Title: ERYTHROMYCIN TREATMENT INHIBITS ALFENTANIL METABOLISM

Authors: RR Bartkowski, M.D. Ph.D., GE Larijani, Pharm.D., ME Goldberg M.D., TF Boerner, M.D.

Affiliation: Department of Anesthesiology, Jefferson Medical College Thomas Jefferson University, Philadelphia, PA 19107

INTRODUCTION. Alfentanil has found a place in anesthetic practice because of its short duration of action. This allows for rapid emergence at the end of surgery. In some instances, however, recovery has been prolonged. After examining records from several of these cases a pattern was noted. In patients who had received a course of erythromycin, there was an unusual incidence of prolonged action which could not be attributed to other causes. Because erythromycin therapy is known to inhibit the elimination of theophylline[1], a similar interaction was suspected. In order to determine the extent of this interaction, this study was undertaken.

METHODS. Six volunteers gave written informed consent to participate in this Institutional Review Board approved study. The protocol specified that each subject would be studied in three sessions separated by at least two weeks. The crossover design consisted of the following preparations for each session:

1. Nothing
2. A single dose of erythromycin-500mg p.o.@ 6 a.m.
3. A 7 day course of erythromycin-500mg p.o. b.i.d.

The order of studies was randomized among the subjects. They were asked to refrain from alcoholic beverages at least seven days prior to each session. For each session, subjects were fasted from midnight and appeared at 7 A.M. Intravenous catheters were placed in opposite arms for drug infusion and collection. Naloxone (0.4 mg) was given five minutes before a five minute infusion of alfentanil (50 µg/kg) and Naloxone (0.4 mg). Blood samples were collected at the following times after the beginning of infusion: 6, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min. The frozen plasma samples were analyzed in duplicate by radioimmunoassay for alfentanil.

Plasma concentration time curves were analyzed by non-compartmental (area under curve) methods. Each was fitted to a sum of two exponentials by non-linear regression to determine the elimination half-life. This was used to extrapolate the tail of the concentration-time curve to determine clearance, volume of distribution and mean residence time from the area under the curve. The parameters obtained were subjected to repeated measures analysis of variance with comparisons by the Least Significant Difference method; $p<0.05$ was considered significant.

RESULTS. Both the clearance and elimination half life were prolonged significantly by the seven day course of erythromycin. The order of administration did not affect the results. Numerical results for all of the parameters are presented in Table 1. Figure 1 shows the average elimination curves for the three treatments. There was notable variability among the subjects in their response to erythromycin. Two subjects had their clearance halved by the seven days of erythromycin while two others were affected only minimally. This is reflected by larger standard deviation in the erythromycin groups.

DISCUSSION. A seven day course of erythromycin clearly inhibited the metabolism of erythromycin. This is evident in the significant change in elimination half-life and clearance as would be expected for a process affecting metabolism. The distribution volume was not affected. The Mean Residence Time was also not affected significantly. This parameter is more dependent on distribution than elimination. The interaction is thus an affect on alfentanil elimination similar to that found for theophylline.

The magnitude of this effect is sufficient to have clinical consequences. An otherwise normal dosage of alfentanil could lead to a prolonged effect if the alfentanil clearance is reduced to one half by this metabolic interaction. It is possible and even likely that higher doses of erythromycin as are often used in a clinical setting could impair hepatic metabolism even further. We find that alfentanil elimination will not be predictable in this setting and we recommend that alfentanil be avoided in patients who have recently received erythromycin therapy.

TABLE 1. Non-compartmental pharmacokinetic parameters for alfentanil after stated duration of erythromycin.

| Parameter | 0 Days | 1 Day | 7 Days |
|---|---|---|---|
| Clearance # | 3.9± 0.8 | 3.9± 1.3 | 2.9 ± 1.2* |
| t 1/2 (min) | 84.0± 8.2 | 105.9± 41.5 | 131.5± 43.4Δ |
| VDSS (ml/kg) | 334.0± 58.8 | 321.0± 60.1 | 285.5± 94.1 |
| MRT (min) | 86.1± 5.0 | 86.4± 19.3 | 104.0± 17.1 |

\# - ml/kg/min
* - $p < .01$ for difference with others
Δ - $p < .05$ for difference with 0 Days

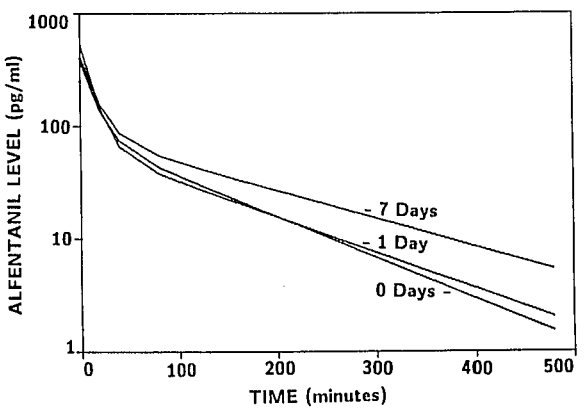


Figure 1. Average plasma decay curves for alfentanil in the six subjects. Noted are the duration of erythromycin therapy prior to each measurement.

Reference.
Prince RA, Wing DS, Weinberger MM, Handeley LS, Riegleman S. J Allergy Clin Immunol 68:427, 1981