ESTIMATION OF ETHYLVINYL ETHER (VINAMAR) IN BLOOD

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IN ORDER to have more complete knowledge of the action of the recently introduced inhalation anesthetic agent, ethylvinyl ether (Vinamar *), it was of interest to have a method to determine the concentration of this agent in the blood of anesthetized subjects. A method for the removal of trifluoroethylvinyl ether from blood, which has been described in a previous paper (1) was adapted for use with this ether. Siggia's (2) iodoacetal procedure was selected as a suitable technique for determining the ethylvinyl ether after it was separated from the blood.

METHOD

In the method described here, ethylvinyl ether and other volatile constituents were steam distilled from the diluted blood sample in a stream of nitrogen. The distillate and nitrogen were then passed into an aqueous-methanolic solution of iodine where the iodoacetal of the ether was formed thus:

$$C_2H_5OCH = CH_2 + I_2 + CH_3OH \rightarrow C_2H_5OCHCH_2I + HI$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OCH_3$$

The excess iodine was then titrated with standard sodium thiosulfate solution. The method is capable of estimating as little as about 0.3 mg. of ethylvinyl ether and has a precision of about ± 8 per cent.

Reagents

Antifoam A compound (Dow-Corning Corp., Midland, Michigan).

Hydrochloric acid, concentrated, reagent grade.

Iodine solution, about 0.05*N*: (100 g. of potassium iodide and 6 g. of iodine per liter of distilled water.)

Methanol-water solution, about 50 per cent by volume.

Starch indicator solution, 1 per cent (3).

Sodium thiosulfate solution, standard, about 0.01*N*: (2.5 g. of $Na_2S_2O_3 \cdot 5\,H_2O$ in 1 l. of sterile distilled water. No stabilizers added and standardized weekly (3)).

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*Vinamar is a proprietary mixture of ethylvinyl ether (97 per cent), ethyl alcohol (3 per cent), and *N*-phenyl-1-naphthylamine (0.01 per cent).

Experimental

Apparatus.—The distilling apparatus is identical with that previously described (1).

Procedure.—Thirty milliliters of water and a small drop of "Antifoam A" were added to the distilling flask, the joint greased and the flask connected to the condenser. The bubble counter was connected to the gas inlet tube of the flask with a piece of rubber tubing. A 100 ml. graduated cylinder was raised around the delivery tube so that the tip just touched the bottom of the cylinder and the cylinder clamped in place. Exactly 5 ml. of 0.05*N* iodine was pipeted into the graduate and about 60 ml. of methanol-water solution added. The blood sample (heparinized or oxalated) was injected into the distilling flask through the serum bottle cap. Cylinder nitrogen was started flowing through the flask at about 1 bubble per second. The heating mantle was placed under the flask, the power turned on for high heat, and the top of the flask loosely wrapped with cloth to provide insulation. When rapid boiling started, the power was reduced and the mixture allowed to boil gently with a continuous stream of nitrogen flowing until 20 ml. of water was condensed in the 100 ml. graduate (40 to 60 minutes). The power was then turned off and the graduate was lowered from the delivery tip and replaced with a 500-ml. Erlenmeyer flask. (This was done carefully so as not to lose any of the iodine solution.) The remaining iodine was completely removed from the delivery tube by increasing the nitrogen flow rate while rinsing with water. The contents of the graduate were rinsed into the flask. (The flask should contain at least 200 ml. of liquid at this point.) The contents were titrated with standard 0.01*N* thiosulfate to a starch end point. The presence of the methanol in the solution tended to make this end point a difficult, but not impossible one.

Since blood contains volatile substances which react with iodine, it is necessary to establish a blank value for the distillation of a similar amount of anesthetic-free blood in the above procedure.

Calculations

$$\frac{(A - B) \times N \times 3{,}600}{\text{ml. of blood}} = \text{milligrams of ethylvinyl ether/100 ml. of blood,}$$

where A = milliliters of thiosulfate required to titrate iodine remaining after reaction with distillate from anesthetic-free blood (blood blank).

B = milliliters of thiosulfate required to titrate iodine remaining after reaction with distillate from blood containing ethylvinyl ether.

N = normality of thiosulfate.

3,600 = 100 × milliequivalent weight of ethylvinyl ether, or $100 \times \frac{72}{2}$.

Results

The procedure was first tested using a 1 per cent solution of ethylvinyl ether in methanol which had been analyzed by the iodoacetal procedure. Aliquots of this solution were added to 35 ml. of water in the distilling flask and distilled according to the procedure given. These data are given in table 1. Aliquots of this solution of ethylvinyl ether in methanol were then added to a mixture of 5 ml. of canine blood (preserved with anticoagulant-acid citrate-dextrose solution, U.S.P.) and 30 ml. of water in the distilling flask and distilled according to the procedure given. These results are given in table 2. The standard deviation, σ, and the 95 per cent confidence limits of the median, $t_{95}\sigma$, for the data of tables 1 and 2, were determined by the procedures of Dean and Dixon (4). Attempts to prepare standard solutions of ethylvinyl ether in blood were unsuccessful presumably because of the high volatility of this ether and because it slowly hydrolyzes to acetaldehyde in aqueous solutions. Solutions in dry methanol were quite stable and lost ethylvinyl ether only slowly.

TABLE 1

Distillation of Ethylvinyl Ether from Water

Ethylvinyl Ether Added (mg.)	Found (mg.)	Recovery (per cent)
2.49	2.43	97.6
1.66	1.67	100.5
3.32	3.30	99.5
4.15	4.36	105.1
5.82	5.95	97.8
0.83	0.79	95.2
4.98	4.92	98.8
5.82	5.81	99.8
	Median	99.1 per cent
	σ	3.2 per cent
	$t_{95}\sigma$	2.9 per cent

TABLE 2

Distillation of Ethylvinyl Ether from Blood

Ethylvinyl Ether Added (mg.)	Found (mg.)	Recovery (per cent)
2.34	2.24	95.8
3.90	3.86	99.0
3.12	3.17	101.0
3.90	3.86	99.0
1.56	1.34	86.0
	Median	99.0 per cent
	σ	6.5 per cent
	$t_{95}\sigma$	7.6 per cent

Discussion

The chemical procedure used here is essentially the iodoacetal method of Siggia (2), but makes use of about a 10-fold dilution of the reagents in order to determine the smaller amounts of ethylvinyl ether. The potassium iodide content of the iodine solution was increased in order to lessen the chance of loss of iodine in the stream of nitrogen bubbling through it. In order to force the iodoacetal reaction to completion, the iodine should remain in excess throughout the distillation, preferably not being more than half consumed (larger amounts of iodine may be used if necessary). Since the reaction liberated a strong acid (HI) and thus the solution becomes acidic and since, in acid solution, potassium iodide may react with atmospheric oxygen to liberate iodine, nitrogen was used for a carrier gas rather than air. For this same reason, the solution should be titrated immediately upon completion of the distillation.

The distillation procedure was arrived at empirically. Preliminary studies indicated that the recommended procedure removes essentially all of the ethylvinyl ether from the blood.

The addition of alkaline stabilizers to sodium thiosulfate apparently interferes with iodoacetal reaction during the titration and tends to cause low results (5). For this reason, all stabilizers are omitted in the preparation of the standard thiosulfate. Thiosulfate solutions prepared with sterile distilled water are reasonably stable.

Summary

A method for the determination of ethylvinyl ether in blood has been described. The ethylvinyl ether is steam-distilled from the blood in a stream of nitrogen and determined by reaction with excess iodine to form its iodoacetal. The excess iodine is titrated with standard thiosulfate. The method is capable of estimating as little as about 0.3 mg. of the ether with a precision of about ± 8 per cent.

References

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