TITLE: QUANTITATIVE ASSESSMENT OF THE ANTINOCICEPTIVE EFFECTS OF MIDAZOLAM, AMITRIPTYLINE AND CARBAMAZEPINE ALONE AND IN COMBINATION WITH MORPHINE IN MICE

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A number of drugs that are not ordinarily classified as analgesics are used for the management of certain types of chronic pain. They are used often in combination with opioid drugs. Most have effects on the central nervous system such as antianxiety, antidepressant and anticonvulsant drugs, so it is difficult to assess in humans, the contribution made by the emotional component of pain. Thus in this study, a quantitative and objective method such as the measurement of nociceptive thresholds in mice (tail-flick assay) was used to assess the antinociceptive effects of midazolam (MDZ), amitriptyline (AMT) and carbamazepine (CBZ) alone and in combination with morphine (M) to quantify the possible additive or synergistic antinociceptive effect of the combinations of drugs. Experimentally we established that MDZ, AMT and CBZ were 19.2, 1.1 and 7.8 times, respectively less potent than M (ED_{50} = 13.2 µmol/kg, s.c.). Thus, when combinations of drugs were studied, the doses that were used to determine the ED_{50} values of the combinations were kept at a fixed molar ratio of 1 : 19.2 (M : MDZ), 1 : 1.1 (M : AMT), 1 : 7.8 (M : CBZ) and 1 : 7.3 (AMT : CBZ). The theoretical additive ED_{50} values of these combinations were calculated to be 133.6 µmol/kg (M-MDZ), 13.6 µmol/kg (M-AMT), 57.9 µmol/kg (M-CBZ) and 58.3 µmol/kg (AMT-CBZ). The experimental ED_{50} values of the combinations were determined to be [ED_{50} (95% confidence interval)] 62.7 (49.9 - 77.7) µmol/kg (M-MDZ), 2.8 (0.9 - 5.6) µmol/kg (M-AMT), 60.6 (45.4 - 82.0) µmol/kg (M-CBZ), and 37.8 (31.0 - 47.5) µmol/kg (AMT-CBZ). When the theoretical and experimental ED_{50} values were compared, it was found that the 95% confidence intervals of the experimental ED_{50} values did not embrace the theoretical ED_{50} values of the combinations of M-MDZ, M-AMT and AMT-CBZ and thus one can conclude that these combinations resulted in a synergistic effect. On the other hand, the 95% confidence interval of the experimental ED_{50} value of the combination of M-CBZ did embrace the theoretical ED_{50} value so this combination resulted in an additive antinociceptive effect. Therefore, the latter combination may not be as advantageous as the other three combinations when employed for analgesic therapy.

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TITLE: SITE OF INTRATHECAL CLONIDINE-INDUCED HYPOTENSION

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INTRODUCTION: Intraspinal administration of the α_2-adrenergic agonist, clonidine, produces analgesia free of side effects common to opioids. Clonidine can, however, decrease blood pressure by actions at several sites. This study examines the effect of the spinal segment of intrathecal injection on hemodynamic effects of clonidine.

METHODS: Intrathecal catheters were inserted in 11 ewes via cervical and mid-lumbar laminectomies with catheter tips at cervical (C_5), upper thoracic (T_5), lower thoracic (T_{12}), and lower lumbar (L_5) levels. In separate experiments 48 hrs apart, animals received intrathecal injections of clonidine, 300 µg via a cervical, thoracic, or lumbar catheter. Blood pressure and heart rate were continuously monitored for 3 hrs following injection. Data obtained at time of peak hemodynamic effect (10-20 min following injection) were analyzed by one-way ANOVA, with $P < 0.05$ significant.

RESULTS: Clonidine's effect on blood pressure varied with spinal cord segment of injection ($P < 0.05$), with maximal blood pressure lowering effect following upper thoracic injection (Fig. 1). In contrast, heart rate decreased similarly following clonidine injection at each site.

DISCUSSION: Intrathecally injected clonidine decreases blood pressure in part by inhibiting preganglionic sympathetic neuronal activity. These results are consistent with a predominant spinal sympatholytic action of intrathecally administered clonidine and are similar to results obtained in rodents, showing peak hemodynamic depression following upper thoracic intrathecal injection of the α_2-adrenergic agonist, guanabenz.[1] These results also agree with initial clinical experience and provide a rationale for the lack of clonidine-induced hypotension following lumbar injection in obstetric patients.[2]

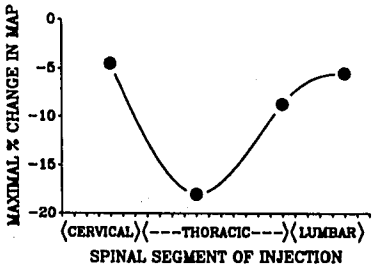

FIG. 1: Effect of Spinal Site on Blood Pressure

REFERENCES:

1. J Pharmacol Exp Ther 240:298-302, 1987
2. Anesthesiology 71:640-646, 1989.

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