Pharmacokinetics and Pharmacodynamics

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Introduction

The theoretical background provided by L. E. Mather and G. K. Gourlay (this volume) indicated that the TTS fentanyl systems can provide a zero order input rate for at least 24 h that would mimic a constant rate intravenous infusion. In fact, the TTS fentanyl systems at a delivery rate of 100 µg/h have been shown to provide similar serum fentanyl concentrations at steady state to the intravenous infusion of fentanyl at an equivalent rate [6]. The currently available methods of treating postoperative pain have also been reviewed (Part 2). The continuous infusion of a number of opioids including morphine [18], pethidine [19] and fentanyl [14] has been shown to provide more reliable postoperative pain relief than that obtained from conventional intramuscular opioid regimens. However, there is at least a five-fold range of interpatient variability in the minimum effective blood opioid concentration (MEC) required to effectively control postoperative pain [2, 5, 8, 20]. Therefore, there are at least two possible approaches in the clinical implementation of zero order infusions to control postoperative pain. Firstly, the physician could use infusion rates which will provide steady-state blood opioid concentrations that are towards the higher end of the range of MECs, thereby providing acceptable pain relief to the majority of patients. The disadvantage of the approach is that the steady-state concentrations will still be inadequate for some patients while being excessive for a significant proportion of patients, probably causing unwanted and unpleasant side effects. The second approach is to attempt to individualize the infusion rate for each patient to maximize pain relief but minimize side effects.

We have conducted both open [9] and double blind (TTS fentanyl versus placebo) [10] evaluations of the TTS fentanyl system in the control of postoperative pain resulting from surgical procedures involving abdominal incisions. We elected to individualize the TTS fentanyl infusion rate by selecting the area of systems applied to each patient for two reasons: (a) we believed this to be the most desirable approach, and (b) concurrent studies [6, 11, 17, 21] intended to use a constant TTS fentanyl infusion rate, invariably, 100 µg/h. This chapter reviews the pharmacokinetics and pharmacodynamic effects from both the open and double blind studies of TTS fentanyl in the treatment of postoperative pain.
Study Design

Patients

Patients were aged between 18 and 70 years and were scheduled to have surgery involving an abdominal incision. Patients with significantly impaired hepatic or renal function, a chronic respiratory illness, documented hypersensitivity to opioids or a history of drug abuse were excluded from the study. Thirteen patients were included in an open study examining pharmacokinetics and pharmacodynamics of the TTS fentanyl systems while forty patients were entered into the double blind comparison of pain relief and side effects of TTS fentanyl \((n = 20)\) and placebo \((n = 20)\) systems.

Psychometric Tests Prior to Surgery

Prior to surgery, each patient completed the following psychometric tests which were required to calculate the area of TTS fentanyl to be applied to individual patients (see below “Calculation of the Dose Rate…”):
1. The Illness Behaviour Questionnaire, which scores seven traits useful in the examination of the impact of the surgical event on the patient [15]
2. The Beck Depression Inventory, a self-rating scale of depression [3]
3. The Eysenck Personality Questionnaire, which examines extroversion/introversion, neuroticism and social conformity (i.e., the tendency for the patient to answer questions to please the investigator rather than truthfully) [7]

Anesthetic Technique

Patients were premedicated with oral diazepam and anesthesia was induced with thiopentone. Muscle relaxation for endotracheal intubation was facilitated with suxamethonium. Anesthesia was maintained with nitrous oxide/oxygen, pancuronium, and enflurane if required. Patients who had TTS fentanyl systems in situ had intraoperative intravenous fentanyl \((2 \mu g/kg)\) administered while those patients who had placebo systems in situ received pethidine \((1 mg/kg)\) instead of the fentanyl. This was achieved using pre coded syringes, thereby preserving the double blind nature of the study design. The intraoperative administration of pethidine \((25 mg\) intravenous increments) was allowed only if the anesthetist judged that the patient required additional opioid analgesia rather than increasing the depth of anesthesia with enflurane.