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INHALATIONAL COMPOUNDS IN THE
BRAIN****Publication Classification**(51) **Int. Cl.⁷** **A61K 49/00**; G06F 19/00;
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A61B 5/00(76) **Inventor: Chung-Yuan Lin, Chicago, IL (US)**(52) **U.S. Cl.** **424/9.1**; 702/19; 600/309Correspondence Address:
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BOSTON, MA 02110 (US)(57) **ABSTRACT**

This invention directs to a method of assessing the concentration of an inhalational compound in the brain of a subject. The method includes administering a gas containing the compound into a subject to fill the pulmonary functional residual capacity, which is defined as the remaining lung volume at the end of an unforced respiration. The method also includes measuring an inspired compound concentration (C_i) and an expired compound concentration (C_e) after having filled the functional residual capacity with the gas. Therefore, a mixed venous compound concentration (C_b) can be assessed based on the formula $C_b = [C_i(M-1) + C_e]/M$, in which M is an alveolar membrane factor for the compound; and a brain compound concentration (C_b) can be assessed based on the formula $C_b = (C_e + C_b)/2$.

(21) **Appl. No.: 10/425,360**(22) **Filed: Apr. 29, 2003****Related U.S. Application Data**

(62) Division of application No. 09/811,316, filed on Mar. 16, 2001, now Pat. No. 6,579,511.

ASSESSMENT OF CONCENTRATION OF INHALATIONAL COMPOUNDS IN THE BRAIN

TECHNICAL FIELD

[0001] This invention relates to a method of assessing the concentration of an inhalational compound (e.g., an anesthetic) in the brain of a subject after administration of the compound.

BACKGROUND

[0002] Minimum Alveolar Concentration (MAC) was introduced in 1964 as a standard of assessing the depth of anesthesia. It is defined as an anesthetic concentration in the alveolar that prevents a response to a painful stimulus in 50% of subjects. Such a definition does not incorporate the time required for an anesthetic concentration in the brain to reach equilibrium with the anesthetic concentration in the alveolar. See Lin, C. Y. (1994) *Anesth Intens Care* 22: 362-373. Thus, the MAC standard cannot be used to accurately assess the depth of anesthesia.

[0003] Practically, most anesthesiologists determine the depth of anesthesia based on exterior symptoms in the patient, such as ocular myosis or abnormal blood pressure. However, these symptoms vary from patient to patient, and reliance on them inevitably involves subjective judgment of the anesthesiologists. Thus, other methods have been developed. For example, one method includes repeatedly administering stimuli to a patient, recording the patient's electrical brain activity after each stimulus, and transforming the record as an indication of the depth of anesthesia. See International Patent Publication No. WO 91/19453.

[0004] There remains a need for an objective method for assessing the depth of anesthesia.

SUMMARY

[0005] In one aspect, this invention directs to a method of assessing the concentration of an inhalational compound in the brain of a subject. Examples of such a compounds include, not limit to, anesthetics (e.g., isoflurane, haloflurane, desflurane, sevoflurane, enflurane, ether, or nitrous oxide) or non-anesthetics (e.g., carbon dioxide or nitrogen). This method includes (1) administering a gas containing an inhalational compound into a subject to fill the pulmonary functional residual capacity; (2) after having filled the functional residual capacity with the gas, measuring an inspired compound concentration (C_i) and an expired compound concentration (C_e); (3) assessing a mixed venous compound concentration (C_b) based on Formula I: $C_b = [C_i(M-1) + C_e]/M$, in which M is an alveolar membrane factor for the compound; and (4) assessing a compound concentration in the brain (C_b) based on Formula II: $C_b = (C_e + C_b)/2$. The alveolar membrane factor M , as will be described below, is mostly a constant parameter for each inhalational compound, may slightly vary among different subjects. It can be assessed based on Formula III: $M = 1 - (C_e/C_i)$, in which C_i and C_e are an inspired compound concentration and an expired compound concentration, respectively, measured at the time when about 90% (i.e., 85-95%) of the functional residual capacity is filled with the gas.

[0006] In another aspect, the invention features an article that includes a machine-readable medium that stores

machine-executable instructions. Such instructions causes a machine to receive values representing the concentration of a compound administered in a gas into a subject to fill the pulmonary functional residual capacity. The values include an inspired compound concentration (C_i) and an expired compound concentration (C_e), wherein the inspired compound concentration (C_i) and the expired compound concentration (C_e) are measured after having filled the functional residual capacity with the gas. The instructions also cause the machine to output a representation of a compound concentration in the brain (C_b), in which the representation of the compound concentration in the brain (C_b) can be assessed by the formula $C_b = (C_e + C_b)/2$, wherein $C_b = [C_i(M-1) + C_e]/M$, M is a given alveolar membrane factor for the compound. Alternatively, the values further include a second inspired compound concentration (C_i) and a second expired compound concentration (C_e), in which C_i and C_e are measured at the time when about 90% of the functional residual capacity is filled with the gas. M is assessed based by the formula $M = 1 - (C_e/C_i)$. The instructions may further cause the machine to trigger a detector to sample the compound concentration at the time when about 90% of the functional residual capacity is filled with the gas; monitor a time interval; and trigger the detector to sample the compound from an inspiration and an expiration after filling the functional residual capacity of the subject.

[0007] In still another aspect, the invention features an apparatus that includes a display and a processor. The processor can be configured to receive values representing the concentration of a compound administered in a gas into a subject to fill the pulmonary functional residual capacity. The values include an inspired compound concentration (C_i) and an expired compound concentration (C_e), wherein the inspired compound concentration (C_i) and the expired compound concentration (C_e) are obtained after having filled the functional residual capacity with the gas. The processor can be also figured to control the display to depict a representation of a compound concentration in the brain (C_b), in which the representation of the compound concentration in the brain (C_b) is assessed by the formula $C_b = (C_e + C_b)/2$, wherein $C_b = [C_i(M-1) + C_e]/M$, and M is an alveolar membrane factor for the compound.

[0008] Other advantages or feature of this invention will be apparent from the following detailed description thereof.

DETAILED DESCRIPTION

[0009] This invention is based on the discovery of a correlation between an inhalational compound concentration in the brain and the average of an expired compound concentration and a mixed venous concentration.

[0010] More specifically, a study was conducted on 16 patients with physical status of American Society of Anesthesiologists Class I and II. See American Society of Anesthesiologists: New classification of physical status. (1963) *Anesthesiology* 24: 111. Each patient was anesthetized with isoflurane, which was administered together with oxygen, air, and nitrous oxide. Catheters were placed in each patient's radial artery and internal jugular bulb for blood sampling. Simultaneously, the inspired isoflurane concentration and the expired isoflurane concentration were recorded. For a total of 192 measurements, a good correlation ($R=0.907$, $R^2=0.823$) was found between the average of

an isoflurane concentration in the radial artery (A) and an isoflurane concentration in the internal jugular bulb (J) and the average of an expired isoflurane concentration (C_e) and an estimated mixed venous isoflurane concentration (C_b). The term "mixed venous isoflurane concentration" refers to an isoflurane concentration in venous blood from inferior and superior vena cava, and coronary sinus. The correlation can be expressed as:

$$(A+J)/2=(C_e+C_b)/2.$$

[0011] Since A represents an isoflurane concentration in the blood that flows into the brain, and J represents an isoflurane concentration in the blood that flows out from the brain, the average of A and J, $(A+J)/2$, represents the isoflurane compound concentration in the brain (C_b). In other words, $C_b=(A+J)/2$. Accordingly:

$$C_b=(C_e+C_b)/2.$$

[0012] As will be discussed below, C_b , like C_e , can also be assessed based on an inspired isoflurane concentration and an expired isoflurane concentration. Therefore, without blood sampling, the concentration of an inhalational compound in the brain can be assessed based on measurements of inspired and expired compound concentrations, thereby providing an objective method for determining the depth of anesthesia.

[0013] To practice the method of this invention, an inhalational compound-containing gas is delivered to a subject to replace the air in a space called the functional residual capacity (FRC). The FRC is the remaining lung volume at the end of a quiet respiration. Typically, its volume is about 2,500 cc. See Nunn, J. F. (1977) *Applied respiratory physiology* 2nd Ed. London Boston Butterworth & Co. pp 4-5. Initially, the FRC is filled with air, which is gradually replaced by the gas. The exchange normally requires a few minutes. After 3-4 min, 85-95% of the FRC is filled with the gas. As the gas penetrates the alveolar membrane (which separates the gas in the alveoli from venous blood flowing through the pulmonary capillaries), it is picked up by the pulmonary capillary blood flow, delivered to various organs including the brain, and continuously circulated.

[0014] As the gas penetrates the alveolar membrane and enters the pulmonary capillary blood flow, it must follow the Fick's principal. See Katzung, R. G. (1998) *Basic principles, introduction in basic and clinical pharmacology* Appleton-Lange p 5. The Fick's principal defines the rate of penetrating the alveolar membrane as:

$$DAk/x (C_i-C_b)$$

[0015] D is a diffusion constant, A is the area of the membrane (proportional to the pulmonary capillary flow or cardiac output), k is a solubility coefficient, x is the thickness of the membrane, C_i is an inspired compound concentration, and C_b is the mixed venous compound concentration. Assuming that the pulmonary capillary flow or the cardiac output is constant, then, for a given inhalational compound, DAk/x is a constant. This constant DAk/x is defined as a membrane factor, M, which varies from one inhalational compound to another. For example, halothane, isoflurane, methoxyflurane, and desflurane have M values of 0.5, 0.4, 0.8, and 0.2, respectively. Since the membrane factor may vary slightly among patients, a more precise determination of the membrane factor can be performed as described below.

[0016] The rate of penetrating the alveolar membrane $DAk/x (C_i-C_b)$ can be expressed as:

$$M (C_i-C_b),$$

[0017] in which M is DAk/x .

[0018] When measuring an uptake of an inhalational compound-containing gas in each breathing cycle, the rate of the uptake is a function of a difference between the inspired concentration (C_i) and the expired concentration (C_e). The difference can be expressed as:

$$C_i-C_e.$$

[0019] C_i-C_e and $M (C_i-C_b)$ both represent the rate of uptake of an inhalational compound:

$$C_i-C_e=M (C_i-C_b), \text{ or}$$

$$M=(C_i-C_e)/(C_i-C_b).$$

[0020] During the initial introduction of an inhalational compound (before the FRC is filled with the gas), the membrane factor M for an individual can be approximated by assuming $C_b=0$:

$$M=(C_i-C_e)/C_i=1-(C_e/C_i).$$

[0021] At the stage of anesthesia (after the FRC is filled with the gas), the equation: $C_i-C_e=M (C_i-C_b)$ can be used to calculate the compound concentration in the mixed venous blood (C_b), in which C_i and C_b are the inspired compound concentration and the expired compound concentration, respectively:

$$C_b=[C_i(M-1)+C_e]/M.$$

[0022] As discussed above, $C_b=(A+J)/2$ and $(A+J)/2=(C_e+C_b)/2$, the compound concentration in the brain (C_b) can be expressed as:

$$C_b=(C_e+C_b)/2.$$

[0023] Thus, with measurements of the expired compound concentration (C_e) and the mixed venous compound concentration (C_b), the compound concentration in the brain (C_b) can be readily obtained. Below are two examples of how to assess brain anesthetic concentrations by this method.

[0024] An endo-tracheal intubation is performed for administering a gas containing a desflurane to a patient. A tube is connected to the circle system of an anesthesia machine consisting of gas flowmeters, a compound vaporizer, supply of oxygen, air and nitrous oxide gas, and a ventilator (e.g., Detex-Ohmeda, Finland, or Drager, Germany). The gas is then delivered to the patient by the anesthesia machine. Desflurane is vaporized, taking up 6-8% of the total gas, and delivered at a flow rate of 3,000 mL/min. Near the connection between the circle system and the tube, a side arm sampling site is linked to a gas monitoring equipment (e.g., an infra-red monitor or a mass spectrometer). Typically, a sampling speed is 200 mL/min. Desflurane has a membrane factor, M, of 0.2 for most patients. A more precise determination of M is performed at the end of 3 min, when 85-95% of the FRC has been filled with the gas. Measuring the inspired desflurane concentration (C_i) and the expired desflurane concentration (C_e) of a patient at this time, the patient's membrane factor M can be obtained by the formula $M=(C_i-C_e)/(C_i-C_b)$, and C_b is 0. Thus, if the inspired desflurane concentration is 6% and the

expired desflurane concentration is recorded as 4.8% at 3-4 minutes, this patient's membrane factor for desflurane is: $M=(6-4.8)/6-0.2$.

[0025] During the course of desflurane anesthesia, the mixed venous desflurane concentration can be assessed according to the formula $C_b=[C_i(M-1)+C_e]/M$.

[0026] For example, if the inspired desflurane concentration is 6.2% and the expired desflurane concentration is 5.4%, the desflurane concentration in the mixed venous blood (C_b) is: $6.2-5.4=0.2$ ($6.2-C_b$), therefore $C_b=2.2\%$.

[0027] Accordingly, based on formula: $C_b=(C_e+C_b)/2$, the desflurane concentration in the brain (C_b) is: $(2.2+5.4)/2=3.8\%$.

[0028] In another example, isoflurane is used. The inspired isoflurane concentration is 1.5% and the expired isoflurane concentration is as 0.8% at 3-4 minutes. Thus, the patient's membrane factor for desflurane is: $M=(1.5-0.8)/1.5=0.406$.

[0029] During a point in the course of anesthesia, if the inspired isoflurane concentration is 1.2% and the expired concentration has risen to 0.9%, the isoflurane concentration in the mixed venous blood (C_b) is: $1.2-0.9=0.406$ ($1.2-C_b$), $C_b=0.46\%$, and the brain desflurane concentration (C_b) is: $(0.9+0.46)/2=0.68\%$.

[0030] After 20 minutes, if the inspired isoflurane concentration is 1.1% and the expired isoflurane concentration remains at 0.9%, the isoflurane concentration in the mixed venous blood (C_b) is:

[0031] $1.1-0.9=0.406$ ($1.1-C_b$), $C_b=0.607\%$, and the brain desflurane concentration (C_b) is: $(0.9+0.607)/2=0.75\%$.

[0032] The methods and formulae described above can be implemented using a variety of software and/or hardware configurations.

[0033] For example, the techniques described here are not limited to any particular hardware or software configuration; they may find applicability in any computing or processing environment. The techniques may be implemented in hardware, software, or a combination of the two. The techniques may be implemented in programs executing on programmable machines such as mobile or stationary computers, devices such as a detector for the inhalation compound, and similar devices that each include a processor, a storage medium readable by the processor (including volatile and non-volatile memory and/or storage elements), at least one input device, and one or more output devices. Each program may be implemented in a high level procedural or object oriented programming language to communicate with a machine system. However, the programs can be implemented in assembly or machine language, if desired. In any case, the language maybe a compiled or interpreted language. Examples of programming languages include C, C++, Java, Fortran, Pascal, and Visual Basic. The programs can also be implemented within other software applications, e.g., a spreadsheet or database program, e.g., using scripts, formulae, and other software tools.

[0034] Each such program may be stored on a storage medium or device that is readable by a general or special purpose programmable machine for configuring and operating the machine when the storage medium or device is read

by the computer to perform the procedures described in this document. The system may also be implemented as a machine-readable storage medium, configured with a program, where the storage medium so configured causes a machine to operate in a specific and predefined manner. Machine-readable media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM, ROM, EPROM, EEPROM, flash memory, and the like; and hybrids of these categories such as magnetic/optical storage media. The processes described here may be executed by an embedded system.

[0035] Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

OTHER EMBODIMENTS

[0036] All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

[0037] From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

What is claimed is:

1. A method of assessing the concentration of a compound in the brain of a subject, the method comprising:

administering a gas containing the compound into a subject to fill the pulmonary functional residual capacity;

after having filled the functional residual capacity with the gas, measuring an inspired compound concentration (C_i) and an expired compound concentration (C_e);

assessing a mixed venous compound concentration (C_b) based on Formula I: $C_b=[C_i(M-1)+C_e]/M$, in which M is an alveolar membrane factor for the compound; and

assessing a compound concentration in the brain (C_b) based on Formula II: $C_b=(C_e+C_b)/2$.

2. The method of claim 1, wherein M is assessed based on Formula III: $M=1-(C_e/C_i)$, in which C_i and C_e are an inspired compound concentration and an expired compound concentration, respectively, measured at the time when about 90% of the functional residual capacity is filled with the gas.

3. The method of claim 1, wherein the compound is an anesthetic.

4. The method of claim 2, wherein the compound is an anesthetic.

5. The method of claim 3, wherein the anesthetic is isoflurane, haloflurane, desflurane, sevoflurane, or enflurane.

6. The method of claim 4, wherein the anesthetic is isoflurane, haloflurane, desflurane, sevoflurane, or enflurane.

7. An article comprising a machine-readable medium that stores machine-executable instructions, the instructions causing a machine to:

receive values representing the concentration of a compound administered in a gas into a subject to fill the pulmonary functional residual capacity, the values including an inspired compound concentration (C_i) and an expired compound concentration (C_e), wherein the inspired compound concentration (C_i) and the expired compound concentration (C_e) are obtained after having filled the functional residual capacity with the gas; and

output a representation of a compound concentration in the brain (C_b), in which the representation of the compound concentration in the brain (C_b) is assessed by the formula $C_b = (C_e + C_b)/2$, wherein $C_b = [C_i(M-1) + C_e]/M$, M being an alveolar membrane factor for the compound.

8. The article of claim 7, wherein the values further include a second inspired compound concentration (C_i) and a second expired compound concentration (C_e), in which C_i and C_e are measured at the time when about 90% of the functional residual capacity is filled with the gas, and M is assessed based by the formula $M = 1 - (C_e/C_i)$.

9. The article of claim 8, wherein the instructions further cause the machine to:

trigger a detector to sample the compound from an inspiration and an expiration measured at the time when about 90% of the functional residual capacity is filled with the gas;

monitor a time interval; and

trigger the detection to sample the compound from an inspiration and an expiration after filling the functional residual capacity with the gas.

10. An apparatus comprising:

a display; and

a processor, the processor configured to:

receive values representing the concentration of a compound administered in a gas into a subject to fill the pulmonary functional residual capacity, the values including an inspired compound concentration (C_i) and an expired compound concentration (C_e), wherein the inspired compound concentration (C_i) and the expired compound concentration (C_e) are obtained after having filled the functional residual capacity with the gas; and

control the display to depict a representation of a compound concentration in the brain (C_b), in which the representation of the compound concentration in the brain (C_b) is assessed by the formula $C_b = (C_e + C_b)/2$, wherein

$C_b = [C_i(M-1) + C_e]/M$, M being an alveolar membrane factor for the compound.

11. The apparatus of claim 10, wherein the values include a second inspired compound concentration (C_i) and a second expired compound concentration (C_e), in which C_i and C_e are measured at the time when about 90% of the functional residual capacity is filled with the gas, and M is assessed based by the formula $M = 1 - (C_e/C_i)$.

12. The apparatus of claim 11 further comprising a detector.

13. The apparatus of claim 12, wherein the instructions further cause the machine to:

trigger the detector to sample the compound from an inspiration and an expiration measured at the time when about 90% of the functional residual capacity is filled with the gas;

monitor a time interval; and

trigger the detector to sample the inhalation compound from an inspiration and all expiration after filling the functional residual capacity with the gas.

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专利名称(译)	评估大脑中吸入化合物的浓度		
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摘要(译)

本发明涉及评估受试者大脑中吸入化合物浓度的方法。该方法包括将含有化合物的气体给予受试者以填充肺功能残余容量，其被定义为非强制呼吸结束时的剩余肺容量。该方法还包括在用气体填充功能性残余容量之后测量吸入的化合物浓度 (C_i) 和呼出的化合物浓度 (C_e)。因此，可以基于式 $C_b = [C_i (M-1) + C_e] / M$ 评估混合静脉化合物浓度 (C_b)，其中M是该化合物的肺泡膜因子；并且可以基于式 $C_b = (C_e + C_b) / 2$ 评估脑化合物浓度 (C_b)。