TITLE: LUNG SEQUESTRATION OF FENTANYL DURING CARDIOPULMONARY BYPASS

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Introduction. Previous investigators have reported disruption of plasma fentanyl (F) concentration-time curves during cardiopulmonary bypass (CPB).[1,2] During this period, F concentrations fluctuate greatly, rising in some patients and falling in others.[1] The purpose of this study was to investigate this phenomenon more completely. In addition to serum F measurements, factors potentially affecting serum F levels during CPB were also measured. These include pH, PCO_2, Hgb, Hct, total protein (TP), and albumin (Alb).[3,4] The goal of the study was to determine factors which affect fentanyl disposition not only in cardiac surgery patients, but in any patient requiring anesthesia.

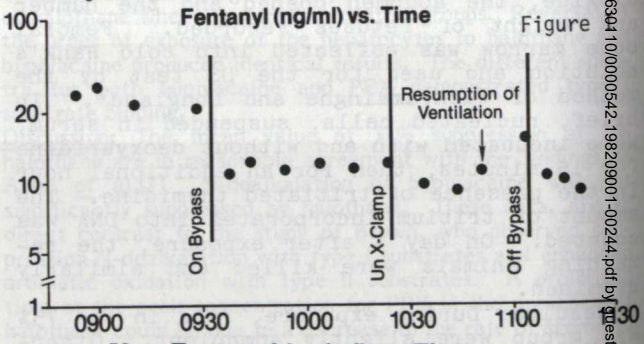
Methods. A total of five consenting patients scheduled for elective coronary artery bypass surgery were studied according to a protocol approved by the Human Subjects Committee of Arizona Health Sciences Center. Each patient was premedicated with IM scopolamine 0.3-0.4 mg and morphine sulfate 0.1 mg/kg. Anesthesia was induced with F (100 ug/kg) and diazepam 10-20 mg, given over 5-10 minutes. Pancuronium bromide was used for muscle relaxation, and ventilation was mechanically controlled. Three blood samples for subsequent serum F determinations were drawn prior to CPB. Additional samples were obtained at 5 minutes after initiation of CPB and then at 10 minute intervals throughout the CPB period. After termination of CPB, blood samples were obtained at 5, 10, and 15 min. In addition, blood samples for PCO_2, pH, TP, Alb, Hct, and Hgb were obtained prior to CPB, 3 times during CPB and after CPB. An additional 3 patients were studied during CPB. Simultaneous pulmonary artery (PA) and radial artery blood samples for fentanyl determinations were obtained before and after initiation of ventilation. Serum F was analyzed by gas chromatography. Analysis of variance with the Student Newman-Keul a posteriori test was used for comparison of group means. Significance was $p \leq 0.05$.

Results. Serum F, Hct, Hgb, TP, and Alb declined significantly with initiation of CPB. After this initial decline, the values of these parameters remained unchanged throughout CPB. PCO_2, and pH remained unchanged throughout the study. No correlation was found between serum F and any of the measured parameters except weight. With initiation of CPB, F levels declined less as patient weight increased ($r = -0.64$, $p < 0.02$). This probably is a reflection of equal pump prime volume in all patients.

Serum F fell proportionally more than Hct (47% vs. 36%, $p \leq 0.01$), suggesting F tissue sequestration as a result of altered circulation during CPB. Unlike previous investigations, F levels were remarkedly stable during CPB. The exception to this was a rise in serum F with the resumption of ventilation after aortic cross clamp removal (Figure I). In this regard, PA F concentrations were lower than radial artery concentrations after the initiation of ventilation (Figure II).

Discussion. Serum fentanyl levels during CPB were surprisingly stable. This occurred despite significant reductions in Hct, Hgb, TP, and Alb. F is bound extensively to these blood elements[3] and decreases in these components should increase the amount of unbound drug (Df). Changes in Df can lead to alterations in drug volume of distribution, clearance, and elimination half life. However, this study demonstrated no relationship between serum F and any of the above blood components during CPB. This finding suggests that changes in these blood components may not alter F pharmacokinetics in noncardiac patients. Clearly, further investigation is necessary to document this speculation.

Lastly, this study demonstrated F sequestration in the lung during CPB. As blood flow through the lungs resumed, and ventilation reopened collapsed alveoli, increases in arterial F concentration were seen. Although this occurred as a result of CPB, a similar situation may exist in patients not undergoing cardiac surgery. That is, F sequestration in the lung might occur during surgery and anesthesia as a result of altered ventilation and perfusion (V/P). Blood levels of F may then rise as V/P relationships return to normal and drug is washed out of the lungs. This mechanism may explain secondary rises in serum F concentrations that have been reported by a number of investigators.



Figure

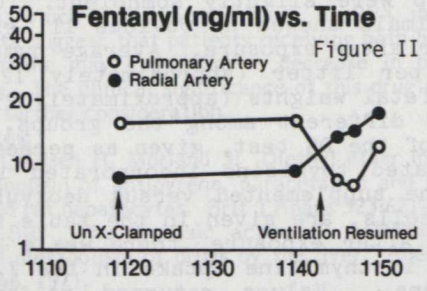


Figure II

1. Bovill JG, Sebel PS: Br J Anaesth 52:795, 1980.
2. Koska AJ, et al: Clin Pharmacol Ther 29:100, 1981.
3. McClain DA,et al: Clin Pharmacol Ther 28:106, 1980.
4. Bower S: J Pharm Pharmacol 33:507, 1981.