Southern African Journal of Anaesthesia and Analgesia 2016; 22(1):4-6
http://dx.doi.org/10.1080/22201181.2016.1141566

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

EDITORIAL

Concentrating on the right measures

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The continued use of "percent" in the labelling and description of many drugs used in the field of anaesthesia is an ongoing source of errors. As part of the modern drive towards safety in medicine it is proposed that the standard of labelling according to mass of the drug per millilitre be universally adopted.

Keywords: drug dosage calculations, drug labelling, medication errors

There are many fields of medicine where small errors may result in significant patient harm. Avoidance of sources of misunderstanding is a fundamental tenet of error reduction strategies.

A recent editorial in the *British Journal of Anaesthesia*,[1] reviewed the time-honoured practice of expressing the effective levels of physiological gases and volatile anaesthetics in units of "percent" or "fractional concentration" (e.g. FiO_2) instead of the physiologically important variable, partial pressure. The nomenclature obscures understanding of the method of action of these agents and may thus negatively impact on the safety of delivered respiratory gases, especially at sites above sea level. While it may be argued that changing this convention will require something akin to a seismic shift in the entire industry, the continuance of an illogical practice is at odds with the growing culture of safety in 21st century medicine.

This discussion also brings to mind the usage of the "percent" terminology to express the concentration of drug and electrolyte solutions. We propose that this latter usage has an even greater potential to increase patient risk - but may also be easily remedied. This issue has previously been highlighted.[2,3] In this editorial, we highlight the errors that may arise from this misleading terminology, especially in the calculation of the administration of drugs in solution, and the consequent hazards across many fields of medical practice.

All but one of the local anaesthetic (LA) solutions available on the South African market is labelled with a concentration expressed in "percent mass per unit volume – (% m/v)". When implementing an anaesthetic technique involving LA, a fundamental risk-reduction strategy is to keep the total amount of LA drug administered below a recognised maximum safe dose expressed in milligrams per kilogram of patient body mass. If the concentration of LA is expressed in milligrams per millilitre (mg/ml) of solution, the calculation of the maximum safe volume of LA solution requires a single multiplication. Thus, any administered dose of local anaesthetic agent should be recorded in milligrams with the volume administered as a secondary descriptor (e.g. 50 mg bupivacaine in 10 ml rather than 10 ml 0.5% bupivacaine).

However, all but one of the local anaesthetics available in South Africa are labelled with a concentration expressed in percent, thus making errors in the calculation of a safe dose much more likely. As a worked example when calculating the safe amount of bupivacaine to be administered:

0.5% bupivacaine = 0.5 g/100 ml = 500 mg/100 ml = 5 mg/ml

Maximum safe dose (plain bupivacaine) = 2 mg/kg = 0.4 ml/kg of the above solution.

Numerous errors are possible at any of the above steps, particularly those related to factors of ten (*vide infra*).

The expression of chemical concentration in terms of "percent" is ambiguous unless it is qualified. The term can be used to express, in percentage terms, the proportion of the mass of substance of interest to the total mass of the solution in which it is dissolved (% m/m). The term could also be used to express in percentage terms the proportion of the volume of the substance to the total volume of the solution (% v/v). In both of these instances the numerator and denominator share the same units, and thus the percentage is (correctly) dimensionless. While neither usage is currently highly favoured in laboratory chemistry, these usages are mathematically logical.

The biological and pharmaceutical sciences have, unfortunately, adopted a third convention: the practice of expressing the concentration of dilute solutions in units of grams of solute per 100 ml of solution, and refer to this as "% m/v". This usage of "percentage" is mathematically bizarre as the numerator and denominator are different physical properties, expressed in different units, and thus cannot generate a dimensionless value. This nomenclature relates rather to the historical choice of the decilitre (100 mL) as the volume of solution being studied. It is this latter convention that is incorporated into the naming of many drugs and electrolyte solutions.

Our main concern with the continuation of this convention is not its inelegance but the way it complicates the education process and opens the door for common errors in the order of magnitude,[4] especially in paediatrics.[5] The most common source of these errors in the order of magnitude is an omitted or misplaced decimal point with the addition or omission of a zero following closely behind. ("Factor of ten error")[6] As generations of anaesthetic trainees have learned by rote, it is necessary for local anaesthetics to multiply "% m/v" by a factor of 10 to obtain the relevant mg/ml to calculate the maximum safe dose. Omission or duplication of this step (both occur) will lead to critical under-dosing or over-dosing, respectively. Moreover, a significant amount of educational time is wasted repeatedly teaching this conversion, and the reasons behind it, to trainees at multiple levels. Surely this constitutes an unnecessary impediment to learning. Expressing dilutions of drugs in terms of the actual mass of agent administered and the volume of diluent in which it is given is both simpler and safer.

The use of "% m/v" is even more obstructive to understanding when used to identify the concentration of electrolyte solutions. Conversion of "15% m/v" of potassium chloride into clinically usable terms of millimoles per litre requires (for the chemist) reference to a periodic table – alternatively (for most clinicians) either blind acceptance, rote learning, or (worst of all) ignorance. Once again, this convention impairs understanding. Similarly, the standard solution of 0.9% sodium chloride requires the user to learn and remember that the solution actually contains 154 mmol/l of sodium and chloride in order to appreciate the solute load being administered. This becomes particularly important in the understanding of the problem of hyperchloraemic acidosis generated by so-called "normal" saline infusions.[7]

Another similar problem occurs during administration of sodium bicarbonate, which is sold in two formulations: 4.0% and 8.5% m/v.[8] Where this formulation deviated from the original preparations (4.2% and 8.4%) is unclear. The original purpose of the 8.4% formulation was to provide a solution 1 mmol/ml of bicarbonate. This allowed the original base excess calculation of Astrup and Siggaard-Anderson[9] to derive the number of millimoles of bicarbonate required by the patient, and for this to be administered as a number of millilitres of the 8.4% solution for "full" correction and millilitres of the 4.2% solution for "half" correction. Given the current controversies over acid base management,[10] it is perhaps wise to move away from this system to one where calculated millimoles of sodium bicarbonate in an appropriate solution are judiciously administered in response to sequential blood gases, rather than as blind administration of various volume amounts.

The problem is yet further compounded when looking at intravenous calcium, which is available in two formulations (gluconate and chloride) each with very different molar masses. However, both solutions are sold in a 10% m/v format and easily leads to the assumption that both solutions deliver similar quantities of calcium. This assumption is seriously mistaken as the gluconate solution has an elemental calcium concentration of 9 mg/ml (0.22 mmol) and the chloride solution has an elemental calcium concentration of 27 mg/ml (0.68 mmol). This represents a threefold difference in administered calcium content for the same volume.[11] This error is so easy to make that noted authors got it wrong in a peer-reviewed article published in a major journal.[12]

Perhaps the most egregious and potentially dangerous of these terminological inexactitudes are those referring to adrenaline preparations.[13] The standard ampoule of adrenaline is widely described as "1:1000", which is, in itself, a meaningless concept. What is meant is that the solution contains 1 g of adrenaline in 1000 ml of solution, or, more usefully, 1 mg (1000 µg) in each millilitre. Since dosages of adrenaline should always be described in terms of micrograms, the only logical description for the standard preparation is 1000 µg/ml. Using this designation makes calculation of the required dilutions of adrenaline relatively simple, whereas the current practice of describing adrenaline mixtures in terms of dilution (1:10,000; 1:100,000; etc.) is confusing and prone to massive dosage errors. This leads to the further dangerous practice of describing adrenaline infusions in terms of millilitres per minute of single, double or triple strength adrenaline. This terminology is open to serious misunderstanding, especially at hand-overs between staff members. The only correct description of an adrenaline infusion dose is in terms of microgram/kilogram/minute. The calculation of such infusion solutions becomes a simple matter if the starting point is to describe the adrenaline in terms of its actual initial concentration of 1000 µg/ml. Anything else is potentially dangerous and should be abandoned.

A survey conducted in 1995 covering 150 teaching hospitals in the United Kingdom found that more than 40% of physicians were unable to convert drug doses correctly from percentage concentrations to more conventional mass concentrations.[14] The frequency of reported drug errors amongst South African anaesthetists leaves us in no doubt that the situation is no different in South Africa today.[15] Although this survey focussed mainly on the administration of the wrong drug, it also reported two deaths related to concentration errors in drug administration.

Expression of drug concentrations in solution in terms of percent is clearly misleading and a potential source of error not only in anaesthesia but also in all disciplines where drugs in liquid form are administered. The industry needs to find the courage to move away from this potentially dangerous practice and to use scientifically rational and practically useful units – partial pressures, mg/ml or mmol/l - instead. We strongly recommend that SASA and other professional representative bodies take a stance on this critical issue and demand a change in drug labelling, mandated through the MCC, as a basic safety issue for medical practice in South Africa.

Ethical Considerations

This article does not fall under the Ethical Principles for Medical research involving human subjects and as such ethical clearance has not been sought.

Acknowledgements – No financial support was received for this work. The authors declare that they have no relevant conflicts of interest with regards to this article

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Received: 21-09-2015 Accepted: 11-01-2016

Erratum:

In the supplement titled *Refresher course and main congress texts*, which was presented at the annual SASA congress of 2016, the following information was documented incorrectly:

- Professor MFM James's affiliation should be noted as Emeritus Professor of Anaesthesia, University of Cape Town.
- P Motshabi was the only author of the main congress text title "Anaesthesia for non-cardiac surgery for children with known congenital heart disease".

The corrected supplement is available electronically at: http://sajaa.redbricklibrary.com.