

elimination (mean  $87.4 \text{ ml kg}^{-1}$ ) is only 50% of the previously recorded values (mean  $157 \text{ ml kg}^{-1}$ ).<sup>4,5</sup> If either the previously recorded elimination rate constants *in vitro* or the distribution volumes are used, values for non-organ clearance are around 25%.

This value is more in keeping with expected values, as up to 10% of a dose of atracurium has been obtained unchanged in the urine of patients<sup>6</sup> and, having a molecular weight of around 1000 and being ionized, hepatic clearance of possibly 15% would occur.

Finally, I must mention that the two-compartment model for atracurium with elimination from both compartments was first described by Ward *et al.*<sup>7</sup>

S. WARD, F.F.A.R.C.S.  
Consultant Anaesthetist  
Southend Hospital  
Prittlewell Chase  
Westcliff-on-Sea  
Essex SSO 0RY  
Great Britain

Anesthesiology  
66:103-104, 1987

*In reply:*—Dr. Ward challenges our conclusion<sup>1</sup> that more than one-half of the clearance of atracurium results from organ-based elimination. He bases his argument on the discrepancy between the *in vitro* half-lives obtained in our study (32 min) and those obtained by Hughes and Chapple<sup>2</sup> (25 min) and Stiller *et al.*<sup>3</sup> (21 min). Unfortunately, Hughes and Chapple provide no details of their experimental design other than their use of plasma (compared with our use of whole blood), so we are unable to explain the differences between their results and ours. Stiller *et al.* added atracurium to plasma maintained at 37° C and determined the concentration of atracurium during a 3-h sampling period; they do not state whether plasma pH was measured repeatedly during the study. When we attempted to replicate their experiment, we found that the pH of the plasma increased during the sampling period, as a result of a decrease in the concentration of carbon dioxide. This increase in pH would be expected to increase the rate of Hofmann elimination, thereby decreasing the *in vitro* half-life of atracurium to a value consistent with the shorter half-life obtained by Stiller *et al.* To simulate physiologic conditions and to prevent problems related to the instability of pH, we believed that it was important to maintain a constant pH throughout our study. Therefore, we kept the blood in a sealed vessel equilibrated with 5% CO<sub>2</sub> and documented that pH did not vary during the study period. Thus, we believe that the shorter *in vitro* half-life obtained by Stiller *et al.* resulted from the instability of pH in their study.

## REFERENCES

1. Fisher DM, Claver Canfell P, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD: Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. *ANESTHESIOLOGY* 65:6-12, 1986
2. Stiller RL, Cook DR, Chakravorti S: *In vitro* degradation of atracurium in human plasma. *Br J Anaesth* 57:1085-1088, 1985
3. Hughes R, Chapple DJ: Experimental studies with atracurium, a new neuromuscular blocking agent. *Br J Anaesth* 52:238P, 1980
4. Ward S, Weatherley BC: Pharmacokinetics of atracurium and its metabolites. *Br J Anaesth* 58:10S, 1986
5. Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis PJ: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. *ANESTHESIOLOGY* 61:699-702, 1984
6. Ward S, Weatherley BC: The pharmacokinetics of atracurium in anephric patients. *Acta Anaesthesiol Scand* 29(Suppl. 80):68, 1985
7. Ward S, Neill EAM, Weatherley BC, Corall IM: Pharmacokinetics of atracurium besylate in healthy patients (after a single iv bolus dose). *Br J Anaesth* 55:113, 1983

(Accepted for publication September 24, 1986.)

Ward is surprised that our value for  $V_{ss}$  (87.4 ml/kg) (which he incorrectly terms distribution volume for elimination) is smaller than the values for  $V_{area}$  ( $V_{\beta}$ ) obtained in other studies. These terms describe different pharmacokinetic volumes and are not interchangeable. In addition, whenever the organ(s) of elimination are located within the central compartment (as we assumed in our pharmacokinetic model),  $V_{ss}$  will be less than  $V_{area}$ . In fact, we<sup>4</sup> reported that  $V_{area}$  for atracurium was  $182 \pm 12 \text{ ml/kg}$ , a value similar to that reported by Ward *et al.*

Finally, Dr. Ward did describe a two-compartment model for atracurium. However, there are marked differences between his model and ours. Dr. Ward's model cannot be used to determine  $V_{ss}$  (or, for that matter, to fractionate clearance into its organ and non-organ components); additional problems with his model have been identified by Hull.<sup>5</sup> In contrast, our model, because it utilizes the *in vitro* rate constant for atracurium elimination, permits determination of these additional pharmacokinetic parameters.

DENNIS M. FISHER, M.D.  
Assistant Professor of Anesthesia and Pediatrics

LEWIS B. SHEINER, M.D.  
Professor of Laboratory Medicine and Medicine  
Departments of Anesthesia and Laboratory Medicine  
University of California  
San Francisco, California 94143-0648

## REFERENCES

1. Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD: Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. *ANESTHESIOLOGY* 65:6-12, 1986
2. Hughes R, Chapple DJ: Experimental studies with atracurium, a new neuromuscular blocking agent. *Br J Anaesth* 52:238P, 1980
3. Stiller RL, Cook DR, Chakravorti S: *In vitro* degradation of atracurium in human plasma. *Br J Anaesth* 57:1085-1088, 1985
4. Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis PJ: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. *ANESTHESIOLOGY* 61:699-702, 1984
5. Hull CJ: A mode for atracurium (editorial)? *Br J Anaesth* 55:95-96, 1983

(Accepted for publication September 24, 1986.)

Anesthesiology  
66:104-105, 1987

## Scented Masks in Pediatric Anesthesia

To the Editor:—I read with interest Yamashita's recent correspondence entitled "Fruit-flavored Mask Induction in Children."<sup>1</sup> I would caution clinicians about aerosolizing fruit flavors into the inhalational gas mixtures in the manner that these authors suggest. I have included a list of the common ingredients of fruit flavors used in this country to scent pediatric masks (Lorann Oils, Inc.) (Table

TABLE 1. Ingredients in Fruit Flavor Extracts\*

Cherry	
Benzaldehyde	Ethyl Isobutyrate
Propylene Glycol Acetal	Ethyl Vanillin
Benzaldehyde	Alpha Ionone
Vanillin	Anisyl Acetate
Tolaldehyde	Frambinone
Heliotropine	Maltol
Amyl Acetate	Red #40
	Blue #1
Grape	
Methyl Anthranilate	Gamma Undecalactone
Ethyl Butyrate	Ethyl Alcohol
Amyl Acetate	Propylene Glycol
Citral	Polysorbate 80
Orange Oil	Red #40
Vanillin	Blue #1
Watermelon	
Ethyl Acetate	Methyl Eugenol
Butyl Heptanoate	Lemon Oil
2,6 Dimethyl 5-Heptenal	Methyl Heptin
Amyl Acetate	Carbonate
Ethyl Isovalerate	Ethyl Caprate
Iso Amyl Valerate	Ethyl Caprylate
Ethyl Pelargonate	Ethyl Alcohol
Strawberry	
Propylene Glycol	Acetic Acid
Aldehyde C-16	Diacetyl
Alcohol 12%	Orange Oil
Ethyl Vanillin	Triacetin
Ethyl Acetate	Red #40

\* Lorann Oils, Inc., Lansing, MI 48910.

1). Aerosolizing a compound with up to 15 ingredients (cherry) may not be ideal.

The issue of the safety in aerosolizing fruit extracts into anesthesia breathing circuits involves the toxicologic, allergic, and airway irritant potential of their chemical ingredients. While there is very little data in this area, there does exist some evidence to support a cautionary note about this practice.

From the toxicologic standpoint, the industrial toxicology literature does cite some evidence for concern. Ethyl acetate (threshold limit value of 400 ppm in air) has caused renal hyperemia, CNS depression, and respiratory tract irritation.<sup>2</sup> In addition, amyl acetate (threshold limit value of 100 ppm in air) has shown renal, hepatic, and CNS toxicity.<sup>2</sup> Propylene glycol is known to be associated with lactic acidosis.<sup>3</sup>

The glycols have been associated with allergic contact reactions.<sup>4</sup> Even without an overt allergic potential, patients with allergic histories (*i.e.*, hay fever, eczema) or reactive airway disease may not benefit from the intrinsic irritant properties associated with inhaling many of these chemicals.

Rather than direct aerosolization of these extracts, it seems safer to either apply small quantities to the face mask in the traditional manner, or to use a specifically designed face mask which has the technology of scent release from the polymer base. Such a scented mask is easier and safer, yet still achieves the advantages of scenting pediatric masks to camouflage the pungent odors of inhalational agents and to improve patient acceptance. Scented pediatric anesthesia masks are available from King Systems Corporation.\*

ALLEN J. HINKLE, M.D.

Assistant Professor of Surgery (Anes.) and Pediatrics  
Dartmouth-Hitchcock Medical Center  
Hanover, New Hampshire 03756

\* 15015 Herriman Boulevard, Noblesville, Indiana 46060