Review Article

Chirality and anaesthetic drugs: A review and an update

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ABSTRACT

Many molecules can exist as right-handed and left-handed forms that are non-superimposable mirror images of each other. They are known as enantiomers or substances of opposite shape. Such compounds are also said to be chiral (Greek *chiros* meaning 'hand'). Such chiral molecules are of great relevance to anaesthetic theory and practice. This review summarizes the basic concepts, pharmacokinetic and pharmacodynamic aspects of chirality, and some specific examples of their application in anaesthesia, along with recent advances to elucidate the anaesthetic mechanisms. Chirality is relevant to anaesthesia, simply because more than half of the synthetic agents used in anaesthesia practice are chiral drugs. Almost all these synthetic chiral drugs are administered as racemic mixture, rather than as single pure enantiomers. These mixtures are not drug formulations containing two or more therapeutic substances, but combination of isomeric substances, with the therapeutic activity residing mainly in one of the enantiomer. The other enantiomer can have undesirable properties, have different therapeutic activities or be pharmacologically inert. Specific examples of application of chirality in anaesthetic drugs include inhalational general anaesthetics (e.g. isoflurane), intravenous anaesthetics (e.g. etomidate, thiopentone), neuromuscular blocking agents (e.g. cisatracurium), local anaesthetics (e.g. ropivacaine and levobupivacaine) and other agents (e.g. levosimendan, dexmedetomidine, L-cysteine). In the recent advances, chirality study has not only helped new drug development as mentioned above, but has also contributed in a more profound way to the understanding of the mechanism of anaesthesia and anaesthetic drugs.

Key words: Anaesthesia, anaesthetic drugs, chirality, enantiomers

INTRODUCTION

Stereoisomers are the compounds that have same chemical structure but differ in the three-dimensional arrangement of their constituent atoms in space. Such isomers may be separated into two groups, enantiomers and diastereoisomers. Our right and left hands are mirror images of each other, but cannot be superimposed on each other when palms are facing the same direction. Similarly, many chemical structures and drugs can exist as right-handed and left-handed forms that are non-superimposable mirror images of each other. These forms are known as enantiomers or 'substances of opposite shape'. Such compounds are also said to be chiral (Greek *chiros* meaning 'hand'). This type of non-superimposable mirror image stereoisomerism ('chirality') is dependent on the presence of a centre of molecular asymmetry in the chemical structure of a drug; this centre is usually a carbon atom with four different atoms or groups attached to it.[1]

Such chiral molecules are of great relevance to anaesthetic theory and practice. This review summarizes the basic concepts, pharmacokinetic and pharmacodynamic aspects of chirality, and some specific examples of their application in anaesthesia, along with recent advances to elucidate the anaesthetic mechanisms. This is a narrative review, for which electronic (followed by manual) search of the literature was made from PubMed and Google Scholar using the following key words in various combinations: chirality,

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stereoisomers, enantiomers, anaesthesia, anaesthetic and specific anaesthetic drugs.

BASIC CONCEPTS

In terms of physiochemical properties, enantiomers differ only in their ability to rotate plane-polarized light in opposite directions and therefore are also referred as optical isomers. A racemate is an equal mixture of two enantiomers and has no optical activity. Since enantiomers differ in the direction of rotation of plane-polarized light, this property is frequently used in their designation. An enantiomer rotating polarized light to the right is known as (+) or d (for 'dextro') isomer, and an enantiomer rotating polarized light to the left is known as (-) or l (for 'laevo') isomer. A racemate is designated by prefix (±) or dl. This nomenclature yields information concerning a physical property of the material and also whether the material is a single isomer or a racemic mixture. However, it does not give information concerning the three dimensional spatial arrangement or the absolute configuration of molecule. Both the magnitude and direction of optical rotation may also vary with experimental conditions. The terms d- and l- should also be distinguished from D- and L-, which do not necessarily indicate the direction of rotation of light. The D/L system relates the stereochemistry of a molecule to that of a standard reference compound, either the carbohydrate D-glyceraldehyde or the amino acid L-serine. Although this is standard nomenclature for simple sugars, amino acids and their derivatives, it can result in problems, because D- and L- are often confused with (d)- and (l)-, which have an entirely different meaning.[2]

The configuration of chiral drugs can be defined in absolute terms by Cahn-Ingold-Prelog sequence rule [Figure 1]. In the sequence rule notation, the substituent atoms attached to chiral centre are placed in an order of priority based upon their atomic numbers, with the ligand having the highest atomic number being assigned the highest priority. The molecule is then viewed from the side opposite to the group of lowest priority and, if remaining, highest to lowest priority atoms or groups are in a clockwise direction, the molecule is assigned the R-configuration from the Latin *rectus* (right). Conversely an anticlockwise order is termed S- from the Latin *sinister* (left). Any chiral molecule can be assigned in this way, whose absolute stereochemistry has been determined. Rectus and Sinister refers to the spatial orientation of groups at

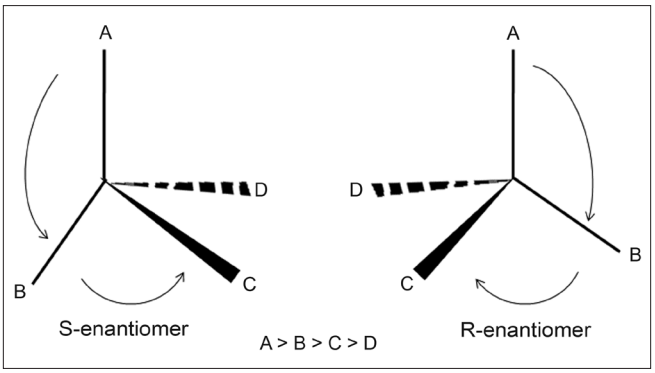

Figure 1: Sequence rule notation. Bonds represented as solid lines are in the plane of paper, those drawn with dotted lines project away from the reader and those represented by a wedge project towards the reader. Group priority (atomic size) is indicated as A>B>C>D, A representing the largest size. Since the group of lowest priority is projected away from the reader, the sequence is clockwise (R) in the enantiomer on the right and anticlockwise (S) in the enantiomer on the left

the chiral centre and not to the direction of rotation of polarized light; hence it is possible for the isomer to be S(+), S(-), R(+) or R(-).[3,4]

The term diastereoisomers refer to all other stereoisomeric compounds that are not enantiomeric, i.e. are not 'nonsuperimposable mirror images' of one another. Diastereoisomerism may be due to presence of more than one chiral centre or geometric isomerism. Geometric isomerism usually occurs when two different groups are attached to adjacent atoms linked by a rigid chemical bond (for example, a carbon–carbon double bond). Cis–trans isomerism is an example of geometric isomerism. In contrast to enantiomers, diastereoisomers differ in their physiochemical properties and can be easily separated.[2]

Relevance of chirality to anaesthesia

Chirality is relevant to anaesthesia, simply because more than half of the synthetic agents used in anaesthesia practice are chiral drugs. Almost all these synthetic chiral drugs are administered as racemic mixture, rather than as single pure enantiomers. These mixtures are not drug formulations containing two or more therapeutic substances, but combination of stereoisomeric molecules, with the therapeutic activity residing mainly in one of the enantiomers. The other enantiomer can have undesirable properties, have different therapeutic activities or be pharmacologically inert.[5-7] It is thus a logical and safer approach to avoid the presence of the therapeutically useless but potentially harmful isomer ('isomeric ballast') in drug formulations.[8]

Recent advances in the chiral technology and the ability to synthesize enantiomerically pure compounds, together with regulatory influences, have led the pharmaceutical industry to attempt, wherever relevant and possible, to develop new chemical entities as single isomers, either *de novo* or by deriving them from racemates marketed previously ('chiral switching').[9] Potential advantages associated with use of single isomer products include an increase in the selectivity of pharmacological profile of the drug, improved therapeutic index and decreased propensity for drug–drug interactions.[10]

In a racemic mixture, two virtually separate drugs are being given at the same time with different pharmacodynamics and pharmacokinetics. Since amino acids and sugars, the major building stones of biological macromolecules, are themselves chiral, the proteins and glycoproteins which constitute enzymes, receptors, carrier macromolecules, etc. are also chiral. This results in stereospecific action and different affinities of enantiomers.[11-13]

The stereospecificity of enantiomers as explained above has important implications not only for pharmacodynamics but also for pharmacokinetics of drugs.[6-8,10-13] Many of the pharmacokinetic processes such as absorption, tissue distribution, plasma protein binding, metabolism and elimination utilize biological macromolecules as their mediators. Thus, different enantiomers may impact upon these pharmacokinetic processes differentially. As an example, Nguyen *et al*.[14] demonstrated that, following an intravenous administration of racemic thiopental, both the total plasma clearance and the volume of distribution at steady state were significantly greater for R-thiopental than for S-thiopental. Thus, these two key pharmacokinetic characteristics of thiopental were both stereoselective. Interestingly, they further showed that this is because the R-enantiomer has significantly larger plasma unbound fraction than the S-enantiomer, resulting in its larger distribution and faster clearance. The accompanying editorial[15] hailed this as 'an example of how the stereospecific study of racemic mixtures can elucidate the clinical implications of chirality that were formerly suspected but unproven'.

It is to be noted, however, that some of the basic mechanisms behind these pharmacokinetic processes (e.g. active transmembrane transport, enzymatic metabolism, protein binding) are more stereoselective than others (e.g. passive transport by diffusion, absorption).[6,10,11,13] As a result, even though the separate pharmacokinetic processes of enantiomers can be quite stereoselective, the overall stereoselectivity may be modest. It has been noted that basic macromolecular-level processes are more stereoselective than whole-body pharmacokinetics such as plasma half-life, distribution and clearance, because these latter parameters depend upon not only stereochemistry but also a host of other factors like formulation and route of administration, drug interactions, disease state, age, gender, race and pharmacogenetics.[16] Nonetheless, there is no denying the fact that stereochemistry does influence pharmacokinetics, so much so that ignoring this basic fact and extrapolating pharmacokinetic data from only the study of racemic mixture of a drug rather than its enantiomers has been dubbed as 'at best misleading'[12] or even 'sophisticated nonsense'.[17] Altered pharmacokinetic properties of enantiomers may also be responsible for different adverse effect profiles. For example, in racemic ketamine, R(-) isomer is less effective agent as an anaesthetic but is associated with higher incidence of side effects including emergence reaction than the S(+) enantiomer.[18,19] S(+) ketamine has recently been approved for clinical use in some European countries and is one of the various instances where one of the enantiomers has a distinct advantage over its racemate mixture.[20]

Examples of stereoisomers in anaesthesia

Inhalational general anaesthetics

Despite the traditional view that general anaesthetics act by non-specific perturbation of lipid membranes, available data point much more plausibly to a direct effect on some protein targets.[21-24] Each of the inhalational anaesthetics halothane, isoflurane and enflurane contains an optically active carbon atom. Optical isomers of isoflurane exhibited stereoselectivity in their effects, (+)isoflurane being about twofold more effective than the (-)isomer,[25-29] though other studies failed to confirm this.[30-32] Since the safety factor for inhalational anaesthetics is very low, even relatively small degree of stereoselectivity can result in one of the enantiomers offering a significant clinical advantage over the racemic mixture.

Intravenous general anaesthetics

Etomidate is unique among intravenous anaesthetics because it is administered as an optically pure R(+) isomer, which is the active component.[33] Many barbiturates including thiopental are chiral compounds, with significant differences in activity

and potencies between optical isomers of these drugs.[34,35] S(-) thiopentone was found to be about twofold more potent than the R(+) thiopentone in the potentiation of gamma-amino butyric acid (GABA) at $GABA_A$ receptors, the major molecular targets underlying anaesthetic action of barbiturates.[36,37] This is consistent with differences in potency for central depressant effects found *in vivo*.[38,39]

Neuromuscular blocking agents

Atracurium is an intermediate-duration, nondepolarizing neuromuscular blocking agent introduced into clinical anaesthesia in the early 1980s. However, atracurium is known to cause histamine release resulting in transient hypotension and tachycardia associated with facial and truncal flushing, especially if a large dose is given rapidly. Moreover, its use by continuous infusion in critically ill patients can lead to the accumulation of laudanosine, a product of Hofmann degradation, which is epileptogenic in animals.[40,41] Atracurium has four chiral centres in its bis-benzylisoquinolinium structure and the marketed product is a mixture of 10 optical and geometric isomers: three cis–cis, four cis–trans and three trans–trans isomers.[42] Cisatracurium is R-R′ optical isomer of the cis–cis configuration, which represents about 15% of atracurium mixture. Since the mid-1990s, a number of preclinical and human studies established the efficacy and safety of cisatracurium.[43-46] The example of cisatracurium demonstrates that isolation of one of the stereoisomer may result in improvement over a parent racemic compound, which can translate into clinical practice.

Local anaesthetics

Racemic bupivacaine is a potent local anaesthetic widely used for long lasting regional anaesthesia. Since its introduction into clinical practice in early 1960s, bupivacaine has been marketed as a 50:50 racemic mixture of two enantiomers. Unfortunately, there have been reports of death attributable to bupivacaine induced cardiotoxicity in patients after accidental intravenous injection. Resuscitation from bupivacaine induced cardiovascular toxicity has been difficult and often unsuccessful.[47] The molecular structure of this highly lipid soluble and protein bound compound contains a chiral centre in the piperidine ring, resulting in two optically active stereoisomers. Accordingly the new long-acting local anaesthetics, ropivacaine and levobupivacaine, have been developed as safer alternatives to bupivacaine. Levobupivacaine and ropivacaine are S(-) enantiomers of two different molecules, 1-butyl-2′6′-pipecoloxylidide and 1-propyl-2′6′-pipecoloxylidide, respectively.[48,49]

In human volunteers, despite higher mean plasma concentration of levobupivacaine than bupivacaine (2.38 vs. 1.87 μg/ml), levobupivacaine had less effect on mean stroke index, acceleration index and ejection fraction.[50] The mechanism of bupivacaine induced cardiac arrhythmias may result from its inhibitory effect on sodium channel current. The bupivacaine induced block of the inactivated state of sodium channels displayed stereoselectivity with R(+) enantiomer interacting faster and more potently. Lower potency of S(-) bupivacaine to block a particular subset of cardiac sodium channels might explain its lower cardiotoxicity.[51]

Other agents

Levosimendan

The administration of levosimendan is approved for short-term treatment of acute decompensated congestive heart failure. Positive inotropic action of levosimendan is correlated to its stereoselective binding to Ca^{2+} saturated cardiac troponin C resulting in enhanced myocardial Ca^{2+} sensization, with levosimendan about 47 times more potent than its stereoisomer dextrosimendan.[52,53]

Dexmedetomidine

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextro-enantiomer of medetomidine that displays specific and selective alpha 2-adrenoceptor agonism. The central alpha 2-adrenoceptor agonist activity is specific to the dextro enantiomer of medetomidine, thus again utilizing chiral principles.[54] The major sedative and antinociceptive effects of dexmedetomidine are attributable to its stimulation of the alpha-2 adrenoceptors in the locus coeruleus and the alpha 2A-adrenoceptor subtype is responsible for relaying the sedative and analgesic properties of dexmedetomidine.[55] The improved specificity of dexmedetomidine for the alpha-2 receptor, especially for the 2A subtype of this receptor, causes it to be a much more effective sedative and analgesic agent than clonidine. Dexmedetomidine was approved by the U.S. Food and Drug Administration at the end of 1999 for use in humans as a short-term medication (<24 hours) for analgesia and sedation in the intensive care unit. Recently it has been approved for use through the epidural route as well, as an analgesic adjunct.[56]

L-cysteine

Gantacurium is an important example of a new class of chlorofumarate muscle relaxants, whose action can be very rapidly terminated by cysteine. Of the two enantiomers of cysteine, the L-cysteine enantiomer acts as a precursor amino acid for the synthesis of several proteins such as coenzyme A. Since D-amino acids are usually harmful for the body, D-cysteine (whether ingested or formed in the body) imposes a metabolic burden on the organism and could therefore be considered toxic. On the other hand, L-cysteine is a sulphate donor in detoxification reactions and hence may have important neuroprotective roles.[57] Another mechanism of neuroprotection by L-cysteine is the interference it provides to the entry of potentially injurious heavy metal ions across the blood-brain barrier.[58] Despite these neuroprotective effects, however, L-cysteine can also be neurotoxic in high concentrations.[59,60] Hence, much work needs to be done before the introduction of L-cysteine into clinical use as a reversal agent.[61]

Recent advances

Chirality study has not only helped new drug development as mentioned above, but has also contributed in a more profound way to the understanding of the mechanism of anaesthesia and anaesthetic drugs. As mentioned earlier, chirality is important in medical sciences because on one hand, most biologically active molecules such as drugs and neurotransmitters are chiral, and on the other hand, most of their biological targets such as enzymes, receptors and ion channels are also chiral in nature. Consequently, there is often stereoselectivity for one enantiomer over another by virtue of that enantiomer's complementarity with its biological target. This fact is potentially important to studies of anaesthetic mechanisms because enantioselectivity observed in behaviours that those molecules mediate may reflect the enantioselectivity on molecular targets of anaesthetic action, such as specific receptors.

To expand the range of studies using chirality that can be performed, in particular, as a test of relevance for anaesthetic targets, Won *et al*.[62] developed a series of secondary alcohols, from 2-butanol till 2-heptanol from commercially available secondary alcohols, and tested their enantioselectivity by recording the minimum alveolar anaesthetic concentration (MAC) for these compounds. They found that the 2-butanol and 2-pentanol isomers were enantioselective, the S isomers having 17–38% higher MAC values than the R isomers. Using this model as a research tool in a companion study, the same group studied three anaesthetic-sensitive receptor-ion channel complexes as potential targets of anaesthetic drugs: GABA-A, N-methyl d-aspartate (NMDA) and Twik-related-spinal cord K^+ channel.[58] Using voltage-clamp techniques, they found that 2-butanol was not enantioselective for any channel, 2-pentanol was enantioselective for GABA-A and 2-hexanol was enantioselective for both GABA-A and NMDA receptors. However, the sensitivity and specificity of chirality as a test of anaesthetic relevance were poor. The authors finally opined that enantioselectivity should not be used as a test of relevance for inhaled anaesthetic targets.[63]

Another example of the potential contribution of chirality to the study of mechanisms of anaesthesia is the use of enantiomers of neuroactive steroid anaesthetics. Neuroactive steroids can either potentiate or inhibit a variety of membrane channels. Most studies have suggested that the effects are mediated by specific association of the steroid with the affected channel. However, a study of the GABA-C receptor concluded that the actions were consistent with an action of the steroid in the lipid bilayer to alter the lateral pressure profile in the membrane.[64] The enantiomers of an optically active compound are expected to have identical physical properties, including interactions with hydrophobic portions of the cell membrane. Li *et al*.[65] used two pairs of enantiomers (pregnanolone and *ent*pregnanolone, allopregnanolone and *ent*-allopregnanolone) to show that the ability to potentiate (allopregnanolone) or inhibit (pregnanolone) the GABA-C receptor is enantioselective. Their results strongly suggest that the actions of these neuroactive steroids are mediated by interactions with chiral regions of the target protein, rather than by a change in membrane properties (including lateral pressure).

Another recent example of how the study of enantiomers can help elucidate the basic mechanisms of local anaesthesia is the study on bupivacaine enantiomers and lipid membrane properties. A recent study concluded that bupivacaine stereostructure specifically interacts with membranes containing cholesterol, which is consistent with the clinical features of S(-)-bupivacaine. Membrane cholesterol appears to increase the chirality of lipid bilayers and enable them to interact with S(-)-, racemic and R(-)-bupivacaine differently.[66]

CONCLUSION

Up to 25% of all therapeutic agents, including many anaesthetics, are incidentally fixed-ratio mixtures, mainly racemates. The problems relating to the composite character of racemic drugs has largely been neglected by authors, resulting in generation of bias in the interpretation of their data and conclusions drawn.[6,7,11] The pharmaceutical industry and contributors to scientific journals should be given clear directives to reveal the constituents of chiral drugs along with pharmacology and toxicology of individual enantiomers. Even the physicians or pharmacists are often not aware of the presence of 'isomeric ballast' in the commonly used pharmaceutical products. The chiral nature of the drug should be apparent from the chemical name of the compound, e.g. rac-ketamine, R(-) or S(+) ketamine. The rationale of using racemate instead of single enantiomers (eutomer) should be made explicit.[67]

To conclude, even after more than 20 years of its publication, an editorial comment has not lost its relevance today: there is an urgent need to reduce the flow of the heavily biased data on racemic drugs in the scientific literature and focus on the specific chiral enantiomers as 'it matters to science, readers of publications and last but not the least to the patients'.[68]

REFERENCES

1. Kelly JG, McIlroy PJ. Chemistry. In: Dundee JW, Clarke RS, McCaughey W, Editors. Clinical anaesthetic pharmacology. Edinburgh: Churchill Livingstone; 1991. p. 3-14.
2. Calvey TN. Isomerism and anaesthetic drugs. Acta Anaesthesiol Scand 1995;39 suppl 106: S83-90.
3. Cahn RS, Ingold CK, Prelog V. The specification of asymmetric configuration in organic chemistry. Experientia 1956;12:81-94.
4. Hill SA. Correct nomenclature for stereoisomers. Anaesthesia 2002;57:200.
5. Calvey TN. Chirality in anaesthesia. Anaesthesia 1992;47:93-4.
6. Drayer DE. Pharmacodynamic and pharmacokinetic differences between drug enantiomers in humans: An overview. Clin Pharmacol Ther 1986;40:125-33.
7. Ariens EJ, Wuis EW, Veringa EJ. Stereoselectivity of bioactive xenobiotics. A pre-Pasteur attitude in medicinal chemistry, pharmacokinetics and clinical pharmacology. Biochem Pharmacol 1988;37:9-18.
8. Ariens EJ, Wuis EW. Chiral cognizance: A road to safer and more effective medicinal products. J R Coll Physicians Lond 1994;28:395-8.
9. Tucker GT. Chiral switches. Lancet 2000;355:1085-7.
10. Hutt AJ, Tan SC. Drug chirality and its clinical significance. Drugs 1996;52 suppl 5: S1-12.
11. Williams K, Lee E. Importance of drug enantiomers in clinical pharmacology. Drugs 1985;30:333-54.
12. Burke D, Henderson DJ. Chirality: A blueprint for the future. Br J Anaesth 2002;88:563-76.
13. Nau C, Strichartz GR. Drug chirality in anesthesia. Anesthesiology 2002;97:497-502.
14. Nguyen KT, Stephens DP, McLeish MJ, Crankshaw DP, Morgan DJ. Pharmacokinetics of thiopental and pentobarbital enantiomers after intravenous administration of racemic thiopental. Anesth Analg 1996;83:552-8.
15. Egan TD. Stereochemistry and anesthetic pharmacology: Joining hands with the medicinal chemists. Anesth Analg 1996;83:447-50.
16. Hutt AJ. Chirality and pharmacokinetics: An area of neglected dimensionality? Drug Metabol Drug Interact 2007;22:79-112.
17. Ariens EJ. Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology. Eur J Clin Pharmacol 1984;26:663-8.
18. Kohrs R, Durieux ME. Ketamine: Teaching an old drug new tricks. Anesth Analg 1998;87:1186-93.
19. White PF, Ham J, Way WL, Trevor AJ. Pharmacology of ketamine isomers in surgical patients. Anesthesiology 1980;52:231-9.
20. Argiriadou H, Himmelseher S, Papagiannopoulou P, Georgiou M, Kanakoudis F, Giala M, *et al*. Improvement of pain treatment after major abdominal surgery by intravenous S (+) ketamine. Anesth Analg 2004;98:1413-8.
21. Franks NP, Lieb WR. Molecular mechanisms of general anaesthesia. Nature 1982;300:487-92.
22. Franks NP, Lieb WR. Selective actions of volatile general anaesthetics at molecular and cellular level. Br J Anaesth 1993;71:65-76.
23. Harrison NL. Optical isomers open a new window on anesthetic mechanism. Anesthesiology 1998;88:566-8.
24. Franks NP, Lieb WR. Do general anaesthetics act by competitive binding to specific receptors? Nature 1984;310:599-691.
25. Franks NP, Lieb WR. Stereoselective effects of inhalational general anesthetic optical isomers on nerve ion channels. Science 1991;30:427-30.
26. Harris BD, Moody EJ, Basile AS, Skolnick P. Volatile anesthetics bidirectionally and stereospecifically modulate ligand binding to GABA receptors. Eur J Pharmacol 1994;267:269-74.
27. Harris B, Moody E, Skolnick P. Isoflurane anesthesia is stereoselective. Eur J Pharmacol 1992;217:215-6.
28. Lysko GS, Robinson JL, Casto R, Ferrone RA. The stereospecific effects of isoflurane isomers *in vivo*. Eur J Pharmacol 1994;263:25-9.
29. Mihic SJ, Ye Q, Wick MJ, Koltchine VV, Krasowski MD, Finn SE, *et al*. Sites of alcohol and volatile anaesthetic action on $GABA_A$ and glycine receptors. Nature 1997;389:385-9.
30. Moody EJ, Harris B, Hoehner P, Skolnick P. Inhibition of [3H] isradipine binding to L-type calcium channels by the optical isomers of isoflurane. Lack of stereospecificity. Anesthesiology 1994;81:124-8.
31. Graf BM, Boban M, Stowe DF, Kampine JP, Bosnjak ZJ. Lack of stereospecific effects of isoflurane and desflurane isomers in isolated guinea pig hearts. Anesthesiology 1994;81:129-36.
32. Eger EI, Koblin DD, Laster MJ, Schurig V, Juza M, Ionescu P, *et al*. Minimum alveolar anesthetic concentration values for the enantiomers of isoflurane differ minimally. Anesth Analg 1997;85:188-92.
33. Tomlin SL, Jenkins A, Lieb WR, Franks NP. Stereoselective effects of etomidate optical isomers on gamma-aminobutyric acid type A receptors and animals. Anesthesiology 1998;88:708-17.
34. Andrews PR, Mark LC. Structural specificity of barbiturates and related drugs. Anesthesiology 1982;57:314-20.
35. Haley TJ, Gidley JT. Pharmacological comparison of R (+), S (-) and racemic thiopentone in mice. Eur J Pharmacol 1976;36:211-4.
36. Cordato DJ, Chebib M, Mather LE, Herkes GK, Johnston GA. Stereoselective interaction of thiopentone enantiomers with $GABA_A$ receptor. Br J Pharmacol 1999;128:77-82.
37. Downie DL, Franks NP, Lieb WR. Effects of thiopental and its optical isomers on nicotinic acetylcholine receptors. Anesthesiology 2000;93:774-83.
38. Kamiya Y, Andoh T, Furuya R, Hattori S, Watanabe I, Sasaki T, *et al*. Comparison of the effects of convulsant and depressant

barbiturate stereoisomers on AMPA-type glutamate receptors. Anesthesiology 1999;90:1704-13.
39. Mather LE, Edwards SR, Duke CC. Electroencephalographic effects of thiopentone and its enantiomers in the rat: Correlation with drug tissue distribution. Br J Pharmacol 1999;128:83-91.
40. Scott RP, Savarese JJ, Basta SJ, Sunder N, Ali HH, Gargarian M, *et al*. Atracurium: Clinical strategies for preventing histamine release and attenuating the haemodynamic response. Br J Anaesth 1985;57:550-3.
41. Parker CJ, Jones JE, Hunter JM. Disposition of infusions of atracurium and its metabolite, laudanosine, in patients in renal and respiratory failure in ITU. Br J Anaesth 1988;61:531-40.
42. Tsui D, Graham GG, Torda TA. The pharmacokinetics of atracurium isomers *in vitro* and in humans. Anesthesiology 1987;67:722-8.
43. Wastila WB, Maehr RB, Turner GL, Hill DA, Savarese JJ. Comparative pharmacology of cisatracurium (51W89), atracurium, and five isomers in cats. Anesthesiology 1996;85:169-77.
44. Lien CA, Belmont MR, Abalos A, Abou-Donia M, Savarese JJ. Dose-response relations of 51W89 under nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 1993;79: A948.
45. Lien CA, Belmont MR, Abalos A, Eppich L, Quissey S, Abou-Donia M, *et al*. The cardiovascular and histamine releasing properties of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 1995;82:1131-8.
46. Smith CE, Vanmiert MM, Parker CJ, Hunter JM. A comparison of the infusion pharmacokinetics and pharmacodynamics of cisatracurium, the 1R-cis 1' R-cis isomer of atracurium, with atracurium besylate in healthy patients. Anaesthesia 1997;52:833-4.
47. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285-6.
48. Burlacu CL, Buggy DJ. Update on local anaesthetics: Focus on levobupivacaine. Ther Clin Risk Manage 2008;4:381-92.
49. McClure JH. Ropivacaine. Br J Anaesth 1996;76:300-7.
50. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol 1998;46:245-9.
51. Valenzuela CV, Snyders DJ, Bennett PB, Tamargo J, Hondeghem LM. Stereoselective block of cardiac sodium channels by bupivacaine in guinea pig myocytes. Circulation 1995;92:3014-24.
52. Sorsa T, Pollesello P, Rosevear PR, Drakenberg T, Kilpelainen I. Stereoselective binding of levosimendan to cardiac troponin C causes Ca^{2+} sensitization. Eur J Pharmacol 2004;486:1-8.
53. Kaheinen P, Pollesello P, Hertelendi Z, Borbely A, Szilagyi S, Nissinen E, *et al*. Positive ionotropic effect of Levosimendan is correlated to its stereoselective Ca^{2+} sensitizing effect but not to stereoselective phosphodiesterase inhibition. Basic Clin Pharmacol Toxicol 2006;98:74-8.
54. Savola JM, Virtanen R. Central alpha-2 adrenoceptors are highly stereoselective for dexmedetomidine, the dextro enantiomer of medetomidine. Eur J Pharmacol 1991;195:193-9.
55. Hunter JC, Fontana DJ, Hedley LR, Jasper JR, Lewis R, Link RE, *et al*. Assessment of the role of alpha 2-adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice. Br J Pharmacol 1997;122:1339-44.
56. Murthy TV, Singh R. Alpha-2 adrenoceptor agonist-dexmedetomidine. Role in anaesthesia and intensive care: A clinical review. J Anaesthesiol Clin Pharmacol 2009;25:267-72.
57. Miyamoto M, Murphy TH, Schnaar RL, Coyle JT. Antioxidants protect against glutamate-induced cytotoxicity in a neuronal cell line. J Pharmacol Exp Ther 1989;250:1132-40.
58. Bradbury MW, Deane R. Permeability of the blood-brain barrier to lead. Neurotoxicology 1993;14:131-6.
59. Olney JW. Role of excitotoxins in developmental neuropathology. APMIS Suppl. 1993;40:103-12.
60. Slivka A, Cohen G. Brain ischemia markedly elevates levels of the neurotoxic amino acid, cysteine. Brain Res 1993;608:33-7.
61. Brull SJ, Naguib M. Selective reversal of muscle relaxation in general anesthesia: Focus on sugammadex. Drug Des Devel Ther 2009;3:119-29.
62. Won A, Oh I, Laster MJ, Popovich J, Eger EI, Sonner JM. Chirality in anesthesia I: Minimum alveolar concentration of secondary alcohol enantiomers. Anesth Analg 2006;103:81-4.
63. Brosnan R, Gong D, Cotton J, Keshavaprasad B, Yost CS, Eger EI, *et al*. Chirality in anesthesia II: Stereoselective modulation of ion channel function by secondary alcohol enantiomers. Anesth Analg 2006;103:86-91.
64. Morris KD, Amin J. Insight into the mechanism of action of neuroactive steroids. Mol Pharmacol 2004;66:56-69.
65. Li W, Covey DF, Alakoskela JM, Kinnunen PK, Steinbach JH. Enantiomers of neuroactive steroids support a specific interaction with the GABA-C receptor as the mechanism of steroid action. Mol Pharmacol 2006;69:1779-82.
66. Tsuchiya H, Mizogami M. Membrane interactivity of charged local anesthetic derivative and stereoselectivity in membrane interaction of local anesthetic enantiomers. Local Regional Anesthesia 2008;1:1-9.
67. Ariens EJ. Racemic therapeutics-ethical and regulatory aspects. Eur J Clin Pharmacol 1991;41:89-93.
68. Ariens EJ. Stereoselectivity in the action of drugs. Pharmacol Toxicol 1989;64:319-20.

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