TITLE: CROSS-TOLERANCE AND SYNERGY BETWEEN INTRATHECAL TIZANIDINE AND MORPHINE

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Tizanidine, an α-2 adrenergic agonist, has been shown to produce spinal analgesia similar to morphine and clonidine.[1] Alpha-2 adrenergic agonists produce spinal analgesia via an interaction with alpha receptors, while morphine exerts its analgesic effect by binding to opiate receptors. There have been no previous studies which examine cross tolerance and synergy between intrathecal tizanidine and morphine. This study examined cross-tolerance and synergy between intrathecal tizanidine and morphine in rats.

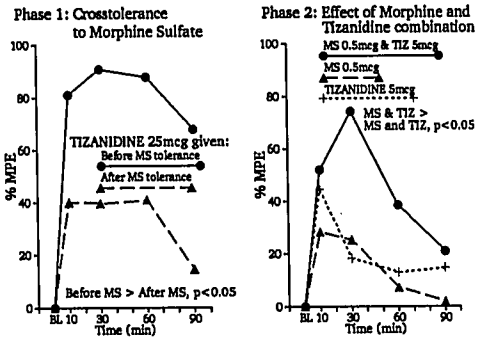
METHODS: Phase 1: 8 male Sprague-Dawley rats (275 ±25gm) had chronic intrathecal catheters placed at the lumbar enlargement. Analgesia was measured using the tail flick response. Animals were allowed a 7 day recovery period. The tail flick response to tizanidine (25ug) was obtained. Rats were then given twice daily intrathecal injections of morphine 8ug for 7 days to produce tolerance. 24 hours later, rats were given a repeat intrathecal tizanidine (25ug) injection, and measurements repeated. Following a 14 day recovery period, testing for synergy was begun.

Phase 2: Rats were given intrathecal morphine .5ug and, 2 days later, tizanidine 5ug and the measurements repeated. Two days later, 0.5ug morphine combined with tizanidine 5ug was given intrathecally. Tail flick response was measured as above.

RESULTS: Phase 1 Tizanidine produced a 40% peak analgesic response with duration similar to that seen in non-morphine-tolerant animals.

Phase 2 Morphine .5ug in combination with tizanidine 5ug produced an analgesic response greater than that of either tizanidine 5ug or morphine .5ug alone and greater than that predicted by additivity at 30, 60, and 90 minutes.

Conclusion: Tizanidine exhibits some degree of cross-tolerance to morphine-induced analgesia. The combination of small intrathecal doses of tizanidine allows for a significant reduction in morphine dose to produce greater analgesia than either agent alone. Tizanidine appears to be a viable adjunct and alternative to intrathecal narcotics.



Reference: McCarthy, Kroin, Lubenow, et al. Pain 40(3)333-338, 1990.

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TITLE: EFFECT OF MAGNETIC FIELD THERAPY (MFT) ON SUBSTANCE P (SP) AND METHIONINE ENKEPHALIN (MEK) IN A RAT MODEL OF CHRONIC PAIN

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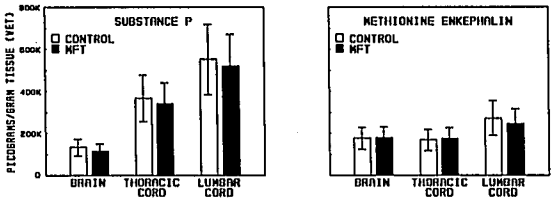
INTRODUCTION: Magnetic field therapy (MFT) is currently being evaluated as a modality for management of chronic pain. There are no well-controlled, randomized studies assessing the efficacy of MFT for chronic pain management. However, several anecdotal reports suggest that MFT is effective in managing chronic pain. We studied the effect of MFT on SP and beta-endorphin in pain-free rats. We found no difference in neuropeptide levels between the MFT group and the control group. Since animals in pain may respond differently to MFT, the purpose of this study was to determine the effect of MFT on SP and MEK in chronic pain using a rat arthritis model associated with chronic pain.

METHODS: Pathogen-free male Sprague-Dawley rats (180-200 g) which had been injected with complete Freund's adjuvant were obtained from Charles Rivers (France). The rats were divided into two groups: control and MFT. Joint size and tail flick latency were monitored daily. The MFT group received twice daily 15 minute exposures to the pulsating magnetic field (180 Gauss, 5 Hertz) for five days. After the final MFT, brain and spinal cord were harvested. Tissues were homogenized in hot acetic acid (1M), centrifuged and the supernatant washed with petroleum ether. The lyophilized extracts were assayed for SP and MEK using radioimmunoassay kits obtained from Incstar (Stillwater, MN). Data were analyzed for statistical difference using ANOVA ($p < 0.05$ was considered significant).

RESULTS: No differences were noted between the SP or MEK levels of the control versus the MFT group in any of the tissues studied (see figures). Changes in joint size and tail flick latency were not significantly different between the groups.

SP and MEK levels in rat tissues



DISCUSSION: Although MFT continues to be an attractive modality for managing chronic pain (because it is relatively non-invasive) our results show that MFT does not alter SP and MEK levels. Thus if MFT is effective in treating chronic pain, changes in these neuropeptide levels (SP and MEK) do not appear to be involved in that mechanism.

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