Title: ALFENTANIL PHARMACOKINETICS: INTRAVASCULAR SPACE AND CARDIAC OUTPUT

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Introduction. Alfentanil, like thiopental, has a very rapid onset of action with very little hysteresis between initial volume of distribution, V_C, and the biophase.[1] Thus it is desirable to describe the initial disposition of alfentanil as accurately as as possible. We have recently described a method of increasing the accuracy of the description of the initial disposition of a given drug by coadministering indocyanine green (ICG) and simultaneously modelling their disposition.[2] We therefore sought to describe the disposition of alfentanil using the newly described model. In addition, because drug distribution by mixing, flow, and diffusion may be influenced by cardiac output (C.O.)[2] we evaluated the relationship between the sum of the intercompartment clearances (ΣCl_I)[3] of alfentanil in the new model and C.O.

Methods. Institutionally approved written informed consent was obtained from 6 healthy volunteers (3 males and 3 females, 23 - 44 years of age). A radial artery was cannulated in each subject for blood sampling. C.O. and blood pressure were monitored continuously before and for at least the first hour after drug administration with the Bomed^R impedance C.O. monitor and the Datascope Accutor^R, respectively. Following an 8 hour fast, volunteers were supine for at least one hour before and 1.5 hours after drug administration. Subjects were then fed a standardized breakfast and allowed to assume a sitting position. Alfentanil HCl, 10 ug/kg, and ICG, 0.5 mg/kg, were injected simultaneously over 15 seconds into the stream of a rapidly running intravenous infusion. Arterial blood samples were obtained at half minute intervals from 1 to 5 minutes after the start of drug administration, at one minutes intervals to 15 minutes, at 17.5, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 135 and 150 minutes, and half hour intervals thereafter to 6 hr. Plasma ICG concentrations were measured using a spectrophotometric technique which has been shown to produce results identical to those obtained by high performance liquid chromatography.[4] Plasma alfentanil concentrations were measured by a modification of the direct RIA method of Michiels et al.[5] in which the sample was added as 200 ul of plasma. Plasma concentrations of both drugs were converted to blood concentrations by multiplying them by (1-Hct) as neither partitions into erythrocytes. The dispositions of ICG and alfentanil were characterized by a 2-compartment and a 4-compartment open mammillary model, respectively, using the CONSAM digital computer program.[2] The models had a common V_c. The peripheral ICG compartment was a subset of a peripheral alfentanil compartment; elimination clearance was from these compartments. Correlations between ΣCl_I[3] and C.O. were sought using a standard linear regression technique.

Results. The pharmacokinetic variables describing the disposition of alfentanil in the present study are summarized in Tables 1 and 2.

Table 1: Volumes of Distribution of Alfentanil (L) $\bar{x}$ (S.D.)

V_1	V_2	V_3	V_4	V_{SS}
2.4	4.7	15.1	7.8	30.2
(0.6)	(1.6)	(6.5)	(3.9)	(7.3)

Table 2: Clearances of Alfentanil (L/min) $\bar{x}$ (S.D.)

Cl_{21}	Cl_{31}	Cl_{41}	ΣCl_I	Cl_E
2.1	0.4	1.8	4.4	0.31
(0.4)	(0.1)	(1.2)	(1.5)	(0.10)

The relationship of ΣCl_I to C.O. is illustrated in Figure 1.

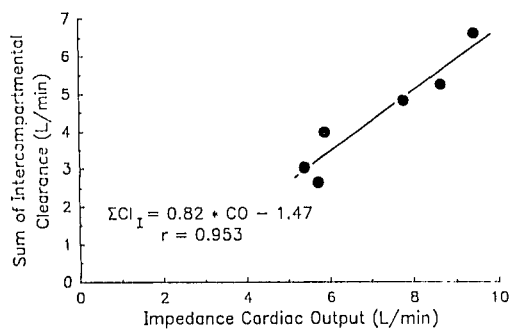

Figure 1

Discussion. The V_C for alfentanil in our model is an intravascular subvolume defined by the early disposition of ICG. From this central blood pool alfentanil and ICG mix with a peripheral blood pool while alfentanil distributes to tissues by blood flow and transcapillary diffusion.[6] Thus, while V_C in this model is independent of C.O. a significant correlation between the distribution of alfentanil (ΣCl_I) and C.O. was found (Figure 1). Because ΣCl_I was always less than C.O., both C.O. and transcapillary diffusion may regulate the distribution of alfentanil as demonstrated for hydrophilic drugs.[7] These factors together determine the time course of early plasma alfentanil concentrations.

References.
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