A47

TITLE: ANALGESIC POTENCY AND ACTION SITE OF EPIDURAL FENTANYL IN PATIENTS FOLLOWING GASTRECTOMY

AUTHORS: Yoshimi Inagaki, M.D., Takashi Hashimo, M.D., Ikuto Yoshiya, M.D.

AFFILIATION: Department of Anesthesiology, Osaka University Medical School, 1-1-50, Fukushima, Fukushima-ku, Osaka 553, Japan

Fentanyl, a liposoluble opioid, produces strong analgesia by not only intravenous but also epidural administration. But it has not been clarified whether the strong analgesia by epidural fentanyl is derived from a spinal or a supraspinal analgesic action, or a combined analgesic action. We carried out this study to clarify this question in terms of the change in pain threshold in patients following gastrectomy.

We obtained our institutional approval and an informed consent from each patient before the beginning of this study.

Sixty-two ASA physical status I or II patients, ages 26-65 yr and weights 43-75 kg, scheduled for gastrectomy by the same surgical team were studied. In the previous day of surgery, all patients received epidural catheterization. An epidural catheter was inserted at the T9-T10 interspace and 7 cm of the catheter remained within epidural space. Through the catheter, 2 ml of 1% lidocaine was administered to rule out intravascular or subarachnoid injection. Twenty minutes after test dose administration, segmental analgesia from nipple to groin was validated by a pin-prick method following epidural administration of 8 ml of 1% lidocaine.

All patients received 0.5 mg of atropine sulfate and 25 mg of hydroxyzine im 1h before anesthetic induction. Anesthesia was induced with 5 mg/kg of thiamylal sodium and the trachea was intubated followed by 0.1 mg/kg of vecuronium bromide iv. Anesthesia was maintained with 1-2% enflurane or 1-1.5% isoflurane and 50-67% nitrous oxide in oxygen. No adjuvant drugs including epidural local anesthetic were administered during anesthesia. All patients were extubated in the operating room. After extubation, the patients were randomly assigned to one of seven groups; epidural administration of 1, 2 or 4 μg/kg of fentanyl diluted with normal saline (groups FE1, FE2, and FE4, respectively) or normal saline (group NS) and intravenous administration of 1, 2, or 4 μg/kg of fentanyl (groups FI1, FI2, and FI4, respectively). Pain threshold was measured by a pressure algesimeter (Kyoto Pain Institute Model-7) before the insertion of epidural catheter (control value 1; CV1) and administration of drugs (control value 2; CV2), and 1, 2, and 3h after administration of drugs. The points at which pain threshold was measured were fore head (V), xyphoid(A), bilateral outer margins of rectus abdominis muscle at the midway from xyphoid to navel(B,C) and on the linea alba 5cm under the navel(D)(refer to fig.1). The change in pain threshold was expressed as percent of CV2 at each measuring point. Furthermore, the intensity of pain was evaluated before each measurement using visual analog scale (VAS) which was graded from 0(no pain) to 10 (maximum pain).

The results of multiple groups were analyzed by one-way analysis of variance, and comparisons between groups were assessed by Mann-Whitney test. A P value < 0.05 was considered significant.

Figure 2 shows time course of the change in pain threshold 1h after the administration. The analgesic potency of epidural fentanyl was much stronger than that of intravenous fentanyl in same dose and tended to increase in a dose related fashion. VAS of epidural fentanyl was significantly lower than that of intravenous one 1h after the administration.

We conclude that the more potent analgesia of epidural fentanyl may be derived from its spinal analgesic action.

MEASURING POINTS OF PAIN THRESHOLD

Fig. 1

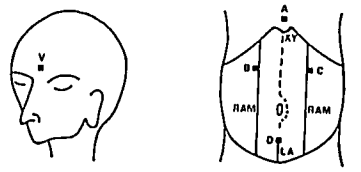
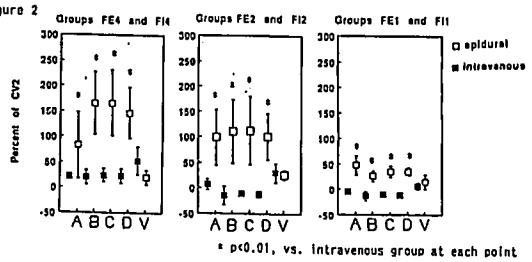


Figure 2



A48

TITLE: INFLUENCE OF PHARMACOKINETIC VARIABILITY ON PHARMACOLOGIC RESPONSE

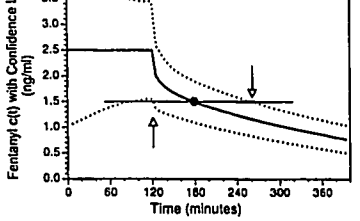
AUTHORS: EA Williams, B.S., LR Smith, Ph.D., and JR Jacobs, Ph.D.

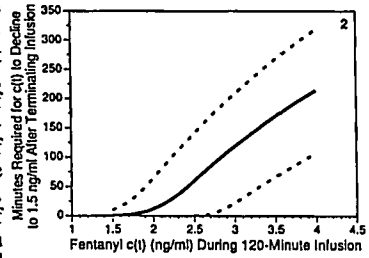
AFFILIATION: Departments of Biomedical Engineering and Anesthesiology, Duke University Medical Center, Durham, North Carolina 27710

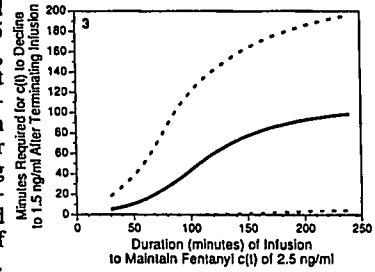
Simulations of pharmacokinetic and pharmacodynamic models have been used in anesthesiology to compare drug properties and teach pharmacologic principles[1] and to provide didactic insight into clinical practices.[2] Pharmacokinetic variability is a source of diversity in pharmacologic response, but statistical uncertainty has rarely been incorporated into simulation procedures. The purpose of this study was to demonstrate the influence of pharmacokinetic variability on simulations of intravenous infusions.

A procedure was developed to compute a "unit error function" (uef) for multi-exponential unit disposition functions (udf). Convolving a dose regimen d(t) with the udf produced the typical simulation of the plasma drug concentration c(t), and convolution of d(t) with the uef produced 95% confidence limits (C.L.) on c(t). The uef accounts for both intra- and inter-patient variability in the data from which the udf was obtained. A udf and uef were derived from pharmacokinetic data[3] for fentanyl. The udf and uef were convolved with d(t) designed to keep c(t) constant for 120 min; in multiple simulations, c(t) was maintained at concentrations ranging from 1.5 to 4 ng/ml. The udf and uef were also convolved with d(t) designed to keep c(t) at 2.5 ng/ml for periods of 30 to 240 min. In all simulations, the times required for c(t) and its C.L. to fall to 1.5 ng/ml after terminating d(t) were determined.

Fig 1 shows a simulation in which c(t) was maintained at 2.5 ng/ml for 120 min. After stopping d(t), c(t) fell to 1.5 ng/ml in 59 min (dot), while the lower and upper C.L. on c(t) reached 1.5 after 1 and 140 min, respectively. In the absence of pharmacodynamic variability or kinetic-dynamic dissociation, the endpoint of 1.5 ng/ml is regarded here as a "recovery" level. Thus, our simulations confirm not only the expected result that higher sustained concentrations (Fig 2) and increasing infusion duration (Fig 3) will increase time to recovery (pharmacologic response) but also that pharmacokinetic variability can affect recovery time. As a result, the striking behavior of some members of the population will be overlooked if conclusions are based on the typical patient (solid lines). For example, of a group of patients receiving a 100 min fentanyl infusion designed to maintain a c(t) of 2.5 ng/ml in the typical patient, most will "recover" in about 40 min, but some will require more than 120 min and some will not have ever achieved 1.5 ng/ml during the infusion. Pharmacokinetic simulations should include interpretations of pharmacokinetic variability.







References: (1) *Anesthesiology* 72:650-658, 1990; (2) *Anesthesiology* 74:53-63, 1991; (3) *Clin Pharmacol Ther* 28:106-114, 1980