Ethchlorvynol Poisoning: Gas Liquid Chromatography in Management

J. Hedley-Whyte, M.B.,* and L. H. Laasberg, Ch.E.†

Management of patients who have ingested toxic doses of drugs is helped by quick identification and determination of drug levels. Upon this information is based the decision whether to employ peritoneal dialysis or hemodialysis. Moreover, urine production and acidity can often be varied to help drug elimination.

Suicidal attempts with nonbarbiturate hypnotics are becoming more common, so that identification and measurement of such drugs as ethchlorvynol (Placidyl), ethinamate (Valmid), glutethimide (Doriden) and meparpyynol (Dormison) present increasing problems. These drugs are suitable for quantification by gas liquid chromatography. A new technique for ethchlorvynol measurement based on gas liquid chromatography is described as a guide to therapy.

CASE REPORT

A 36-year-old man was taken, unconscious, to another hospital, two hours after having been seen alert. On admission the patient was breathing spontaneously, but 30 minutes later he vomited and aspirated gastric contents. Auffed endotracheal tube was passed. Hydrocortisone, 300 mg, was injected intravenously; 1,000,000 units penicillin and streptomycin 0.5 g were given intramuscularly. Gastric contents were aspirated via nasogastric tube. One hour later spontaneous respirations became inadequate and controlled ventilation was started. It was presumed that the patient had ingested a toxic dose of one or more drugs. Four hours after admission cardiac arrest occurred. Prompt external cardiac massage and D.C. defibrillation were immediately successful. Peritoneal dialysis was started and the patient was transferred to the Beth Israel Hospital, where we immediately attempted to identify the drug or drugs he was presumed to have ingested. Tracheostomy was performed. Peritoneal dialysis was discontinued after 23 l peritoneal dialysis solution 1 had been used in ten exchanges. Ventilation was controlled for the next eight days with an Emerson constant-volume ventilator; conventional chest physiotherapy and nursing techniques were used. The alveolar-arterial oxygen tension gradient (measured on 100 per cent oxygen) fell from 330 to 35 mm Hg in seven days. The electroencephalographic pattern initially consisted of 1-3/sec slow waves; by the eighth day of ventilation 10 to 12/sec alpha waves of 25-50 microvolts were present. The patient recovered consciousness late on the ninth hospital day and was sent home five days later. The suicidal attempt was thought to be due to an acute depressive episode.

DRUG ISOLATION, IDENTIFICATION AND MEASUREMENT

Five-ml aliquots of plasma or whole blood, hemolyzed by adding 2 ml distilled water, and 25 ml urine or peritoneal dialysate were shaken for two minutes with 2 ml chloroform. The chloroform phase was separated from the mixture by centrifugation at 15,000 rpm for five minutes. Aliquots of 3 μl of the chloroform phase were injected into a Hewlett-Packard 5750 Gas Chromatograph, equipped with a hydrogen flame ionization detector.

Ethchlorvynol was identified by measurement of retention times with three different liquid phases on chromosorb W (SE-30 1 per cent w/w, SE-33 10 per cent w/w and diethylene glycol succinate 6 per cent w/w) in six-foot stainless steel columns (i.d. 3/4 inch). The 6 per cent w/w diethylene glycol succinate as liquid phase on the chromosorb W (80-100 mesh) column was used for quantitation. Helium (flow rate 60 ml/min) was the carrier gas.

* Anesthetist-in-Chief, Beth Israel Hospital; Associate Professor of Anaesthesia, Harvard Medical School.
† Chemical Engineer, Department of Anaesthesia, Beth Israel Hospital; Research Associate in Anaesthesia, Harvard Medical School.

Received from the Department of Anaesthesia, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts. Supported by Grants 1 PO 1 CN 15904-01 and HE 12164-01 from the National Institutes of Health.

† Impersol (560 mg NaCl, 36 mg CaCl₂, 15 mg MgCl₂, 500 mg sodium lactate, 1.5 g dextrose per 100 ml water), Abbott Laboratories, Chicago, Illinois.
The flow rates of hydrogen and air through the flame jets were 35 ml/min and 350 ml/min, respectively. Temperature of the injection port (250 C), columns (168 C) and detector (310 C) were kept constant. The changes in flame current caused by the chemical ionization of ethchlorvynol during combustion in hydrogen flame were recorded by means of a Hewlett-Packard strip chart recorder Model 7127 A. A span setting ranging from zero to one millivolt for full-scale deflection of the recorder pen was used for recording the chromatograms.

The instrument was calibrated with known amounts of ethchlorvynol in normal urine, plasma and blood specimens. Because of the symmetrical peaks of the drug on the chromatograms, it was sufficient to measure the peak heights of ethchlorvynol for quantitation of the drug.

Responses of the flame ionization detector, columns and recording apparatus, evaluated by injection of various concentrations of ethchlorvynol in chloroform into the gas chromatograph, were found to be linear (fig. 1). The mean response factor of ethchlorvynol measured as peak height in mm/μg drug had a relative standard deviation of 1.8 per cent obtained from 33 determinations.

The mean recovery of the drug from urine was 94.2 per cent (S.D. 4.2 per cent); from whole blood 94.7 per cent (S.D. 3.1 per cent); from plasma 96.7 per cent (S.D. 2.4 per cent). Concentrations of ethchlorvynol as low as 0.05 mg/100 ml plasma can be measured accurately.

RESULTS

The initial plasma level of ethchlorvynol was 6.0 mg/100 ml; by the ninth day the plasma level had fallen to 0.25 mg/100 ml (fig. 2). The urinary level decreased from 0.65 to 0.11 mg/100 ml (fig. 2). At first, twice as much ethchlorvynol was present, per unit volume, in red blood cells as in plasma, so that the initial whole blood level was 9 mg/100 ml (initial hematocrit 50 per cent). By the ninth day the red blood cell level (0.25 mg/100 ml) was the same as the plasma level. The level of ethchlorvynol in the peritoneal dialysate was 0.72 mg/100 ml. Consequently, 166 mg (one-third of a tablet) were removed by peritoneal dialysis. Fifty-nine mg were excreted in urine in eight days (fig. 2). Gastric aspiration, seven hours after ingestion, removed only 3.8 mg ethchlorvynol.

No ethyl alcohol, opium alkaloids, barbiturate, salicylate, meprobamate, phenothiazines, organic bases or heavy metals were found in the urine.² No carboxyhemoglobin was present in blood.

![Figure 1](image)

**Fig. 1.** Linearity of response of the gas chromatograph’s flame ionization detector, columns and recording apparatus was evaluated by injection of various concentrations of ethchlorvynol in chloroform. Each point represents mean value (±S.D.) of eight determinations.

![Figure 2](image)

**Fig. 2.** Average plasma and urine levels of ethchlorvynol for each day of coma. Unfortunately, only part of the urine passed on the day of ingestion was available.
**CLINICAL WORKSHOP**

**DISCUSSION**

Quick and accurate determination of levels of a nonbarbiturate hypnotic, ethchlorvynol, is possible by gas liquid chromatography. Several measurements by gas liquid chromatography showed that in our patient the plasma level at awakening after ingestion was 0.3 mg/100 ml; colorimetrically-determined values at the times of awakening of other patients who ingested ethchlorvynol have ranged from 3 to 0.005 mg/100 ml plasma. These discrepancies are presumably due to use of colorimetric techniques at the limits of their accuracy.

Measurement of blood levels of drugs that cause coma has in the past been time-consuming. Moreover, until the application of chromatography and mass spectrometry it was difficult to identify unknown drugs. Recently, schemes for screening barbiturates and tranquilizers have been presented, but little attempt has been made to measure drug levels. The combination of gas liquid chromatography with high-level mass spectrometry and computer storage of data provides a technique which should be able to identify quickly and to quantify hypnotic drugs in blood. In this instance we did not find it necessary to employ mass spectrometry for identification of the ethchlorvynol—this was accomplished by gas chromatography with three different columns. Identification of an unknown peak of the chromatogram was achieved by mass spectrometry, however (fig. 3).

During peritoneal dialysis urinary output is suppressed; thus, despite dialysis there is negligible gain in ethchlorvynol excretion. The addition of either albumin or tromethamine to the dialysate has appeared to increase the ethchlorvynol excretion; however, data of these authors are insufficient for reliable evaluation and changes are not of clinical importance when urinary output is adequate.

Hemodialysis may be useful in removing ethchlorvynol. A ten-hour dialysis with a Travenol twin-coil dialyzer removed 5.49 g ethchlorvynol from a woman with a predialysis blood level of 21.6 mg/100 ml (determined by the colorimetric technique of Wallace et al.). She recovered conscious-

---

**Fig. 3.** Representative gas chromatogram from blood drawn on the sixth day of coma. A six-foot stainless steel column (i.d. 1/4") filled with Chromosorb W and impregnated with 6 per cent w/w diethylamine propyl succinate was maintained at 168 C. Peak 1 is due to solvent (chloroform). Peak 2 is ethchlorvynol, peak 3 was later identified by a mass spectrometer attached to a gas chromatograph as due to benzyl alcohol, a preservative of heparin.

---

*Hitachi Perkin-Elmer RMU 6-D and Varian Aerograph 500D courtesy R. A. Hites and Prof. K. Bliem, Department of Chemistry, Massachusetts Institute of Technology.*
Fig. 4. Colorimetric method based on reaction of phloroglucinol and concentrated HCl with the aldehyde group of ethchlorvynol was inaccurate below 3.0 mg/100 ml whole blood. Mean values and ranges for 3-6 determinations made at each concentration are shown. The difficulty of using this method explains previous discrepancies.8, 11, 13, 14, 15, 16, 17, 18, 19

Phloroglucinol levels at awakening approximately ten times (3 mg/100 ml serum) as great as the level at which our patient regained consciousness (fig. 2). We believe that the reason for these discrepancies is that the phloroglucinol colorimetric technique used by Westervelt2 is difficult to perform at levels below 3 mg/100 ml blood (fig. 4). This view is shared by Wallace11 and Ogilvie et al.20 At higher levels the phloroglucinol technique appears satisfactory.21

When sleep was induced in normal persons by the ingestion of 500 mg ethchlorvynol, the blood level was found by Wallace and co-workers21 to be 0.4 mg/100 ml— a figure almost identical to the level at the awakening of our patient. Neither hepatic damage nor nephrectomy was thought to prolong ethchlorvynol sedation in dogs.22 More recently, however, it has been stated that coma caused by ethchlorvynol is considerably prolonged in rats with hepatic damage induced by carbon tetra chloride.23 Our data show that almost all ethchlorvynol is metabolized.

Recent efforts of the pharmaceutical industry have provided a great number of lipophilic non-barbiturate hypnotics.24 Treatment of patients who have ingested these drugs is more difficult than treatment after equipotent barbiturate ingestion because metabolism is slow, excretion poor, and circulatory depression often profound, as in this patient. However, quick identification and measurement of the drugs greatly help management.

SUMMARY

Excretion of ethchlorvynol (Placidyl) after ingestion of a near-fatal dose is slow. Treatment of a man with an initial whole-blood level of 9 mg/100 ml (plasma level 6.0 mg/100 ml) was aided by a new gas chromatographic technique for quick and accurate quantification of ethchlorvynol in plasma, whole blood, urine, and peritoneal dialysate. Unconsciousness persisted for nine days: the patient awakened at a blood level of 0.3 mg/100 ml ethchlorvynol. Peritoneal dialysis did not significantly help drug excretion. Only 59 mg of ethchlorvynol were excreted in 13.5 liters of urine between the end of the first and the end of the ninth day of coma. The coma level after ingestion of ethchlorvynol is probably 0.3 mg/100 ml, not 3 or 0.005 mg/100 ml plasma as previously reported. We suggest that colorimetric techniques for measuring ethchlorvynol are unreliable at concentrations below 3 mg/100 ml plasma.

The help and encouragement of G. Paladino, B.S., R.Ph., Pharmacist, Beth Israel Hospital, is gratefully acknowledged.

REFERENCES

screening of toxicological extracts for alka-
loids, barbiturates, sympathomimetic amines
and tranquilizers, Anal. Chem. 35: 356,
1963.
8. Thompson, H. L., and Decker, W. J.: Analy-
sis of blood: A simplified gas chromato-
graphic approach for toxicologic purposes,
9. Schultz, J. C., Crowder, D. C., and Medart,
W. S.: Excretion studies in ethchlorvynol
(Placidyl) intoxication, Arch. Intern. Med.
10. Ogilvie, R. I., Douglas, D. E., Lochead, J. R.,
Moscovich, M. D., and Kaye, M.: Eth-
chlorvynol (Placidyl) intoxication and its
treatment by hemodialysis, Canad. Med.
11. Wallace, J. E., Wilson, W. J., Jr., and Dahl,
E. V.: A rapid and specific method for de-
termining ethchlorvynol, J. Forensic Sci. 9:
342, 1964.
12. Algeri, E. J., Katas, G. G., and Luongo,
M. A.: Determination of ethchlorvynol in
biologic mediums, and report of two fatal
13. I'Anc, S. Y., Kodet, M. J., Gardoki, J. F.,
McLamore, W. M., and Bavley, A.: Phar-
macological studies on the hypnotic anti-
convulsant actions of ethyl beta-chlorovinyl
ethyl carbinal, J. Pharmacol. Exp. Ther.
14. Carr, D. J., and Crampton, R. F.: Ethchlor-
15. Sedative-hypnotic drugs. V. The nonbarbi-

A Simple Method of Anesthetizing the Nasopharynx
Prior to Awake Nasal Intubation

JERRY A. SHOKAS, M.D., THEODORE R. STONE, JR., M.D.,
KARL F. URBACH, M.D.

A simple method of anesthetizing the naso-
pharynx and larynx prior to awake nasal intu-
bation is described.

A 20-ml syringe is fitted with a Toomey
urological adapter and an 18-cm length of the
tip end of a suction catheter (fig. 1). The
syringe is filled with 5–15 ml of viscous 2 per
cent lidocaine (xylocaine® viscous) and the
catheter is inserted into the nasal orifice.
The lidocaine is forced into the nasal passage and
slowly advanced into the pharynx and to the
larynx. During this procedure, successive ap-

Received from the Department of Anesthesi-
ology, U. S. Public Health Service Hospital, Staten
Island, New York.

ACTIONS of the local anesthetic are made
until the entire nasopharyngeal area and larynx
are anesthetized. This results in profound an-
esthesia with minimum discomfort and allows
accurate measurement of the amount of lidoc-
aine used. Experience in approximately 100
cases has shown excellent patient acceptance.