

TITLE : PHARMACOKINETICS OF LONG-TERM ALFENTANIL INFUSION (72 HOURS) USED FOR SEDATION IN PATIENTS IN THE I.C.U.

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In I C U patients undergoing prolonged mechanical ventilation, a rapid reversibility of sedation is needed to assess neurological status and avoid unnecessary prolongation of mechanical ventilation. To date, little information is available on the use of alfentanil for prolonged sedation (1,2).

After institutional approval and informed consent from the family were obtained, 10 consecutive patients were studied. There were 8 males and 2 females with a mean age of  $33 \pm 17$  years ( $\pm$  SD) and a mean body weight of  $74 \pm 13$  kg. The patients had no history of cardiovascular, renal or hepatic abnormalities. Patients were first given a bolus induction dose of 90 mcg.kg<sup>-1</sup> i.v. alfentanil administered in 3 min. The drug was then administered by continuous infusion at a constant flow rate of 0.7 mcg.kg<sup>-1</sup>.min<sup>-1</sup> for 72 h. Blood samples were obtained before injection and at 3, 10, 20, 40 min and at 1, 2, 4, 6, 18, 30, 48, 54, 66, 72 h. after the beginning of infusion. Further samples were taken 5, 10, 20, 40 min and 1, 2, 6, 12, 24, 36, 48, 60, 72 h after the end of infusion. The tubes were centrifugated and plasma was stored at -20 °C until assayed. Alfentanil concentrations were determined by Radio Immuno Assay (3). Individual pharmacokinetic parameters were estimated by non-compartmental analysis for all patients.

Alfentanil plasma concentrations plotted against time are

shown in the figure. A plateau was nearly reached at the 30<sup>th</sup> hour and maintained up to the 72<sup>nd</sup> hour when the infusion was stopped. The elimination half-life (T<sub>1/2</sub>β) was  $5.5 \pm 3.9$  h (range: 1.8 - 15.7 h), the total body clearance (Cl) was  $1.57 \pm 1.36$  ml.min<sup>-1</sup>.kg<sup>-1</sup> (range: 0.3 - 4.2 ml.min<sup>-1</sup>.kg<sup>-1</sup>) and the volume of distribution (Vdβ) was  $0.46 \pm 0.24$  l.kg<sup>-1</sup> (range: 0.23 - 1.02 l.kg<sup>-1</sup>).

The principal finding of the present study is that during prolonged infusion of alfentanil, T<sub>1/2</sub>β was found to be very high. Vdβ was not modified as compared with previous studies, but Cl was found to be dramatically decreased. The alteration of Cl was not explained by a concomitant change in the renal or in the hepatic status of the studied patients.

References

- 1) Anesthesiology 57 : 439 - 443, 1982.
- 2) Clin. Pharmacokinet. 15 : 216 - 226, 1988.
- 3) J. Pharm. Pharmacol. : 93 : 86 - 93, 1983.

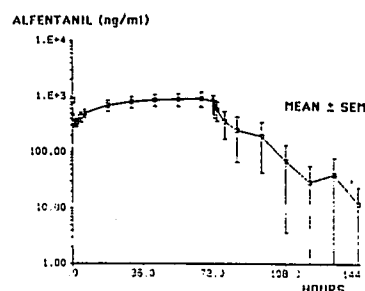


Figure : Alfentanil concentrations.

TITLE: ISOFLURANE PARTIALLY PROTECTS ENERGY BALANCE IN ISOLATED HEPATOCYTES DURING IN VITRO ANOXIA

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Added fructose but not glucose was reported to support glycolytic ATP production in anoxic perfused livers from fasted rats.<sup>1</sup> Because anesthetics might also affect ATP supply or demand, we studied effects of these substrates plus isoflurane (ISO) on ATP/ADP in isolated hepatocytes during in vitro anoxia.

**Methods** Hepatocytes were isolated from fed or 48 hr-fasted rats by in situ liver perfusion using Krebs HCO<sub>3</sub> buffer containing collagenase. The cells were incubated in fresh buffer + 10 mM glucose or fructose at 37°C. The gas phase was O<sub>2</sub>/CO<sub>2</sub> (95/5) for 10 min, followed by either O<sub>2</sub>/CO<sub>2</sub> or N<sub>2</sub>/CO<sub>2</sub>, ±1.4% ISO, for 20 min. ATP/ADP was measured to indicate ATP supply-demand balance; lactate, the extent of impaired mitochondrial ATP formation. ANOVA and  $\bar{x}$  test assessed statistical significance.

**Results and discussion** In cells from fed rats, under O<sub>2</sub>, fructose decreased ATP/ADP and increased lactate, as previously described.<sup>2</sup> Similar changes occurred with glucose under N<sub>2</sub>. In cells from fasted rats, neither fructose nor glucose supported ATP/ADP adequately under either O<sub>2</sub> or N<sub>2</sub>, although fructose did slightly better than glucose under N<sub>2</sub>.

+ISO gave higher ATP/ADP than -ISO with either substrate, but only under N<sub>2</sub> in cells from fed rats. This ISO effect was not due to increased ATP supply, because lactate was unchanged and O<sub>2</sub> absent.

**Conclusions** 1. ISO partially protected ATP/ADP during anoxia in cells from fed rats, probably by decreasing ATP demand. 2. Added fructose did not support ATP/ADP well under N<sub>2</sub> in cells from fasted rats and was only slightly better than glucose.

- References 1. Am J Physiol 253:G390-G396, 1987. 2. Curr Topics Cellular Regulation 13:98-135, 1978.

|          | O <sub>2</sub>                       |                      | N <sub>2</sub>       |                       |
|----------|--------------------------------------|----------------------|----------------------|-----------------------|
| fed rats | glucose                              | fructose             | glucose              | fructose              |
|          | ATP/ADP                              |                      |                      |                       |
| -ISO     | 4.9±1.2                              | 3.0±1.2 <sup>a</sup> | 0.9±0.5 <sup>b</sup> | 0.9±0.3 <sup>b</sup>  |
| +ISO     | 5.2±1.3                              | 3.0±0.7 <sup>a</sup> | 1.8±1.5 <sup>b</sup> | 1.8±1.3 <sup>bc</sup> |
|          | lactate (umol/10 <sup>7</sup> cells) |                      |                      |                       |
| -ISO     | 2.3±1.2                              | 6.1±1.1 <sup>a</sup> | 4.2±1.1 <sup>b</sup> | 7.4±2.3 <sup>a</sup>  |
| +ISO     | 3.1±1.6                              | 5.8±1.8 <sup>a</sup> | 4.3±1.5              | 6.0±1.3 <sup>a</sup>  |
|          | fasted rats                          |                      |                      |                       |
|          | ATP/ADP                              |                      |                      |                       |
| -ISO     | 2.6±0.8                              | 2.9±1.0              | 0.4±0.3 <sup>b</sup> | 0.6±0.4 <sup>ab</sup> |
| +ISO     | 3.3±1.3                              | 3.0±1.1              | 0.5±0.5 <sup>b</sup> | 0.9±0.8 <sup>ab</sup> |
|          | lactate (umol/10 <sup>7</sup> cells) |                      |                      |                       |
| -ISO     | 1.4±1.0                              | 3.0±1.8 <sup>a</sup> | 1.7±1.0              | 3.3±2.0 <sup>a</sup>  |
| +ISO     | 2.0±1.6                              | 3.8±1.3 <sup>a</sup> | 2.5±1.8 <sup>b</sup> | 3.3±1.8               |

Values are mean  $\pm$  sd; N = 10. Different at p < .05 for <sup>a</sup>fructose vs glucose, <sup>b</sup>N<sub>2</sub> vs O<sub>2</sub>, <sup>c</sup>+ISO vs -ISO. (Support Fndn Anesth Educ Research / ASA)