Partition Coefficients of I-653 in Human Blood, Saline, and Olive Oil

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The purpose of this study was to determine partition coefficients for a new, inhaled anesthetic, I-653. Blood samples were taken from 11 patients scheduled for elective surgery who were ASA physical status I-III and ranged in age from 25 to 76 yr. At 37°C, we found a blood/gas partition coefficient of 0.424 ± 0.024 (mean ± SD); a saline/gas partition coefficient of 0.225 ± 0.002; and an oil/gas partition coefficient of 18.7 ± 1.1. These values indicate that I-653 will have a minimum alveolar concentration (MAC) required for anesthesia that is four to five times that of isoflurane and that I-653 will produce a rapid induction of and recovery from anesthesia.

Key Words: ANESTHETICS, VOLATILE—I-653. SOLUBILITY—I-653 partition coefficients.

Rapid recovery from anesthesia is an increasingly important goal of clinical practice, particularly for outpatient surgery. Although currently available potent inhaled anesthetics act rapidly and with minimal or no toxicity, recovery from the effects of these agents is still less rapid than might be desired. Consequently, interest has revived in the experimental inhaled anesthetic, sevoflurane (1), the low solubility of which (blood/gas partition coefficient of 0.59-0.69) (1,2) indicates a considerably more rapid recovery than that associated with the next least soluble anesthetic, isoflurane (blood/gas partition coefficient 1.4) (3).

However, sevoflurane appears to have limitations. It is metabolized (4) and unstable in the presence of soda lime (1,5). In addition, although it offers the advantage of low solubility, a still lower solubility seems possible. The partition coefficient of nitrous oxide, the least soluble of presently available inhaled anesthetics, is 0.47 (6).

I-653 is a new experimental inhaled anesthetic. Its MAC is slightly less than 6% in rats (unpublished data). It has the same structure as isoflurane except for the substitution of fluorine for chlorine on the α-carbon of the ethyl moiety. It is flammable at a concentration of 17% (unpublished data supplied by Ana-
quest). This compound has a relatively high vapor pressure (about 700 mm Hg at 22–23°C) (unpublished data). These properties indicate a lower solubility and greater stability than found with sevoflurane, and our initial studies have confirmed these differences (unpublished data). Recovery is extremely rapid with I-653, a finding also consistent with an agent having a very low solubility in blood (unpublished data). The role of the present study was to determine the solubility of this new agent in saline, oil, and human blood.

Methods

With approval from our Committee on Human Research and consent from each patient, we obtained 30 ml of venous blood from each of 11 patients ranging in age from 25 to 76 yr. All patients were ASA physical status I–III. There were four women and seven men.

The method of Lerman et al. (7–9) was used to determine the blood/gas and saline/gas partition coefficients of I-653. Fifteen-milliliter samples of blood or 0.9% saline were placed in 50-ml syringes and equilibrated by tonometry with 20 ml of 1.6–2.6% I-653 for 90 min in a waterbath at 37°C. The syringes were shaken vigorously every 15 min. The concentration of I-653 in the gas phase over each sample was determined by gas chromatography.

The oil/gas partition coefficient was obtained by the method described by Tanifuji et al. (10). Liquid I-653 (0.15 ml) was added to 100 ml of pure virgin olive oil and thoroughly mixed. Twelve milliliters of this mixture was equilibrated by tonometry with 20 ml of air.
The syringes were shaken vigorously once per hour for the last 4 hr of tonometry. The concentration of I-653 in the gas phase over the olive oil was then determined by gas chromatography.

For chromatography we used a 30-m, fused silica open tubular capillary (0.53-mm internal diameter) column coated with a layer of methylsilicone oil (J & W Scientific DB-1), which was 1.5-μm thick. A nitrogen carrier stream of 6 ml/min was directed through the column with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop.

After analysis of the gas phase in the syringes, aliquots of 10.069 ml of each of the equilibrated substances were transferred to 581-ml flasks. The blood and saline aliquots were transferred anaerobically to flasks from which a portion of the air had been evacuated to produce a negative pressure. The negative pressure drew the aliquot into the flask through a needle that pierced the Teflon stopper. A one-way stopcock was affixed to the needle. Each sealed flask containing blood or saline was placed in a 37°C water bath and shaken every 15 min for the ensuing 90 min, after which the concentration of I-653 was determined by gas chromatography.

Similarly, an aliquot (10.069 ml) of the equilibrated mixture of olive oil was placed in a 581-ml flask, but the aliquot was directly injected into the open flask. The flask then was sealed with a Teflon stopper pierced with a needle to which a one-way stopcock was affixed. The flask was equilibrated at 37°C and was shaken vigorously once an hour for 6 hr. After 6 hr, the concentration of I-653 in the gas above the mixture in the flask was determined by gas chromatography.

The partition coefficients (λ) were determined using the following equation:

\[ \lambda = \frac{C_g(V_g/V_s)}{C_i - C_s} \]

where \( C_g \) is the concentration of I-653 in the gas phase in the 30-ml syringe used for tonometry; \( C_i \) is the concentration of I-653 in the gas phase of the flask; \( V_i \) is the volume of the flask; and \( V_s \) is the volume of the aliquot of blood, saline, or oil.

Dual determinations of the blood/gas partition coefficient were made for each patient. The paired values were averaged for each patient, and the averaged value assumed to represent the partition coefficient for that patient's blood. Averaged values for the partition coefficient were regressed against patient age and hematocrit. Eight unpaired determinations were obtained for the saline/gas partition coefficient and seven unpaired determinations for the oil/gas partition coefficient.

Results

Patients' ages averaged 59.9 ± 15.4 (mean ± sd) yr. Hematocrit concentrations averaged 43.1 ± 5.0%. The blood/gas partition coefficient was 0.424 ± 0.024; the saline/gas partition coefficient, 0.225 ± 0.002; and the oil/gas partition coefficient, 18.7 ± 1.1. There was no significant correlation (\( P > 0.05 \)) between patient age or hematocrit and the blood/gas partition coefficient, although the slope of the relationship between hematocrit and the blood/gas partition coefficient approached significance (\( t = 1.90; \) partition coefficient = 0.312 + 0.0026 × hematocrit).

Discussion

The blood/gas partition coefficient of 0.424 suggests that I-653 will move into and out of the body as rapidly or more rapidly than nitrous oxide. Thus I-653 should anesthetize quickly and should permit prompt recovery from anesthesia. Our unpublished observations support the prediction of an extremely rapid rate of recovery, even from deep levels of anesthesia. These characteristics recommend its use for outpatient surgery, provided I-653 also possesses the attributes which make current, clinically applied inhaled agents safe and desirable to use. These properties include resistance to breakdown, minimal or absent toxicity, minimal or absent pungency, and a reasonable margin of safety. Resistance to breakdown is suggested by the similarity of the structure of I-653 to that of isoflurane and the known resistance of the latter to breakdown. Again, our unpublished data indicate that I-653 is resistant to breakdown and that this resistance appreciably exceeds that of any of the presently available potent inhaled anesthetics. The rapidity with which I-653 leaves the body should further reduce any possibility of breakdown and hence toxicity. These desirable properties may be counterbalanced by a predicted, clinically useful anesthetic concentration that is considerably higher than that required for anesthesia with currently used volatile anesthetics (see later). A higher concentration would increase the amount of agent available for biodegradation.

The blood/gas partition coefficient for I-653 was not significantly affected by hematocrit or patient age. However, the correlation with hematocrit approached significance, and a correlation such as increased sol-
ubility with increased hematocrit would be consistent with results reported for other inhaled agents in a previous study (9). The absence of a correlation with age distinguishes I-653 from other volatile inhaled anesthetics (8).

The product of MAC times the oil/gas partition coefficient equals a constant for most volatile anesthetics in humans (11). For isoflurane, the anesthetic structurally most similar to I-653, this product equals 104 (that is, 1.15% × 91). Thus an oil/gas partition coefficient of 18.7 predicts an MAC for I-653 of 5.6%. As indicated earlier, unpublished data support this prediction for MAC. A MAC of 5.6% would be disadvantageous if, as appears likely, I-653 is an expensive anesthetic to manufacture. A closed system may be used for reasons of economy. The low solubility of I-653 may be a particular advantage in a closed system because, at a given alveolar concentration, the need to replenish the supply of anesthetic will be much less than that needed with any other potent inhaled anesthetic.

References


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