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Temporal changes in bupivacaine kinetics

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The chronokinetics of bupivacaine have been examined in the mouse. Different groups of adult male NMRI mice maintained under controlled environmental conditions received a single intraperitoneal injection of bupivacaine (20 mg kg^{-1}) at one of four different fixed time points in a 24 h period i.e. 1000, 1600, 2200 and 0400h. Blood samples were taken 0·25, 0·5, 0·75, 1, 1·5, 3, 4 and 6 h after drug administration and total serum levels of bupivacaine were determined by a gas–liquid chromatography with a flame ionization detector. Statistically significant temporal changes were found in the following pharmacokinetic parameters: highest C_{max} value = 0·900 ± 0·080 μg mL^{-1} at 2200h (amplitude, maximum–minimum/mean × 100, is 64%); highest C_{max}/T_{max} ratio = 3·596 ± 0·339 at 2200h (amplitude = 85%); highest β elimination half-life, $T_{\frac{1}{2}}\beta$, = 3·950 ± 0·246 h at 2200h (amplitude = 35%); area under concentration curve (AUC_0^∞) was not found to be significantly different among the hours of administration. The temporal kinetic changes demonstrated suggest a possible circadian difference in bupivacaine efficacy and/or toxicity.

The existence of a temporal pattern of drug kinetics is well known and has been demonstrated for many drugs in animals and man (Reinberg & Smolensky 1982: Bruguerolle 1983; Lemmer 1981). Local anaesthetic drugs have been little studied from a chronopharmacokinetic view. We have reported data on the chronokinetics of lignocaine in the rat (Bruguerolle et al 1982) and in man (Bruguerolle & Isnardon 1985). This report examines the pharmacokinetic changes of bupivacaine related to the time of its administration by assessing temporal changes in its pharmacokinetic parameters after a single intraperitoneal dose in the mouse.

Materials and methods

Adult male NMRI mice (n = 160) (~30 g) were housed, ten to a cage, for a minimum of three weeks before use, with free access to food and water. Environmental conditions were controlled at a relative humidity of 50–55% and temperature 25 ± 1 °C during the month of October. Animals were synchronized with natural day/light alternation; on the day of the experiment sunrise occurred at 0602h and sunset at 1700h.

At 1000, 1600, 2200 and 0400h a total of 160 animals, 40 per chosen time, were given bupivacaine chlorhydrate solution (2·5 mg mL^{-1}) intraperitoneally as a single 20 mg kg^{-1} dose; blood samples were collected after decapitation 0·25, 0·5, 0·75, 1, 1·5, 3, 4 and 6 h after drug administration. Total bupivacaine serum levels were determined by GLC with a flame ionization detector according to Desch et al (1981) modified by Prat & Bruguerolle (1986).

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Bupivacaine serum concentrations were plotted against time and pharmacokinetic parameters were determined assuming a two compartment open model: maximum concentration (C_{max}), time to reach it (T_{max}), the ratio C_{max}/T_{max}, α and β phase elimination half-lives ($T_{\frac{1}{2}}\alpha$, $T_{\frac{1}{2}}\beta$) and area under the serum concentration curve extrapolated to infinity (AUC_0^∞) were assessed according to conventional methods (Wagner 1975) by a computer program. The curve fitting of the data was done by the method of residuals according to Wagner (1975): for instance α and β phases were assessed by linear regression (3 to 4 points for α and 4 to 5 points for β phase).

All data were quantified (mean ± s.e.m.) and compared by statistical analysis (analysis of variance, ANOVA). For each parameter the amplitude of the temporal change was calculated as maximum–minimum/mean × 100 giving percentage of the 24 h mean.

Results

Table 1 shows the different pharmacokinetic parameters (mean ± s.e.m.) of bupivacaine after a single 20 mg kg^{-1} i.p. dose at 1000, 1600, 2200 and 0400h and statistical analysis (ANOVA) of the comparison. For each parameter the amplitude of the temporal change is also shown in Table 1.

Fig. 1 shows serum concentration-time curves of bupivacaine according to the hour of administration. These results indicate a significant change in distribution and elimination half-lives, $T_{\frac{1}{2}}\alpha$ and $T_{\frac{1}{2}}\beta$ being highest at 1000h and lowest at 1000h, respectively. C_{max} value and the C_{max}/T_{max} ratio are highest when the drug is administered at 2200h, indicating a better absorption of the drug at this time. AUC_0^∞ is not significantly different according to time of administration.

Discussion

Our data demonstrate for the first time that the pharmacokinetics of bupivacaine depend on the time of its administration. It is known (Reinberg & Smolensky 1982; Bruguerolle 1983; Lemmer 1981) that chronokinetic differences can occur at one or more stages, i.e. absorption, distribution, metabolism and excretion of the drug.

Even if bupivacaine is administered by the intraperitoneal route, involving relatively rapid resorption processes, our data reveal temporal changes in its absorption (see C_{max}, T_{max} and C_{max}/T_{max} ratio values in Table 1). Bupivacaine resorption is highest when the

Table 1. Bupivacaine pharmacokinetic parameters related to the time of administration in mice. C_{max} ($\mu g\,mL^{-1}$) = maximum concentration, T_{max} (h) = time to reach it, $T_{\frac{1}{2}}\alpha$(h) = α phase elimination half-life, $T_{\frac{1}{2}}\beta$(h) = β elimination half-life, AUC_0^{∞} ($\mu g\,mL^{-1}\,h$) = area under the serum concentration curve.

Time	C_{max}	T_{max}	C_{max}/T_{max}	$T_{\frac{1}{2}}\alpha$	$T_{\frac{1}{2}}\beta$	AUC_0^{∞}
1000h	0·494 ± 0·088	0 350 ± 0·050	1·579 ± 0·355	0·359 ± 0·034	2·790 ± 0·210	1·978 ± 0·367
1600h	0·570 ± 0·080	0·300 ± 0·040	1·965 ± 0·266	0·192 ± 0·025	3·390 ± 0·660	1·459 ± 0·122
2200h	0·900 ± 0·080	0·250 ± 0·000	3·596 ± 0·339	0·119 ± 0·063	3·950 ± 0·246	1·877 ± 0·124
0400h	0·570 ± 0·020	0·250 ± 0·000	2·262 ± 0·084	0·317 ± 0·064	2·950 ± 0·768	1·645 ± 0·126
ANOVA	$P < 0·025$ F = 5·24	NS	$P < 0·005$ F = 7·70	$P < 0·05$ F = 3·40	$P < 0·01$ F = 5·83	NS F = 1·44
Amplitude: % of the 24 h mean	64·14	35·08	85·83	97·16	35·47	29·84

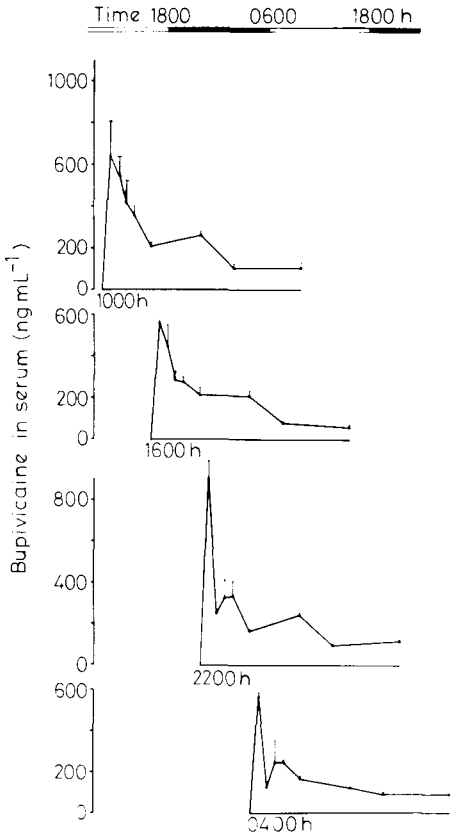

FIG. 1. Bupivacaine serum levels (means ± s.e.m.) after intraperitoneal injection of a single 20 mg kg^{-1} dose at four different fixed time points 1000; 1600, 2200 and 0400h.

drug is administered at 2200h. These results agree with data reported by Bruguerolle et al (1982) for another amide-type anaesthetic, lignocaine, which is better absorbed during the dark phase in the rat (Bruguerolle et al 1982). This may be related to temporal variations of peritoneal blood flow not yet demonstrated although possibly based in part on circadian variations of peripheral blood flow, highest in rodents during the dark period (activity span) (Lew 1976).

Since bupivacaine is 90% bound to plasma proteins, circadian changes in protein binding, as demonstrated for other local anaesthetics such as lignocaine (Bruguerolle et al 1982), would affect the kinetic changes observed and are under investigation.

Bupivacaine is known to be principally 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. Our data reveal a temporal change in bupivacaine elimination half-life with highest values when the drug is given at 2200h. The metabolic pattern of bupivacaine involving oxidation by *N*-dealkylation may vary with time as demonstrated for other drugs (see Bruguerolle 1983).

The temporal kinetic changes demonstrated in this study may suggest temporal differences in bupivacaine toxicity and/or efficacy. Preliminary results from our laboratory, not yet published, on bupivacaine chronotoxicity, seem to agree with the present data: the highest mortality occurs when the drug is given at 2200h.

In conclusion the temporal changes in bupivacaine as well as those reported for some other drugs suggest that the time of administration must be taken into account.

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