LOCAL ANESTHESIA AND PAIN III

A363

INTRODUCTION: Inadequate analgesia is often a major complaint following surgical procedures. One concern with parenteral administration of narcotics for post surgical pain is the wide fluctuations observed in the plasma concentration and its association with periods of inadequate analgesia or the risk of respiratory depression. Fentanyl, a potent synthetic opioid, has been recently incorporated into a Transdermal Therapeutic System (TTS) which consists of a rate-limiting membrane to provide constant release of fentanyl (Alza Corporation, Palo Alto, CA). The potential advantages of this system, therefore, are not only avoidance of parenteral administration but also achievement of a constant therapeutic blood concentration without untoward consequences. The serum concentration time profile of fentanyl following single day application of the TTS delivering fentanyl at a rate of 100 mcg/hour has been reported previously. The aim of the present investigation was to evaluate the pharmacokinetics of fentanyl after a single TTS application delivering 75 mcg/hour of fentanyl for 3 consecutive days in post surgical patients.

METHOD: Five male and five female patients (ASA I-II), ages 56 to 72 years, scheduled to undergo intrabdominal colorectal surgery, gave their written informed consent to participate in this Institutional Review Board approved study. None of the patients had a history of chronic narcotic use, liver dysfunction, CNS deficit, PaCO₂ greater than 45 Torr on room air, or body weight greater than 100 kg were included in this study. Approximately 2 hours prior to the scheduled surgery the TTS delivering 75 mg/day of fentanyl was placed on the upper chest of the patients. Premedication was with diazepam (10 mg, PO) one hour prior to the induction of anesthesia. Anesthesia was induced with thiopental (4 mg/kg) and intubation facilitated by succinylcholine (1.5 mg/kg). Each patient also received 300 mcg of fentanyl during induction and the first hour of the operation. Maintenance of anesthesia consisted of N₂O/O₂ (60/40 ratio), isoflurane and pancuronium as needed. The TTS was left in place for 72 hours. Twenty serial blood samples were obtained for up to 48 hours after the removal of TTS (total 120 hours collection). Immediately after collection, serum samples were harvested and stored at -80°C until analysis. Plasma concentrations of fentanyl were measured by radioimmunoassay method of Michiels et al. The lower sensitivity of this assay is 0.1 ng/ml. Lagrange technique was employed to measure the total area under the plasma concentration-time curve (AUC). The elimination-rate constant was measured by least squares linear regression utilizing at least 5 points on the terminal phase of the plasma-concentration-time curve. The expected average steady-state serum concentration (cp) of fentanyl was measured as the ratio of AUC/T where T is the duration of fentanyl administration (72 hours). Mean residence time (MRT) was measured as the ratio of AUTC/AUC where AUTC is the first moment of the fentanyl plasma concentration-time curve. Data is presented as mean (SD).

RESULTS: Figure 1 depicts the plasma concentration-time curve of fentanyl administered for 72 hours through a TTS delivering 75 mcg/hour of fentanyl. The mean (SD) terminal elimination half-life of fentanyl was 19.6 (5.2) hours with a range of 13.7 to 29.2 hours. The average plasma concentration of fentanyl had a Mean (SD) of 1.5 (0.5) ng/ml.

DISCUSSION: The systemic clearance or the steady-state volume of distribution of fentanyl were not measured after the transdermal application since the dose of fentanyl ultimately reaching the blood stream of the patients were unknown. The elimination half-life of fentanyl in our study is significantly longer than following the intravenous administration, most likely due to continued systemic absorption from skin depot for some time after the removal of the TTS. Clinical respiratory function in our patients were good with respiratory rates always falling within acceptable range during the patch application. Overall the system is expected to provide a steady-state mean serum concentration of 1.7 ng/ml on an every 3 day regimen and appears to be an important advance in the treatment of perioperative pain.

FIGURE 1:

REFERENCES: