Title : PHARMACOKINETICS OF FENTANYL (F) DURING CONTINUOUS INFUSION IN CRITICALLY ILL PATIENTS

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INTRODUCTION : F is a narcotic agent widely used in intensive care units to provide sedation and adaptation to mechanical ventilation. Under these conditions, F is infused at a constant rate for very long periods, requiring high total doses (2). At present there are few data available about the pharmacokinetics of F in this clinical use. The aim of this study was to evaluate the pharmacokinetic parameters of F after continous perfusion for over three days.

METHODS AND MATERIALS : Six critically ill patients (4 men, 2 women, age 44 ± 15 years) without renal, cardiac, or hepatic disease received a constant infusion of F (500 $\mu g.h^{-1}$ = 7.55 ± 1.6 $\mu g.kg^{-1}h^{-1}$) for a minimum period of 72 h (119 ± 77 h). Venous blood was sampled every 24 h during the infusion and at : 5, 10, 15, 20, 30, 45, 60, 90 min. and at 2, 2.5, 4, 5, 5.5, 8, 10, 12, 16, 24 and 36 h. Plasma was separated from the blood by centrifugation and stored at - 20°C. until assay F plasma concentrations were determined in duplicate by radioimmunoassay. The following model independent pharmacokinetic parameters were calculated using the habitual equations : elimination half-life ($t\ 1/2\beta$), total volume of distribution ($Vd\beta$), total body clearance (Cl), and steady state plasma concentrations (Css). Plasma protein binding was measured by equilibrium dialysis at 37°C for 4 h ; plasma samples were incubated with F^{3H} at a total concentration of 10 $ng.ml^{-1}$ and dialyzed against phosphate buffer at a ph of 7.4. Hematocrit (Ht) and blood protid levels were determined each day.

RESULTS : They are summarized in tables I and II (mean ± standard deviation).

DISCUSSION : The comparison of these results with other pharmacokinetic F studies is difficult because of the long duration of infusion and the physiological state of critically ill patients. All the data available concern bolus or short duration infusion (< 6 h), except for one case (5). In our study, the terminal half-life measured was prolonged significantly ($t\ 1/2\beta$ = 25 h), being approximately two times longer than the maximum values observed in surgical patients receiving a simple dose of 500 µg (3) or a constant infusion of 0.3 $\mu g.kg^{-1}.min^{-1}$ for 4 h (4) ; in these studies terminal half-life ranged between 2.5 and 11 hours. The augmentation of $t\ 1/2\beta$ in critically ill patients is due to the enlargement of the total volume of distribution, while total clearance did not differ from other studies (3,4). This change in $Vd\beta$ has also been reported in criticaly ill patients (1,5). The explanation for this phenomenon could be the enhanced penetration of F into highly perfused tissues. Two hypotheses can be proposed : 1/. Low hematocrit values (29 %) can decrease the fixation of F in erythrocytes (40 % in normal subjects) and facilitate its diffusion outside the blood compartment. However, plasma protein-binding is not notably diferent from the normal values (80.9 % versus 85 % in normal subjects). In addition, blood protid levels (61.6 $g.l^{-1}$) remain normal. These results do not explain the increase in the plasmatic free fraction of F. 2/. Numerous associated drugs used in intensive care units are capable of interfering with F pharmacokinetics. Cimetidine, when administered to this kind of patient (1.2 $g.24\ h^{-1}$) could prolong the terminal half-life of F but this interaction is not clear (1). Dopamine was used at efficient doses producing an increase in regional blood flow leading to an increase in F tissular distribution.

CONCLUSIONS : In critically ill patients, a long duration F infusion produces a larger total volume of distribution and a longer elimination half-life than in normal anesthetized patients. In this study, it is difficult to determine a therapeutic model due to the great interindividual variations in pharmacokinetics.

Table I : pharmacokinetic parameters $\bar{X}$ ± SD

T 1/2β (h)	Vdβ ($l.kg^{-1}$)	Cl ($ml.kg^{-1}mn^{-1}$)	C^{-1} ss ($ng.ml^{-1}$)
25.03 ±16.2	25.1 ±17.6	12.03 ± 4.44	9.75 ±2.75
min.-max	min.-max	min.-max	min.-max
10 - 56	14.1-58.4	7.3-20.1	5.5-12.5

Table II : biological parameters $\bar{X}$ ± SD

plasma protein-binding (F=10ng.ml^{-1})	Hematocrit (%)	Blood protid ($g.l^{-1}$)
80.88 ± 2.38	29.3 ± 3.3	61.58 ± 6.57

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