POTENTIAL ANALGESIC CONTRIBUTION FROM MORPHINE METABOLITES FOLLOWING INTRA-THECAL MORPHINE.

AUTHORS: P.D. McDonagh, J.Billett, W.P. Blunnie, N. Murphy

INSTITUTION: Department of Anaesthesia / Intensive Care, Mater Misericordiae Hospital, Eccles Street, Dublin 7, IRELAND.

INTRODUCTION. Intra-thecal morphine provides safe, effective and sustained analgesia for patients following cardiac surgery.(1) Recently a metabolite of morphine, morphine 6 glucuronide (M6G) has been shown to be present in cerebro-spinal fluid (CSF) after both oral and intramuscular administration of morphine sulphate (2), while the analgesic activity of M6G has been confirmed following intravenous administration in patients with chronic pain. (3) Experimentally, direct intracisternal administration of M6G revealed an analgesic potency 44 times that of the parent drug(4) In a prospective clinical trial, we analysed CSF and plasma samples to assess the potential analgesic effects of morphine metabolites following intra-thecal administration of morphine sulphate.

METHODS. Following ethics committee approval and informed patient consent, 14 male patients undergoing elective coronary artery bypass grafting were studied. Following induction of anaesthesia, patients were placed in the lateral position and under strict asepsis lumbar puncture was preformed using a 25g spinal needle at the L 2-3 or L 3-4 space. Paired control samples of CSF (1 ml) and blood were taken and then 2mg preservative free morphine was injected. All patients were transferred to the operating theatre where the surgical procedure was carried out under moderate hypothermic (28°C) cardiopulmonary bypass. Following surgery all patients were transferred to the intensive care unit. Blood samples were taken at 4 hourly intervals following intra-thecal administration, the plasma immediatley seperated, placed in plastic tubes and frozen until analysed. At 24 hours all patients were assessed and if indicated a repeat lumbar puncture was preformed, a second CSF sample taken, and each patient given additional 1mg intra-thecal morphine. All plasma and CSF samples were analysed using High Performance Liquid Chromatography (HPLC) for the following, (1) Morphine (2) Morphine 3 glucuronide, (3) Morphine 6 glucuronide and (4) Normorphine. Normocapnic ventilation was maintained in ITU until body temperature had returned to normal, patients were haemodynamically stable and extubated when breathing was adequate and sufficiently alert. Pain scores, sedation scores, respiratory status and additional requests for analgesia were recorded. Pain occuring in the 24 hours after intra-thecal morphine was controlled with intravenous Pethidine 10mg I.V. as requested.

RESULTS. 10 patients satisfied the protocol requirements. 2 patients withdrew voluntarily and 2 patients were surgically unstable to permit repeat lumbar puncture. Only 2 patients had morphine and morphine 3 glucuronide in the plasma samples after 4 hours, and in only 1 of these patients was morphine 3 glucuronide detected at 8 hours. Morphine was detected in the CSF of 9 patients after 24 hours. (Range 10 - 290 ug/ml $x10^{-3}$) No morphine metabolites were detected in the CSF of the 10 patients sampled. Analgesia was deemed excellent as documented by the low pain scores and small requirement for additional analgesia. (Range 0 - 70 mg in 48 hours).

DISCUSSION. Although M6G has been shown to be a highly active analgesic agent in animals and following intravenous use, we found no evidence of potential analgesic contribution following intra-thecal placement. This may be in the fact that the liver is the major site of opiate metabolism although extra-hepatic sites of metabolism have been postulated. Morphine having low lipid solubility is confined to the CSF, and consequently only extremely small ammounts are detected in plasma following intrathecal administration. Additionally our study shows that no local metabolism of morphine occurs. and that morphine metabolites do not contribute to analgesia following intra-thecal administration.

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