h and statistical analysis (ANOVA) of the comparison.

Discussion

Chronokinetics (i.e. temporal variations of kinetics) of lignocaine, bupivacaine and mepivacaine, have been previously reported from our laboratory (Bruguerolle et al 1982; Bruguerolle & Prat 1987, 1988). The present study reports chronokinetics of another amide type local anaesthetic agent, etidocaine. Fig. 1 shows that the temporal variations of mortality (LD 50) mirror the temporal changes of C_{max} in serum and in brain. The highest resorption, as assessed by C_{max} at the earliest time point, 5 min, in the dark period, and the lowest resorption during the resting period, are similar to those previously reported for bupivacaine (Bruguerolle & Prat 1987), lignocaine (Bruguerolle et al 1982) and mepivacaine (Bruguerolle & Prat 1988). The amplitude of the temporal changes of etidocaine resorption are similar to bupivacaine but only one half those observed for mepivacaine; there were no significant temporal changes in maximum brain concentrations even though the maximum

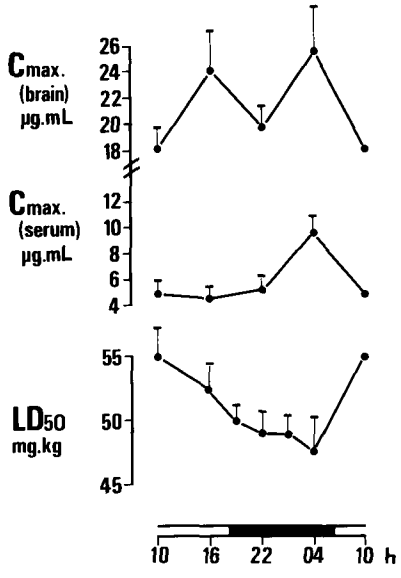

FIG. 1. Temporal variations of etidocaine acute toxicity (LD 50), C_{max} in serum and C_{max} in brain.

Table 1. Acute toxicity (LD50, mg kg^{-1}) according to the hour of administration and cosinor analysis.

	Time of administration (h)					
	10·00	16·00	19·00	22·00	01·00	04·00
LD 50 ± s.e.m.	55·0 ± 2·3	52·5 ± 2·1	50·0 ± 1·2	49·0 ± 1·8	49·0 ± 1·4	47·5 ± 2·8
Cosinor Analysis		Amplitude	3·4 ± 0·9		R: 82·8	
		Mesor:	51·2 ± 0·6			
		Acrophase	12·18 ± 0·59		$P = 0·05$	

Table 2. Circadian variations of the pharmacokinetic parameters of etidocaine in serum after a single 40 mg kg^{-1} i.p. dose at four different hours. C_{max} ($\mu g\ mL^{-1}$) = maximum concentration. V_d (kg^{-1}) = apparent volume of distribution. $t_{\frac{1}{2}}\alpha$ and $t_{\frac{1}{2}}\beta$ (h) = α or β phase elimination half life. CL L $kg^{-1}\ h^{-1}$) = total plasma clearance. AUC_0^∞ ($\mu g\ mL^{-1}$ h) = area under the serum concentration curve.

Time (h)	C_{max}*	V_d	$t_{\frac{1}{2}}\alpha$	$t_{\frac{1}{2}}\beta$	CL	AUC_0^∞
10·00	4·91 ± 1·17	0·79 ± 0·11	0·055 ± 0·004	1·51 ± 0·06	0·355 ± 0·037	2·00 ± 0·27
16·00	4·55 ± 1·01	0·67 ± 0·09	0·470 ± 0·004	1·48 ± 0·04	0·312 ± 0·038	2·31 ± 0·33
22·00	5·17 ± 1·21	1·13 ± 0·29	0·073 ± 0·022	2·06 ± 0·32	0·357 ± 0·039	1·99 ± 0·25
04·00	9·64 ± 1·31	0·65 ± 0·09	0·028 ± 0·04	1·57 ± 0·03	0·281 ± 0·027	2·48 ± 0·27
ANOVA	$F = 3·51$ $P < 0·05$	$F = 1·36$ ns	$F = 2·08$ ns	$F = 2·10$ ns	$F = 0·82$ ns	$F = 0·70$ ns
Amplitude %	83·8	59·7	52·0	34·9	23·0	22·4

* In all cases the maximum concentration was observed in the earliest sample taken (5 min).

value occurred at the same time as the serum C_{max}. This may be explained by the high lipophilicity of etidocaine.

Etidocaine, is mainly metabolized in the liver where it undergoes dealkylation and hydrolysis (Lund et al 1974; Tucker & Mather 1975). Our data confirm its shorter elimination half life compared with bupivacaine or mepivacaine. Nevertheless, no statistically significant temporal changes in elimination were seen whereas bupivacaine and mepivacaine elimination half lives were previously reported to be longest at 22·00 h with amplitudes of 35% and 145%, respectively (Bruguerolle & Prat 1987, 1988). The lack of significant circadian rhythm in etidocaine elimination may be interpreted in terms of differences between different metabolic patterns of the drugs (oxidation by *N*-dealkylation for bupivacaine and *N*-demethylation or hydroxylation for mepivacaine).

Concerning brain tissue levels, a significant temporal change was found for elimination half life and hence AUC with highest values at 22·00 h. These findings must be interpreted taking into account the high liposolubility of etidocaine.

In conclusion, the chronokinetics of etidocaine have been demonstrated in serum for absorption processes and in brain for elimination processes; these findings agree well with previously reported chronokinetics of bupivacaine and mepivacaine, but reveal a less pronounced circadian effect for etidocaine: the detection of a significant variation, and its amplitude, may depend on differences in distribution, protein binding and metabolic pathways related to physicochemical differences amongst the three drugs. The present work also shows temporal changes in etidocaine-induced acute toxicity similar to that demonstrated for bupivacaine and mepivacaine; this chronotoxicity may be, in part, explained by the chronokinetic data.

Table 3. Circadian variations of the pharmacokinetic parameters of etidocaine in the brain after a single 40 mg kg^{-1} i.p. dose at four different hours. C_{max} ($\mu g\ mL^{-1}$) = maximum concentration. $t_{\frac{1}{2}}\beta$(h) = β phase elimination half-life. AUC_0^∞ ($\mu g\ mL^{-1}$ h) = area under the brain concentration curve.

Hour	C_{max}*	$t_{\frac{1}{2}}\beta$	AUC_0^∞
10·00	18·06 ± 1·94	1·42 ± 0·03	7·54 ± 0·64
16·00	24·11 ± 3·13	1·47 ± 0·09	9·08 ± 1·02
22·00	19·74 ± 1·75	6·26 ± 0·62	27·14 ± 3·37
04·00	25·64 ± 3·83	2·80 ± 0·17	15·04 ± 2·37
ANOVA	$F = 1·61$ ns	$F = 38·79$ $P < 0·0001$	$F = 12·05$ $P < 0·005$
Amplitude %	34·64	161·9	133·2

* In all cases the maximum concentration was observed in the earliest sample taken (5 min).

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