BRIEF COMMUNICATIONS

Calculation of the percentage of a narcotic gas to permit abolition of the high pressure nervous syndrome

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Simon, S., Y. Katz, and P. B. Bennett. 1975. Calculation of the percentage of a narcotic gas to permit abolition of the high pressure nervous syndrome. Undersea Biomed. Res. 2(4):299-303.—A theoretical method is derived for computation of the interaction of pressure and a weak anesthetic such as nitrogen or other narcotic gases in a two-dimensional material so as to prevent signs and symptoms of the high pressure nervous syndrome. A ratio of one part nitrogen to 9 parts helium (pressure) is derived, which is in excellent agreement with previous human experiments in men at 31 ATA, with PO_2 = 0.5 ATA.

HPNS
pressure
anesthesia
helium
trimix

Exposure to increased hydrostatic or oxygen-helium pressures results in a number of signs and symptoms in animals as well as in man that are collectively called the high pressure nervous syndrome (HPNS). This disorder is characterized by tremors, dizziness, nausea, increase in electroencephalographic activity (4-6 Hz), and depression of other activities. At sufficiently high pressure HPNS is characterized in man by lapses of consciousness and in animals by convulsions (Bachrach and Bennett 1973; Hunter and Bennett 1974).

A number of workers, as described in a recent review (Hunter and Bennett 1974), have suggested that incorporation of an anesthetic gas into the oxygen-helium mixture will prevent HPNS.

Such suppression or prevention of HPNS in human divers exposed to pressures as great as 31 ATA (1000 fsw) has been confirmed by recent studies at this laboratory (Bennett, Blenkarn, Roby, and Youngblood 1974; Bennett, Roby, Simon, and Youngblood 1975). A satisfactory amount of the narcotic gas nitrogen was 1 part nitrogen to 10 parts helium. This paper presents a simple model for predicting corrective concentrations of anesthetic to nullify a given effect of hydrostatic pressure.

There are many reasons why nitrogen may negate the effects of high helium pressures, but the most likely is that while helium—because of its extremely low water solubility—acts on cell membranes in a manner that effectively decreases their size (Bennett, Papahadjopoulos, and Bangham 1967; Bennett, Simon, and Katz 1975; Trudell, Hubbell, and Cohen 1973), nitrogen mixes with such biological systems in a manner that counteracts their size-reducing effect (Bennett et al. 1967). Thus the correct mixture of nitrogen, or any other anesthetic gas added to helium-oxygen mixtures, should prevent membrane contraction due to the hydrostatic pressure, resulting in no change in size and, thereby, no HPNS.

There has been much controversy in the literature concerning whether the *site* of interaction of anesthetic gases is first in the bimolecular lipid region of a biological membrane (Miller 1974) or in a protein embedded in the lipid matrix (Eyring, Woodbury, and d'Arrigo 1973). It is beyond the scope of the following analysis to differentiate between these hypotheses.

For our purposes it is only necessary to postulate that the site where the gases first partition is a two-dimensional material, such as a monolayer (Gaines 1966), a lipid bilayer (Evans and Simon 1975 a,b) or a biological membrane (Evans 1973).

THEORY

Consider a gas in equilibrium with a two-dimensional material which is in turn in equilibrium with an aqueous subphase. By the definition of equilibrium, the chemical potential of the gas must be equal in all three phases. For simplicity we will confine the rest of the analysis to a monolayer. For monolayers it has been shown that the Gibbs adsorption equation (Gaines 1966) can be written:

$$\Sigma_i - \partial\gamma_i = \Sigma\Gamma_i\partial\mu_i \qquad \text{(T constant)} \qquad (1)$$

where

T = temperature

γ_i = surface tension in presence of gas *i*,

μ_i = chemical potential of gas *i*, and

Γ_i = surface excess in presence of gas *i*.

The above equation may be approximated for small concentrations of gas in the monolayer for a single component (Ross and Chen 1965) as

$$-\partial\gamma = \partial\Pi = mX_L \qquad (2)$$

where

X_L = mole fraction of gas in monolayer and

m = a constant at constant temperature.

Equation (2) simply states that the change in surface pressure will be directly proportional to the mole fraction of gas in the monolayer. The mole fraction of gas in the monolayer is related to the mole fraction of gas in the water, X_W, via the partition coefficient, K. Hence $X_L = KX_W$. We may relate X_W to the external pressure P via Henry's Law

$$P = K_H X_w$$

where

$$K_H = \text{Henry's constant.}$$

Upon substituting the above relations into Equation (2) one gets for a particular gas

$$\left(\frac{\partial \Pi}{\partial P}\right)_T = \frac{K}{K_H} m \qquad (3)$$

Since the right-hand side of Equation (3) is constant (K_H by definition is independent of pressure), which it will be at moderate pressures, then the change in surface pressure will be directly proportional to the external pressure.

Physically this means that as inert gases (other than neon or helium) are adsorbed, the area per molecule of the surface-active molecule will increase. Thus the tension in the membrane increases or the surface pressure decreases. If, however, gases such as helium or neon act in a manner that decreases the area per molecule, then the tension will decrease and the surface pressure increase.

From the above discussions we will now *assume* that the necessary condition for the elimination of HPNS is that the area per molecule at the interface must remain unchanged or that the sum of the changes in surface pressure for the three gases must algebraically add to zero. Thus

$$\sum_i \Delta\Pi_i = 0 \qquad (4)$$

so that upon integrating Equation (3)

$$\Delta\Pi_{N_2} = (\pi_{N_2} - \Pi^0) = -\frac{K_{N_2}}{K_{H\,N_2}} m\ P_{N_2} \qquad (5)$$

$$\Delta\Pi_{O_2} = (\Pi_{O_2} - \Pi^0) = -\frac{K_{O_2}}{K_{H\,O_2}} m\ P_{O_2} \qquad (6)$$

$$\Delta\Pi_{He} = (\Pi_{He} - \Pi^0) = \frac{K_{He}}{K_{H\,He}} mP_{He} \qquad (7)$$

where Π^0 = standard reference state of monolayer.

Since the sum of the terms on the left-hand side must equal zero to prevent HPNS (membrane contraction) or anesthesia (membrane expansion), and since the oxygen partial pressure is determined from experimental conditions (usually at 0.5 ATA for divers exposed to great depths) and used in Equation (6), it is then possible to calculate the ratio of helium to nitrogen by substituting the handbook values of Henry's Law and the partition coefficient and using Equation (4) with Equations (5) and (7).

Following the above prescription for dives of 1000 fsw (31 ATA) we calculate that for about every 9 atm helium, 1 atm nitrogen would be required for the prevention of HPNS. This result is in good agreement with experiments exposing men to 1000 fsw (Bennett, Roby et al. 1975) with 10% nitrogen added to the oxygen-helium mixture. Calculations indicate that at 31 ATA the percentage required in man for nitrous oxide would be 0.5% and for hydrogen 16%. These values are in reasonable agreement with the relative biological effectiveness of nitrogen (10% ± 2%) and of nitrous oxide (0.25% ± 0.05%) to elevate the pressure at which mice convulse, a common HPNS measurement in animals (Brauer, Goldman, Beaver, and Sheeham 1974). Hydrogen, however, appears to be an exception; Brauer et al. (1974) found that 29 ±6% was required for mice compared to our calculated value of 16%. Part of this small discrepancy could be due to the fact that Henry's Law cannot be applied without corrections at the very high pressures utilized in the mice investigations.

CONCLUSIONS

Using only minimum assumptions it was possible to calculate the correct proportion of gases in a gas mixture necessary to eliminate complex physiological responses to hydrostatic pressure (HPNS) in men and animals. Further, these calculations agree with proportions that have been examined experimentally in human divers and found effective (Bennett et al. 1974; Bennett, Roby et al. 1975). All that is required is reference to the handbook values for Henry's constant at the experimental temperature[1] and the oil-water partition coefficients at 37°C[2].

Although this paper does not resolve the speculation as to the site where gases partition in connection with both HPNS and anesthesia mechanisms, it is pertinent that relationships similar to those obtained theoretically were found previously for gases adsorbed to an egg phospholipid monolayer (Bennett et al. 1967).

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Simon, S., Y. Katz, and P. B. Bennett. 1975. Méthode pour le calcul du pourcantage d'un gaz narcotique nécessaire pour abolir le syndrome nerveux des hautes pressions. Undersea Biomed. Res. 2(4):299-303.–Une méthode théorique pour le calcul de l'interaction de la préssion et d'un gaz à faible action anesthésique tel que l'azote ou autre gaz narcotique dans une matière à deux dimensions pour empecher l'apparition des signes et symptomes du syndrome nerveux des hautes pressions est dérivée. Un rapport d'une partie d'azote à neuf parties d'hélium (pression) est dérivé, ce qui s'accorde très bien avec les expériences humaines à 31 ATA, avec un PO_2 = 0.5 ATA.

[1]Handbook of Chemistry and Physics (1961); see REFERENCES.

[2]Handbook of Respiration (1958); ibid.

pression hélium
anesthésie mélange ternaire
syndrome nerveux des hautes pressions

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