Losing concentration: time for a new MAPP?

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Anaesthetic vapour analysis is an essential element of monitoring during inhalation general anaesthesia,1 and recent publications have re-emphasized the importance of monitoring end-tidal anaesthetic concentrations as a means of minimizing the risks of awareness in this setting.2–4 Consequently, the question arises as to whether expired vapour concentration is a valid measure of the dose of volatile anaesthetic gases in all circumstances. More specifically, can such measures be misleading in conditions of altered barometric pressure that occur with increasing altitude? A quarter of the world’s population live at more than 500 m above sea level and nearly 10% reside higher than 1500 m,5 many in highly populated cities, including Denver, Mexico City, La Paz, Quito, Lhasa, Nairobi, and Johannesburg. Inhalation anaesthesia at such altitudes is common. Might practices suitable for sea-level environments result in increased risk of awareness and injury at these elevated altitudes? If so, how can this risk be mitigated? To this end, we propose minimal alveolar partial pressure (MAPP) as the safest universal measure of anaesthetic dose, as opposed to the concentration-based variable, minimal alveolar concentration (MAC).

The physical concept underlying this proposal is beautifully illustrated by the classical teaching (and erstwhile common final fellowship question) about the degree to which an anaesthetist delivering volatile anaesthesia at altitude would need to alter the fractional concentration set on a variable bypass vaporizer in order to achieve the same level of anaesthesia as at sea level. The answer to this thought experiment is that the same settings as at sea level will result in the same proportion of the saturated vapour pressure of that volatile and therefore the same partial pressure and pharmacological effect at any altitude (although this theoretical degree of precision is not entirely accurate because alterations in flow splitting ratios with changes in barometric pressure may have minor, unpredictable effects; see http://www.openanesthesia.org/vaporizer_output_at_altitude/). This is because all variable bypass vaporizers deliver varying dilutions of saturated vapour pressure, and not a concentration5 (the desflurane vaporizer functions on a different principle). However, the fractional concentration will be dependent on the barometric pressure. Thus, a variable bypass vaporizer set to deliver 2% at sea level will deliver a partial pressure of 2 kPa regardless of the barometric pressure. The same vaporizer in Johannesburg or Denver, CO, USA [at an altitude of ~1700 m (5500 feet) and a barometric pressure of ~80 kPa] will continue to deliver the same partial pressure of 2 kPa, but at a concentration of 2.5%. At half of the sea-level barometric pressure (say ~5300 m), the concentrations will be double. Therefore, if the anaesthetist were to titrate anaesthetic agent dosage to end-tidal volatile concentration, the partial pressure would be half that delivered at sea level and the risk of underdosing (and in some circumstances accidental awareness under anaesthesia) would be substantial. Modifying the vaporizer to deliver the set concentration will almost certainly result in a significantly lower partial pressure of the agent being delivered. It is thus illogical to calibrate these instruments in terms of concentration. Importantly, the most widely used device for the factory calibration of vaporizers is the refractometer, a device that measures partial pressure, not concentration.

The exception to this principle, the desflurane vaporizer, features dual circuits that function by blending gas and vapour and behaves much like a nitrous oxide cylinder, delivering a volume of vapour that will expand on exposure to reduced barometric pressure. This vaporizer will either need to be recalibrated at altitude to ensure that the appropriate partial pressure is delivered or a calculated higher setting on the dial must be selected. At an altitude of 2000 m, the operator must manually increase the fractional concentration set on a variable bypass vaporizer in order to achieve the same level of anaesthesia as at sea level. The answer to this thought experiment is that the same settings as at sea level will result in the same proportion of the saturated vapour pressure of that volatile and therefore the same partial pressure and pharmacological effect at any altitude (although this theoretical degree of precision is not entirely accurate because alterations in flow splitting ratios with changes in barometric pressure may have minor, unpredictable effects). Henry’s law states that, at a constant temperature, the amount of a given gas dissolved in a liquid is directly proportional when the physical concept underlying this proposal is beautifully illustrated by the classical teaching (and erstwhile common final fellowship question) about the degree to which an anaesthetist delivering volatile anaesthesia at altitude would need to alter the fractional concentration set on a variable bypass vaporizer in order to achieve the same level of anaesthesia as at sea level. The answer to this thought experiment is that the same settings as at sea level will result in the same proportion of the saturated vapour pressure of that volatile and therefore the same partial pressure and pharmacological effect at any altitude (although this theoretical degree of precision is not entirely accurate because alterations in flow splitting ratios with changes in barometric pressure may have minor, unpredictable effects; see http://www.openanesthesia.org/vaporizer_output_at_altitude/). This is because all variable bypass vaporizers deliver varying dilutions of saturated vapour pressure, and not a concentration5 (the desflurane vaporizer functions on a different principle). However, the fractional concentration will be dependent on the barometric pressure. Thus, a variable bypass vaporizer set to deliver 2% at sea level will deliver a partial pressure of 2 kPa regardless of the barometric pressure. The same vaporizer in Johannesburg or Denver, CO, USA [at an altitude of ~1700 m (5500 feet) and a barometric pressure of ~80 kPa] will continue to deliver the same partial pressure of 2 kPa, but at a concentration of 2.5%. At half of the sea-level barometric pressure (say ~5300 m), the concentrations will be double. Therefore, if the anaesthetist were to titrate anaesthetic agent dosage to end-tidal volatile concentration, the partial pressure would be half that delivered at sea level and the risk of underdosing (and in some circumstances accidental awareness under anaesthesia) would be substantial. Modifying the vaporizer to deliver the set concentration will almost certainly result in a significantly lower partial pressure of the agent being delivered. It is thus illogical to calibrate these instruments in terms of concentration. Importantly, the most widely used device for the factory calibration of vaporizers is the refractometer, a device that measures partial pressure, not concentration.

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to the partial pressure of that gas in equilibrium with that liquid. Thus, alveolar partial pressure is the factor that determines the content of that gas in the blood, and thereby, its physiological or pharmacological effects. This is true of all gases and vapours. The physiological gases, oxygen and carbon dioxide, are routinely measured in the blood as partial pressures, but inhaled anaesthetic agents are almost exclusively measured in the anaesthesia delivery system as concentrations. The use of concentration as a measure of inhaled gas is the result of long tradition dating from the time of the early pioneers of pneumatic chemistry, such as Priestley, Lavoisier, Cavendish, and Dalton, when only volumetric analysis of gas mixtures was available. Consequently, the majority of anaesthetic monitors in current use report gas composition as a percentage or concentration.

Modern gas and vapour analysers use physical properties to detect specific gases in a mixture, ignoring others. This results in the measurement of the partial pressure of that gas, not its concentration, from which the concentration is derived and almost invariably reported. Most contemporary machines allow the user to choose concentration or partial pressure for carbon dioxide but not for other gases and vapours. Thus, an oxygen analyser displaying concentration that gives a reading of 20.9% oxygen at sea level will report decreasing ‘concentrations’ as barometric pressure reduces. At simulated altitudes of 1800 and 3300 m, an oxygen analyser calibrated to measure 21% oxygen at sea level reported values of approximately 17 and 14% at each respective barometric pressure. Therefore, the analyser is in fact measuring partial pressure, and the calibration scale expressed as percentage concentration is simply wrong. The real measurement for all anaesthetic gas analysers in current use (with the possible exception of the mass spectrometer) is partial pressure. The most rational approach would be for these analysers to report the units of real measurement (kilopascals or millimetres of mercury), rather than a derived variable, such as concentration.

Concentration is an inadequate measure of inspired gases unless it is accompanied by the value of the barometric pressure at the location where the concentration is being measured. This phenomenon is well known in high-altitude physiology, where the fractional concentration of oxygen remains at just under 21%, regardless of altitude, whereas the partial pressure ranges from 20.9 kPa (159 mm Hg) at sea level to approximately one-third of that value at the top of Mount Everest. Consequently, the alveolar partial pressure of oxygen as determined by the alveolar gas equation falls from 13.3 to 4.51 kPa, a value at which an unacclimatized individual would lose consciousness within 3 min. Conversely, in hyperbaric situations, such as deep sea diving, low concentrations of oxygen are included in the breathing mixture in order to maintain safe partial pressures, thereby preventing oxygen toxicity. A dramatic example of the importance of partial pressure as opposed to concentration is that of shallow water blackout. A breath-hold diver at moderate depth will have sufficient partial pressure of oxygen in the lungs to sustain consciousness. However, as the diver ascends towards the surface, decreasing ambient pressure results in a sharply reduced partial pressure of oxygen in the lungs and arterial blood, leading to severe hypoxia and loss of consciousness, with potentially catastrophic consequences.

The uptake of anaesthetic agents into the blood is determined by a combination of the partial pressure and the solubility of the agent in blood. In a situation analogous to that of protein binding of intravenously administered drugs, inhaled agents must first saturate the plasma before they can develop a significant partial pressure (comparable to ‘free fraction of drug’). It is the partial pressure of the agent in the blood that determines the amount of agent available to reach the effect site and exert clinical effects. Thus, a highly soluble agent, such as ether, will be taken up rapidly into the bloodstream and develop a substantial concentration in plasma (mass per unit volume, analogous to the protein-bound drug fraction), but the partial pressure will remain low until the plasma is saturated. Therefore, the onset and offset of anaesthesia will depend on the time taken to develop a sufficient partial pressure of the agent in the blood. Despite the fact that ether is a more potent anaesthetic than either desflurane or sevoflurane (MAPP 1.9 vs 6.7 or 2.0 kPa, respectively), high inhaled concentrations are required to achieve an effective partial pressure in the blood. The less soluble agents will saturate the plasma much more rapidly, with an effective partial pressure more quickly and easily attained. Again, concentration is a poor indicator of anaesthetic level, whereas exhaled partial pressure will reflect the amount of drug at the effect site.

Nitrous oxide is equally dependent on partial pressure rather than concentration. The reduced effectiveness of N₂O at the altitude of Johannesburg was noted as long ago as 1913. Powell concluded that the efficacy of N₂O was decreased at an altitude of 5280 feet (1670 m). Cleaton-Jones and colleagues reported that there were only marginal differences between a group studied at sea level and a different group studied at 1670 m. However, they did not measure objective end points and there were strong trends suggesting a lower potency of N₂O at altitude, particularly in conscious level, at 60 and 70% concentrations between the two altitudes. In a pressure chamber experiment, in which the same subjects were tested at various simulated altitudes, it was shown that the analgesic efficacy of an inhaled mixture containing 50% N₂O and a constant partial pressure of oxygen was reduced by 44% from the sea-level effect at an altitude of 1460 m and to negligible levels at 3300 m. A study of anaesthesia using volatile agents and N₂O in combination at sea level and at altitudes >1300 m showed a significantly greater consumption of volatile agents at higher altitudes, suggesting a diminished effect of N₂O. Furthermore, a comparative trial of i.v. anaesthesia in conjunction with 66% N₂O at high and low altitudes demonstrated significantly higher propofol requirements at altitude. It can be safely concluded that the efficacy of N₂O is entirely dependent on the partial pressure of the agent and not the concentration. With the recent ENIGMA-II study showing no increased risk of myocardial injury or other adverse events other than nausea and vomiting, there is likely to be a resurgence in the use of this agent. An appreciation of the difference between concentration and partial pressure, particularly at altitude, will be critical if adverse incidents resulting from inadequate anaesthetic dosage are to be avoided.

Given that all modern vaporizers (bar desflurane) actually deliver a partial pressure, all analysers actually measure partial pressure, and partial pressure is the measurement that determines depth of anaesthesia, it is irrational to continue to use concentration to express anaesthetic gas composition. Fortunately, for those working in SI units, it is easy to make the shift to expressing values as partial pressures. Given that barometric pressure closely approximates 100 kPa, units of partial pressure are almost identical to sea-level concentration. The conversion is not as easy in millimetres of mercury, because the concentration must be multiplied by ~7.6 to calculate the partial pressure.

These considerations have a major import for the outdated concept of MAC. As concentration in terms of requirements for anaesthesia is barometric pressure dependent, MAC needs to be adjusted for altitude, or substantial underdosing will result in an increased risk of awareness. At sea level, 1 MAC of isoflurane is 1.15 vol %. This corresponds to an end-tidal partial pressure of 101.3 kPa×0.0115=1.16 kPa. To achieve an end-tidal isoflurane
partial pressure of 1.16 kPa in Mexico City (barometric pressure 76.4 kPa), one should aim for an end-tidal concentration of 1.16 kPa/76.4 kPa=1.5%. Consequently, when using isoflurane in Mexico City, its MAC is 1.5 vol %, not the standard 1.15%. It is far more logical, therefore, to use the concept that is independent of altitude, and thus applicable throughout the world, MAPP.13 Again, in SI unit terms this conversion is simple because the kilopascal MAPP value and the sea-level MAC value are essentially the same.

Similar considerations apply to the measurement of carbon dioxide, where the clinically relevant value is partial pressure, not concentration. Fortunately, most CO2 analysers allow this display as an option.

A subsequent important consideration is the manner in which commercial anaesthesia machine companies calibrate their instruments, particularly at altitude. While refractometers (measuring partial pressure) are widely used to calibrate vaporizers, predetermined gas mixtures are extensively used to calibrate vapour analysers. This means that a calibration gas that is produced at sea level will expand at altitude to give the same concentration as the sea-level standard, but a reduced partial pressure. If vapour analysers are then put into service with altitude-adjusted outputs, lower than anticipated partial pressures are inevitable, and the risks of awareness are greatly increased.

Counterintuitively, it is indefensible to incorporate a barometric pressure correction factor into gas analysers so that they report corrected concentration and not the measured partial pressure. This will inevitably lead to serious errors in clinical management, particularly in terms of anaesthetic dosage administered and adjustment of ventilators to achieve the ‘correct’ concentration of CO2. An end-tidal concentration of 5% CO2 measured using a recalibrated device in Mexico City would be, in fact, a partial pressure of 3.8 kPa, which could represent substantial hyperventilation. Likewise, an end-tidal isoflurane concentration of 1.15% at the same altitude would be a partial pressure of only 0.87 kPa, leading to potentially serious errors in dosage and risk of awareness.

What should we do? The only logical answer is that all anaesthesia systems—including gas/vapour analysers and vaporizers—should be designed to display partial pressure and not concentration. In practice, this is a simple matter for areas using SI units, because the sea-level numbers for concentration are interchangeable with partial pressure. It is less simple for those still using other units. Such a change would be considerably simpler than the change to SI units that was implemented many years ago, but the impact on patient safety would be substantially greater. This is a change in practice that the anaesthesia community should strongly consider adopting. We should report quantities in units in which they are measured rather than ones which are derived. Ultimately, this will result in improved accuracy, reliability, universal applicability, and thereby, enhanced patient safety.

In summary, all inhaled gases exert their effects through partial pressure, not concentration. Modern anaesthetic analysers measure partial pressure but report the derived variable, concentration. Furthermore, almost all vaporizers deliver a partial pressure, not a concentration. The time has surely come to move from the traditional, outdated use of volumetric reporting to the much more appropriate and safer use of partial pressure. The way forward is clearly indicated by the MAPP!

Declaration of interest


References