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Clonidine does not reduce postoperative meperidine requirements

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Aim of the study: Clonidine is an alpha$_2$-adrenergic agonist that inhibits the synaptic transmission of sympathetic impulses. Clonidine is also assumed to have an analgetic potency, at least after intrathecal (2), epidural (3,4) and intramuscular administration (1). The question was whether it is possible to reduce the postoperative intake of meperidine by additional intravenous clonidine infusion.

Methods and patients: 30 females, having undergone cholecystectomy, were examined in a randomized, doubleblind prospective study. On arrrival in the recovery room 15 patients received clonidine infusion of 150 µg over a period of 30 min., and an additional 150 µg during the following 90 min. (Cl. group). The other 15 patients received identical volumes of NaCl (placebo group) over an identical time interval. All patients were connected to a PCA-machine (Life-Care 4200, Abbott) and received an initial dose of 16 mg meperidine, the following demands were 8 mg of meperidine each. Background-infusion was 2.5 mg of meperidine per hour, lockout time was 5 min.

During the clonidine or NaCl infusion pain was evaluated every 10 min. with the aid of a verbal rating scale and a 101-point numerical rating scale. Bloodpressure, arterial oxygen saturation (via pulse oximeter), respiratory rate and any side effects were registered.

The patients of the Clonidine-group had an average age of 42 years (range 23 - 60) and an average body weight of 68.3 kg (range 58 - 93). The average age and body weight of the patients of the placebo goup was 47 years (range 35 - 62) and 68.6 kg (range 56 - 94).

Results: There was no statistically significant difference in age, body weight, pain scores or blood pressure between the two groups.
The patients of the Cl. group required a mean meperidine dose of 78.3 mg (range 53.2 - 131.4), compared to 71.9 mg (range 37.3 - 137.3) in the placebo goup. The cumulative meperidine intake for the Cl. and placebo group, calculated per minute, is plotted in fig. 1.

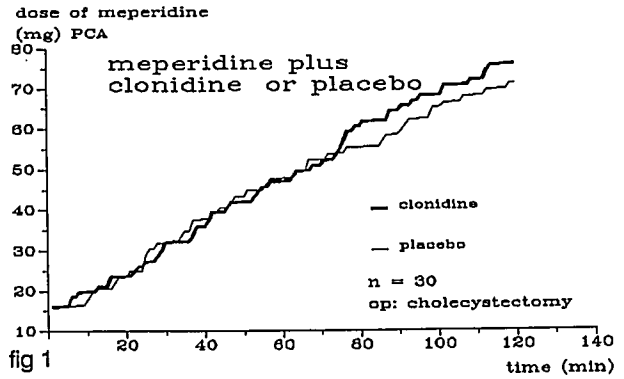

fig 1

Discussion: These results demonstrate that the postoperative meperidine intake during the first 2 postoperative hours after cholecystectomy can not be reduced by intravenous application of 300 µg clonidine.

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Title: SIGNIFICANT SYNERGISM BETWEEN INTRATHECAL MORPHINE AND CLONIDINE FOR VISCERAL ANTINOCICEPTION

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Introduction: Clinically, the management of visceral pain is important. It has been demonstrated that intrathecally coadministered opioids and alpha-2-adrenergic agonists produce synergistic action for somatic antinociception. However, such pharmacological interactions have not been examined for visceral pain processing. This study is part of a series of experiments aimed at determining optimum drug combinations that, at minimal doses, produce maximal analgesic effect at the spinal level. The present study examined interactions between morphine and clonidine using isobolographic analysis of the effects of the two drugs on colorectal distension as a visceral pain model.
Methods: This protocol was approved by the Yale Animal Care and Use Committee. Male Sprague-Dawley rats (280-360 g) were used. Drugs were administered intrathecally in a volume of 5 µl through a chronically implanted catheter whose tip was located near the lumbar enlargement of the spinal cord. Morphine (M) was administered at doses of 0.5 (n=10), 1 (n=11), 2.5 (n=11) or 5 µg (n=12). Clonidine (C) was administered at doses of 1 (n=10), 2.5 (n=11), 5 (n=12) or 10 µg (n=13). In some studies, drugs were co-administered. When drugs were coadministered we maintained a fixed ratio of M to C, 1:2. Doses (µg) of combinations (M/C) were 0.1 / 0.2 (n=9), 0.25 / 0.5 (n=9), 0.5 / 1 (n=9) or 1 / 2 (n=8). In this study, a modified colorectal distension technique was used. The minimal pressure of the distension balloon at which abdominal constrictions were evoked was defined as responding threshold. A cut-off distension pressure was set at 80 mmHg to avoid tissue damage. Thresholds were measured before and at 5, 10, 15, 20, 30 45 min after drug injection. Data were converted to %MPE by the following equation: %MPE = 100 X (postdrug pressure - control) / (80 - control). A50 (Dose producing 50 %MPE) and its 95% confidence limits were calculated by linear regression lines at 15 min after drug administration. An isobologram for A50 was constructed using these data and then the interaction between morphine and clonidine was evaluated by isobolographic and potency ratio analysis.[1,2]
Results: Isobolographic analysis allows a statistical evaluation of the type of interaction that occurs when the effects of combined drugs are studied. Fig. 1 shows the isobolographic plot of the A50 values and 95% confidence intervals for each drug alone (M,C), in combination (A) and the theoretical point (B) if the drug combination produced an additive effect. As seen in Fig. 1 point A lies to the left of the additive line and there is a significant difference between the confidence intervals of points A and B indicating a synergistic interaction. This difference was confirmed by analysis of the potency ratios ($P<0.05$).
Comment: It is concluded that the interaction between morphine and clonidine is synergistic for visceral antinociception. This is the first demonstration of mu opioid - alpha-2 adrenergic agonist synergistic interaction in visceral pain processing at the spinal level. Further study of interactions between other opioid subtypes with adrenergic systems in the visceral pain model is warranted.

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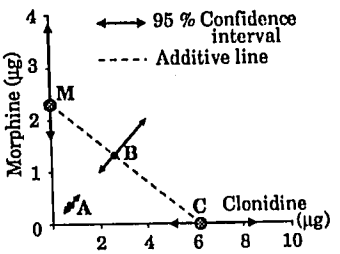

References:
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