AANA Journal Course

Update for Nurse Anesthetists

6

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A pathway toward safer anesthesia: Stereochemical advances

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Advances in organic analytical chemistry recently have led to the ability to produce medications that are stereochemically pure. At present, most medications commercially available are racemic mixtures, which are 50%-50% mixtures of the constituent stereoisomers. The human body is a chiral system and, as a result, exhibits stereoselectivity in its utilization of medications. When a racemic mixture is administered, all the stereoisomers must be metabolized. Development of stereochemically pure medications can lead to safer medications, reduce the amount of medication needed to produce the desired effect, and, potentially, reduce untoward and/or toxic effects of a medication.

Key words: **Chiral, racemic mixture, enantiomers, geometric isomers, optical activity, stereoselectivity.**

OBJECTIVES

At the completion of this course, the reader should be able to:

1. List the types of stereoisomers.
2. Differentiate among stereoisomers.
3. Identify the implications of using racemic mixtures as opposed to stereochemically pure medications.
4. List 2 potential benefits of stereochemically pure medications.
5. List 2 stereochemically pure medications.

Almost every time an anesthetist administers a medication, 2 or more medications are, in fact, given. That would seem to be quite an inflammatory statement, one that requires an explanation. How can that possibly be true? Only one syringe or vaporizer is used, and those are clearly and correctly labeled as to the contents. How, then, could 2 or more medications have been administered? Can such a statement be accurate? The simple answer is: Yes! The purpose of this article is to present an overview of a "new" avenue for pharmacological research and development. Such an overview must, of necessity, begin with a review of chemistry.

Chemistry is divided into 2 broad headings: the first is inorganic chemistry and the second, organic chemistry. Organic chemistry is concerned primarily with the composition, formation, and reactions of carbon-based compounds produced within or as a by-product of either the plant or the animal kingdoms. It is the area of organic chemistry with which the anesthetist is most concerned and from which the answers to the initial questions will be gleaned.

Within the broad area of organic chemistry are numerous, more specialized subdivisions, such as stereochemistry, which is the focus of this article. Stereochemistry is the branch of organic chemistry that deals with the spatial arrangement of atoms' and molecules' attachment at a specific carbon atom and the resultant relationship to the physical properties exhibited by the molecule as a whole. Table 1[1] is a compilation of definitions of terms specific to stereochemistry.

In any basic study of chemistry, one learns the concept of isomers. *Isomers* are chemical compounds that have identical empirical formulas but are structurally different. In anesthesia, we probably are most familiar with this concept through the volatile anesthetics, enflurane and isoflurane. Both of these anesthetics have the same empirical formula, $C_3H_2ClF_5O$, but the struc-

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Table 1. Stereochemistry terms and definitions[1]

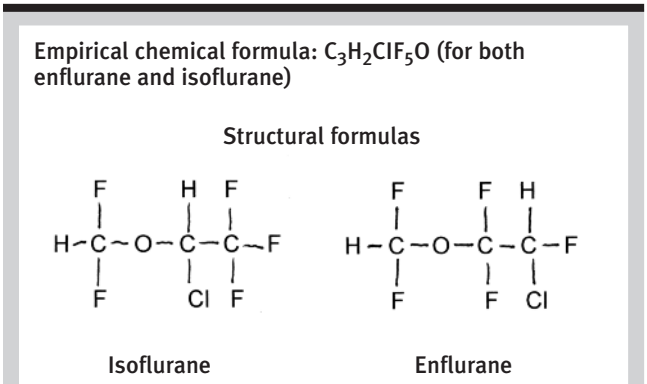
Term	Definition
Achiral	A molecule devoid of chirality
Antipode	The opposing optical isomer
Chiral (asymmetrical) center	Typically refers to a carbon atom to which 4 different atomic or molecular substituents are bonded
Diastereoisomer (diastereomer)	Stereoisomers with 2 chiral centers physiochemically different from one another
Distomer	Enantiomer with the least activity
Enantiomer	One of the mirror images
Eutomer	Enantiomer with the majority of a given effect
Geometric isomers	Molecules formed by limitation of the rotation of molecules and/or atoms around a carbon atom; restriction by either a double bond or a rigid carbon ring system
L- and – and D- and +	Descriptors of optical activity: L- and – refer to levorotary enantiomers; D- and + refer to dextrorotary enantiomers
Optical activity	A molecule that can change the direction of plane-polarized light
Racemic mixture	An equal proportion of stereoisomers; a solution containing the possible stereoisomers in equilibrium
S and R	Absolute configuration or spatial arrangement of optical isomers independent of the direction of optical activity
Stereoselective	Preferentially related to one stereoisomer
Stereospecific	Specific to only one stereoisomer
Tautomeres	Conformational isomeric forms that exist in equilibrium but change from one form to another with ease depending on the physical conditions surrounding them

tural placement of the chlorine atom (Cl) yields entirely different compounds. Figure 1 shows the 2-dimensional, structural formulas for enflurane and isoflurane.

There are 3 types of stereoisomers: optical, geometric, and conformational. *Optical* isomers, or enantiomers, are compounds that have identical empirical and structural formulas; however, enantiomers differ in the 3-dimensional spatial arrangement of the atoms and/or molecules bonded to the carbon atom. Actually, these forms of stereoisomers are mirror images of each other that cannot be superimposed on one another, just as one's left hand cannot be superimposed on the right hand. Figures 2 and 3 demonstrate the spatial differentiation of optical isomers.

Not all organic compounds are capable of forming optical isomers. For an organic molecule to have optical isomers, that molecule must have at least 1 chiral carbon, sometimes called an asymmetrical carbon. The word *chiral* comes from the Greek word, *chiros,*[2] which translates as "hand;" therefore, a chiral compound may be right-handed or left-handed. Whether a molecule is right- or left-handed is determined by the relative strength of forces exerted on the chiral carbon by the atoms and/or molecules bonded to it. A right-handed molecule is designated by the letter "R" for rectus; a left-handed molecule is designated by the letter "S" for sinister.

Figure 1. Structural isomers



In addition to spatial or 3-dimensional differences, optical isomers differ as to the direction in which they cause plane-polarized light to rotate. One enantiomer will produce counterclockwise rotation; the other will produce clockwise rotation of this type of light. The direction to which the light is rotated is symbolically designated as follows: counterclockwise rotation is termed *levorotatory*

Figure 2. Generic optical isomers

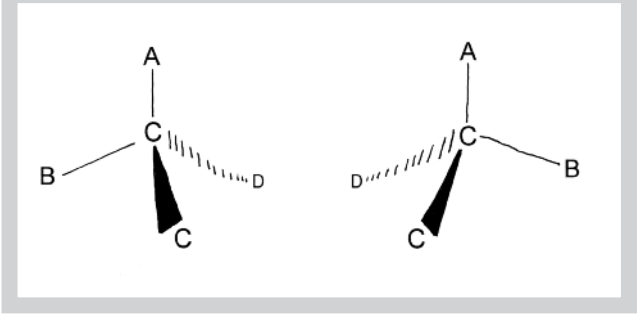
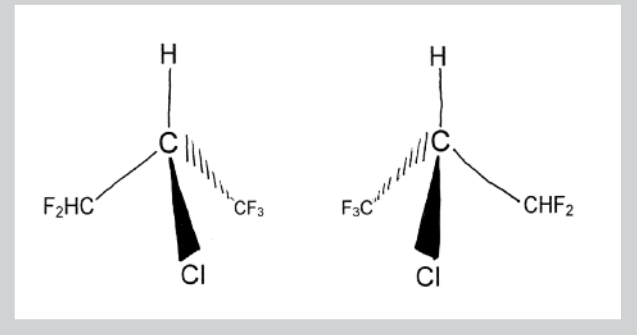


Figure 3. Isoflurane optical isomers



and symbolized by an "L-" or "–" notation; clockwise rotation of plane-polarized light is termed *dextrorotatory* and is symbolized by a "D-" or "+" notation. Thus, enantiomers have 2 independent descriptive designations. There is *no* relationship between the handedness of a molecule and the direction to which the molecule causes plane-polarized light to rotate.[3,4]

Geometric isomers constitute the second group of stereoisomers. This type of stereoisomer arises when molecular rotation around a carbon atom is restricted or prohibited by a carbon-to-carbon double bond or by the presence of a rigid carbon ring system. With single carbon-to-carbon bonds, the attached molecules or atoms are able to rotate rather freely around the carbon atom. Carbon-to-carbon double bonds are shorter and more rigid than single bonds. Visually, the rotation around a carbon single bond is similar to the rotational ability of the humerus, whereas the rotation around a carbon-to-carbon double bond is similar to the rotational ability of the radius and ulna, which is somewhat more restricted, more rigid. Geometric isomers have been differentiated, traditionally, by the following prefixes: *cis-*, from Greek, which translates as "same," and *trans-*, also from Greek, which translates as "opposite." More recently, these designations have been indicated by the letters "*Z*-" and "*E*-" for the German words, *zusamman* and *entgegen*, respectively. The *Z*- and *E*- roughly correspond, respectively, to the traditional *cis-* and *trans-* nomenclature, although both methods continue to be used. Figure 4 shows a generic representation of geometric isomers.

Figure 4. Geometric isomers

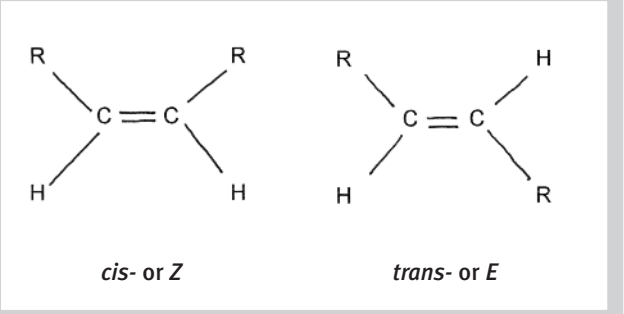
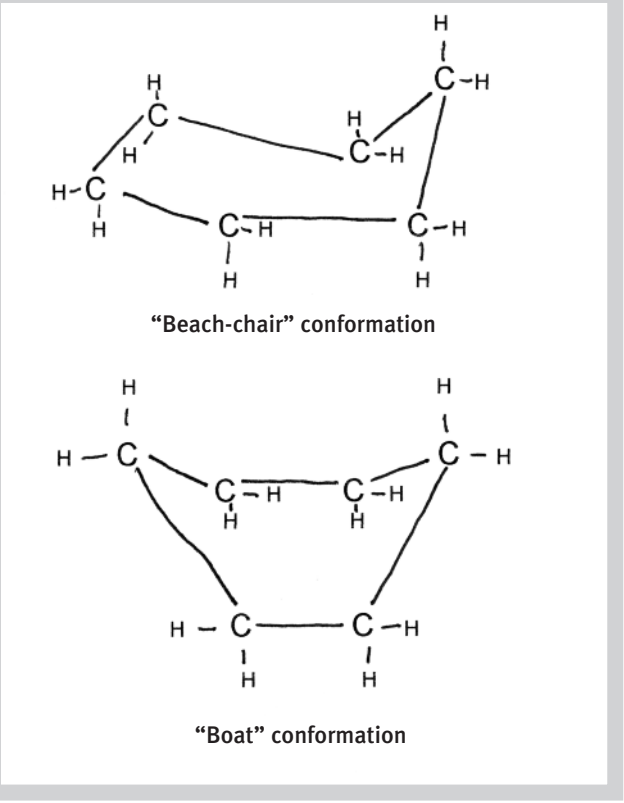


Figure 5. Conformational isomers



Conformational isomers, or conformers, are the last subset of stereoisomers. These isomers have nonidentical spatial arrangements of the atoms and/or molecules bonded to a particular carbon. This subset of stereoisomers occurs as a result of the rotation of the bonded constituents around 1 single carbon bond or around more than 1 single carbon bond. Essentially, this molecule must twist, contort, or fold to bind to a target receptor and produce the desired effect. Figure 5 is a representation of conformational isomers.

Biological significance

Biological systems are, of a sort, living chemical labo-

ratories, some obviously more complex than others. Arguably the most complex such living laboratory is the human body. In most plants and animals, enzymes and other biologically active molecules contain a chiral carbon, sometimes more than one such carbon. The human body can be considered a collection of chiral compounds and, therefore, a chiral system.[5] For example, to be used in protein synthesis, amino acids must be L- enantiomers.[6] Receptor sites are protein molecules built from specific enantiomers and are optically active. Thus, receptors are able to distinguish between stereoisomers, that is, they exhibit stereoselectivity, so that only medications with the "proper" optical activity, geometric structure, or conformation are able to interact with the receptor protein.

Traditionally, medications developed in a laboratory, whether chiral, geometric, or conformational compounds, have been racemic mixtures, which are solutions containing all the possible isomers in equilibrium. Therefore, a single vial or ampule of such a medication may contain 2 or more stereoisomers or medications. Biologically active molecules within the body are able to distinguish between stereoisomers.[6,7] As a result of the body's ability to distinguish between stereoisomers, administration of a racemic mixture can be viewed as administering 2 or more medications, all of which may behave differently with regard to toxicology, pharmacodynamics, and pharmacokinetics (Table 2).[1,8]

During the 1990s, advances in analytical chemistry specifically applied to medication design have allowed scientists to more easily separate and manufacture specifically oriented molecules. In other words, rather than producing racemic mixtures, a stereochemically pure compound can be produced. Recognizing the advances in analytical chemistry technology in recent years, the US Food and Drug Administration, in 1992, issued guidelines[7] for pharmaceutical companies regarding investigation of the pharmacological properties of various medications. In essence, these guidelines put forth 3 cases for specific testing of pure stereoisomers:[7] (1) both stereoisomers demonstrate desirable effects, (2) one stereoisomer demonstrates pharmacological activity, while the other does not, and (3) the stereoisomers demonstrate completely different pharmacological activities or have a different concentration-response relationship for a certain property.

Anesthesia implications

One of the goals of studying, developing, and marketing a medication composed of a single, pure stereoisomer is to produce a decided benefit for the patient who receives that medication. For many medications, one stereoisomer will exhibit greater potency than another. Greater potency often translates into a reduction in the amount required to produce the desired effect. Often, one stereoisomer will demonstrate a greater safety index compared with the racemate(s) or with the racemic mixture. For the anesthetist, both of these are highly sought-after potential patient benefits. Increasing the safety index of an anesthesia medication is a benefit to all involved, patients and practitioners. There are several examples of newly developed medications in which one stereoisomer demonstrates greater pharmacological activity than another. One is dexmedetomidine. Dexmedetomidine is the dextrorotatory optical isomer of the imidazole compound, medetomidine, that acts specifically and selectively as an alpha$_2$-adrenoceptor agonist.[9] Dexmedetomidine has demonstrated 8 times the specificity for alpha$_2$-adrenoceptors compared with clonidine.[10] As a potent alpha$_2$-adrenoceptor agonist, dexmedetomidine produces significant sedation, analgesia, and anxiolysis while maintaining hemodynamic stability without respiratory depression, ease of arousal, and patient cooperation. Currently, dexmedetomidine is marketed in the United States primarily for continuous infusion for intensive care

Table 2. Some achiral and chiral anesthesia-related drugs[8]

Achiral	
Chloroprocaine	Neostigmine
Dopamine	Nitrous oxide
Edrophonium	Propofol
Fentanyl	Sevoflurane
Gallamine triethiodide	Tetracaine
Lidocaine	
Chiral	
Alcuronium	Hyoscine
Atropine	Isoflurane
Bupivacaine	Ketamine
Cisatracurium	Levobupivacaine
Desflurane	Mepivacaine
Dexmedetomidine	Methohexital
Dobutamine	Morphine
Enflurane	Prilocaine
Etidocaine	Remifentanil
Etomidate	Ropivacaine
Fenoldopam	Thiopental
Glycopyrrolate	Tubocurarine
Halothane	

patients who require mechanical ventilation. Dexmedetomidine also significantly reduces anesthetic requirements,[11] postoperative analgesic requirements,[12] and the vasoconstriction and shivering thresholds.[13]

An example of a pure stereoisomer that demonstrates a greater safety index is levobupivacaine, or L-bupivacaine. Levobupivacaine is the most recently introduced amide local anesthetic. Pharmacologically, L-bupivacaine seems to be equally potent with racemic bupivacaine, or bupivacaine, with onset of action and duration of effect also similar to those of the racemic mixture. The major issue regarding L-bupivacaine is the significantly greater safety index it has demonstrated thus far and its reduced risk of toxic effects. For example, the lethal dose of L-bupivacaine, from animal studies, has been consistently 1.3 to 1.6 times greater than that for the racemic mixture.[14] Central nervous system toxic effects seem to be less common with L-bupivacaine, and larger doses are necessary to produce seizure activity or apnea compared with racemic bupivacaine.[14,15]

Pure stereoisomeric medications can be an improvement particularly if metabolic products of a parent compound are toxic or deleterious, an example of which is atracurium. Atracurium, introduced to anesthesia in 1982, is characterized by significant histamine release when injected rapidly. Atracurium is eliminated by both ester hydrolysis and Hofmann degradation. One metabolite of atracurium is laudanosine, which is a known epileptogenic compound. Higher plasma levels of laudanosine tend to be formed when atracurium is used via continuous infusion.[16] Cisatracurium, or 1R-cis, 1'R-cis atracurium, is 1 of 10 geometric isomers of atracurium. Cisatracurium is about 5 times more potent than atracurium and produces significantly less histamine release than the racemic mixture. The predominant metabolic route of elimination of cisatracurium is Hofmann degradation, with lesser elimination via ester hydrolysis; however, cisatracurium results in 5 times less laudanosine production than atracurium.[17] This represents a significant development when continuous infusions are used, for example, with mechanically ventilated intensive care patients or patients undergoing prolonged surgical procedures.

In addition to potentially increased drug potency and safety indices, the development of stereochemically pure medications may yield other benefits. The additional benefits include simplification of dose-response relationships, reduced intersubject variability, and minimization of toxic effects resulting from metabolism of the pharmacologically inactive or less active stereoisomer.[18]

Conclusion

The dramatic advances in analytical chemistry pertaining to stereochemistry have given rise to a new "class" of medications: stereochemically pure medications. Many of these single isomer medications demonstrate significantly greater potency and higher safety indices compared with the complementary stereoisomers or with the racemic mixtures from which they are derived. By producing stereochemically pure medications, potentially toxic metabolic products can be dramatically reduced, if not eliminated. The increased potency may translate into a reduced dosage and reduce the overall cost to the patient. Because of the high number of anesthesia and anesthesia-related medications that form stereoisomers, the anesthetist can look forward to exciting advances in the safety of the medications that are used on virtually a daily basis.

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