EDITORIAL

When less is more – efficacy with less toxicity at the ED50

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Introduction

The individualization of drug dosage to maximize benefit and minimize risk is always a challenge since desired benefit is often associated with many dose-related adverse effects. Most disease is subacute and mild to moderate in severity. Doses that give around 50% of the maximum possible drug effect [the effective dose 50 (ED50)] often prove to be sufficient. An analysis of the dose–response relationship for most drugs shows that above the ED50, efficacy increases only marginally, whilst adverse effects continue to increase (Figure 1), especially with agonist agents. Using the lowest effective dosage is particularly desirable when drugs are used long term in prevention, as is the case with most cardiovascular drugs.

This Editorial explores factors that drive the highly prevalent but often unnecessary dose-escalation many fold above the ED50 that may be associated with unintended toxicity and negative outcomes.

Evidence-based dosing

The ED50 is the dose required to achieve 50% of the desired response in 50% of the population. It is thus calculated from

a dose–response curve by dropping a line on the dose axis where 50% of the desired response is seen. As with LD50 and TD50, ED50 is usually reported in regulatory submissions of a new drug.

Manufacturer dose-finding studies sometimes provide a dose estimate and the range of a drug's population ED50 but this information appears to have little bearing on prescribing. Clinicians or pharmacists are either not aware of it, or, if they are, tend to ignore it once the drug is marketed with recommended dosage guidelines. Also ignored are the practical implication of variation in individual ED50 depending on body size, pharmacokinetics and pharmacodynamics. Variation in individual ED50 leaves a situation where the effective dose may be less in many patients compared to participants in clinical trials [1, 2]. A major concern is that much of what is known about ED50 is not disclosed to practitioners or pharmacists and that this may partly be to assist finding marketing advantage. Manufacturers have dose response data for some efficacy endpoints (albeit often not clinical or much to do with outcomes) on which dose recommendations are based. If they have data for at least four doses, a very approximate ED50 might be estimated.

Dose finding studies, and hence dosage guidelines, are often based on surrogate measures such as a cholesterol concentration at a particular timepoint rather than major

Figure 1

A graphical representation showing relationship of drug dose and effect – toxicity and clinical

long-term outcomes such as mortality [3]. In addition, many trials use composite outcomes. With cardiovascular trials, many of the contributors to a composite outcome are intercorrelated, and in modern times have become substantially driven by excess weight [4]. Whilst the use of such endpoints reduce the patient numbers needed to show small benefits, it gives the same weighting to new angina as death. Dose-finding studies can also be problematic regarding dose translatability as adverse effects appear relatively uncommon – due both to a more robust population than often encountered in the clinic, and because adverse events can be difficult to ascertain and quantify. In addition, total mortality may be presumed too small to be of interest. However, mortality is an unambiguous and pivotal endpoint as it summates both efficacy and safety. For example, digoxin had been promoted for its efficacy, reduction in ventricular rate in atrial fibrillation and rehospitalization for left ventricular failure, but later systematic review showed digoxin at routine doses increases net total mortality [5]. Higher serum digoxin concentrations in particular are associated with increased mortality [6]. Digoxin is no longer recommended first line.

Clinical trials that address outcomes such as total mortality must be larger and longer term and usually cannot be undertaken without industry funding. There are notable exceptions, such the independently conducted UK Prospective Diabetes Study, which showed improved diabetic and cardiovascular outcomes, including mortality, on metformin [7]. Interestingly, metformin is often used *below* its ED50, which is around 2 g. In the RALES study, spironolactone, a mineralocorticoid receptor antagonist dosed around ED50 reduced total mortality in cardiac failure [8] as substantially as the newer, heavily promoted angiotensin receptor blocking agents which are used at

several fold above their ED50s. For example, candesartan is used at up to 32-fold ED50 in the absence of convincing evidence for superior outcomes. In cardiac failure, losartan 150 mg compared to 50 mg daily [9] and lisinopril 33 mg compared to 4 mg [10] did not improve total mortality. Higher doses of these drugs reduced the softer endpoint of rehospitalization but increased the incidence of potentially serious side effects such as renal impairment, hyperkalaemia and symptomatic hypotension, each by >40%.

Total mortality is reduced by doses of β -blockers around ED50 in cardiac failure and hypertension. Higher doses confer little advantage, partly because the slowed heart can systolic blood pressure, associated with increased mortality [11, 12].

Unintended adverse effects

Prescription medicines have been shown to contribute to, or cause, at least 12% of hospital admissions [13] and 16% of hospital mortality [14]. Although not all adverse effects are caused by high plasma concentrations, adverse effects in initially asymptomatic patients on long-term preventive drug treatment are usually unacceptable. Persistence with high doses is not justified when lower doses confer sufficient protection and avoid detrimental adverse effects. For example, statins dosed around ED50 (based in this case on low-density lipoprotein-lowering) have been shown to reduce coronary events, by about 30% after 3 years [15].

The only placebo-controlled statin trials that have shown statistically convincing reductions in total mortality employed doses just below [16] and just above [17] the ED50. However, statins are approved at doses of up to 40-fold ED50. Such high doses do not improve survival but can increase adverse effects, for example myalgia and liver

dysfunction, up to 10-fold compared to the incidence at around ED50 [18]. Clinical trials recruit younger patients with less comorbidity and adverse effects are likely to occur more frequently in older clinic patients with multiple comorbidities.

High-dose statins have been recommended in acute coronary syndrome based on just two industry-sponsored studies, neither of which demonstrated a statistically significant survival advantage, compared to doses around ED50 [19]. The Cochrane meta-analysis of all 18 relevant studies of a wide range of statin dose compared to placebo showed some reduction in recurrent angina by 4 months but no significant impact on any of the major outcomes: myocardial infarction, stroke or mortality [20].

Selective serotonin reuptake inhibitors (SSRIs) are the drugs most commonly used to treat depression. However, contrary to the implication in their name, their actions are not specific and they may be more effective for treating anxiety. Further, it is unclear as to whether their common long-term use is as treatment or prevention of recurrent illness, lower dose may be appropriate for the latter. Despite knowledge of SSRI dose response, manufacturers have had doses of over 30-fold ED50 approved (e.g. venlafaxine 225 mg, with an ED50 of 5.8 mg) and there are no available strengths <3-fold ED50. Early data on the effects of different doses on effective receptor occupancy appear to have been overlooked [21]. Meta-analysis [22] has shown that SSRIs provide only limited clinical efficacy. This may be explained in part because adverse effects, which include sleep disturbance, agitation, fatigue, weight gain, hyponatraemia, mood deterioration, sexual dysfunction and movement disorders, cloud benefits and lessen compliance.

Clinical trials have rarely addressed comparative effectiveness at different doses. This leaves the task of optimal individual dosing to close clinical monitoring by the treating clinician. For example, if gastroesophageal reflux symptoms remit on esomeprazole 5 mg daily, which is around the mean population ED50, higher proton-pump inhibitor dose may be futile and unnecessarily increases the risk of adverse effects. If reflux persists and proton-pump inhibitor adverse effects emerge, a lower dose combined with domperidone and intensive lifestyle measures may prove effective and more sustainable.

Disease prevention is best treated with small doses

Lower doses are likely to be effective in prevention, when the pathophysiology is less advanced and potentially more readily arrested. This has been clearly shown with aspirin [23] and statins [24] with doses not much above ED50.

The ratio of benefit to risk is necessarily lower in prevention because the risks of toxicity are no different but the mean benefit to the individual is only small in absolute terms and may prompt clinicians to increase the dose. However, as has been settled with aspirin in coronary disease and stroke, a small dose provides the best balance of risks with benefit. A dose of 75 mg of aspirin even after a first clinical event, so-called secondary prevention, is often sufficient

compared to previously approved doses of up to 1300 mg daily [23].

In a competitive market, promotion of drugs asserts greater efficacy with higher doses, often supported by evidence based only on surrogate markers. Practitioners and Guidelines groups may be influenced unduly by the marketed data taken from publications in high profile journals [25]. For example, clinicians are encouraged to lower blood pressure, cholesterol or glucose towards numerical targets, and in doing so, tend to ignore an individual patient's pharmacology and pathophysiology. Lowering blood pressure to 120/80 mmHg, cholesterol to 4 mmol l⁻¹ and glycated haemoglobin to 6% may be appropriate in younger populations or if achieved with long-term lifestyle measures such as dietary improvement, weight loss and regular exercise. However, to achieve these targets routinely with drugs, necessarily brings the risk of adverse effects which usually degrade outcomes. For example, intensive pharmacological efforts to target blood glucose [26], triglyceride [27] and high-density lipoprotein concentrations [28] all increased total mortality, which is surely of greater importance to patients.

Conclusion

ED50 appears to be a useful guide to help physicians choose appropriate starting doses. In fact, it is usually prudent and safest to start dosing below the ED50. This is because many drugs can worsen morbidity, particularly in the elderly and this is often dose related. Close clinical monitoring is essential to ensure optimal individual dosing and to detect adverse effects early. Whilst ED50 is calculated by examining the dose-response curve, it is often not translated into clinical guidelines. But the ED50 alerts a clinician to the likely useful and safe dose range and should be more widely available. ED50 should be an important variable in drug approval, marketing and most importantly prescribing.

Competing Interests

There are no competing interests to declare.

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References

- 1 Peck C, Urquhart J. Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980-1999. *Pharmacoepidemiol Drug Saf* 2002; 11: 439-46.
- 2 Cross J, Lee H, Westelinck A, Nelson J, Grudzinskas C, Peck C. Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980-1999. *Pharmacoepidemiol Drug Saf* 2002; 11: 439-46.
- 3 Martin JH, Fay MF. Surrogate end-points in clinical practice: are we providing worse care? *Intern Med J* 2010; 40: 395-8.

- 4 Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrback K, *et al.* Bariatric surgery. A systematic review and meta-analysis. *JAMA* 2004; 292: 1724–37.
- 5 Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. *Eur Heart J* 2015; 36: 1831–8.
- 6 Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; 289: 871–8.
- 7 Turner RC, Holman RR, Stratton IM, Cull CA, Matthews DR, Manley SE, *et al.* Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352: 854–65.
- 8 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341: 709–17.
- 9 Konstam MA, Neaton JD, Dickstein K, Drexler H, Kamajda M, Martinez FA, *et al.* Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009; 374: 1840–8.
- 10 Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, *et al.* Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999; 100: 2312–8.
- 11 Bangalore S, Sawhney S, Messerli FH. Relation of Beta-Blocker Induced Heart Rate Lowering and Cardioprotection in Hypertension. *J Am Coll Cardiol* 2008; 52: 1482–9.
- 12 Dimmitt SB, Stampfer HG, Warren J. β -adrenoceptor blockers -valuable but higher doses not necessary. *Br J Clin Pharmacol* 78: 1076–9.
- 13 Al Hamid A, Ghaleb M, Aljadhey H, Aslanpour Z. A systematic review of hospitalization resulting from medicine-related problems in adult patients. *Br J Clin Pharmacol* 2013; 78: 202–17.
- 14 Moulton JP, Mehta U, Parrish AG, Wilson DPK, Stewart A, Njuguna CW, *et al.* Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. *Br J Clin Pharmacol* 2015; 80: 818–26.
- 15 Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease and stroke: systematic review and meta-analysis. *BMJ* 2003; 326: 1423–9.
- 16 The long-term intervention with pravastatin in ischaemic disease (LIPID) study group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339: 1349–57.
- 17 Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Thorgerirsson G, *et al.* Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994; 344: 1383–9.
- 18 LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352: 1425–35.
- 19 Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomized controlled trials. *Heart* 2007; 93: 914–21.
- 20 Nordmann A, Schwartz G, Vale N, Bucher HC, Briel M. Cochrane corner: early statin therapy in acute coronary syndromes – what clinical benefit? *Heart* 2016; 102: 653–4.
- 21 Meyer JH, Wilson AA, Sagrati S, Hussey D, Carella A, Potter WZ, *et al.* Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses. An [¹¹C]DASB positron emission tomography study. *Am J Psychiatry* 2004; 161: 826–35.
- 22 Linde K, Kriston L, Rücker G, Jamil S, Schumann I, Meissner K, *et al.* Efficacy and acceptability of pharmacological treatments for depressive disorders in primary care: systematic review and network meta-analysis. *Ann Fam Med* 2015; 13: 69–79.
- 23 Campbell CI, Smyth S, Montalescot G, Steinhilber SR. Aspirin dose for the prevention of cardiovascular disease. A systematic review. *JAMA* 2007; 297: 2018–24.
- 24 Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, *et al.* Efficacy of statins in familial hypercholesterolaemia: a long-term cohort study. *BMJ* 2008; 337: a2423.
- 25 Miller JD. Study affirms PhRMA's influence on physicians. *J Natl Cancer Inst* 2007; 99: 1148–50.
- 26 Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, *et al.* Effect of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358: 2545–59.
- 27 Warren JB, Dimmitt SB, Stampfer HG. Cholesterol trials and mortality. *Br J Clin Pharmacol* 2016; 82: 168–77.
- 28 Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJP, Komajda M, *et al.* Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007; 357: 2109–22.