

TITLE: EEG EFFECTS DURING 'STEADY STATE' INFUSION OF MIDAZOLAM: DEVELOPMENT OF ACUTE TOLERANCE?

AUTHORS: L.T.M. Breimer, M.D., A.G.L. Burm, Ph.D., M. Danhof*, Ph.D., P.J. Hennis, M.D., Ph.D., Joh. Spierdijk, M.D., Ph.D.

AFFILIATION: Dept of Anesthesiology and *Centre for Bio-Pharmaceutical Sciences, University of Leiden, Leiden, The Netherlands

The EEG effects during 'steady state' infusion of midazolam (M) (concentrations of 200 and 300 ng/ml) were quantified with TNW_{12-30}^1 (total number of waves between 12-30 Hz). This parameter is derived from an aperiodic EEG analysis technique. This study was conducted in order to get information about the stability of the CNS effect of midazolam with stable concentrations.

After obtaining institutional approval and informed consent, 11 male volunteers participated in the study. Infusion schemes for M were designed such that 'steady state' M concentrations of 200 (6 subjects) and 300 ng/ml (5 subjects) were reached in 40-60 min and maintained for a further 2 h. The EEG was recorded between Fp_1-M_1 and Fp_2-M_2 . After a 15 min baseline registration M infusion was started. Venous blood samples were collected for 9 h. Plasma M concentrations were measured with HPLC. $T_{1/2}$, the half-time for plasma concentration and effect equilibration, was determined by a nonparametric method. Subsequently a sigmoid E_{max} model was used to characterize the concentration- TNW_{12-30} relationship for the first 40-60 min. The pharmacodynamic data obtained, along with the measured plasma M concentrations were used to predict the effect during the 'steady state' period over the next hour. AUC's from 60-120 min of the measured and the predicted

effect versus time curves were compared with the Wilcoxon paired sample test.

One subject was excluded from evaluation because he showed an irregular hypnosis pattern. One subject showed a clockwise hysteresis and in another subject the effect remained close to E_{max} during the 'steady state' period, which prevented pharmacodynamic evaluation.

In the remaining 8 subjects measured plasma concentrations were close to the target 'steady state' concentrations, but the predicted TNW_{12-30} , based on the measured concentrations was higher than the measured TNW_{12-30} (fig. 1). There was a significant ($p < 0.05$) difference between the predicted and the measured AUC's under the effect vs time curves.

The results from this study suggest that acute tolerance for midazolam for the parameter TNW_{12-30} may occur.

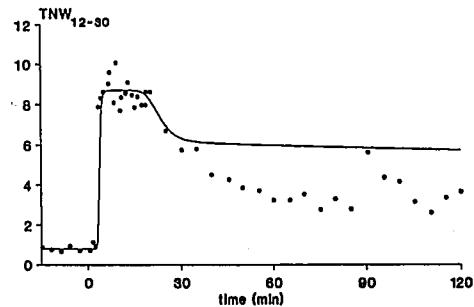


Fig. 1. : measured TNW_{12-30} , - : predicted TNW_{12-30}

Reference
1. Anesthesiology 71:A119, 1989.

A1214

TITLE: PARABEN PRESERVATIVES DO NOT CAUSE INCREASED ICP IN CATS.

AUTHORS: L. Pompy, M.D., A. Karlin, M.D., C.M. Capuano, B.S., J. Hartung, Ph.D. J.E. Cottrell, M.D.

AFFILIATION: Anesthesiology Dept. State University of New York Health Science Center, Brooklyn, NY 11203

Introduction: Hamilton et al have shown that paraben preservatives are potent vasodilators *in vitro*,¹ suggesting that succinylcholine-induced increases in ICP may be due to the preservatives contained in multidose vials.

We tested this hypothesis with preservative-free succinylcholine (S) (Anectine® Brand) vs. succinylcholine from multi-dose vials (SP) (Quelcin® Brand) which contain both propylparaben (PP) (0.2 mg/ml) and methylparaben (MP) (1.8 mg/ml). S and SP were also tested against the preservatives alone, administered in the same volume and concentration contained in Quelcin®. A previously described model² was used to determine the increase in ICP caused by injection of S, SP, PP/MP and an equal volume of normal saline.

Methods: Adult, male, mongrel cats (n = 6), were anesthetized via spontaneous respiration of 70% N₂O/30% O₂ and isoflurane titrated to enable endotracheal intubation without use of muscle relaxant (2.5 ± 1%).³ Inspired concentration was then reduced with mechanical ventilation adjusted to maintain mean arterial pressure (MAP) at 110 ± 20 mmHg and end-tidal CO₂ at 35-40 mmHg. Intermittently measured arterial blood gases correlated well with end-tidal CO₂. Drugs and fluids were administered via the cephalic vein. Intravenous fluids (4 ml/kg/hr) were monitored to avoid hypervolemia. Under conditions of

normotension, normothermia, normocapnea and elevated ICP (22 ± 2 mmHg) each cat received standardized injections of S, SP, PP/MP in random sequence. Each injection was preceded and followed by an equal volume of normal saline. Effectiveness and duration of muscle paralysis was determined with a train-of-four nerve stimulator before and after each injection.

Results: S, SP and PP/MP increased intracranial pressure by 4.2 mmHg ± 1.0 mmHg (SEM), 3.8 mmHg ± 0.7, and .08 mmHg ± 0.08 respectively, while normal saline had no effect. There was no statistically significant difference between SP and S, but both were significantly different from PP/MP ($p < 0.002$ ANOVA, $p < 0.01$ on 2-tail T-tests).

Discussion: Although the paraben preservatives may be vasodilators *in vitro*, our *in vivo* model indicates that paraben does not augment the ICP increase caused by succinylcholine in cats. In the concentrations found in multi-dose vials of succinylcholine, paraben preservatives caused an ICP increase of less than 0.42 mmHg (upper 99% Confidence Limit). This result suggests that pure succinylcholine is as contraindicated as succinylcholine with paraben preservatives when ICP is elevated and intracranial compliance is poor.

References:

1. Canadian J. Anaest., 1989, pp. S85.
2. Anesth. & Analg., 1983, pp. 1006-9.
3. Am. J. Vet. Resp., 1977, pp. 1833.