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Biotransformation of Drugs Used in Anesthesia

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WRITING about biotransformation of drugs presents a dilemma. On one hand, the material is clinically important because some breakdown products of drugs are themselves pharmacologically active or even toxic; on the other hand, complicated techniques and chemical terms that describe events in biotransformation discourage the clinical anesthesiologist who needs this information in his daily work. The present review, therefore, will look at the subject from the point of view of a clinical consultant with the objective of making the material more meaningful to the clinical practice of anesthesiology. To avoid repetition, the discussion will not emphasize information covered in the 1968 review by Greene [1] or the 1971 review by Cohen.[2]

Assume a patient had a cholecystectomy under general anesthesia four days ago. He now has a mild fever, and vague complaints of general malaise and nausea. Work-up includes a detailed urinalysis. The clinical chemist (using analytical methods not generally available to us) reports that the urine shows elevated levels of chlorides, bromides, and fluorides, as well as the presence of methoxydifluoroacetic acid, dichloroacetic acids, trifluoroacetic acid, oxalic acid, trifluoroethanol glucuronide, 2-amino-3 methylbenzoic acid, 4-hydroxy-2,6-xylidine, nor-fentanyl, desproprionol-fentanyl, and a glucuronide form of tropanyl tropate. A clinical consultant called in on such a case would attempt to reconstruct the drug history of this patient, concentrating on the last four or five days, since preoperative urinalysis revealed no abnormal levels of any substance.

The Ions

Chloride occurs abundantly in nature, and short of employing a specifically labeled chlorine, it would be impossible to trace its origin. Fluoride and bromide, however, are not present in any significant degree in normal urine.

These halogens will let us immediately think of halogenated anesthetics, and we should, for the sake of thoroughness, start with the discussion of simple agents such as chloroform, CCl_3H, and carbon tetrachloride, CCl_4.

Although chloroform had been used as a major volatile anesthetic for more than 120 years, it was not until 1963 that Paul and Rubenstein [3] reported on the biotransformation of chloroform in animals. They showed that chloroform is converted to CO_2 in rats. However, data concerning the metabolic fate of chloroform in man have been lacking until quite recently. Fry *et al.*[4] investigated the fate of chloroform in nine volunteers. The chloroform was labeled with the nonradioactive isotope, ^{12}C, and given orally in gelatin capsules. For eight hours thereafter the subjects exhaled through a gas mask, with the expired gases measured and assayed for chloroform and CO_2 at 10-minute intervals. In addition, blood samples were drawn and urine collected for 24 hours after the administration of chloroform. Eighteen to 67 per cent of the chloroform was exhaled in eight hours. Although chloroform could be detected in the breath of some of the subjects 24 hours after dosing, the concentration was below quantitative measurable limits and most of the chloroform excreted through the lungs was expelled in eight hours. The pulmonary excretion of $^{12}CO_2$ was measured in two subjects. The maximum $^{12}CO_2$ concentration appeared 75–220 minutes after administration of the capsule. Forty-nine per cent of the dose appeared as exhaled CO_2 in one woman, 51 per cent in one man, and it was concluded that about half of the ingested dose of the chloroform was broken down to carbon dioxide and excreted through the lungs. The authors postulated the following biotransforma-

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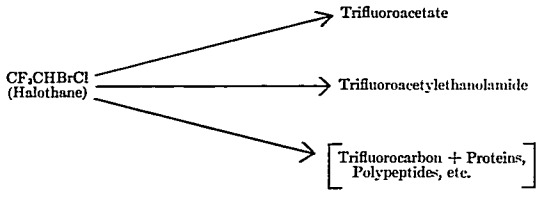

FIG. 1. Halothane and its metabolites.

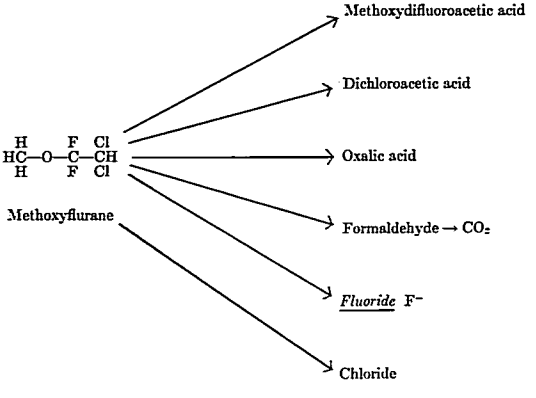

FIG. 2. Methoxyflurane and its metabolites.

tion of chloroform in man:

$$CHCl_3 \text{ (chloroform)} + H_2O + O \rightarrow CO_2 + 3\ HCl \text{ (hydrochloric acid)}$$

This is an overall reaction. The authors thought it unlikely that the initial reaction was homolytic fission of the C–Cl bond with formation of chlorine radicals, since reaction products like methylenedichloride and 1,1,2,2,-tetrachloroethane could not be found by very sensitive gas chromographic methods in any of their experiments. This is in contrast to Butler's finding of methylene chloride in mouse livers *in vitro*.[5] Yet, the chlorines must be disposed of during the biotransformation of chloroform to CO_2 and could appear in urine as inorganic chloride.

Carbon tetrachloride is also metabolized in the liver. Its carbon–chlorine bond cleavage is of interest because it seems to result in lipid peroxidation which has been linked with the chemical events leading to hepatic cellular necrosis.[6-9]

The other urinary metabolites in our fictitious case cannot help us in deciding whether our patient had been exposed to chloroform or carbon tetrachloride.

The presence of bromide in the urine of our patient suggests the ingestion of bromides. For many years bromides were used as sedatives, but they have now largely disappeared from the medical armamentarium. Bromine, of course, can be part of the molecule of a volatile anesthetic, and the list of metabolites will have

to be examined for other clues indicating a brominated inhalation anesthetic.

Fluorides occur in toothpaste, in water, and in several solid drugs, but in such low concentrations that noticeably elevated urinary fluoride levels should be alarming. Again, several inhalation anesthetics and the convulsant flurothyl (Indoklon) contain fluorine, and so the other metabolites in the patient's urine will have to be examined to see which hydrocarbons or ethers might have served as sources of this halogen.

The Acids

Several of the acids listed as being found in the urine of this patient invite close scrutiny, particularly in light of a general rule that the biotransformation of ethers and hydrocarbons often leads to formation of organic acids.

Trifluoroacetic acid: There is little likelihood that the body would have fixed three fluorines to a single carbon in the process of intermediary metabolism of a drug. Indeed, it is very difficult for intermediary metabolism to remove a fluorine from a carbon that carries three fluorines.[10] Trifluorocarbons are biostable, whereas difluorocarbon bonds can break in the body. The CF_3 radical found in the urine of the present patient must, therefore, be listed as a constituent molecule of one of the drugs to which the patient was exposed.

Dichloroacetic acid: It is unlikely that the body chlorinated an acetic acid radical, but it is possible that the parent drug carried two or more chlorines on a carbon.

Methoxydifluoroacetic acid: We have already seen that the parent substance for this particular acid could not have been a compound containing a trifluorocarbon because of the stability of CF_3-. Furthermore, the methoxydifluorocarbon configuration (CH_3—O—CF_2) shows an oxygen bridge of an ether.

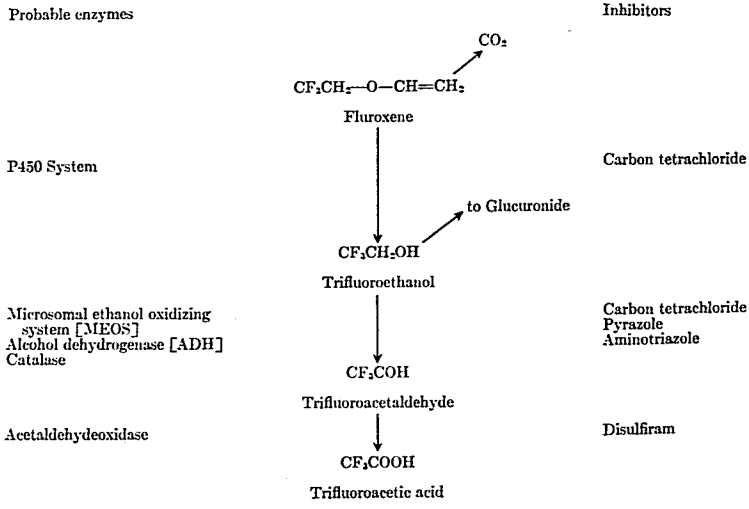

FIG. 3. Postulated pathways of fluroxene biotransformation.

Oxalic acid: This acid has been postulated as a potential metabolite of methoxyflurane and is said to contribute to the nephrotoxicity of methoxyflurane, which will be discussed later.

At this point it is time to sketch the commonly used inhalation anesthetics that contain bromine, chlorine, and fluorine, and list their products of biotransformation [11-24] (see figs. 1, 2, and 3). Methoxyflurane (Penthrane), halothane (Fluothane), and fluroxene (Fluoromar) are agents that might explain the acids and ions already discussed.

Metabolism of Anesthetics in General

At first glance it is surprising that volatile anesthetics which are taken up by the lung and to a large degree leave the body by the same route can be transformed into nonvolatile products as well as into volatile CO_2. The nonvolatile products are excreted in the urine, bile and feces.[22] The most important avenue for excretion, however, is the kidney, and nonvolatile metabolites of inhalation anesthetics can be found for many days in the urine of patients after a single exposure.

The long delay in excretion may be caused not only by limitations in renal transport of these metabolites, but also by the fact that anesthetics are fat-soluble and are, therefore, stored in body compartments for many days. These compartments slowly feed anesthetic into the metabolic biotransformation process, which deposits its end-products in the urine. Thus, radioactivity, presumably labeled trifluoroacetic acid, a halothane metabolite, was found in the urine 24 days after a single exposure to halothane.[23] With refined methodology, trace amounts of anesthetic metabolites might be detected for even longer periods.

Factors Influencing Metabolism of Volatile Anesthetics

It has been suggested that anesthetics might inhibit their own metabolism, *i.e.*, the more volatile anesthetic present, the less metabolism should take place.[25, 26] This was based on studies in miniature swine in which the amount of anesthetic taken up by the liver was assumed to be equal to the amount metabolized. Several other observations, however, indicate that the rate of metabolism of volatile anesthetics is not decreased during anesthesia. Topham *et al.*,[27] for example, have shown in mice that the *rate* of halothane metabolism is highest during halothane anesthesia and declines progressively after anesthesia. Yet, the *amount* of metabolites excreted during halothane anesthesia may be small in comparison with the amount excreted after anesthesia, the latter presumably derived from metabolism of halothane released from body depots.

In experiments on ourselves, we injected very small amounts of radioactive halothane intravenously (about one ten-thousandth of an anesthetic dose) and measured the amounts of radioactive metabolite in the urine. At a suitable time later we repeated the experiment after being anesthetized with halothane. The difference between labeled metabolite production two hours after injection of tracer was surprisingly small.[23] Furthermore, E. Cohen reported the appearance of nonvolatile metabolites almost immediately after onset of anesthesia in mice.[28, 29] Finally, we studied the effect of fluroxene anesthesia on postanesthetic mortality in mice and found that postanesthetic death occurred earlier and more frequently when the mice had been pretreated with phenobarbital, which increases the production of a toxic metabolite (*vide infra*). If anesthesia suppresses fluroxene metabolism, mice should not die more frequently during anesthesia. We, therefore, took two groups of mice, one pretreated and one nontreated, and anesthetized them for four hours with fluroxene. The pretreated mice (fast metabolizers) died *during* anesthesia, whereas the nontreated mice (slow metabolizers) recovered from anesthesia and died later.[30]

Genetic Factors in Metabolism

The center of metabolism is the liver, and particularly its P-450 system, a nonspecific drug-metabolizing enzyme system. The activity of this system is dependent on two factors, *i.e.*, environmental and genetic influences.

The metabolism of halothane is powerfully influenced by the genetic make-up of an individual, but is probably also affected by the environment. Genetic studies in man are severely limited by the techniques available to-

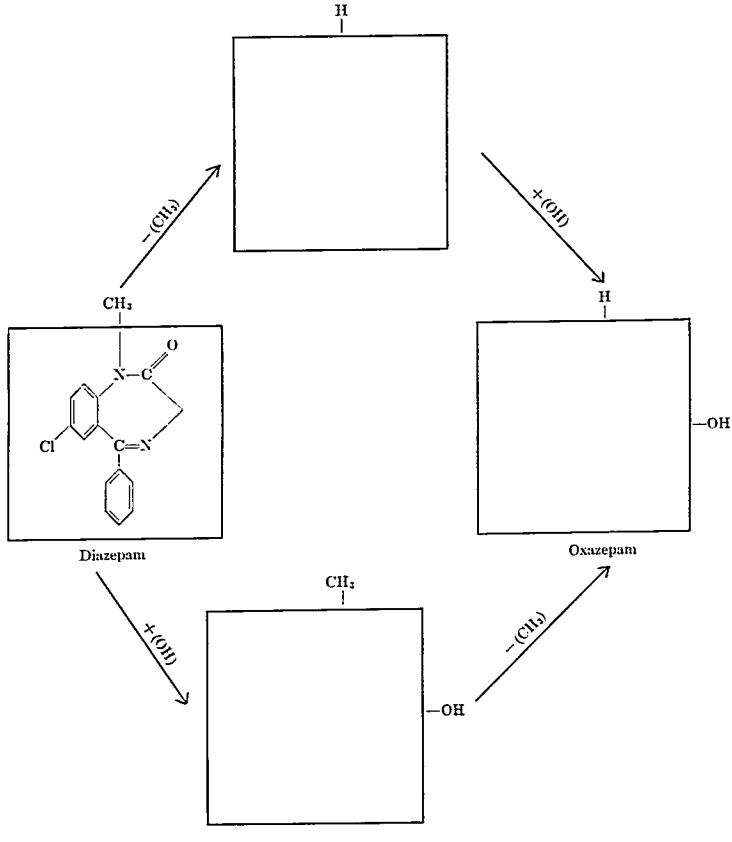

FIG. 4. Chemical structure of diazepam and major metabolites.

day. One can really study this only in identical twins who have identical genes. If drug metabolism of identical twins in different environments is always identical, but large differences exist between sets of twins, genetic factors must be assumed to control drug metabolism. This is numerically expressed by the h factor, which can vary from 0.0 to 1.0. An h factor of 1.0 means complete genetic control, and a factor of 0.0, no genetic control, of the modality under study. For halothane, the h factor is 0.89.[31] This means that almost 90 per cent of halothane metabolism in identical twins is controlled by genetic factors. The

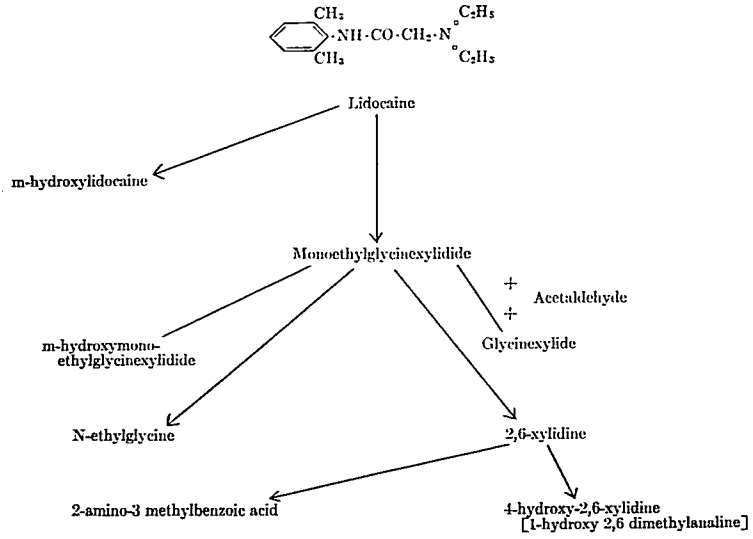

FIG. 5. Lidocaine and major metabolites.

genetic make-up of an individual may also determine the degree to which biotransformation can be influenced by the environment.[22, 23] Some evidence [23] indicates that anesthesiologists metabolize more halothane than persons not exposed to this anesthetic. Environmental factors facilitate or inhibit metabolism, and the effects vary from individual to individual, presumably because of genetic differences.

Toxicity of the Metabolites of Volatile Anesthetics

Nonspecific Toxicity

Strong organic acids tend to be bound to plasma proteins. This creates opportunities for drug interaction, because organic acids may displace other protein-bound drugs from their binding sites. Recently much has been said about drug interactions in general and protein binding in particular, and many examples in which the displacement of a protein-bound drug from its binding site can lead to adverse drug reactions have been cited.[24] Whether the concentrations of organic acids derived from volatile anesthetics are sufficient for clinically demonstrable drug reactions to occur on this basis remains to be seen.

Specific Toxic Effects

More important than this type of nonspecific toxicity are fairly specific toxic effects produced by metabolites. We have already mentioned the toxic effects of the metabolites of carbon tetrachloride, a model extensively used in studies of hepatotoxicity produced by halogenated hydrocarbons. Carbon tetrachloride, however, may be a unique example, and the toxicity seen with the more complex halogenated hydrocarbons and ethers may not be based on the carbon tetrachloride mechanism.[25]

Recently, Johnston [26] reported that four hours of anesthesia with fluroxene kills dogs

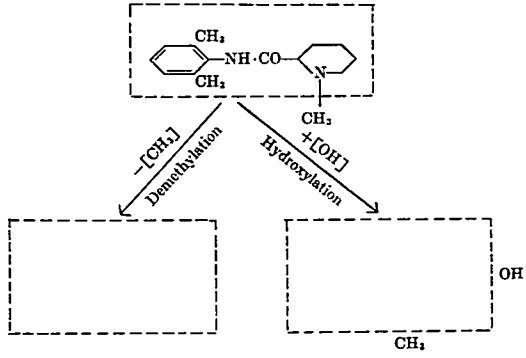

FIG. 6. Mepivacaine and two metabolites.

after anesthesia. This led us [37] to investigate the pharmacology and toxicology of fluroxene and its products of biotransformation in mice. We found that mice which had recovered from four hours of light fluroxene anesthesia invariably died within a day in a characteristic crouching position, with an unusually early onset of rigor mortis. Since fluroxene is transformed to trifluoroethanol in mice [22] and trifluoroethanol is quite toxic,[38, 39] we suspected trifluoroethanol (fig. 3) as the offending agent. To test this, we manipulated the metabolism of mice by pretreating them with drugs that either increase or decrease the metabolizing enzymes in the liver. We found that more mice died when hepatic enzymes had been increased. Suppression of hepatic enzymic activity protected the animals against death after fluroxene anesthesia. This strongly supports the thesis that biotransformation of volatile anesthetics occurs and that the ability of the organism to metabolize these anesthetics is variable and subject to manipulation. Most important, however, is the emerging concept that the metabolites may be toxic.

Trifluoroethanol fulfills all requirements of a toxic substance: it is toxic regularly and predictably, which is not the case with agents causing sensitivity reactions, and there is a relationship between dose and toxic effect.[38]

Today it is accepted that the renal damage after methoxyflurane anesthesia is a reproducible, dose-dependent phenomenon related directly to the levels of inorganic fluoride in the patient's serum.[40-44] The critical serum threshold for fluoride is between 80 and 100 μM/l. At these levels one can expect laboratory evidence of renal dysfunction. When fluoride levels rise higher than 150/200 μM/l, clinical evidence of renal dysfunction occurs. This may suggest that small amounts of methoxyflurane can be employed safely because only low concentrations of fluoride will be produced. However, patients who are capable of metabolizing methoxyflurane faster than normal because of genetic and environmental influences and whose renal tubular cells are unusually sensitive to fluoride could suffer renal damage from methoxyflurane in doses that are innocuous to most people.

Trace Amounts of Anesthetics

Continuously improving methods for demonstrating trace amounts of anesthetics and their metabolites have provided data indicating that operating room personnel frequently have minute amounts of anesthetics in their expired air and trace amounts of metabolites in their urine.[45, 46, 47] If such occupational exposures to traces of anesthetics in the operating room lead to measurable amounts of urinary metabolites, slight contamination of soda lime canis-

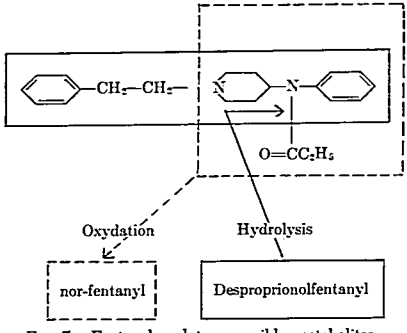

FIG. 7. Fentanyl and two possible metabolites.

ters from previous anesthetics or a leaky vaporizer can also contaminate a patient's air and may lead to "inexplicable" metabolites in his urine.

The Other Metabolites

The *diazepam* and *oxazepam* discovered in the urine of our hypothetical patient are, of course, easily traced to the ingestion of diazepam (Valium), which the patient presumably received because of anxiety. The metabolism of agents of this nature (fig. 4) can follow various pathways,[48-53] including demethylation and hydroxylation, which in turn result in metabolites which become hydroxylated–demethylated to form oxazepam. The formulas suggest that the less polar diazepam is converted to a more polar, more water-soluble form, and is therefore more easily excreted in the urine. The changes in structure are slight, and consequently there are only minor changes in biologic activity. All diazepam metabolites are active CNS depressants, oxazepam being about half as active as diazepam on a molar basis.[48] Most of diazepam is excreted in the urine, some of it in the feces and the saliva.[51] The half-life of diazepam, between 7 and 10 hours, is the result of a combination of the activities of all metabolites. After four hours de Jong [54] found a slight increase in diazepam activity (bioassayed by measuring protection against convulsions in cats), which he attributed to peaking of oxazepam levels.

Other substances in our patient's urine, such as 2-amino-methylbenzoic acid and 4-hydroxy-2,6-xylidine, are the principal breakdown products of *lidocaine* (Xylocaine) (fig. 5).[55-58] There are other pathways for the metabolism of lidocaine, but they are of minor importance in most individuals. One can speculate whether there are patients who metabolize lidocaine by one of the unusual pathways and whether this might have adverse effects on them. Since the amount of lidocaine metabolism depends on the activity of the microsomal hepatic enzymes,[56] large differences in quantities of lidocaine metabolites are to be expected in man.

One of the intermediary metabolites of lidocaine, monoethylglycinexylidide, has marked antiarrhythmic activity in mice and dogs, and it has been postulated that this metabolite may contribute to or be responsible for the antiarrhythmic action of lidocaine.[59]

The formula of *mepivacaine* (Carbocaine) is shown in figure 6. The metabolites of mepivicaine, once again, are demethylation and hydroxylation products, which make the compounds more polar and easier to excrete in the urine.[60, 61]

The demonstration of breakdown products of *fentanyl* (Sublimaze) and atropine in urine of our patient four days postoperatively suggests that the patient had these drugs only recently, because these drugs are given in small doses and have short half-lives and current assays for them are not highly sensitive. Indeed, study of the metabolism of fentanyl in man is at present almost impossible because of its high degree of biologic activity. Studies in rats indicate two possible metabolic end prod-

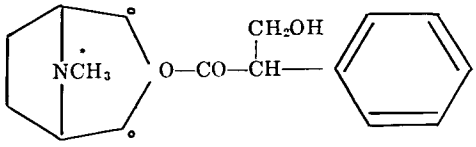

FIG. 8. Atropine with two different ^{14}C labels. * = N-methyl label; ° = 2,4-tropine label.

ucts—one produced by hydrolysis of the side chain leading to desproprionolfentanyl, and the other by oxygenation at the nitrogen, forming nor-fentanyl (see fig. 7).[62] In either case, the biologic half-life of fentanyl in man is considerably shorter than the half-life of any other opioid drug.[63] The major route of excretion of fentanyl and its metabolites is undoubtedly the urine.

Atropine is usually depicted by a formula that shows the tropine moiety as a rectangle. Figure 9 shows a structure that is somewhat closer to reality, a peculiarly formed ring. A very thorough study of radioactively labeled atropine in man showed that 77–93 per cent of injected atropine is excreted in the urine.[64, 65] The investigators used two labels, one at the methyl connected to the nitrogen in the ring, the other at the two carbons adjacent to the oxygen in the ring. Only the methyl label was excreted as CO_2, indicating that demethylation at this point is one pathway of metabolic disposition of atropine in man. About 3 per cent of the label was exhaled as CO_2 in three hours. The bulk of the metabolite was excreted in the urine, mostly as a glucuronide. Urinary excretion of atropine occurs at two rates, which seems to indicate that there are at least two different metabolic events, one slower than the other.[65, 66] It is also interesting that the blood levels of atropine could be related to its pharmacologic activity.[64] Low blood levels slow the heart rate and high blood levels increase it.

Conclusion

What anesthetics did the patient receive? The elevation of urinary fluorides together with methoxydifluoroacetic acid and dichloroacetic acid suggests methoxyflurane. Trifluoroethanol is a breakdown product of fluroxene.[22] Trifluoroacetate can be derived from either fluroxene or halothane.[24] If the latter two compounds are present in trace quantities only, and if they are not listed on the anesthetic record, contamination of soda lime or rubber equipment is their most likely source. The other metabolites can be explained by premedicants and postoperative analgesic drugs. However, we cannot say whether the patient's symptoms are related to drug intake and to the potential toxicity of metabolites. Much remains to be learned about the symptomatology produced by metabolites of inhalation anesthetics and other drugs extensively used in medicine.[67, 68]

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