The Role of Organic Volatile Profiles in Clinical Diagnosis

Albert Zlatkis, Roswitha S. Brazell, and Colin F. Poole

The organic volatile constituents of biological fluids contain clinically useful diagnostic information for the recognition of metabolic disorders in man. To gain access to this information, it was necessary to develop the methodology for reproducibly stripping the trace concentrations of volatiles from biological fluids (dynamic headspace, gas phase-stripping, solvent extraction, and the transevaporator technique), to separate the complex extracts by high-resolution capillary column gas chromatography, and to develop computer-aided data-handling and pattern-recognition techniques for analyzing the immense amount of information generated. The normal and pathological organic volatiles identified by gas chromatography–mass spectrometry in urine, serum, and breast milk are tabulated. Clinical applications of the above techniques to the study and diagnosis of diabetes mellitus, respiratory virus infection, renal insufficiency, and cancer are described.

Additional Keyphrases: mass spectrometry · biochemical individuality · diabetes mellitus · respiratory virus infection · cancer · renal insufficiency · urine · breast milk · chromatography, gas

The last few decades have witnessed extraordinary developments in the chromatographic separation of complex mixtures. In particular, gas chromatography has revolutionized analysis for small molecules in biological systems, and much of our knowledge of their importance in medicine stems from such research during the last 30 years. Gas chromatography has evolved into a sophisticated separating and measuring technique for detecting several hundred substances in a single sample. This capability has made possible the use of broadly based “profiling” techniques in clinical chemistry. The concept of metabolic profiling was summarized by Jellum et al. as follows, “it seems reasonable to assume that if one were able to identify and determine the concentration of all compounds inside the human body, including high molecular weight as well as low molecular weight substances, one would probably find that almost every known disease would result in characteristic changes of the biochemical composition of the cells and the body fluids” (1). This statement is in keeping with Pauling’s concept of “orthomolecular medicine,” defined as the preservation of good health and the treatment of disease by varying the concentrations in the human body of substances that are normally present and required for health (2). As early as 1908, Sir A. Garrod, a physician, suggested that pathological states could possibly be reflected in characteristic changes in the profiles of the constituents in biological fluids (3). The most advanced analytical techniques yet devised do not allow a full inventory to be taken of all the chemical substances making up the essential biological fluids. Progress has been made by restricting the inventory to physiologically important biological materials such as carbohydrates, amino acids, steroids, and peptides, and relating changes in their average concentration to particular diseases. Approximately half of the 200 or so clinically recognized metabolic disorders can be studied by gas-chromatographic profile techniques (4–9).

This review is concerned specifically with the use of profiles of the organic volatile fraction of biological fluids as an aid to the clinical diagnosis of disease. The “organic volatiles” consist of certain of the essential nutrients, intermediates, waste products, environmental contaminants, and other substances of low molecular mass involved in metabolism. Chemically a diverse group of substances of widely different polarity, most are alcohols, ketones, aldehydes, O- and N-heterocyclic compounds, isocyanates, sulfides, and hydrocarbons. They contain 1 to 12 carbon atoms and have boiling points <300 °C; ideally, they are sufficiently thermally stable to survive the chromatographic process intact without the need for derivatization. Table 1 lists those organic volatiles identified by gas chromatography and mass spectrometry in human urine, serum, and breast milk.

Sampling and separation of the organic volatile fraction of biological fluids presents several specific problems. The broad range of polarity, the low concentration, and the complex nature of the organic volatile fraction all contribute to the difficulty of their quantitative analysis. Sampling techniques are required that will separate the organic volatiles from their biological matrix and concentrate them before their resolution. The complex nature of the organic volatile fraction requires the use of high-resolution capillary column gas-chromatographic techniques for their separation and computer-aided data-handling methods for collecting, storing, and comparing the profiles generated. The various methods used to overcome the above difficulties will be outlined in subsequent sections.

Sampling Techniques and Analytical Techniques for Organic Volatiles in Biological Fluids

Techniques for isolating the organic volatile fraction from urine include dynamic headspace analysis with condensation of the stripped volatiles in a cryogenic trap (2, 10–13) or adsorption onto a porous polymer (7, 14–27). Isolation by dynamic headspace sampling has also been used for the analysis of serum (28–31), saliva (32), tissue homogenates (28, 33), and cerebrospinal fluid (34). Solvent extraction has been used for the sampling of urine (34–36), plasma (36–38), tissue homogenates (38), blood (39), breast milk, and amniotic fluid (36). The transevaporator sampling apparatus has been used for the analysis of urine, serum, amniotic fluid, breast milk, cerebrospinal fluid, and saliva, the sample volume required being 5–500 μL (26, 40–45).

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2 Oak Ridge National Laboratory, P.O. Box X, Oak Ridge, TN 37830.
3 Department of Chemistry, Wayne State University, Detroit, MI 48202.
4 A “profile” is a complete analysis of all those substances related by physical or chemical properties which might be recognized as comprising a distinct group.

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<table>
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<tr>
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<td>acetones</td>
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The dynamic headspace sampling technique can also be used for breath analysis (2, 10, 12, 15). Certain experimental difficulties make breath less suitable for diagnostic purposes than other biological media: the large amount of water vapor present in expired air, the very low concentration of volatile organic metabolites, the poor reproducibility of the profile unless precautions are taken to use very pure air, and the long equilibration time needed to flush out the lungs and remove interfering air pollutants. Scrupulous cleaning of the oral cavity is essential to eliminate contamination from oral bacteria and food. The selective detection of a few specific volatile metabolites in expired air can be diagnostically useful; for example, above-normal concentrations of mercaptans and dimethyl sulfide in expired air are associated with hepatic cirrhosis (12).

**Dynamic Headspace Analysis**

Dynamic headspace sampling is best suited to the analysis of urine and other biological fluids for which the sample volume is not so restricted. Figure 1 illustrates a suitable apparatus for sample volumes in the range 25–250 mL. In a typical experiment, an aliquot of a 24-h urine, ammonium sulfate (200 g/L), and a magnetic stirrer bar are placed into the 500-mL sampling bottle, which has a ground-glass joint at its neck. The sample bottle is fitted with a condenser connected to a thermostatically controlled water circulator. To the other end of the condenser is attached a Y-connector holding two adsorbent traps filled with Tenax (2,6-diphenyl-p-phenylene oxide polymer). A flow-rate of helium through the apparatus is established at 20 mL/min. The organic volatile fraction is collected by heating the rapidly stirred sample in a waterbath set at 90 °C, the sampling time usually being 1 h.

The yield of collected volatiles depends on such experimental variables as duration of sampling, sample temperature, cooling-water temperature in the condenser, helium gas flow-rate, and the interfacial surface area between liquid and gas phases. Liebich found that the optimal temperature for the condenser was 12 ± 1 °C (24). At lower temperatures, the

![Fig. 1. Headspace sampling apparatus](image-url)
organic volatile profile is lacking in the higher-boiling constituents, and at temperatures above 16 °C there was a distinct loss of low-boiling materials. The dynamic headspace sampling technique is semiquantitative, but is reproducible if experimental conditions are adequately controlled. In general, higher-boiling compounds are less well accounted for than lower-boiling constituents, but the reproducibility is better for the higher-boiling constituents. Incubating the urine samples with Glucurase [Sigma Chemical Co.; a β-D-glucuronidase (EC 3.2.1.31)/sulfatase (EC 3.1.6.1) mixture] releases further volatiles that were conjugated as glucuronides and sulfates (18). The whole sampling, separation, and data-recording operations can be completely automated. Two research groups have described the construction of mechanized analyzers for urine organic volatiles (13, 23).

Because the organic volatiles in the urine sample equilibrate slowly with the gas phase above the fluid, the minimum sample volume of urine for a detailed profile is 25.0 mL. The passage of organic volatiles from urine into the gas phase is also influenced by their solubility in water, the possibility that selective adsorption to high-molecular-mass biological molecules will diminish their vapor pressure, and the area of contact between the gas and liquid phases. Transfer of organic volatiles to the gas phase is favored by adding a salt to the sample, maintaining an increased temperature, and vigorously stirring the sample so as to create a vortex. Because the equilibration of volatiles between the gas and liquid phases is slow, sampling times are comparatively long; thus it is possible to trap several samples, in series, during the same experiment. Not surprisingly, such samples may differ quantitatively, a further reflection of the fact that the volatiles are removed gradually and incompletely.

Ordinarily, clinical laboratories assay blood rather than urine for diagnostic purposes, because the composition of blood varies less. Analysis of blood for organic volatiles presents several problems. First of all, less sample is easily available than is the case for urine. Although most of the organic volatiles present in urine are also present in serum, their concentration is much lower. The dynamic headspace sampling technique has been used to obtain profiles for blood and serum, but the sample volume required for a diagnostically useful profile is too large for clinical purposes (28, 29, 31). Alternative sampling procedures have been developed for the analysis of less than a few milliliters of biological fluids.

**Gas-Phase Stripping Analysis**

Use of gas-phase stripping techniques may improve the yield of organic volatiles from small volumes of biological fluids by facilitating the transfer of volatiles from the liquid to gas phase (27). With this apparatus, the sampling gas is introduced below the liquid level; the finely dispersed bubbles provide maximum surface contact between the gas and liquid phases. As the organic volatiles move into the gas phase, they are rapidly and continuously carried away, thus favoring the stripping process.

Initial trials, in which helium was dispersed through a glass frit, were unsuccessful because of excessive foam formation, which could not be controlled by antifoaming agents. As an alternative the surface area of the liquid can be increased by packing the sampling apparatus with glass beads. The gas-phase stripping apparatus (Figure 2) consists of a glass cylinder (15 cm × 2.4 cm i.d.) about half filled with 3-mm glass beads (26). A water-cooled condenser is attached to the cylinder and at its lowest end is fitted a glass frit. A Tenax trap is attached to the top of the condenser, the stripping gas flow-rate established at 10 mL/min, and the apparatus immersed in a constant temperature hot-water bath set at 55 °C. For analysis 2.0 mL of urine or serum is required, with a sampling time of 30 min.

**Solvent Extraction of Organic Volatiles**

When applied to serum, gas-phase stripping techniques failed to reveal the complete complexity of the organic volatile fraction, and the several-milliliter sample required was too large for some problems, e.g., pediatric chemistry or studies with laboratory animals. This prompted investigations into the use of solvent-extraction techniques for profiling organic volatiles in microliter sample volumes. Profiles so obtained are selective because extraction efficiency depends on the value of the partition coefficient of the solutes and the area of contact between the solvent and sample. Limitations of the solvent-extraction technique are: very pure extracting solvents must be used, evaporation of the extracting solvent is usually accompanied by a loss of compounds of low boiling point, and no one solvent will extract to an equal extent the complete range of volatile compounds present in biological fluids. The principal advantage of the micro-scale solvent-extraction technique is the small volume required for profiling. Only 100 μL of serum, 3.0 mL of urine, 20 μL of breast milk, or 500 μL of amniotic fluid is needed; these samples are saturated with ammonium carbonate and extracted with 500 μL, 1.0 mL, 100 μL, or 750 μL of ether, respectively (30). The organic volatiles in saliva, cerebrospinal fluid, and semen can also be extracted by the above technique.

The solvent extraction of plasma (37) and the continuous liquid-liquid extraction of urine (34) with ether was used to prepare concentrates of the organic volatiles in biological fluids before identification by gas chromatography–mass spectrometry. The urine extract was neutralized with sodium bicarbonate to prevent the very large acetic acid peaks from obscuring the early part of the chromatogram. At the opposite scale of operation, Düngees and Kiesel (39) described the use of specially designed microwave for the extraction and concentration under partial reflux of microliter samples.

**The Transevaporator Sampling Apparatus**

General improvements in the methods for the microliter
solvent extraction of biological fluids resulted in the development of the transevaporator sampling apparatus.

The transevaporator is a sampling apparatus for the solvent stripping of organic volatiles in small (5–500 µL) samples of biological fluids with collection and separation of the organic volatiles from the extracting solvent on an adsorbent column. This technique is suitable for the analysis of serum, urine, saliva, cerebrospinal fluid, breast milk, amniotic fluid, sweat, and tissue homogenates.

The transevaporator sampling apparatus is shown in Figure 3; details of its operation are given elsewhere (26, 43, 45). The sample is injected by syringe into the base of a micro-column packed with Porasil E (controlled pore silica gel; Waters Associates, Milford, MA 01757). The micro-column retains most of the water, the high-molecular-mass polar organics, and the inorganic salts that are present in the biological fluids. It also distributes the sample as a film over a large surface area and thus improves the efficiency with which the organic volatiles are extracted. The stripping gas passes through the micro-column, removing the organic volatiles, which are then collected on a Tenax trap to provide a modified headspace sample. A solvent-extraction profile is obtained by using gas pressure to force a volatile solvent such as 2-chloropropane through the micro-column; this solvent carries the solvent- soluble organic volatiles to the glass bead trap, where the volatiles are collected and the solvent is evaporated.

The transevaporator sampling apparatus provides a semi-quantitative profile that is reproducible but only fairly representative of the actual concentration of organic volatiles in the sample. In absolute terms, the percentage recovery of test compounds depends both on the volatility and the chemical nature of the compounds being studied. For aqueous standards containing n-propanol, n-butanol, 2-decanone, 2-heptanone, and benzaldehyde prepared to cover the range 0.5 to 5.0 mg/L, the percentage recovery was consistent for each compound throughout the concentration range and averaged 20, 40, 50, 55, and 70%, respectively (47).

The thermal and chemical stability, high collection efficiency, gas permeability, and hydrophobicity (low retention of water) of Tenax has led to its almost universal acceptance as an adsorbent for headspace analysis. When Tenax was used to trap the organic volatiles from the transevaporator in the solvent-extraction mode, results were poor because of the low recovery of the volatiles when they were collected in the presence of the extracting solvent. This led to the evaluation of other trapping agents (glass wool, glass beads, textured glass beads, Teflon wool, and carbon fibers). Glass wool and glass beads were found to be superior (38, 40). The glass bead traps efficiently retain the organic volatiles, allowing the extraction solvent to evaporate by forced convection. Other advantages are the low desorption temperatures for sample transfer to the chromatographic column and the low background contamination.

Chromatographic Analysis of the Organic Volatile Fraction

The organic volatile fraction is so complex that high-resolution capillary column gas chromatographic techniques must be used. The limited sample capacity of these capillary columns presents certain injection problems if their high resolution is not to be degraded. For the separation of the organic volatiles, the sample on the glass beads or Tenax trap is thermally desorbed in a stream of helium and condensed in a short capillary precolumn cooled in liquid nitrogen. This condensation serves to "refocus" the sample. The capillary precolumn constitutes the injection device, and the analysis is commenced by coupling it to the analytical column, establishing the carrier gas flow-rate, and removing the cooling bath from the precolumn before beginning the temperature program.

The organic volatiles have been separated on glass, nickel, or stainless-steel capillary columns coated with non-polar to medium-polar stationary phases. Either glass or metal capillary columns are used routinely. Fused silica capillary columns have recently become commercially available; they are inherently more mechanically stable and chromatographically inert than glass columns and are likely to be widely used for the separation of organic volatiles in the future. The chromatographic performance of glass capillary columns, after careful deactivation, is better than that of metal columns, their main limitation being their greater fragility. The principal disadvantage of stainless-steel columns is the partial desorption of aldehydes, the possibility of catalytic alteration of the sample by the metal surface, and the general trend for polar compounds to exhibit peak tailing. Nickel columns, as well as showing some of the above features, partially adsorb sulfur-containing compounds.

Data Handling and Pattern-Recognition Techniques

Figure 4 illustrates the complexity of the organic volatile fraction and the problems associated with collecting and evaluating the chromatographic data. Modern computing integrators are commercially available that can store the chromatographic data as absolute retention times (used to identify a particular peak in the chromatogram and relative peak areas (a measure of the concentration of that compound in the sample). This information forms the data base by which different chromatograms are compared. When there is a consistent large change in the areas of a few peaks in the chromatogram of the organic volatiles obtained from a pathological sample, compared with their mean average peak area in normal samples, then visual inspection of the chromatograms usually suffices for clinical diagnostic purposes. But there are exceptions, when a more sophisticated procedure, computer-aided pattern-recognition, is required.

Reliable visual comparison of large numbers of profiles, each containing more than 200 peaks, obviously is not feasible. Three research groups have described pattern-recognition
procedures for use in interpreting organic volatile chro-
matograms (19, 25, 42). Each of these techniques involves the
use of clinically defined samples to provide training sets, which
are used to establish pattern vectors characteristic of the
sample type. These pattern vectors are then used to classify
a further set of samples, not used in the training set, to test the
efficiency of the pattern-recognition algorithm. In one study of
urinary organic volatiles from diabetic patients, 93.75% of
the test samples were successfully classified by using threshold
logic units as being normal or diabetic (25). In another study
(42), the K-nearest-neighbor pattern-recognition procedure
was used to classify correctly 87.5% of serum samples from
normal controls and virus-infected patients.

Organic Volatile Profiles and Biochemical
Individuality

The organic volatile profiles will be more or less affected by
factors such as genotype, diet, circadian and seasonal varia-
tions, occupation, physical exercise, and physiological and
clinical status. For volunteers on a standard chemical diet
composed almost entirely of small molecules (Vivonex-100),
after the fourth day, when intestinal flora had disappeared,
the average standard deviation for individual gas-chromato-
graphic peaks in the urine profile on successive days was about
10% (2). For volunteers on a normal diet, individual differ-
ces in average concentrations were several times greater.
In general, as far as urinary volatiles are concerned, the vari-
bance between individuals is significant, whereas for the same
individual the profile from urines collected on different days
remains remarkably constant (16). The chromatograms of
the urinary volatiles can be considered to be characteristic for
the individual and little influenced by diet, sex, and circadian or
seasonal changes (14, 22, 24, 34). Concentrations of the or-
ganic volatiles in normal urines are subject to physiological
variations, with relatively narrow normal ranges for compo-
sounds such as 2-pentanone, 4-heptanone, 2-heptanone, and
pyrrole and very broad normal ranges for some other con-
stituents (e.g., allyl isothiocyanate and carvone) that are ab-
sent from some normal urines (24). This biochemical individ-
uality is much more suppressed in serum than in urine,
making comparison of different profiles less troublesome.

Clinical Use of Information on Organic Volatiles

Diabetes Mellitus

Diabetes mellitus has been carefully studied by profiling
techniques during recent years. The deficiency in effective
insulin that characterizes this disorder drastically alters the
metabolism of carbohydrates, lipids, and proteins. In its fully
developed form, the disease is manifested by increased blood
sugars, inadequate glucose tolerance, glucose excretion in the
urine, ketosis, acidosis, and increased protein breakdown (46).

Zlatkis et al. (16, 22, 34, 44) and Leibich et al. (24, 35, 47)
have studied the profiles of urinary volatile metabolites for
both normal and diabetic individuals. The diabetic patients
were seen to develop distinct changes in their excretion of
volatile alcohols and ketones. Analysis of 54 urine samples
from 18 hospitalized patients with overt diabetes mellitus
showed increased excretion of ethanol in 87%, isobutanol in
69%, n-butanol in 66%, and isoamyl alcohol in 26% of the samples
(25). The patients studied were receiving different forms of
therapy (control by diet, insulin, or oral antiabetic medica-
tion). In a study (22) of 100 urine samples from 25 diabetic
patients (juvenile and adult types in the age group 16 to 75
years) characteristically increased excretion of ethanol and
n-propanol was found in 85% of the cases, of isoamyl alcohol
and butanol in 60%, and of isoamyl alcohol in 26%. These increases not only varied from patient to patient but also from day to day
in urine samples from the same patient. There was no obvious
correlation between the excretion of alcohols and the type of
therapy—increased alcohol concentrations were found in
the urines of patients on insulin, sulfonylurea, or biguanide, and
in patients whose diabetes was controlled by diet only. The
concentrations of alcohols were highest in the urines of several
patients being treated with insulin (16, 22). 4-Heptanone is
consistently found in normal urines among the compounds
of higher concentration (estimated mean excretion 50 μg/24
h), whereas cyclohexanone is either absent or detected only
in trace amounts (24, 47). Of 54 diabetic urines, increased
4-heptanone excretion was found in 38% and cyclohexanone
in 54%. Because the concentration of alcohols and cyclo-
hexanone is low in normal urines, the use of mass fragment-
ography as a selective detector for ethanol, n-propanol, iso-
butanol, n-butanol, isopentanol, and cyclohexanone in dia-
betic urines has been proposed for therapeutic monitoring and
disease control (47). The excretion of 4-heptanone in normal
urines ranges between 10 and 50 μg per day. By heating the
urine samples (90 °C, 60–90 min) to complete the conversion
of precursors to the corresponding ketone, the measured 4-
heptanone is increased five- to 15-fold. The same is true of
2-heptanone. The apparent 24-h excretion of 4-heptanone in
urine after heat treatment was 184 μg for normal urines and
900 μg for diabetic urines. For 2-heptanone, the corresponding
values were 27 μg and 62 μg.

Abnormal concentrations in urine of certain aliphatic al-
cohols, ethanol, n-propanol, n-butanol, and isopentanol and
certain ketones (4-heptanone and cyclohexanone) reflect
the metabolic disorders in patients with diabetes mellitus. De-
pending on the form, stage, and severity of the disease, the
excretion of one or several of these analytes is changed. This
information, combined with the standard glucose tolerance
test, provides a positive diagnosis of diabetes. In nearly 90% of
the urine samples studied, ethanol and n-propanol were
increased; these seem to be the analytes most indicative of
diabetes mellitus. Isopentanol, cyclohexanone, and 4-hepta-
none are more specific for certain forms, stages, and situations
of the disease (24). Further studies are required to find more
detailed correlations between these metabolites and the
clinical aspects of diabetes mellitus.

In addition to the primary metabolic disorders of diabetes
mellitus, neurological abnormalities are also associated with
the disease. The diabetic neuropathy or diabetic neuritis that
occurs rather commonly is associated with changes in both the
central and peripheral nervous systems. The pattern of axonal
degeneration and symmetrical polyneuropathy found in pa-
in patients with long-standing diabetes is similar to the distal
neuropathy found in cases of prolonged exposure to certain

Fig. 4. Example of organic-volatile profile by solvent extraction of
serum, obtained from a long-standing diabetic on no drug
therapy, with the use of the transevaporator
Separations done on a 106 x 0.25 mm I.D. glass capillary column coated with
Silar 10C; helium flow-rate 1.5 mL/min; temperature program: isothermal 40
°C for 6 min, then 2 °C/min to 180 °C and finally isothermal at 180 °C for 30
min

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aliphatic hexacarbon compounds such as n-hexane, 2-hexane, and 2,5-hexanedione (48, 49). To test the hypothesis that the diabetic state produces endogenous neuroretic diketones that could account for the sensory loss affecting many patients with diabetes mellitus, profiling experiments were undertaken to determine quantitative variations of the ketones, especially those that can undergo \( \omega-1 \) oxidation to form \( \gamma \)-diketones (26, 44). 2-Hexanone and 3-heptanone were the only ketones found in diabetic sera that could undergo \( \omega-1 \) oxidation to form \( \gamma \)-diketones. Intermediate metabolites of these ketones, which could also lead to the formation of the diketones, were not detected, nor were the \( \gamma \)-diketones themselves. When individual serum profiles were compared, no correlation between the severity of the neuropathy and the concentrations of 2-hexanone or 3-heptanone was found. When the overall profiles were compared, significant quantitative variations were found between normal subjects and patients with long-standing diabetes on no therapy, especially at the high-temperature end of the chromatograms. However, serum profiles for diabetics on insulin closely resembled normal profiles. In contrast, the urinary volatile profiles of insulin-treated diabetics differ distinctly from normal.

Respiratory Virus Infection

A total of 36 serum samples from 12 men volunteers who had been exposed to either “England virus” or “Rhinovirus” were studied by profiling techniques to establish a method for both the detection and the assessment of the volunteer’s susceptibility to virus infection (34). The concentration of four organic volatiles—2-ethylhexanol, 2-ethylhexan-1-ol, 6-methyl-2-heptanone, and a trimethyl-2-cyclohexanone (tentative identification)—were found to be important for indicating virus infection. A two-peak ratio method was used to characterize the various serum samples. On virus infection, the 6-methyl-2-heptanone/2-ethylhexanol ratio decreased from the normal value and the 2-ethylhexanol/trimethyl-2-cyclohexanone ratio increased. By use of the two-peak ratio method, 86% of 14 blind-selected unknown serum samples were correctly classified as normal or virus infected. Concentrations of the four organic volatiles in serum and the susceptibility of the volunteers to virus infection were well correlated.

Renal Insufficiency

The percentage of alcohols among the total volatile components in serum is higher and the percentage of ketones is lower than in urine (31). Presumably, the alcohols are better adsorbed in the kidneys and further metabolized. n-Pentanol was found in serum samples but is generally not detected in urine samples. The concentrations of 4-heptanone in serum from normal subjects ranged between 10 and 50 nmol/L. By comparison, the 24-h urinary excretion is 900–3500 nmol. In cases of renal insufficiency, less 4-heptanone is excreted. In five patients undergoing hemodialysis, concentrations between 3250 and 1000 nmol/L were found before dialysis.

There are certain characteristic alterations in the profiles of organic volatiles in plasma from patients in chronic renal failure who are treated by intermittent maintenance hemodialysis (30). Less dimethyl disulfide, methyl mercaptan, carbon tetrachloride, benzene, chloroform, and toluene were present in plasma after a dialysis treatment, but only the first four of these returned to as low a value as found for normal plasma. In contrast, certain compounds of higher molecular mass, including cyclohexanol and xylene, were present in increased concentration after dialysis.

Cancer

Profiling studies of cancer patients have been aimed at identifying characteristic changes in the concentration of organic volatiles in serum samples, which might be used for the early diagnosis of cancer, when treatment might be expected to be the least traumatic and successful. Sera of patients with leukemia, multiple myeloma, breast cancer, lymphoma, or melanoma showed patterns virtually indistinguishable from normal (26, 45), even when selective chromatographic detectors (e.g., electron-capture, nitrogen-phosphorus selective, flame-photometric detector for sulfur) were used to maximize the information content of the samples. These selective-detector profiles from normal and pathological samples were very similar, and no diagnostically useful trends were found.

The organic volatile profile of biological fluids is a promising technique for the study of a diverse series of metabolic disorders. Many problems of analytical methodology have been solved, and we are entering an era when profiling of organic volatiles can be developed into a clinically useful tool. Besides the diseases discussed here, heart, liver, and mental disorders are being investigated, but results have not yet been published.

References


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