TITLE: Plasma Protein Binding Determines Partitioning of Lidocaine into Brain and CSF Following Intravenous Bolus Administration in Dogs

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Traditional dogma in pharmacology suggests that plasma protein binding of drugs restricts their movement from blood into tissues. While this concept appears logical, it has been confirmed for only a few drugs, and has not been confirmed for local anesthetics. The purpose of this study was to test the hypothesis that plasma protein binding determines partitioning of lidocaine into brain and CSF, following iv bolus administration of lidocaine to dogs.

13 mongrel dogs were studied with approval of the local committee on animal experimentation. Six dogs were pretreated for 14 days with rifampin, which is known to substantially increase the principal plasma protein that binds lidocaine, alpha-1-acid glycoprotein (AAG). All dogs were anesthetized with halothane and nitrous oxide, intubated and ventilated. Six dogs (3 rifampin treated) were designated for CSF sampling from the cisterna magna, and 7 dogs (3 rifampin treated) were designated for cortical brain tissue sampling. Lidocaine 3 mg/kg was administered iv over 15 sec. Samples of arterial blood and either brain tissue or CSF were obtained over a 60 min period. AAG level, total lidocaine level and lidocaine free fraction were determined for each blood sample. Lidocaine level was determined for each brain and CSF sample.

Rifampin pretreatment resulted in a 4 fold increase in mean AAG concentration ($p=0.023$). The area under the curve (AUC) of lidocaine concentration vs. time plots for each dog were used to compare lidocaine concentrations in serum, brain and CSF. A ratio between AUC for brain or CSF and AUC for serum were calculated. Higher ratios indicate relatively greater partitioning of lidocaine into brain or CSF. The correlation betweeen the ratio of brain/serum lidocaine and lidocaine free fraction in plasma was $r=0.92$ ($p=0.003$, Figure). The correlation between the ratio of CSF/serum lidocaine and plasma free fraction was $r=0.90$ ($p=0.01$)

Increased plasma protein binding of lidocaine restricted entry of lidocaine into the CNS, as shown by the positive correlation between free fraction and the ratio of brain/serum and CSF/serum lidocaine. The results of this study are consistent with clinical observations that local anesthetic toxicity appeared related more closely to free than total concentration. Clinical monitoring of local anesthetic plasma levels should include determination of *free* levels.

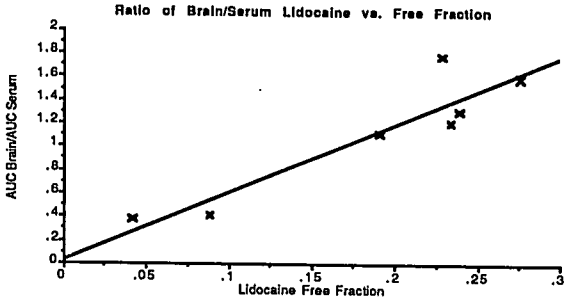

Figure. Each (x) represents one dog.

TITLE: THE PHARMACOKINETICS OF NALMEFENE, AN OPIOID ANTAGONIST

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Nalmefene is a novel, 6-methylene analogue of naltrexone(1). Preclinical studies indicate that it is a pure opioid antagonist (1, 2).

In the present study, the pharmacokinetics of single-doses were evaluated in healthy male subjects. Eighteen subjects, ranging in age from 19 to 35, were divided into three groups of six subjects each. In ascending fashion, single doses of 0.5 mg, 1.0 mg and 2.0 mg were given as a rapid intravenous bolus injection, one dose per group.

All subjects gave informed consent and the protocol was approved by the Institutional Review Board of Harris Laboratories.

Safety was evaluated through pre- and post-dose physical examinations and clinical laboratory tests. Determinations of heart rate, blood pressure, respiratory rate and body temperature were conducted at frequent intervals throughout the 48-hour study.

Multiple plasma samples were drawn prior to dosing and at multiple intervals over the 48-hour post-dose period. Samples were assayed for nalmefene by radioimmunoassay with a limit of quantitation of 0.1 ng/ml.

The calculated parameters of area-under-the-plasma-concentration vs. time curve from 0 to 48 hours (AUC 0-T), AUC from 0-infinity, half-life of elimination (T1/2), and the volume of distribution (Vd) are shown in the following table:

Mean (SEM) Kinetic Parameters of Nalmefene

Dose (mg)	AUC 0-T (ng·hr/ml)	AUC 0-inf (ng·hr/ml)	T1/2 (hr)	Vd (l/kg)
0.5	6.79 (0.49)	7.84 (0.43)	9.53 (0.56)	11.2 (0.6)
1.0	17.83 (1.77)	18.78 (1.81)	7.77 (1.14)	9.1 (1.4)
2.0*	37.75 (3.10)	39.09 (3.21)	9.86 (0.71)	10.0 (1.2)

*n=5, one subject was excluded from the kinetic analysis, but was included for safety

The data indicate that there is linear dose proportionality among the doses tested. Compared to naloxone, the half-life of nalmefene is 8 times longer and the volume of distribution is 5 times greater (3).

There were no serious adverse events during the study.

References

1. Journal of Medicinal Chemistry, 1975, Vol. 18, 259-262

2. Journal of Pharmacology and Experimental Therapeutics, 1977, Vol 200, No.3, p.496-500

3. Goodman and Gilman's The Pharmacological Basis of Therapeutics, Seventh Edition, 1985, p. 1698