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Commentary

Are we using the right dose? – A tale of mole and gram

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'The initial dose of pralidoxime is 1 g administered intravenously over a period of 20 to 30 min.' [1]

'An oxime, such as pralidoxime chloride or mesilate, should be administered in a dose of 30 mg kg^{-1} bodyweight intravenously every 4–6 h to patients with systemic features and who require atropine. Alternatively, an infusion of pralidoxime 8–10 mg kg^{-1} h^{-1} may be administered.' [2]

In reading original publications, we frequently find imprecise descriptions of dosage. This flaw is usually not due to the author's uncertainty about the dosage they have used, but to an ambiguous definition of the chemical. This error is then perpetuated and magnified through to reviews, meta-analyses and commentary (in even the most prestigious journals and by internationally acknowledged experts) [1, 2].

For example, 'pralidoxime', an antidote against certain organophosphorus compounds, is a poor description of the drug proper. As a quaternary ammonium compound the cation requires an anion. It is available as pralidoxime chloride (172.6 Da), pralidoxime mesilate (or methanesulfonate, 232.3 Da), pralidoxime metilsulfate (248.6 Da), and pralidoxime iodide (264.1 Da). The term 'pralidoxime sulfate' is also found in literature [3], a compound that does not exist. Is it referring to one of the compounds above, or to pralidoxime hydrogen sulfate or bis(pralidoxime) sulfate? At any rate, it should be obvious that a precise instruction (prescription) requires the correct name of the chemical compound. It is perhaps less obvious that the same precision is required in the dose.

When considering dose equivalence of these various salts in the market and comparing their price, the unit mol or mmol is particularly helpful and should be used more frequently than usually done. From the molecular weight it can be seen that 1 g of pralidoxime chloride contains 1.5 times more pralidoxime than 1 g pralidoxime iodide (and neither contains a gram of pralidoxime). If one adheres to the frequently used protocol [4, 5] with a continuous infusion of pralidoxime chloride at 8 mg kg^{-1} h^{-1} following a short infusion of 30 mg kg^{-1} (Table 1), it is evident that a considerably higher amount of pralidoxime iodide is needed to reach a concentration of about 100 μmol/l [5, 6].

Table 1

Dosage of pralidoxime predicted to reach a plasma concentration of about 100 μmol/l

	Loading dose over 30 min 175 μmol kg^{-1}	Continuous infusion 50 μmol kg^{-1} h^{-1}
Salt	mg kg^{-1}	mg kg^{-1} h^{-1}
Chloride	30.2	8.6
Mesilate	40.7	11.6
Metilsulfate	43.5	12.4
Iodide	46.2	13.2

The use of molarity has a further advantage: when dealing with plasma concentrations of a salt, e.g. pralidoxime, the accompanying anion is mostly the abundant chloride and in part bicarbonate, but hardly the original anion, such as iodide or mesilate. Hence, presentation of 'pralidoxime' in mg l^{-1} of body fluid is vague. Does it relate to the cation only (137.1 Da), to the salt administered or to pralidoxime chloride, the most abundant pralidoxime counter-ion in the body? It is obvious that presentation of the molarity, e.g. μmol l^{-1}, circumvents this ambiguity. We are accustomed to using this unit when dealing with electrolyte concentrations in blood.

The problem is not confined to pralidoxime. Any drug with a narrow therapeutic index present in various salts may suffer from this dosing equivocation. A more widely used example is lithium. In manic patients, the targeted plasma concentration is in the (narrow) range of 1.0 to

1.25 mmol l^{-1}. The drug may be available as lithium carbonate (Li_2CO_3, 73.9 Da; 1 g is equivalent to 27 mmol lithium) or lithium citrate (tri-lithium citrate tetrahydrate, 282.0 Da; 1 g is equivalent to 10.6 mmol lithium). It is clear that lithium carbonate contains 2.5 times more lithium than lithium citrate. The very low molecular weight of the active cation (7 Da) hardly contributes to the total mass of the salt (roughly 19% and 7.5% of the two salts). Lithium is an unusually extreme case in this regard, for most drugs the molecular weight of the base (e.g. erythromycin, 733.9 Da) outweighs the molecular weight of the anions by far and the therapeutic index is much larger. It seems likely that the fact that these distinctions can thus be safely ignored for many drugs has lead to the widespread imprecision. Nonetheless, it might be better practice to consistently relate dose recommendations in terms of the active moiety.

Similar problems can occur in the presentation of analytical data. Dosage recommendations of atropine (hyoscyamine) usually refer to racemic atropine sulfate, which is in fact bis(atropinium) sulfate monohydrate (CAS 45-48-1, 694.8 Da). It is crucial when plasma concentrations are reported in μg l^{-1} that it should clearly indicate whether the atropine base is meant or the salt equivalent. Moreover, in presenting pharmacokinetic data it needs to be unambiguously stated whether a given concentration in biological material refers to the pharmacologically active l-hyoscyamine as measured by radioreceptor assays [7], or to the racemic atropine as determined by GC-MS [8], or predominantly to the inactive d-hyoscyamine when using a radioimmunoassay [9].

These few examples are presented to encourage researchers to present their methodology exactly and alert reviewers to the need to insist on unambiguous descriptions. Our comment has been criticized by its reviewers in that we might open Pandora's box again and reopen the intensive quarrel on the value of introducing SI units in medicine in general and clinical pharmacology in particular. Furious articles have been written in the past against using amount units (mole) and have highlighted the problem of mixing-up normal or toxic values that are known only as numbers and not along with their units [10–13]. We will not add to this dispute but would like to recommend the Salomonian wisdom: In case of doubt, we should report both molar and mass units [14]. It is not always easy to improve precision in scientific research, but in this case a lot can be done with the simple stroke of a pen!

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