SI units-common sense not dogma is needed

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Introduction

Although the role of Napoleon's wallpaper on St Helena in his demise remains a subject of controversy, the metric system of weights and measures is perhaps the major legacy from his era which has a direct impact on clinical pharmacology and toxicology. But what would this man of action have said to the fact that after many years of debate there is still no consensus as to the units to be used in routinely reporting the results of analytical measurements? In the United Kingdom and in other parts of Europe some clinical chemistry and occupational toxicology laboratories report such data in what purport to be Systeme International (SI) molar units (e.g. μ mol Γ^{\prime}), while others are sometimes vilified for using 'traditional' units (e.g. mg l^{-1} , or even mg dl^{-1}) which in fact have equal validity as regards SI. Reporting the results of analytical measurements of drugs and poisons in mass units is logical whilst drugs are still dispensed and pesticides and other chemicals are still quantified for use in mass units. It is more important to an improved understanding of drug/poison concentration/effect relationships that reliable, selective analytical methods are used with appropriate quality assurance procedures than that the results are reported in molar units.

The International System of Units (Systeme International d'Unites, SI)

Originally promulgated in 1948, the 10th (1954) and 14th (1971) General Conferences on Weights and Measures (Conférence Général des Poids et Mesures, CGPM) agreed the basis of the system which aims to provide a coherent set of units of measurement for use in all branches of science $[1-3]$. The name Système International d'Unités was introduced in 1960 (11th CGPM). The system of quantities used with SI units is

the province of the International Organization for Standardization (International Standards Organization, ISO). Various additional national and intemational bodies such as the British Standards Institution (BSI), the International Union of Pure and Applied Chemistry (IUPAC) and the International Federation for Clinical Chemistry (IFCC) contribute to the continuing evolution of SI. The IUPAC manual 'Quantities, Units and Symbols in Physical Chemistry' [4] contains much of relevance to the analysis of drugs and poisons.

Base units and supplementary units

There were originally six base units which are regarded as independent of each other 'in respect of dimension'. A seventh base unit, that for 'amount of substance' (mole), was added in 1971 (see Table 1). When using the mole the elemental entity referred to (molecule, ion, etc.) must be specified. (N.B. 'Molarity' or 'molar solution' (symbol M) and 'normality' or 'normal solution' (symbol N) as expressions of concentration are not consistent with SI). There are in addition two dimensionless 'supplementary' units, the unit of the plane angle, the radian (symbol rad), and the unit of the solid angle, the steradian (symbol sr). Note finally that unit symbols are unaltered in the plural (e.g. kg not kgs) and full stops should not be used after symbols except at the end of a sentence.

Derived and 'allowed' units

Further SI units are normally derived by taking products of base or supplementary units raised to appropriate powers. These include those for area $(m²)$, volume $(m³)$, mass density (kg m⁻³), linear velocity (m s⁻¹), angular velocity (rad s^{-1}), acceleration (m s^{-2}) and electric linear current density $(A m^{-1})$. Some derived SI units have special names (Table 2). In addition, a

<i>Quantity</i>	Name	Symbol	Derivation
Celsius temperature	degree Celsius	°C	K^*
Energy, work, quantity of heat	joule	J	W s (= N m = kg m ² s ⁻²)
Force	newton	N	m kg s ⁻² (= J m ⁻¹)
Frequency	hertz	Hz	s^{-1}
Power, radiant flux	watt	W	$J s^{-1} (= N m s^{-1} = m^2 kg s^{-3})$
Pressure	pascal	Pa	N m ⁻² (= m ⁻¹ kg s ⁻²)
Capacitance	farad	F	$A s V^{-1}$
Electric conductance (direct current)	siemens	${\bf S}$	$A V^{-1}$
Electric flux	coulomb	C	A _s
Electric potential difference	volt	v	A^{-1} m ² kg s ⁻³
Electric resistance (direct current)	ohm	Ω	$V A^{-1}$
Magnetic flux	weber	Wb	V _s
Magnetic polarization	tesla	T	$Wb m^{-2}$
Permeance	henry	H	$V s A^{-1}$
Illuminance	lux	\mathbf{I}	$\text{Im}~\text{m}^{-2}$ (= cd sr m ⁻²)
Luminous flux	lumen	lm	cd sr
Absorbed radiation dose	gray	Gy	$J kg^{-1} (= m^2 s^{-2})$
Radioactivity	becquerel	Bq	s^{-1}

Table 2 Some derived SI units with special names

Key: * But $0 °C = 273.15 K$

number of non-SI units may be 'allowed' in conjunction with SI units. These include the minute (min), hour (h), day (d), degree of arc (°) = $(\pi/180)$ rad, litre or liter (1 or L) = dm^3 , electronvolt (eV) approximately $= 1.60218 \times 10^{-19}$ J, bar (bar) = 10³ Pa, and unified atomic mass unit (u) approximately = 1.66054×10^{-27} kg. (N.B. The dalton (Da), a name for atomic mass unit, is not yet approved for use with SI.)

A raised dot (\cdot) or a space may be used to indicate the product of two or more units (e.g. $A \cdot s$ or $A \cdot s$). A solidus $('')$, a horizontal line, or negative exponents may be used to express a unit formed from two others by division. However, the solidus must not be repeated on the same line unless ambiguity is avoided by use of brackets (e.g. m kg/(s^3 A) or m kg s^{-3} A⁻¹ are both acceptable but m $kg/s^3/A$ is not). Negative exponents have to be used in some instances $(m^{-1}$, for example). Note that if intrusive numbers or words are used (e.g. mg per 100 ml, mmol mandelic acid per mmol creatinine) then use of either the solidus or the negative superscript convention is ambiguous unless brackets are employed.

Multiples, submultiples and dimensionless quantities

The prefixes and symbols used to denote multiples and submultiples of SI units are listed in Table 3. Compound prefixes (as in millimicrometre, for example) are not allowed. The use of decimal points should be kept to a minimum (i.e. use 12 g not 0.012 kg). It is often stated that centi, deci, deca and hecto should not be used as these multiples and submultiples are not factors of 10^3 or 10^{-3} , but there is no official recommendation to this effect. The use of multiples and submultiples in complex units should be kept to a minimum (i.e. use mg m^{-3} not μ g dm⁻³). Dimensionless quantities such as percent (part per hundred, %), part per million (ppm) and part per billion (ppb), may be used in conjunction with SI but should be defined carefully whenever they are employed [4]. Using ppb especially without definition can still cause confusion since the American billion $(10⁵)$ traditionally differs from the European billion (10^{12}) . Decimal fractions may also be used (e.g. $0.40 = 40\%$).

Inconsistencies within SI

One obvious inconsistency within SI is that the base unit of mass, the kilogram, appears to be a multiple of the gram. This could only be solved by adopting a new name for the kilogram. Another seeming inconsistency is that the base unit of 'amount of substance' (mole) is defined in terms of another base unit, that of mass

Key: \dagger Not to be used with $\lceil \n\mathbf{C} \rceil$

*Base unit of mass carries the prefix kilo-multiples and submultiples of the unit of mass are formed by attaching prefixes to the word 'gram' or symbol 'g'.

(molar mass of $^{12}C = 0.012$ kg mol⁻¹). This quantity was chosen to maintain the connection with the old gram atom/molecule and it seems silly to pretend that this definition is not based on the gram (molar mass of 12^1 C = 12 g mol⁻¹). It has been suggested that the mole should be redefined a thousand times larger (molar mass of $^{12}C = 12$ kg mol⁻¹) [5].

The latest version of SI [2, 3] lists the degree Celsius as a derived unit when it is only the kelvin with a different zero point. A further inconsistency is that it is conventional that units named after individuals should be all lower case (newton, etc.), but that the first (or only) letter of their symbols should be upper case (N, etc.). In the case of units not named after individuals lower case should be used throughout. However, exceptions now include degree Celsius and capital 'L', which it was agreed in 1979 may be used in addition to lower case '1' as the symbol for the litre in order to avoid confusion with numeral '1'. However, 'L' has been used as the symbol for the lambert $[1 L = (10^4/\pi)cd \text{ m}^{-2}]$ [1], and both '1' and 'L' have or have had many other connotations (e.g. laevo-rotatory, lake, learner, left, length, lethal, licentiate, lumbar, £ Sterling).

SI in clinical science

Despite a programme of 'SI conversion' initiated in the United Kingdom 20 years ago [6] the adoption of SI in clinical science has been at best half-hearted. This is partly because of compromises intended to facilitate the continued use of some 'traditional' units and partly because some national programmes have been implemented with little reference to primary SI documentation [2,3]. Even the 'SI Unit Conversion Guide' recently published by the New England Journal of Medicine [7] perpetuates a number of basic errors.

A fundamental problem is posed by the continued use of the litre (10^{-3} m^3) . Although this may be convenient for laboratory and domestic use and should be 'allowed' in conjunction with SI units, some journals published by the Royal Society of Chemistry have refused to use it in recent years. The 12th CGPM (1964) recommended that the cubic metre and not the litre should be used for 'very precise' volume measurements. The widespread adoption of the litre in clinical chemistry has led to contradictions such as the substitution of the microlitre (not an SI unit) in place of the cubic millimetre (an SI unit) in the course of 'SI conversion'! A further argument has been over the symbol to use for the litre-some editors/publishers have changed to capital 'L' whilst others stick to lower case '1'. If SI really is to be implemented in clinical science then the litre should be abandoned in favour of the (derived) SI unit of volume, the cubic metre and sub-multiples thereof $dm³$ = litre; cm³, the old c.c. = millilitre; mm^3 = microlitre; and so on). The argument against the superscript notation (that it was difficult to reproduce on a conventional typewriter) surely now fails with the widespread availability of word processing packages.

Other changes will be needed if SI really is to be implemented. For example, enzyme activity should be expressed in terms of conversion of moles per second (the name katal, symbol kat, has been suggested here: 1 kat = conversion of 1 mol s^{-1}) and not in International Units (IU, conversion of 1 mmol min^{-1}). Such a change is needed because the minute is not an SI unit. It would also avoid any potential confusion between 'SI' and 'IU', but would only make sense if the data were expressed as katals per cubic metre of plasma/serum and not per litre since the minute and the litre both have the same status with respect to SI. Quantities of vitamins, hormones, etc. should be expressed in grams or moles and not in International or other units. Blood pressure, cerebrospinal fluid pressure, partial pressures of blood gases, should be expressed in pascals $(1 \text{ mm Hg} = 0.1333 \text{ kPa})$. Work, energy, 'quantity of heat' should be expressed in joules (1 15 \degree calorie = 4.1855 J). Osmolality should be expressed in millimoles per kilogram (1 mOsm kg^{-1} = 1 mmol kg^{-1}).

However, with the best will in the world ^I can see no advantage to abandoning the use of minutes, hours and days for recording time. These units are simply (approximate) multiples of the second which relate to human experience and not powers of ten. Similarly I can see no point in abandoning the degree Celsius in favour of the kelvin or in reporting hydrogen ion concentration rather than pH.

SI in analytical pharmacology and toxicology

Some of the inconsistencies in SI implementation in clinical science have been noted above since much of the impetus for the use of amount concentration ('amount-of-substance' concentration, 'molar units') in analytical pharmacology and toxicology has come from clinical chemists, spurred on no doubt by the belief that such a change was needed in the name of 'SI conversion'. In truth, however, both mass and amount concentration are equally acceptable measurements within SI provided that the atomic or molecular entity being measured is known. The choice of unit lies with the user and should be governed by the primary purpose for which the measurement has been undertaken.

Quantities and SI units important in concentration measurements are given in Table 4. The relationships between these quantities are summarized in the following equations (note that the numbers in the examples are arbitrary):

 $n = m/M$ For example: $(3.5 \text{ mol}) = (70 \text{ g})/(20 \text{ g/mol})$ $\rho = m/V$ For example: $(1.2 \text{ g/dm}^3) = (0.3 \text{ g})/(0.25 \text{ dm}^3)$ $c = n/V$ For example: $(0.15 \text{ mol/dm}^3) = (0.3 \text{ mol})/(2.0 \text{ dm}^3)$ $c = \rho/M$ For example: $(0.15 \text{ mol/dm}^3) = (3.0 \text{ g/dm}^3)/(20 \text{ g/mol})$

<i>Quantity</i>	Symbol for quantity	SI unit	Symbol for SI unit
Mass	m	kilogram	kg
Amount of substance	n	mole	mol
Volume		cubic metre	m ³
Molar mass	M	kilograms per mole	$kg \, mol^{-1}$
Mass concentration	o	kilograms per cubic metre	kg m^{-3} mol m ⁻³
Amount concentration	C	moles per cubic metre	

Table 4 Ouantities and SI units important in measurements of concentration

If the chemical entity being measured is not known then use of amount concentration is inappropriate [2, 3]. Thus mass concentration has to be used in the case of gentamicin and other analytes with no fixed relative molecular mass ('molecular weight'). By the same token mass concentration should be used if there is uncertainty as to the entity being measured by a particular method. Examples of non-selective methods used in biomedical analysis are legion and include immunoassays and achiral measurements of chiral compounds-even if only one stereoisomer is given racemisation may occur in vivo, as exemplified by ibuprofen [8]. A classic error of this nature was using amount concentration to report the results of serum 'digoxin' measurements in samples from neonates and other patients who had not been given the drug [9].

Amount concentration if a specific method is used?

Most routine analytical measurements of drugs and other chemicals are performed to assess dose or exposure, compliance with prescribed therapy, or risk of toxicity. In my opinion mass concentration is better for drugs, solvents and other xenobiotics if the intended use of the measurement is simply to relate to, for example, dosage of a drug in mass units or ambient air concentrations of a pollutant expressed in mass units. Most of the published information about the vast majority of xenobiotics in the clinical pharmacology and toxicology literature is in mass units. Pharmacokinetic data are normally derived from dose and the results of plasma, urine or indeed expired air concentration measurements expressed in mass units. A further factor is that data enshrined in legislation are often expressed in mass concentration. In Great Britain the Control of Lead at Work Regulations [10], for example, specify airborne and blood lead concentrations in mg m^{-3} and μ g dl⁻¹, respectively. Similarly in England and Wales the Road Traffic Act of 1972 and subsequent amendments cite blood and urine ethanol concentrations in mg per 100 ml, i.e. mg dl^{-1} ; reporting mass concentration is logical here since it is sometimes necessary to back-calculate the ethanol dose in grams. By the same token back-calculation in order to estimate dosage may be required in other areas of forensic toxicology.

One argument put forward in favour of using amount concentration for reporting the results of drug/ poison measurements is to facilitate correlation with the results of clinical chemistry tests. Increases in plasma osmolality may follow the absorption of relatively large amounts of poisons with a relative molecular mass <150, notably methanol, ethanol,

2-propanol, ethylene glycol and acetone. It has been suggested that this provides an example where reporting toxicological data in amount concentration would aid interpretation since the compounds of interest are osmotically active in proportion to their molar concentration. However, in practice there is nothing to be gained from this exercise. In the case of methanol and ethylene glycol poisoning, treatment is initiated either on the basis of the clinical presentation or more usually after a toxicological measurement has been performed. Moreover, none of these substances behaves as ideal solutes in plasma hence the factors relating plasma concentration to osmolality are only approximate even after adjustment for the proportion of water in plasma. The relationship:

serum ethanol = $0.83 \times$ osmolal gap

indicates the magnitude of the deviation from ideal behaviour which is observed with ethanol when the serum ethanol and osmolal gap are expressed in mmol dm^{-3} and in mmol kg⁻¹, respectively [11].

Another argument which has been put forward to support the use of amount concentration for drug/ poison measurements is that which claims pharmacological response to be directly related to amount rather than mass concentration at the site of action of the drug/poison. It is logical that when ideal solutes react in dilute solution they do so in proportion to the number of molecules present. Plasma, however, is a very complex fluid. Few drugs are freely soluble in plasma water let alone act directly in plasma, and many factors may affect pharmacological response in addition to plasma concentration (e.g. route of administration, production of active metabolites, age, sex, race, length of treatment, use of other drugs, diet, disease). If the solvation, ionization/protonation, or binding to any carrier molecules is different at the 'receptor', whatever and wherever that may be, as opposed to that in plasma then any amount concentration/effect relationship between the two sites may be further compromised.

With ethylene glycol, methanol, paracetamol and some other poisons giving rise to toxic metabolite(s), attempts to derive information on amount concentration/effect relationships in tissues from measurements of the parent compound in plasma are clearly fraught with added difficulty. In the case of paracetamol especially many factors may influence toxicity in addition to the amount of drug absorbed. The use of amount concentration to report the results of emergency paracetamol measurements can present a real danger to patients since reference to published work

will often provide interpretation in mass concentration. A complicating factor here is that the time the sample was obtained in relation to the estimated time since ingestion is important in assessing the risk of toxicity—such information is more usually available to clinical rather than laboratory staff. The interpretation of plasma paraquat concentrations is a further example where information as to the time of the sample in relation to the time of the ingestion/exposure may be important in assessing toxicity. On the other hand, interpretation of plasma bromide concentrations is dependent on knowing whether inorganic bromide has been ingested or if exposure to organobromines such as bromomethane has occurred.

Reporting the results of measurements of urine or expired air concentrations of poisons or of active or indeed inactive metabolites in amount concentration will clearly not aid study of molecular interactions at 'receptors'. There are also many situations where reporting the results of drug measurements in blood in amount concentration will not aid such studies. Examples include 'total' plasma concentration measurements if a high proportion of the drug is strongly bound to plasma protein, or if an unstable metabolite such as an N-glucuronide is present in much higher concentrations than the parent compound (nomifensine provides a good example here), measurements in haemolysed blood if the plasma:red cell distribution ratio is not unity, and measurements performed using blood specimens obtained postmortem if redistribution of the drug between blood and other tissues may have occurred after death.

There are in addition many well described situations where the relation between blood concentration and pharmacological effect is poor. If volatile compounds are inhaled, for example, toxic concentrations can be rapidly attained in the brain even though venous blood concentrations remain low-after ingestion or chronic low-level inhalational exposure much higher blood concentrations of volatiles may be associated with no CNS toxicity. With some relatively water-soluble acidic compounds (salicylate, 2,4-dichlorophenoxyacetate) blood/tissue distribution is strongly dependent on blood pH. With other compounds tolerance may occur because of a decrease in the number of active receptors, drug concentration at the receptor and in plasma remaining relatively constant. In yet other cases the plasma concentrations associated with serious toxicity after acute overdosage may be much lower in patients already taking a drug than in previously unexposed subjects, possibly because of prior accumulation of active drug at receptor sites. The very water-soluble compound lithium provides an example here. Some compounds (organophosphate insecticides, monoamine oxidase inhibitors) even bind 'irreversibly' to receptors.

Clearly these problems in interpretation apply if either mass or amount concentration is used to report the analytical data. However results reported in mass units do not imply information about amount concentrations at receptors or elsewhere. In my opinion it is far more important to an improved understanding of drug/poison concentration/effect relationships that reliable, selective analytical methods and effective quality assurance procedures are used than that the results are reported in amount concentration.

This being said, reporting analytical data in amount concentration may be useful when compounds undergo metabolic or other reactions and measurement of the product(s) is undertaken in order to relate to, for example, a portion of the dose administered or reacting with cell macromolecules. However, the number of such measurements is small even though data derived in this way may be widely used (proportion of a dose following a particular metabolic pathway, for example). Reporting amount concentration could also be useful in theory if two or more compounds have been measured and the sum is to be reported, although in practice the actions of most drugs and metabolites are sufficiently different for this not to be done. Measurements of tricyclic antidepressants such as amitriptyline and their demethylated metabolites do provide one example where such an addition is sometimes performed. However, here the difference in relative molecular mass (5% or so) is such that the uncertainties introduced by analytical and biological variation are far greater than the error introduced by simply adding the drug and metabolite mass concentration.

Mass/amount concentration interconversion

Conversion from mass concentration to amount concentration and vice versa is simple if the molar mass of the compound of interest is known. Thus using the symbols for quantities defined in Table 4 and, in the example, a compound with a molar mass of 151.2 g mol^{-1} :

$$
c = \rho/M
$$
 For example:
\n(1 mol dm⁻³) = (151.2 g dm⁻³)/(151.2 g mol⁻¹)
\n $\rho = c M$ For example:
\n(151.2 g dm⁻³) = (1 mol dm⁻³) × (151.2 g mol⁻¹)

However, such conversions always carry a risk of error. This risk is enhanced if the calculation has to be performed by busy clinical staff in the middle of the night. Especial care is needed in choosing the correct molar mass if the drug is supplied as a salt, hydrate, etc. This can cause great discrepancies especially if the contribution of the accompanying anion or cation is high [12]. Most analytical measurements are expressed in terms of free acid or base and not salt. A further factor is that laboratory balances are calibrated in mass units. The use of programmable balances is of no help here since the risk of entering the wrong molar mass remains. There is an added complication if the measurement is to be related to creatinine excretion since nowadays creatinine excretion may well be expressed in moles. However, there is nothing to stop excretion of the analyte being reported in mass units per millimole creatinine.

Reporting blood manganese in amount concentration (nmol dm^{-3}) and recommended daily requirement in mass units (μ g kg⁻¹) may have confused the assessment of paediatric manganese supplementation. In the United Kingdom manufacturers had until recently recommended that babies weighing less than 10 kg

should receive a daily manganese supplement of 44-55 μ g kg⁻¹ (800-1000 nmol kg⁻¹). This may have given rise to manganese poisoning in some patients [13]. In contrast, in 1988 the American Society for Clinical Nutrition recommended daily manganese supplementation of 1 μ g kg⁻¹ [14].

Concluding remarks

The use of amount concentration ('molar units') for reporting the results of analytical measurements of drugs and other chemicals is inappropriate if the chemical entity being measured is not known, i.e. if the substance being measured has no fixed relative molecular mass or if a non-selective analytical method has been used. In my opinion, the use of amount concentration is also out of place even if a specific method is used whilst (i) drugs are dispensed in mass units, and pesticides and other potential analytes are provided for use in mass units, (ii) most pharmacokinetic and toxicological data are derived or presented in mass units, (iii) measurements of environmental (air, water, etc.) concentrations of chemicals are reported in mass units, and (iv) if the purpose of the measurement is simply to relate to one of the above variables.

Most published analytical data on drugs are presented in SI mass units per millilitre or per litre of the appropriate fluid, or units which are numerically equivalent in the case of aqueous solutions:

[parts per million] =
$$
\mu
$$
g g⁻¹ = μ g cm⁻³ = μ g m⁻¹
= mg l⁻¹ = mg dm⁻³ = g m⁻³

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It would thus seem sensible to standardise on SI mass and SI volume units when reporting such measurements. Clinical pharmacologists are after all quite accustomed to calculating drug dosage per square metre body surface area and thus expressing drug concentrations per cubic metre of plasma would be consistent here. For measurements of concentrations in solid tissues (e.g. hair, nails, liver) then SI mass units should be used throughout (e.g. μ g g⁻¹). Clearly the use of either the solidus or the negative superscript convention to mean 'per' or 'divided by' in conjunction with symbols in written reports is a matter for local decision taking into account SI guidelines [2-4]. An exception is when preparing written statements for a court of law or other purpose outside the normal reporting channels. In such cases ^I suggest that symbols should not be used and the whole unit of measurement should be written out in full (e.g. grams per cubic metre) on every occasion.

One final point. Many editors of books, journals and other printed works now ask their contributors to present their data in 'SI units'. ^I think it should be incumbent upon all such editors to (i) familiarise themselves with primary SI documentation and associated material [1-4], and (ii) ensure not only that their own guidelines are consistent with SI, but also that their guidelines are adhered to in their pages. If as much attention had been paid to this important topic as to the relatively trivial matter of reference style the present situation as regards 'SI conversion' might have been resolved long ago.

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