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A328

TITLE: EFFECT OF FENTANYL ON ANP SECRETION IN NEONATAL RAT CARDIOMYOCYTES

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Although fentanyl was introduced to clinical anesthesia two decades ago [1], little is known about its effects on cardiac muscle cells at the subcellular level, and its relation to ANP secretion has not been clarified [2]. Ultrastructure, protein biosynthesis and atrial natriuretic peptide (ANP) secretion were studied in neonatal rat cardiomyocytes (CM) grown in tissue culture and incubated with fentanyl. Ventricles from 2-day-old American Wistar rats were digested with 0.5% collagenase in perfusion buffer. Under serum free conditions, 0.8-1 million cells/ml were incubated in tissue culture and exposed to fentanyl as 50 ng/ml. Fentanyl increased the spontaneous beating rate of CM. Cells were incubated for 4h with H^3 leucine 2 mcci/ml (50 ci/mmole) in the presence and absence of fentanyl. Cells were solubilized and proteins were precipitated and counted by liquid scintillation for radiolabelled leucine. Culture media were collected at 24h and 48h, and tested for ANP by radio-immunoassay. Fentanyl increased CM protein biosynthesis in a time-related manner (Fig. 1). Simultaneous incubation with naloxone (10^{-6}M) did not alter protein biosynthesis (Fig. 1). Fentanyl increased ANP secretion in tissue culture media (Fig. 2). Simultaneous incubation of CM with naloxone (10^{-6}M) blocked the fentanyl-induced increase in ANP secretion (Fig. 2). Ultrastructurally, the number of ANP granules in neonatal rat CM increased with fentanyl treatment. At the same time the number, organization and complexity of the developing sarcomeres exceeded the control CM. Organized sarcoplasmic reticulum with T-tube system, adult type mitochondria and well developed intercalated discs were observed in the fentanyl treated CM. It appears that fentanyl induces the intercellular protein biosynthesis machinery in CM. Such proteins are mainly domestic proteins utilized in cell maturation and sarcomere development. Such action appeared to be non-opiate receptor-mediated. Though it also appears that ANP was also induced by fentanyl as part of protein biosynthesis stimulation, its secretion was most probably mu receptor mediated. ANP secretion adds another advantage to fentanyl-based anesthesia, especially in patients with cardiac disease, by virtue of its natriuretic and vasodilator properties.

REFERENCES:
1)Anes Analg 57:411, 1978. 2)European J Endocrinol 143:315-21, 1987.

Fig. 1: Effect of Fentanyl on Cardiomyocyte Protein Synthesis

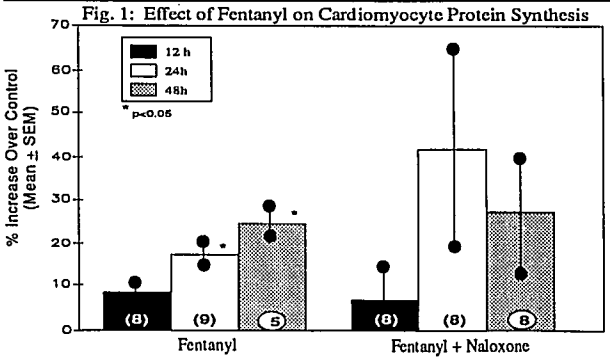
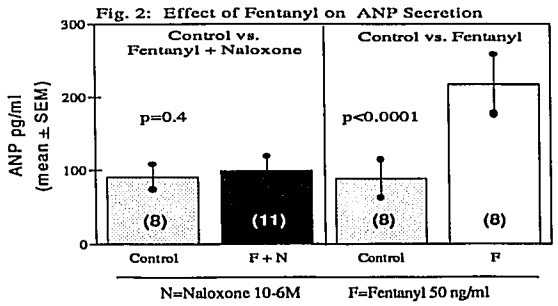


Fig. 2: Effect of Fentanyl on ANP Secretion



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Title: 'IVA-SIM' AN INTERACTIVE COMPUTER PROGRAM TO SIMULATE INTRAVENOUS ANESTHESIA

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Introduction: Computer simulation with intravenous anesthetics based on pharmacokinetic-dynamic model assumptions has recently become more and more important for the development of dosing strategies (1). This approach, however, is limited to a small group of specialists, only, with kinetic-dynamic knowledge and computer programming skills. To enable the common anesthetist to perform computer simulation of intravenous anesthesia in his daily practice a user friendly and simply to use simulation program was developed.
Methods: In the current version of the program it was attempted to offer software to be operated on a wide variety of hardware configurations. It runs on most IBM- and compatible machines with a common graphics card such as CGA, EGA, VGA or Hercules. The simulation program requires the operating system by IBM or Microsoft (DOS) with versions 2.1 or higher. IVA-SIM is completely menu-driven, so that the user does not need any kind of special experience in computer programming. Thereby it is possible to gain first simulation results very fast. Out of 13 different drugs one can choose up to two drugs for simultaneous simulation. Pharmacokinetic and -dynamic data are provided for the hypnotics: propofol, methohexitone, thiopentone, and etomidate; the opioid agonists and antagonist: fentanyl, alfentanil, sufentanil, and naloxone; the benzodiazepine: midazolam; the nondepolarizing musclerelaxants: pancuronium, vecuronium, and atracurium as well as ketamine. If applicable population kinetic data were applied to adapt the kinetic data to age, gender and body weight. Algorithms have been developed to cover the age and weight period from neonates to geriatric patients with the age of more than 80 years to achieve a wide individualization of the simulated concentration courses and pharmacological effects. The validity of the pharmacokinetic and -dynamic data which are used for the calculations was analyzed in a group of 20 patients undergoing total intravenous anesthesia with propofol and alfentanil. Frequent blood samples were taken and analyzed by HPLC and radioimmunoassay. Measured to predicted ratios were calculated and regression analysis was used for data analysis.
Results: The program was evaluated in the clinical situation for more than 500 patients and was able to predict the anesthetic requirements for neonates as well as for geriatric patients with an age of more than 80 years with propofol, fentanyl, alfentanil, and vecuronium. In addition, offset of drug action could be predicted with a high degree of confidence. Thereby the recovery period became more predictable with an enhancement of patients safety. Measured concentrations showed good accordance to the predicted ones by IVA-SIM with a highly significant ($p<0.001$) correlation for alfentanil (Fig.1) and propofol.

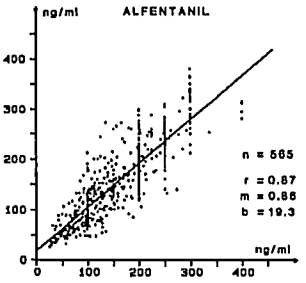

Fig.1

Conclusions: The aim of the program IVA-SIM is to explain the very complex relationship of dose, application time course, and pharmacological effect in intravenous anesthesia. In addition, the effects of age and sex, systemic diseases and drug interactions upon pharmacokinetics and dynamics can be assessed. Optimized dosing strategies and predictive drug level monitoring in real-time mode can be easily performed in the operation room using a laptop computer. And finally this program can be applied for education and training in anesthesia and as a practical tool for demonstrations and presentations at research meetings, exhibitions, and workshops. The predictive power of the program proved to be very satisfactory by clinical measures and correlation to real drug level measurements.
References: 1. Anesthesiology 74:53 (1991)