Effect Of Clonidine On Bupivacaine Clearance In Tunisian Patients: Population Pharmacokinetic Investigation.

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OBJECTIVES

Combined lumbar and sciatic nerve blocks is associated with an increased plasmatic concentrations of bupivacaine (BPV), sometimes reaching toxic concentrations, with a large inter and intraindividual variability. The addition of a vasonstrictor is intended to reduce local perfusion and thereby reduce systemic absorption limiting systemic toxicity.

Our team aimed to study the effects of clonidine, an α-2 mimetic known to affect systemic clearance, on bupivacaine pharmacokinetics when given as an adjuvant.

METHODS

PATIENTS AND PROTOCOL

The protocol of this study was reviewed and approved by the committee on medical ethics of Aziza Othmana Hospital in Tunis; Tunisia.

62 ASA physical status I or II patients, who have given written informed consent, were enrolled in this prospective study for elective lower extremity surgery. Exclusion criteria were patient's refusal, age < 18 years, contraindication to peripheral nerve block, history of known hypersensitivity to local anesthetics.

A dose of 150 mg of bupivacaine (for each nerve) was administered with 1 mcg/kg of clonidine (19 patients, group 1) or without clonidine (43 patients, group 2).

We collected plasma samples, for each patient, before the blocks and at 5, 10, 30, 45, 60, 120 and 240 minutes post-second injection.

Time between both injection (lag time) was recorded

PHARMACOKINETIC ANALYSIS

To assess the BPV pharmacokinetic profile of each patient, individual analysis of the plasma concentration data were performed by nonlinear regression using **NONMEM VI software** (NONMEM Project Group, University of California, San Francisco, USA).

The structural model was established initially, followed by development of the covariate model. The pharmacokinetic parameter estimates of BPV were determined by compartment analysis. Model selection was based on the Akaike information criterion (AIC): An additional parameter was included in the model, if the resulting decreasing the AIC the parameter was accepted.

Two compartment model with first order absorption rate constant (Ka) and central elimination was selected.

The population means parameters; between-subject variance and residual variance were estimated using the first order conditional estimate (FOCE) interaction method (residual intraindividual variability was modeled as log-normally distributed, by log transforming the concentrations using an exponential model to describe residual variability of BPV concentration using the PREDPP subroutine ADVAN 5 of NONMEM VI (level 1.1).

Convergence criterion was three significant digits and MAXEVAL=9000. Microsoft windows Vista ™ was used to compile and execute NONMEM.

The most important covariates included body weight and age which affect respectively the volume of distribution and clearance.

The final model was evaluated by the bootstrap method.

Normalized Prediction Distribution Error (npde) for the Evaluation of Nonlinear Mixed-Models:

npde was used for model evaluation in population pharmacokinetic using **R** software . It's based on the whole predictive distribution.

RESULTS

Table 1: Patient characteristics. Data are Mean (range) for age (AGE), weight (WT), height (HT)

	Group 1	Group 2
Age(yrs)	59 ± 26	51 ± 22
Wight (Kg)	71 ± 11	70 ± 10
Height (cm)	168 ± 11	167 ± 8
Time between both injections (min)	9 ± 4	11 ± 7

Figure 1. Scatter plots of individual model predicted concentration versus observed concentrations

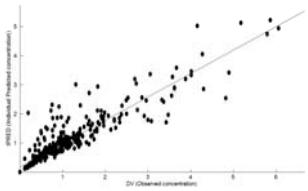

Figure 3: Diagrammatic representation of the selected model with two compartments.

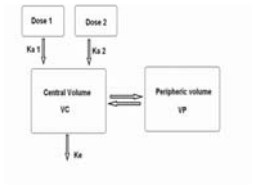

Table 2: Population pharmacokinetic parameters

	V1 (l)	V2 (l)	Ka1 (min^{-1})	Ka2 (min^{-1})	Ke (min^{-1})
Population mean	266.43	10.68	0,181	0,180	0,0039

Ka1: absorption rate constant
Ka1: absorption rate constant
Ke: elimination rate constant from the central compartment.
VC: central volume of distribution
VP: peripheral volume of distribution

Figure 2: graphically representation of npde distribution for the Evaluation of Nonlinear Mixed-Models

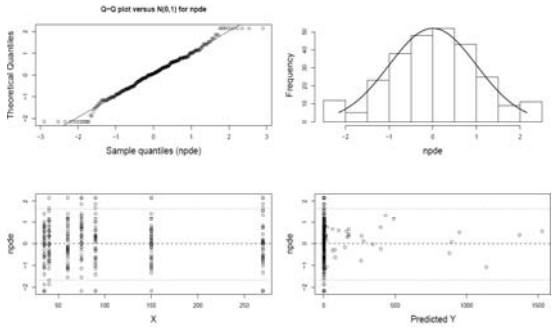

Table 3 Normalized prediction distribution error (npde) for the evaluation of nonlinear mixed-models one and two compartments:

	npde distribution and statistical analysis
Mean	0.05795 (SE= 0.061)
Variance	0.989 (SE= 0.086)
Skewness	-0.09105
kurtosis	-0.1368
Wilcoxon signed rank test	0.281
Fisher variance test	0.921
Shapiro-wilks test of normality	***0.00672 *****
Global adjusted p-value	0.0202 *

Significant codes: '**' p<0.01 and '*' p<0.05

Table 3 systemic clearance in two groups :

	Group 1 (n=19)	**Group 2 (n=43)**
Clearance (l/h)	32.6	60.74

ANOVA test , P= 0.0429 <0.05

CONCLUSION

Our results shown that bupivacaine absorption is fast in the both sites of injection, despite clonidine administration. Moreover, clonidine decreases bupivacaine's clearance only. In fact, several studies have previously shown the effect of clonidine on local anaesthetics: Kopacz J (2001) reported that clonidine decrease lidocaine clearance *in vivo*, Mazoit JX (1996) demonstrated how clonidine decrases lignocaine peak plasma concentration when used as an adjuvant and Bruguerolle B (1996) detailed the decreasing effect of clonidine pre-treatment on bupivacaine metabolism in mice. Altogether, these data along with our results, shall allow us to better predict bupivacaine concentrations to administer in the presence or absence of clonidine. Furthermore, our pharmacokinetic model will be used to determine an individual dosage for each patient and insure a better risk/benefit ratio.

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