Chemical Aspects of General Anesthesia: Part I. From Ether to Halothane

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General anesthesia is characterized by unconsciousness, analgesia (relief of pain), amnesia, muscle relaxation, and depressed reflexes, while avoiding cardiovascular instability, shivering and convulsions, and postoperative vomiting and nausea. These ground rules emerged gradually as the use of ether spread from Boston, Massachusetts in 1846 to the rest of the world. An all-inclusive noun, etherization, came into being; pundits quickly coined the word anesthesia.

Under local anesthesia (1) it is possible for the patient to be awake at all times during a surgical procedure. Even so the patient may express a desire to be asleep. The guiding principle is to be sensitive to the concerns of the patient, but also to avoid overmedication. In choosing general over local anesthesia, a major factor is the complexity of the procedure. A knee replacement can be carried out under regional anesthesia; a heart bypass involving several hours of surgery within the chest cavity needs be carried out under general anesthesia. A decisive call (5) for change was made in 1926 by John S. Lundy, a young physician at the Mayo Clinic. He was not willing to wait for marginal improvements in what was in essence a single-agent inhalational approach and believed the time had come to adopt a new way. He advocated a balanced system in which one or more supplemental drugs were administered intravenously.

Several decades of change were needed before ether anesthesia would be superseded by “balanced” general anesthesia. In 1934 Lundy and Waters (University of Wisconsin) independently (6) induced hypnotic sleep with thiopental, a new barbiturate (vide infra). The next advance came in 1942 when Griffith and Johnson (7) injected intravenously a therapeutic dose of the deadly arrow poison and neuromuscular blocker curare, 1 (Figure 1), reducing concurrently the quantity of inhalational anesthetic. Before this time satisfactory skeletal muscle relaxation was not possible until stage three of etherization, one step removed from near cessation of respiration.

Figure 1. The deadly arrow poison and neuromuscular blocker curare.
The appearance of halothane, 2-bromo-2-chloro-1,1,1-trifluoroethane (vide infra), in the 1950s as a potent and comparatively inert inhalational anesthetic meant that the basic rudiments of balanced general anesthesia were in place. It is a liquid polyhalogenated alkane with a low boiling point, just as chloroform is. Hospital trials of the new agent in conjunction with the ultrashort-acting barbiturate thiopental and the synthetic muscle relaxant succinylcholine (vida infra) were conducted successfully by Johnstone (8) and Bryce-Smith and O'Brien (9) in England in 1956.

Preparation of Compounds

Although the first synthesis of ether, 2, cannot be reliably documented,

\[
\begin{align*}
2 \text{EtOH} + H_2SO_4 & \xrightarrow{\text{distill}} \text{EtO}_2\text{H} \\
\text{wine spirits} & \text{oil of vitriol} \\
\end{align*}
\]

the compound received attention from the middle of the 16th century on; at the time its anesthetic properties were regarded as novel, but not significant.

Discovery of nitrous oxide, 3, is credited to the eminent English chemist Joseph Priestley in his pioneering studies of gases beginning in the 1770s. Within a short time the careful thermal decomposition of molten ammonium nitrate would become the standard synthetic pathway to the gas:

\[
\begin{align*}
\text{NH}_4\text{NO}_3(s) & \xrightarrow{\text{heat}} \text{N}_2\text{O}(g) + 2\text{H}_2\text{O} \\
\end{align*}
\]

Chloroform, 4, was discovered independently in three different laboratories in 1831:

\[
\begin{align*}
2 \text{CH}_3\text{CH}_2\text{OH} + \text{excess Ca(OCl)}_2 & \xrightarrow{\text{distill}} 2 \text{CHCl}_3 + \text{Ca(O}_2\text{CH)}_2 \\
\end{align*}
\]

As noted by Moseley (10), priority is to be given to the American chemist Samuel Guthrie, who produced the agent together with calcium formate by distilling a mixture of bleaching powder, Ca(OCl)_2, and ethyl alcohol.

As the 20th century began, synthetic organic chemistry was in full bloom. The first commercial sedative–hypnotic barbiturate, barbital or 5,5-diethylbarbituric acid, appeared in 1904, and the straightforward preparation of other barbiturates from diethyl malonate, 5, was repeated countless times (Scheme I). Thiopental sodium, 11 (Scheme I) (11), was the first of the intravenous induction (ultrashort-acting) anesthetics; thiamylal, 14 (Scheme I) (12), and methohexital sodium, 22 (Scheme II) (13), would also find use in this way.

Scheme I. Synthesis of thiopental sodium, 11, and thiamylal, 14.

\[
\begin{align*}
\text{MeCH}==\text{O} + \text{EtC}==\text{CMgBr} & \xrightarrow{\text{EtC}==\text{CCHMe}} \text{EtC}==\text{CCHMe} \\
\text{MeCH}==\text{O} + \text{EtC}==\text{CMgBr} & \xrightarrow{\text{EtC}==\text{CCHMe}} \text{EtC}==\text{CCHMe} \\
\text{MeCH}==\text{O} + \text{EtC}==\text{CMgBr} & \xrightarrow{\text{EtC}==\text{CCHMe}} \text{EtC}==\text{CCHMe} \\
\end{align*}
\]

Scheme II. Synthesis of methohexital, 22.
The monoalkylated malonate ester 7 (Scheme I) was a common intermediate in the preparations of compounds 11 and 14. It arose via the $\text{Sn}_2$ C-alkylation of the enolate anion of diethyl malonate with the secondary alkyl halide, 2-bromopentane, 6. A second alkylation with ethyl bromide, 8, or allyl bromide, 12, yielded the disubstituted malonate ester 9 or 13, as shown. Ring formation then occurred as the two nucleophilic nitrogen atoms of thiourea, 10, bonded to two electrophilic ester carbonyls. The emergence of a stable charge-delocalized anion (seen in structure 11 but not in 14) helps to bring this reaction to completion.

Presence of the carbon–carbon triple bond in one side chain of methohexitol, 22, required the preliminary synthesis of 2-bromo-3-hexyne, 18. As outlined in Scheme II, a Grignard reaction between acetaldehyde, 15, 1-butynylmagnesium bromide, 16, led to 3-hexyn-2-ol, 17. Careful treatment of 17 with phosphorous tribromide and pyridine then gave the alkylating agent 18.

Note as well the slight change from diethyl malonate, 5 (Scheme I), to ethyl cyanoacetate, 19, its bisalkylation [18 followed by 12 (allyl bromide)] leading to structure 20 (Scheme II). Reaction of 20 with methylurea, 21, in the presence of sodium ethoxide yielded a cyclic imino (C=NH) compound that, following hydrolysis ($\text{H}_3\text{O}^+$), gave barbiturate 22.

The appearance of curare in surgery prompted the development of succinylcholine dichloride, 25 (I4), as an alternative neuromuscular blocker. It was obtained via the direct reaction of the quaternary aminium salt with succinyl chloride, 24.

$$2\left(\text{Me}_3\text{NCH}_2\text{CH}_2\text{OH Cl}^-\right) + \text{Cl}_2\text{CCH}_2\text{CH}_2\text{Cl} \rightarrow \text{Me}_3\text{N}(\text{CH}_2)\text{O}_2\text{C}(\text{CH}_2)\text{CO}_2(\text{CH}_2)\text{NMe}_3 \quad \text{Cl}^-$$

Both steps in the preparation of halothane, 27, from 1,1,1-trifluoroethane, 26 (Scheme III) (I5), invoked free radical vapor phase halogenation at high temperature. If bromination preceded chlorination, then the overall yield of 27 was lower.

**Correlation between Structure and Activity**

It is essential to restrict the sphere of influence of a local anesthetic, but in general anesthesia direct access to the blood stream and the brain is required. The nature of the anesthetic receptors in the brain is still unclear. Individual drug-substrate binding studies are suggestive, but the questions of their importance in an overall mechanism go unanswered (2, 16).

In this context it is useful to observe how slight changes in the lipophilic character of the barbiturates can have a major effect upon their ability to reach the brain as well as their susceptibility to metabolism in the liver.

With an onset time of 15 to 30 minutes, oral phenobarbital, 28 (Figure 2) (17), can induce hypnotic drowsiness at dosage levels of 100 mg and continue to be effective for 12 hours or more. Under similar conditions amobarbital, 29, is a sedative of lesser duration (3 to 6 hours) and secobarbital, 30, of least duration (less than 3 hours). By comparison the intravenous induction anesthetics thiopental sodium, 11, thiopental sodium, 14, and methohexitol, 22, all produce unconsciousness within seconds, albeit losing their effectiveness only minutes later.

These behavioral patterns are related to subtle structural differences. Generally speaking, barbiturate molecules with greater lipophilicity will cross the blood–brain barrier more rapidly (rapid induction), but also readily migrate in reverse (short duration) to be sequestered in other lipid reservoirs and, to some extent, penetrate liver microsomes (metabolism). The enhanced lipophilic character of thiamyal, 14 (Scheme I) compared to secobarbital, 30, is attributed to the replacement of one of the oxygens in 30 by sulfur in 14; otherwise their structures are the same. Note in this regard the presence of sulfur in 11. Changes in the hydrocarbon substitu-
ents attached to the geminal ring carbon are also involved. The drop in lipophilicity when the C₂H₅ alkyl group in amobarbital, 29, a sedative of intermediate duration, is replaced by phenyl translates into the long-lasting barbiturate known as phenobarbital, 28. In fast-acting methohexital, 22, the absence of a sulfur atom is apparently offset by virtue of its having the largest number of lipophilic side chain carbons (including the N-methyl) of the six compounds under discussion.

The intravenous induction anesthetics (Schemes I and II) are administered as freshly reconstituted aqueous solutions (including the N-methyl) of the six compounds under discussion. Although their pH is close to 7.4, there is a major portion of each drug present in the molecular form and a noticeable, but transient, precipitate may form at the injection site. There is rapid induction of unconsciousness, quickly followed by redistribution of the agent from the injection site. There is rapid induction of unconsciousness, quickly followed by redistribution of the agent from the blood–brain to peripheral tissues. Thiopental, 14, and thiopental, 11, (each having a single asymmetric carbon atom) are administered as racemates. Methohexital, 22, (two asymmetric carbon atoms) forms two separate racemates: the more potent α-modification (R,R- and S,S-) produces excessive motor activity, and it is the α-racematé (R,S- and S,R-) that is marketed (18).

The chemistry of the muscle relaxants is closely tied to that of acetylcholine, 31 (Figure 3). In the organism muscle relaxation is preceded by the migration of the neurotransmitter acetylcholine (ACh) from nerve cells to receptors on the endplate region (surrounding membrane) of adjacent muscle cells. The transfer triggers depolarization across the membrane, immediately followed by a rapid decline in the potential gap between the inner and outer walls of a (resting) muscle cell, initiating the muscle response. Spent acetylcholine is recycled as it undergoes rapid enzymatic hydrolysis (acetylcholinesterase or AChE) in the intercellular plasma, followed by reconstitution (choline acetyltransferase) within the nerve cell. The chiral muscle relaxant tubocurarine, 1, is classified as a competitive agent because this non-activating drug sequesters acetylcholine receptors and prevents membrane depolarization; endogenous ACh is denied access to the endplate receptors. In contrast succinylcholine dichloride, 25, produces membrane depolarization but remains on-site; when present it will inhibit the subsequent event of muscle cell depolarization, and so the drug is classified as a depolarizing blocker.

As the developer of halothane, 27, Suckling worked with three outcomes in mind: (a) lack of chemical toxicity, (b) no significant risk of fire and explosion, and (c) viability as a potent anesthetic (19). Two earlier trials of fluorinated alkanes had sparked little interest. In the first instance (20a) dichlorofluoromethane and chlorodifluoromethane as anesthetics produced convulsions in mice. Later in 1946 Robbins (20b) evaluated forty-two compounds in mice; the more promising candidates were then tested in dogs but no clinical trials followed.

Nevertheless, from the standpoint of toxicity the merit of the inherently less reactive C–F bond vis-à-vis a C–Cl bond (as in chloroform) was self-evident; a ~CF₂— or CF₃ group should also lower the reactivity of any adjacent C–Cl or C–Br bond. As to point (b), fewer hydrogen atoms is better. In the end, the single hydrogen in halothane was essential; without it a much higher concentration of the perhalo compound was required to achieve anesthesia. The Meyer–Overton correlation between enhanced gaseous anesthetic potency and high lipid solubility was implicit in the selection of molecules to be synthesized. In addition, Suckling deliberately aimed for a boiling point range from 30 °C to about 60 °C; a coworker (Ferguson) had pointed out that existing examples of effective anesthesia in this range of volatility involved lung concentrations by percent volume in the low single digits or less. An individual halothane molecule (one asymmetric carbon atom) is chiral; it is the racemate that is administered as an inhalational anesthetic.

**Summary**

By the middle of the 20th century administration of liquid anesthetics by classical “open drop” induction was rare in the developed world. In its earliest and simplest form, a moist sponge was fitted over the nose and the open mouth, additional ether or chloroform being supplied dropwise as warranted. In the beginning gaseous nitrous oxide was supplied from a bag and delivered through a flexible face piece. Time was needed to improve delivery system technology, particularly in medicine, and to develop the necessary professional skills. It was in 1899 that the S. S. White Dental Manufacturing Company produced the first commercial gas–oxygen apparatus for health professionals. Thirteen years later (1912) the American Association of Anesthetists came into being. By 1960 trained hospital personnel, equipped with reliable and versatile anesthetic machines, could implement the changeover to balanced general anesthesia. Mixtures in the range of 70% nitrous oxide and 30% oxygen were commonly used to convey halothane vapor into the patient’s lungs.

**Notes**

1. The scope of this presentation is limited by and large to developments during the first half of the 20th century.


Out of all the interim challengers to ether and chloroform, gaseous cyclopropane had the greatest impact. It was introduced in 1934 by Waters.

Dentists who erred on the side of no oxygen put their patients in dire risk of anoxia; in the presence of sufficient oxygen at normal room pressure anesthesia was incomplete.

Purified curare extract is a complex mixture of alkaloids, with the major component being \((-\text{tubocurarine})\). The terms are used interchangeably.

Efficient transmittal of the information in schemes and elsewhere is facilitated by using the following abbreviations: Me = methyl, Et = ethyl, Pr = propyl, and Ph = phenyl.

Literature \(p_K\) values can be at 20°C, 25°C, or 37°C (normal body temperature). At the lower temperatures, a \(p_K\) is generally larger by 0.1 (25°C) or 0.2 units (20°C).

At a body temperature of 37°C, the equilibrium vapor pressure of halothane, bp 50.2°C, is calculated to be 0.829 atm or a gas phase molarity of 0.033. Based upon an oil/gas partition coefficient of 224, halothane’s concentration in olive oil would be 7.3 molar.

Early practitioners often used simple inhalers, for example, glass vases with embedded sponges.

The issues of anesthetic toxicity and removal of carbon dioxide and rebreathing will be included in the third and final installment.