

Position Statement

Subject: Reporting Drug Concentrations: Mass or Molar Units?
Approval Date: November 2010
Review Date: March 2015
Review By: Chemical Pathology AC
Number: 3/2010

This document is the result of a recommendation from the AACB, ASCEPT, RCPA, RACP Common Units for Reporting Drug Concentrations Working Party.

Executive Summary

Recommendation:

It is recommended that mass units be used routinely for reporting results of therapeutic drug concentrations measured by pathology laboratories in Australia and New Zealand. It is also recommended that the litre (L) be used as the denominator when expressing the concentration. Examples of these units are mg/L and µg/L. Recommended exceptions to these principles are as follows:

- Drugs where there is current uniformity of reporting in molar units: eg lithium (mmol/L) and methotrexate (µmol/L).
- Drugs which are also present as endogenous substances where the units used routinely should be used. Examples include iron (µmol/L), vitamin D (nmol/L) and thyroxine (pmol/L).
- Drugs where the denominator is not a volume of fluid and there is international uniformity, for example per 10⁹ red cells.

These recommendations relate to drugs which are normally given therapeutically, whether measured for therapeutic drug monitoring purposes or assessment of overdose. Other substances such as drugs of abuse, heavy metals or environmental toxins were not considered by the Working Party and are thus not covered by this document.

Background:

Drug concentrations are generally reported to requesting doctors using either mass units (e.g. mg/L) or molar units (e.g. mmol/L). There is currently significant variation in the units used to report drug concentrations by pathology laboratories in Australia and New Zealand. This produces a clinical risk if results are interpreted using decision points in different units. Uniformity of units will reduce this risk and facilitate electronic and other communication of results.

A Working Party (WP) was established by the Royal College of Pathologists of Australasia (RCPA), the Australasian Association of Clinical Biochemists (AACB) and the Australian Society for Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) to address this issue. The process adopted by the WP was to identify and consider all issues relevant to the topic, assess the importance of each factor, and prepare a discussion document on the issue. This included:

- assessment of current guidelines and practice, in Australasia and overseas;
- review of units used in published literature and other supporting information;
- the link between units and drug dosing information;
- the purpose for which drug concentrations are used;
- assay standardization and measurement issues.

The draft document was widely distributed for comment and revised following a range of written responses. The issue was presented and discussed at a number of national meetings. In response

to feedback the document has been revised and is now submitted for formal approval. In making assessment of the issues the WP considered patient safety and clinical decision making as the most important factors.

Discussion:

The WP recommends the use of mass units for reporting drug concentrations with a number of specified exceptions. The reasons for this recommendation are as follows:

- Drugs are dosed in mass units and reporting in mass units facilitates drug dosage (and other pharmacokinetic) calculations, either manually or in dose prediction software.
- The major English language sources of information use mass units (USA) or have recently recommended mass units (UK).
- Toxic concentrations of therapeutic drugs are likely to be interpreted using information sources other than the therapeutic intervals supplied with the result.
- Concentrations of many drugs e.g. immunosuppressants and antibiotics are already reported in mass units.
- Mass units are more widely used in other areas such as toxicology and forensics.

It is recognized that there are advantages to the use of molar units such as the clear definition of the molecular entity for assay standardization and understanding of the molecular interactions involved in drug metabolism and binding. While these may have advantages in some settings, it is felt that these factors do not outweigh those favouring mass units for routine reporting.

The WP recognizes that for a number of common drugs there are more laboratories in Australia reporting in molar rather than mass units and that the benefits of adopting mass units for these drugs must be weighed against the risks associated with changing. The working party also recognizes that for some common drugs molar units are universally used in New Zealand and the risks of change in that environment are consequently higher. It therefore may be appropriate for some of these recommendations to be considered separately in New Zealand.

The working party also recognizes that full benefits of a single unit for each drug will only be realized if associated material such as clinical guidelines, textbooks, journals, and websites also adopt these principles.

These recommendations are related specifically to measurements of therapeutic drugs, whether measured for therapeutic monitoring or overdose assessment. This document does not refer to other exogenous agents which may be consumed or otherwise absorbed, e.g. metals, chemicals or other toxins.

Exceptions to the recommendation to use mass units are as follows:

1. Lithium, methotrexate and thiopurine metabolites: molar units. There is currently complete use of molar units in laboratories and in supporting information.
2. Endogenous substances such as minerals e.g. iron, vitamins such as vitamin D, and hormones such as thyroxine: molar units or other units as are commonly used to report the concentrations of these endogenous substances.

There may be other substances or circumstances that are not clearly covered by these guidelines where laboratories and clinical groups may need further discussion to reach a consensus position.

Reporting Drug Concentrations: Mass or Molar Units?

Full Report

Introduction

Goal: The goal of the Common Units for Reporting Drug Concentrations Working Party (the Working Party) is to recommend uniform units for reporting drug concentration measurements by pathology laboratories in Australia and New Zealand.

Rationale: The aim of the adoption of common units for reporting drug concentrations is to reduce patient harm which may be caused by misinterpretation of drug concentrations where test results and decision points are expressed in different units (see Table 1 for examples).

This type of error occurs most often when a clinician, familiar with one unit, encounters a result expressed in different units without recognizing the difference. It may occur when a result is separated from its report which specifies the units, or when a clinician is unaware of unit differences when consulting a textbook, journal article or guideline. The chance of this happening is increased if a drug is reported in more than one system of units. Reports of patient harm due to misinterpretation of drug concentrations lead to establishment of the Working Party.

Another issue increasingly relevant to uniformity of reporting units is the rise of health databases containing results from more than one laboratory. These databases may cover whole cities or larger regions and may be integrated with individual health records. They usually have a single access portal drawing together the results from all participating laboratories. The use of more than one reporting unit for a pathology result leads to unnecessary complexity in these databases and increased risk of clinical error.

Background: There are two main systems used for drug concentration reporting, mass units (e.g. mg) and molar units (e.g. μmol) per unit volume. There are also variations within these systems such as the choice of multiplier (eg nano, micro or milli) and the choice of denominator (ie L, dL or mL). Other units are also occasionally used such as % (g/dL) for reporting blood alcohol.

Systeme Internationale (SI) has been formally adopted in Australia and many parts of the world for pathology reporting although the implementation is far from complete. We note that both forms of drug reporting units, moles (amount of substance) and grams (mass) are fundamental SI units although the mole is commonly interpreted as the appropriate SI unit for pathology reporting.

A recent publication has highlighted the variability in units used for reporting drug concentration measurements in Australian and New Zealand pathology Laboratories (1). While many drugs are reported in entirely in mass units, some are consistently reported in molar units and some with different units in different laboratories. It is this variability in reporting that unnecessarily increases risk and should be removed.

Drug concentrations are requested for both therapeutic monitoring and toxicological assessment and the laboratory may not be aware of the purpose of the measurement for drugs with a routine clinical use (eg digoxin). It is important that the same units are used for both purposes for the same drug. It is also more likely that external references will be sought for overdose situations to assess severity, whereas in therapeutic monitoring the therapeutic range on the report often provides the target concentration.

While it is preferred that a single primary system of units be defined for all drug testing, it is recognized that there will be some drugs where an alternate unit may be more appropriate. The Working Party aims to recommend a primary system with appropriate exceptions. The aim is also to obtain common a uniform numerator and denominator for each drug. All parties consulted agree that commonality of units for reporting each drug assay is more important than the choice of unit.

The purpose of this paper is to identify and discuss issues relevant to choice of units for drug concentration reporting and make an initial recommendation of a solution to this issue. The Working Party has considered existing recommendations, current practice, clinical decision making, assay standards and other information. Where published sources were not available Working party members have sought advice from relevant colleagues. These are discussed in detail and our recommendations follow.

The paper has been distributed to members of the participating societies and other interested organisations and individuals for consultation. The Working Party has considered the submissions in this paper. The final version will be submitted to the participating societies for ratification.

Issues relevant to choice of drug reporting units.

EXISTING RECOMMENDATIONS

1. Previous Australian Recommendations.

There are no recent relevant Australasian guidelines related specifically to the topic of therapeutic drug concentrations. Of those sources below the RCPA guideline is the most specific for serum drug measurements but has not been revised for over 20 years. The outcome of the Working Party will be to provide Australasian guidelines.

- Australian National Measurement Institute (NMI). The NMI has responsibility for implementation of SI in Australia. However, it currently offers no specific guidance on the issue of drug measurements in serum (2).
- Royal College of Pathologists of Australasia. An RCPA broadsheet in 1985 regarding introduction of SI reporting units specifically recommended the use of molar not mass units for therapeutic drugs. This was predicated on drug prescribing becoming molar units (3). The RCPA has membership on the Working Party.
- Australian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) recommends the use of mass units. These recommendations have not been published. ASCEPT has membership on the Working Party.
- Standards Australia, in AS4308, specifies cutoffs for urine toxicology interpretation in mass units (5).

2. International Recommendations.

There are a number of international bodies with recommendations in this area:

- International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and International Union of Pure and Applied Chemistry (IUPAC) specify molar units as the agreed communication terminology for therapeutic drugs (6). The purpose of this standard is not specifically to guide reporting of patient results for clinical use, but to provide unambiguous terminology for data exchange.
- The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Provides detailed recommendations relating to drug measurement and reporting in humans but does not specify units (7). Mass units are consistently used in documents expressing drug concentrations. (NB ICH includes the regulatory authorities of Europe, Japan and the United States and the pharmaceutical industry in the three regions along with the World Health Organisation (WHO), European Free Trade Association (EFTA), and Canada.)
- The World Anti-Doping Agency (WADA) specifies the use of mass units for results (8).
- The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), the regulatory body for pharmaceuticals in the European Union, does not have a stated position (9).
- The Food and Drug Administration (FDA) the regulatory body for pharmaceuticals in the USA, does not have a stated position (10) although mass units are universal in the USA.

Some documents (eg Guidance for bioequivalence studies, 11) recommend mL as the denominator.

- The Association of Clinical Biochemistry (ACB), Royal College of Pathologists (RCPATH), National Poisons Information Service (NPIS), Forensic Science Service (FSS) and International Association of Therapeutic Drug Monitoring & Clinical Toxicology (IATDMCT) recently issued a joint recommendation in the UK for the use of mass units for routine reporting (12), with the use of the litre (L) as the denominator for all drugs whether for therapeutic or toxicological purposes. Specific exceptions for thyroxine, lithium, methotrexate and iron where molar units are recommended.
- NPIS and ACB (UK) recommendations for “poisoned patients” proposed mass units for drugs with the exception of lithium, methotrexate and thyroxine in 2002 (13).
- Société Française de Biologie Clinique (SFBC). Officially recommends that all drugs with a known molar mass be reported in Molar units. (personal communication)
- The International League Against Epilepsy (ILAE) has no specific recommendation. It has issued a best practice guidelines for therapeutic drug monitoring, which uses mass units and provides conversion factors to molar units (13a).

3. Recommendations for reporting drug concentrations in other biological fluids.

Australian and international guidelines recommend that results of urine drug screens are expressed in mass units (ng/mL, µg/L) (5).

RECOMMENDATIONS - COMMENT. The 1986 Australasian pathology recommendations specifically recommend molar units (3). However this recommendation is followed by the statement that “It is rational and possibly a long term expectation that drugs also will be labeled and administered in molar terms.” As drug dosing remains firmly in mass units without movement for change this recommendation should be revisited. Amongst the other recommendations and usages above, the combined UK consensus is the most specific to the current situation as it relates directly to pathology reporting, is the product of wide consultation, and has been produced recently. The Australian Standard on urine toxicology, albeit restricted to urine samples is also a relevant document as it relates to current Australian practice. It is also notable that with the exception of the UK and French guidelines we have been unable to identify any other national or international recommendations or guidelines specifying drug units for routine pathology reporting.

PUBLISHED LITERATURE AND REFERENCES

4. Units used in published literature, textbooks and other reference sources.

Drug measurement results are compared with information from various reference sources and so the units used in these sources is a relevant factor. These sources include refereed journal articles, textbooks, websites, standards, guidelines and handbooks. These may be produced for use in Australia and New Zealand or, more commonly, for international use.

A summary of the units used in major journals and textbooks is shown in Appendix A. With regard to the use of units in Journals, the recommendation from the International Committee of Medical Journal Editors (ICMJE) (14) states: “Drug concentrations may be reported in either mass or SI units, but the alternative should be provided in parentheses where appropriate”.

The most widely available first-line references for drug information in Australia are the Australian Medicines Handbook (15), MIMS (16) and the Therapeutic Guidelines series (17). These works, available in paper and web-based formats use a mixture of molar and mass units and often both (1).

LITERATURE – COMMENT: Textbooks and Journals are not consistent with the use of units. There is a tendency for those sourced in the USA to use mass units and from the UK to use molar units but this is not universal. There is also a tendency for international textbooks to provide both units for some drugs. Australian journals have not been uniform with regard to units. Use of units in the literature varies according to drug and context, with some drugs being reported exclusively in

mass units, some in molar units and others inconsistently. Any recommendations for drug reporting units should be shared with local journals and guideline organizations to move towards standardization of all relevant information. Additionally, given the lack of uniformity in the information sources that may be used it would seem appropriate for pathology laboratories, following the recommendation of the Medical Journal Authors, that whatever units are in use, to provide information on factors for converting results from one unit system to the other on their websites or laboratory manuals.

CURRENT PRACTICE

5. Current reporting practice in Australia and New Zealand.

As indicated above, a recent review of data submitted to the RCPA QAP has indicated considerable variability in reporting drug concentrations in blood (1). This data is shown in Table 1, separated separately for Australia and New Zealand as well as combined. Some drugs currently have near or complete use of mass units, e.g. gentamicin, and a few have complete use of use of molar units, e.g. lithium. However, some are split between the two systems e.g. phenytoin and paracetamol. Of note the uptake of molar units in New Zealand appears complete for a number of commonly measured drugs such as digoxin, the anticonvulsants and salicylate and nearly 100% for paracetamol and theophylline. By contrast there is less uniformity for these drugs in Australia. Our personal experience suggests that some classes of drugs, for example immunosuppressants, are reported almost entirely in mass units as are many specialised tests performed in dedicated clinical pharmacology laboratories. Lithium and methotrexate are the two notable exceptions for which molar units are used exclusively.

The decision points for urine drug screens, although not always included on pathology reports, are expressed in mass units (ng/mL, µg/L) consistent with Australian and international guidelines (5).

While not part of the routine pathology environment, drug concentrations in forensic pathology are routinely determined in mass units.

6. Current reporting practice internationally.

We have been unable to identify any surveys or references regarding actual practice in overseas locations. Members of the Working Party have sought information from international colleagues on practice in their countries. USA: The use of mass units seems to be the most common practice although mL and dL are frequently used as the denominator. Canada: A mixed system with some drugs entirely mass, eg gentamicin, and some entirely molar, eg digoxin. Germany: Largely mass units. Spain: Molar units for methotrexate and otherwise mass units. UK: progressing well with implementing guidelines recommending mass units with specified exceptions (12); Sweden: Molar units in general use for some common drugs with well established molecular entity, like digoxin, paracetamol, salicylic acid, antiepileptic and antiarrhythmic drugs and mass units for drugs of abuse and some others such as immunosuppressants and antibiotics; Hong Kong and Singapore: variable use of units.

CURRENT REPORTING PRACTICES – COMMENT: For drugs where there are clearly dominant units in use in Australia and New Zealand it seems appropriate to formally adopt these units unless there is an overwhelming indication to introduce a change. It is recognized that during a changeover period there is an increased risk of interpretive error. Where there is variability in units used locally, changes at some laboratories will be required to achieve uniformity. In making these decisions about drug units it is appropriate to take into consideration the units used by overseas countries in cases where there is general agreement. Although some countries are using molar units for some drugs (eg Sweden, Canada) more countries appear to be using mass units and mass units are used for more drugs.

CLINICAL DECISION MAKING

7. Units used for prescribing drugs

Mass units are almost universally used for prescribing drugs. Exceptions to this include electrolytes in solution e.g. sodium chloride which are described in percent terms, e.g. 0.9% saline which is an expression of mass units (g/100mL) as well as molar units, and biological preparations such as vitamin D, heparin, insulin or antithrombin which are prescribed in international units. This is relevant to drug reporting where there is a direct relationship between the numerical value of the result and the dose or change in dose prescribed. This issue is explored further under items 8 - 9.

8. The relationship between drug concentration and drug dose

In or near the therapeutic range drug concentrations usually vary in direct proportion to dose and therefore drug dose can be considered relative to the therapeutic range. A drug which is present at twice the target concentration can be adjusted by halving the dose. The units used for the concentration reporting and the dosing need not be aligned for this type of dose adjustment. However, there are a number of exceptions to this causing both within-patient and between-patient variability.

- Drug factors such as saturable clearance (e.g. phenytoin) or saturable protein binding (e.g. valproate)
- Patient factors such as hypoalbuminaemia due to liver dysfunction or nephrotic syndrome; or competition with binding sites e.g. uraemia or co-prescribed drugs.
- Higher drug concentrations such as occur in overdose.

In these cases the drug concentration may not be directly proportional to drug dose requiring a more complex application of pharmacokinetics in interpretation of drug concentrations.

At steady-state, drug concentrations are directly related to dose via drug clearance. Physicians are expected to understand this pharmacokinetic relationship which can be described as follows:

Maintenance dose = systemic clearance x target concentration at steady-state

Similarly drug concentration after a loading dose is determined by apparent volume of distribution.

Loading dose = volume of distribution x target concentration

Thus the dose and target concentration are linked by a constant for which reference values can be obtained. When performing calculations it is feasible to convert between units but the process is simplified when common units are used. Note that the unit of volume used for pharmacological constants such as the volume of distribution is the litre, supporting the case for litre (L) to be the volume unit for drug concentrations.

9. Decision support software that predict dose from drug concentrations

For complex dose-concentration relationships decision support software may be used with a range of inputs including drug dose and drug concentration. The process is simplified if the same units are used throughout. As with simple calculations described in 8 above, conversion can be performed but risk of error is reduced if the same units are used. Software may be able to reduce this risk by providing unit conversion as part of the program.

10. Stoichiometric relationship between circulating components

Circulating components interact on the basis of moles rather than mass. This may be relevant in interpreting drug concentrations in the following circumstances:

- Metabolites: Some drugs are administered as prodrugs or have active metabolites. The relationship between moieties is molar rather than mass and the relationship may be clarified by the use of molar units.
- Protein binding: For example the calculation of free drug concentration from total drug concentration and concentrations of binding proteins. Although not all drugs are bound with the same stoichiometry, calculation of free drug concentration may be facilitated if both drug and ligand are in molar units. However we note that albumin, the most common

binding protein, is reported in mass units. When software is used to calculate free drug concentration differences between units could be handled by the software provided the relevant units are specified.

CLINICAL DECISION MAKING – COMMENTS: For the majority of drug dosing decisions based on measured drug concentrations the interpretation is made by comparing the result with the therapeutic range. Provided the result and the range are both in the same units there is little chance of confusion. As noted above there are some circumstances where the use of mass units, i.e. the same units used to prescribe the drug, may be a benefit and some occasions where molar units may facilitate understanding. The primary aim of unit standardisation is to reduce the risk of errors affecting patient care, therefore the use of the same units for reporting and prescribing seems to be the most important factor. Conversion between units during dosing calculations is an unnecessary source of potential error.

ASSAY STANDARDS AND ANALYTICAL SYSTEMS

11. International Reference Preparations.

There are very few reference measurement systems for therapeutic drugs listed on the JCTLM database (Joint Committee for Traceability in Laboratory Medicine, 18). Reference methods and reference laboratory services are available for digoxin, digitoxin and theophylline with reports issued in molar units. The JCTLM lists reference preparations from NIST (National Institute of Science and Technology, USA) for carbamazepine and valproate (SRM 1599, anticonvulsant drug level assay standard in human serum); for ethosuximide, phenobarbital, phenytoin and primidone (SRM 900, antiepilepsy drug level assay standard in human serum); for lithium carbonate (SRM924a – Lithium carbonate (clinical)). Reference materials are additionally available for many of the endogenous substances also used therapeutically e.g. some steroids, vitamins, electrolytes. In each case the entity is uniquely defined allowing use of either molar or mass units for measurement systems traceable to these systems.

Other reference materials are available but without highest level certification and with reference laboratory services. The U.S. Pharmacopeia has a reference standards catalogue for a wide range of drugs listed in mass units (19).

The International Program on Chemical Safety (IPCS), established in 1980, is a joint program of three Cooperating Organizations - WHO, International Labour Organisation (ILO) and United Nations Environment Program (UNEP). IPCS have a catalogue of approximately 75 reference drugs and provide a conversion table between mass and molar units for toxicology reporting in mass units (20).

12. Analytical Systems, Drug Structures and Related Issues.

Most measurement systems identify the relative number of molecules rather than the mass of the drug in the sample. For example, immunoassay systems measure the number of immunoreactive particles, irrespective of other variations in the molecule. Thus a doubling of the result for a drug assay is more closely related to a doubling in the number of moles of substance, rather than a doubling of the mass of analyte, even if the structure and mass of the analyte is variable in the sample. Further, a failure in many immunoassay systems to adequately distinguish active drug molecules from other immunoreactive molecules in patient samples (including metabolites of the drug, endogenous molecules, other drugs and their metabolites and other exogenous molecules) is a significant source of error in some commercial reagents. Such 'interference' interactions occur on a molar basis.

A limited number of drugs are mixtures of compounds, and the molecular weight is thus uncertain and may be dependent on the relative abundance of the various components. This may make molar units variable and unreliable, for example gentamicin. If the primary standard is weighed-out drug, then reporting in mass units provides a direct link to the primary standard. However, the

IFCC/IUPAC guidelines have assigned molecular weights for many drugs for the purposes of conversion between mass and molar units (6).

Many drugs are dosed and measured as racemic mixtures, but usually one enantiomer is active and the molar proportion of the active moiety(ies) may not be known. Further the activity (effects) of the drug may in part be due to metabolites as well as the parent drug. Thus the relationship between drug concentration and drug target (effects) is more complex than the molar relationship that is sometimes assumed.

ASSAY STANDARDS – COMMENT: For any assay it is important to understand the analytical basis on which it is defined and to understand the relationships between the measured concentration, the reference standard, the drug in clinical use, and the primary research literature guiding that use. Issues related to units used to define standards are relevant to decisions made in laboratories when preparing assay standards and comparing results between laboratories. While it is of vital importance in the laboratory that errors due to assay standards are avoided, this has little relevance to routine clinical decision making. This matter can be handled with appropriate definition of the standards, relevant conversion factors and attention to these matters in the laboratory. We believe these factors to be less relevant with respect to the choice of unit system. The information provided by a drug concentration is an intermediate point between drug dose and effect and clinical interpretation should be on this basis.

It is also a recognized problem in both TDM and Toxicology that there is often a lack of Certified Reference Materials on which to base a calibration. Hence the plethora of sources of ‘pure compound’ as a great source of variability between assay methods, perhaps particularly with ‘in house’ methods where the source is likely to be inconsistent across a range of laboratories performing the same test, with the resultant source of error.

13. Drug formulations and different molecular complexes.

Some drugs are available in a number of different molecular complexes, eg hydrates and various salts. However, drug doses are defined on the basis of bioequivalence, usually in relation to the free base. Thus “100 mg” of a drug is the same number of moles regardless of the preparation (salt, ester or other) and will give rise to the same concentration. The TGA endorses the following statement in this regard:

By definition it is considered that different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy (21).

The definition of the drug as the base compound has not been universally adopted previously. For example phenytoin is referred to as both phenytoin and phenytoin sodium with the molecular weights of 252 and 274 respectively and thus the opportunity for confusion. For the future the US Pharmacopoeia is recommending the use of the base name as the official name of the drug and thus for the amount to be included in preparation of the medication. The issue here is the need for an agreed definition of the drug for the purposes of preparation of the medication, but also to allow drug assays to be standardized in the same unambiguous manner as the therapeutic formulation. While the universal use of molar units in preparation, dosing and measurement would be beneficial, the important issue for drug laboratories is uniformity (to give the same results from different laboratories) which is also aligned with the drug preparation process.

COMMENTS: The process of standardizing drug assays is far from simple with a lack of certified reference materials, different formulations of the same drug and a definition of drug amount which may not be well known or understood. It is important that both clinicians and laboratories are aware of this issue when considering different drug formulations. If drugs were dosed in molar units the risk of errors in pharmaceutical preparation and labeling might be reduced, but we are unaware of any active discussions in this direction.

OTHER FACTORS

14. Drugs also present endogenously.

Some substances used therapeutically are also endogenous compounds which are measured for purposes other than therapeutic monitoring and toxicology. Examples include the hormones cortisol (nmol/L), testosterone (nmol/L) and thyroxine (pmol/L) as well as iron ($\mu\text{mol/L}$) and vitamin D (nmol/L). For these examples the commonly used reporting units in Australia are shown in brackets. The units used for reporting these analytes should be the same regardless of endogenous or exogenous origin.

COMMENTS: For the analytes that may be used therapeutically and are also present endogenously it is important that the same units are used for both. Where a unit type is in common use in Australia and New Zealand for such analytes this unit should be adopted.

Conclusions and Overall Recommendations

The Working Party believes that it is important that serum drug concentrations for clinical use are reported with the use of one unit type throughout Australia and New Zealand, irrespective of the location of the laboratory or the purpose of the measurement. The primary purpose of this is to reduce the clinical error that may occur if a result is interpreted against a decision point using different units. The focus of this document is to determine which units are most appropriate for this standardized use.

We believe that the factors outlined above support the use of mass units for most drugs, unless there are specific reasons for the use of other units. In summary the reasons for this recommendation are as follows:

- Drugs are almost universally prescribed in mass units, and there is a generally direct relationship between dose and concentration. Mass units facilitate the understanding of the relationship between serum concentration and dose and of calculations.
- While internationally there is much variability in practice, the UK has recently adopted mass units (with a number of specified exceptions) and mass units are generally used in the USA, making the use of mass units concordant with two major English-language countries and increasing the likelihood of widespread international agreement.
- While there is variability in the units used in textbooks and research journals, mass units are used for the majority of drugs and in the majority of references.
- Drugs in urine are reported in mass units.

We also note that the previous RCPA recommendation for the use of molar units presupposed that drug doses would eventually be expressed in molar units, an outcome that has not eventuated. However it is worth noting that drugs are actually dosed in molar units disguised as mass units (see section 13 above). If we could do so, we would recommend that drugs be prescribed and measured in molar units. Whilst there is a sound argument that drugs be prescribed in molar units, the Working Party believes that this change is unlikely in the foreseeable future. While drugs are dosed in mass units we recommend that the laboratory data be consistent with the units of drug prescription except where there are good reasons to do otherwise.

Although molar units may facilitate definition of the active moiety when standardising assays and allow improved understanding of the relationship between interacting components, we do not believe these factors outweigh the issues cited above.

With regard to the exceptions to mass units we recommend the use of the alternate units for the following drugs:

Therapeutic drugs not present endogenously

- Lithium – mmol/L (currently local uniformity of this unit and commonly used internationally)
- Methotrexate – $\mu\text{mol/L}$ (currently local uniformity of this unit and commonly used internationally)

For all hormones, minerals and vitamins also present endogenously we recommend the same unit as is used endogenously, most commonly molar units (this is consistent with current practice and will not require changes). Examples include:

- Non-peptide hormones: thyroxine, tri-iodothyronine, cortisol, testosterone, estrogen, adrenaline, noradrenalin, cholecalciferol (25-hydroxy-vitamin D) – all molar units
- Peptide hormones: insulin, growth hormone – common units pending.
- Electrolytes and minerals: iron, sodium, potassium, calcium, magnesium, bicarbonate, zinc, selenium – all molar units

We also recommend the universal use of the litre (L) as the denominator for reporting drug concentrations unless there are specific reasons for the use of other units. In summary the reasons for this recommendation are as follows.

- Litre is the SI unit for volume.
- Internationally litre is almost universally used as the unit of volume for drug concentrations, including the recent UK guidelines, with the exception of the USA where mL or dL are used.
- Litre is used for other laboratory measurements.
- Litre is clinically meaningful, as physiological volumes, e.g. extracellular fluid volumes are expressed in litres.
- The unit for the volume of distribution, used in the calculation of loading dose, is litre.

Analysis of units currently used in Australia and New Zealand (table 1) indicates that these recommendations will confirm the majority current practice for many drugs, either because molar units (e.g. lithium, methotrexate) or mass units (e.g. immunosuppressants, antibiotics, antifungals, antidepressants, antipsychotics) are almost consistently used.

The current situation in New Zealand is different to Australia in that there is a higher level of uniformity, with several common drugs entirely in molar units in opposition to the recommendations above. Any change in this setting must be very carefully considered. It may be appropriate, in some regions, for exceptions to be made to these recommendations. If this is to be done, it should only be done with full input of relevant stakeholders and an assessment of any benefits derived from the position compared to the risks associated with adopting units different to the majority of other laboratories.

There are a number of common drugs for which the use of mass units would require a change at a significant number of laboratories. These are considered in more detail below.

Carbamazepine, paracetamol, phenytoin, and valproate are widely measured and over 50% of laboratories currently report in molar units. These are well defined molecular entities where conversion between the unit types can be reliably performed and both formats of units are generally included in the common drug references Australian Medicines Handbook, MIMs, and Therapeutic Guidelines. Carbamazepine, paracetamol, phenytoin sodium, and sodium valproate have molecular weights of 236.27, 151.17, 274.25 and 166.2 respectively. Due to the large difference in numerical values with the different units changes in the units for reporting drug concentrations of these four drugs are the most likely to be subject to major interpretative errors.

Digoxin, which is also widely measured in both mass and molar units, has a molecular weight of 780.95 and thus the therapeutic ranges for mass and molar units differ by only 30%. While a change is less likely to cause major clinical errors, care must be taken to ensure the change is recognised. Salicylate, although widely measured in both mass and molar units, is rarely encountered at dangerous concentrations, thus problem scenarios are less likely and clinicians are more likely to make use of the reference range provided rather than a “remembered” range.

Practical issues with changes in reporting units.

In order to achieve unity for the units used for drug concentration reporting, some laboratories will need to change their units. This must be carefully managed in order to avoid errors during the

transition period. Some strategies for such a change are discussed further below and include notification of stakeholders, annotation of the change on pathology reports and the provision of alerts at both the requesting and reporting interfaces. We recommend collaboration between laboratories and clinical services and making all necessary changes at one time where possible.

Changes should be supported with notifications to clinicians. This may include letters, handouts, or website information. A notification of the changes in the units should also be included in a comment on the report for a period of time.

Information to provide to clinicians should include the numerical difference in results; the change in reference intervals or decision points and a conversion factor to allow interchange of results.

Dual reporting is discouraged as this is known to increase misinterpretation.

Laboratory handbooks and websites and other relevant material in the area or the hospital should be updated at the next available opportunity.

Major uses of the TDM service in particular should be notified, eg the Emergency Department for paracetamol and salicylates; neurology for anticonvulsants.

Laboratories are also encouraged to provide ready access to conversion factors between mass and molar units for drugs so that interpretations against decisions points in alternate units can be facilitated if the event arises. Note the conversion factor provided must relate to the appropriate drug formulation, see section 14 above.

All efforts will be made to request compliance with these guidelines by other sources such as journals, practice guidelines, textbooks and websites.

Processes must be put in place to ensure that proposed changes are widely promulgated and cemented in place – i.e. as formal college policies or similar.

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- 2008-11-25 accessed Dec 2008 – NB Australia (TGA) uses the European Standards.

Table 1. Reporting Units for drugs in Australia and New Zealand.

The number of laboratories (percent of laboratories) reporting in mass and molar units based on choice of units used to report QAP results. Data from RCPA-QAP Chemical Pathology (with permission). GSC – data from the general Serum Chemistry and Therapeutic Drugs program; TDM – data from the Special Drugs program. Data where over 90% of the participants report in the same unit type are highlighted in bold.

TEST	Program	Australia		NZ		Combined	
		Mass	Molar	Mass	Molar	Mass	Molar
AMIKACIN	TDM	19 (100%)	0 (0%)	3 (100%)	0 (0%)	22 (100%)	0 (0%)
TOBRAMYCIN	TDM	45 (100%)	0 (0%)	5 (100%)	0 (0%)	50 (100%)	0 (0%)
GENTAMICIN	GSC	199 (97%)	7 (3%)	23 (100%)	0 (0%)	222 (97%)	7 (3%)
VANCOMYCIN	GSC	133 (96%)	6 (4%)	13 (100%)	0 (0%)	146 (96%)	6 (4%)
AMIODARONE	TDM	7 (64%)	4 (36%)	0 (0%)	1 (100%)	7 (58%)	5 (42%)
TRICYCLIC SCREEN	TDM	7 (58%)	5 (42%)	1 (50%)	1 (50%)	8 (57%)	6 (43%)
LIGNOCAINE	TDM	3 (50%)	3 (50%)	0 (0%)	1 (100%)	3 (43%)	4 (57%)
QUINIDINE	TDM	2 (40%)	3 (60%)			2 (40%)	3 (60%)
PARACETAMOL	GSC	92 (39%)	144 (61%)	3 (10%)	27 (90%)	95 (36%)	171 (64%)
SALICYLATE	GSC	43 (45%)	53 (55%)	0 (0%)	25 (100%)	43 (36%)	78 (64%)
PHENOBARBITONE	GSC	20 (33%)	40 (67%)	0 (0%)	8 (100%)	20 (29%)	48 (71%)
THEOPHYLLINE	GSC	30 (35%)	56 (65%)	1 (5%)	19 (95%)	31 (29%)	75 (71%)
VALPROATE	GSC	40 (33%)	83 (67%)	0 (0%)	31 (100%)	40 (26%)	114 (74%)
CARBAMAZEPINE	GSC	40 (31%)	87 (69%)	0 (0%)	34 (100%)	40 (25%)	121 (75%)
PHENYTOIN	GSC	43 (31%)	97 (69%)	0 (0%)	34 (100%)	43 (25%)	131 (75%)
DIGOXIN	GSC	69 (28%)	179 (72%)	0 (0%)	39 (100%)	69 (24%)	218 (76%)
METHOTREXATE	TDM	0 (0%)	19 (100%)	0 (0%)	3 (100%)	0 (0%)	22 (100%)
LITHIUM	GSC	0 (0%)	163 (100%)	0 (0%)	34 (100%)	0 (0%)	197 (100%)

Note: This list is limited to drug assays included in the RCPA QAP with a choice of units to report. The experience of Working Party members is that more specialised drugs are usually reported in mass units.

APPENDIX A: UNITS USED IN JOURNALS AND TEXTBOOKS

With regard to the use of units in Journals, the recommendation from the International Committee of Medical Journal Editors (ICMJE, 11) is the most widely used guideline. It states: "Drug concentrations may be reported in either mass or SI units, but the alternative should be provided in parentheses where appropriate"

The following table provides policies from major reference sources and provides examples of usage for several drugs where changes in units may be required in a significant number of laboratories.

International Clinical Pharmacology Journals

Name: **Clinical Pharmacology and Therapeutics**

About: Journal of the American Society for Clinical Pharmacology and Therapeutics (ASCPT)

Advice to authors: Specifies mass units

General comments: mass units dominate

Carbamazepine: $\mu\text{g/ml}$

Paracetamol: $\mu\text{g/ml}$

Phenytoin: $\mu\text{g/ml}$

Valproate: $\mu\text{g/ml}$

Name: **Therapeutic Drug Monitoring**

About: Journal of IATDM

Advice to authors: "Molarity is preferred to units of weight/volume when expressing the concentration of a drug or drugs".

General comments: mass units dominate, published units conflict with authors advice.

Carbamazepine: $\mu\text{g/ml}$ and mg/L

Paracetamol: $\mu\text{g g/ml}$ and mg/L

Phenytoin: $\mu\text{g/ml}$ and mg/L

Valproate: $\mu\text{g/ml}$, $\mu\text{mol/L}$ and mg/L

Name: **British Journal of Clinical Pharmacology**

About: Clinical Pharmacology Journal of the British Pharmacological Society

Advice to authors: "SI units (mass or molar units) should be used. If other units are used, a conversion factor should be included in the Methods section."

General comments: mass units dominate

Carbamazepine: $\mu\text{g mol/L}$ and mg/L

Paracetamol: mg/L and mmol/L

Phenytoin: mg/L and $\mu\text{g g/ml}$

Valproate: mg/L and $\mu\text{g g/ml}$

International Clinical Medicine Journals

Name: **New England Journal of Medicine**

About: Journal of the Massachusetts Medical Society, USA

Advice to authors: "Authors should express all measurements in conventional units, with Système International (SI) units given in parentheses throughout the text."

General comments: mass units dominate

Carbamazepine: $\mu\text{g/ml}$

Digoxin: ng/mL , nmol/L or both

Paracetamol: $\mu\text{g/ml}$

Phenytoin: $\mu\text{g/ml}$

Valproate: $\mu\text{g/ml}$

Name: **British Medical Journal**

About: General Medical Journal

Advice to authors: As per ICMJE

General comments: Most articles do not refer to units but to text e.g. "a defined therapeutic range".

Carbamazepine: mg/L

Digoxin: nmol/L

Paracetamol: mg/L

Phenytoin: mg/L

Valproate: mg/L and $\mu\text{mol/L}$

Australian Clinical Medicine Journals

Name: **Medical Journal of Australia**

About: Journal of the Australian Medical Association

Advice to authors: As per ICMJE

General comments: Not many articles including drug concentrations.

Carbamazepine: mg/L and μmol

Digoxin: $\mu\text{g/L}$

Paracetamol: $\mu\text{mol/L}$ and mg/L

Phenytoin: NA

Valproate: $\mu\text{mol/L}$

International Pathology or Clinical Biochemistry Journals

Name: **Clinical Chemistry**

About: Journal of the AACC (USA)

Advice to authors: "SI units must be used throughout your submission. Conventional units may only be added as additional information in parentheses after the SI units." The use of SI is defined with a link to BIPM. Note that units for drugs are not specified at this site.

General comments: Examples found in mass units with L as denominator

Carbamazepine: mg/L

Digoxin: $\mu\text{g/L}$

Paracetamol: mg/L

Phenytoin: mg/L

Valproate: mg/L

Name: **Annals of Clinical Biochemistry**

About: Published on behalf of the Association for Clinical Biochemistry. The official journal of NVKC (de Nederlandse Vereniging voor Klinische Chemie), JSCC (Japan Society of Clinical Chemistry) and the AACB Australasian Association of Clinical Biochemists

Advice to authors: "All measurements should be expressed in SI units (see Baron DN, et al. The use of SI units in reporting results obtained in hospital laboratories. *Ann Clin Biochem* 1974; 11: 194-202)."

General comments: Mixture of units in use.

Carbamazepine: mg/L and μmol

Paracetamol: mg/L and μmol

Phenytoin: mg/L and μmol

Valproate: mg/L and μmol

Name: **Clinical Chemistry and Laboratory Medicine**

About: Published in association with the International Federation of Clinical Chemistry and Laboratory medicine and the European Federation of Clinical Chemistry and Laboratory Medicine

Advice to authors: "The preferred way of expressing concentration in this journal is as substance concentration in moles per litre and its submultiples (mmol/L, $\mu\text{mol/L}$, etc.)." CCLM, 2005;43(1):108–123.

Digoxin: ng/mL

Carbamazepine: mg/L, $\mu\text{g/mL}$

Phenytoin: mg/L

Valproate: mg/L

Name: **Epilepsia**

About: The journal of the International League Against Epilepsy (ILAE)

Advice to authors: Units not specified – cite ICMJE

General comments: Mass units used, occasionally molar units also provided in brackets

Carbamazepine: $\mu\text{g/ml}$ and mg/L

Phenytoin: $\mu\text{g/ml}$ and mg/L

Valproate: $\mu\text{g/ml}$ and mg/L

Name: **Neurology**

About: The journal of the American Academy of Neurology (AAN)

Advice to authors: Units not specified – cite ICMJE

General comments: Mass units used, occasionally molar units also provided in brackets

Carbamazepine: $\mu\text{g/ml}$ and mg/L

Phenytoin: $\mu\text{g/ml}$ and mg/L

Valproate: $\mu\text{g/ml}$ and mg/L

Name: **Emergency Medicine Journal**

About: The journal of the British Association for Accident & Emergency Medicine and is the official journal of the British Association for Immediate Care and the Faculty of Prehospital Care of the Royal College of Surgeons of Edinburgh.

Advice to authors: Units not specified – cite ICMJE

General comments: Limited relevant articles molar units mostly used

Carbamazepine: $\mu\text{mol/L}$ and mg/L

Paracetamol: $\mu\text{mol/L}$ and mg/L

Phenytoin: $\mu\text{mol/L}$ and mg/L

Valproate: $\mu\text{mol/L}$ and mg/L

Name: **Emergency Medicine Australasia**

About: The journal of The Australasian College for Emergency Medicine (ACEM) and the Australasian Society for Emergency Medicine (ASEM)

Advice to authors: SI units as outlined in the latest edition of Units, Symbols and Abbreviations: A Guide for Medical and Scientific Editors and Authors (Royal Society of Medicine Press, London).

General comments: Limited articles pertaining to drug concentrations

Paracetamol: $\mu\text{mol/L}$ and mg/L

Toxicology and Clinical Pharmacology Textbooks

Name: **The Pharmacological Basis of Therapeutics, Goodman and Gilman**

About: 11th Edition, 2006. USA

General comments: All mass units with mL as denominator

Name: **Ellenhorns Medical Toxicology**

About: 2nd Edition 2007

General comments: All mass units. Predominantly mL as denominator but occasionally L.

Name: **Clarke's Analysis of Drugs and Poisons**

About: 3rd Edition 2004 (Pharmaceutical Press, UK)

General comments: All mass units. Predominantly L as denominator.

Name: **TOXINZ**

About: <http://www.toxinz.com>

General comments: Most widely used primary toxicology reference in Australasia. Mass units used.

Name: **Toxicology Handbook**

About: 2007 Elsevier Australia

General comments: Both provided, a mixture of primary units used with the alternative provided in brackets.

General Medical Textbooks and Websites

Name: **UptoDate**

About: <http://utdol.com> 2008

General Comments: Uses mass units mostly $\mu\text{g/ml}$

Name: **Harrisons Textbook of Medicine**

About: 17th edition 2008

General comments: Mass units in text for anticonvulsants and digoxin, both units in comprehensive table in appendix.

Name: **Oxford Handbook of Clinical and Laboratory Investigation**

About: Proven and Katz (UK)

General comments: Mainly mass units, some both and some molar only.

Paracetamol: both

Phenytoin: mg/L

Carbamazepine: Both

Valproate: mg/L

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