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Extraordinary popular delusions and the madness of crowds: puncturing the epoetin bubble—lessons for the future

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Abstract

Recent trials, and meta-analyses, have cast further doubt on the clinically desirable and safe range for increasing haemoglobin in chronic kidney disease using erythropoiesis-stimulating agents. In this article, I review the current dilemmas we face, suggest key clinical and biological research priorities, and conclude that we need to be brave enough to admit our present shortcomings, and then perhaps adopt a more patient-focused, individualized approach to anaemia management.

Keywords: anaemia; epoetin; mortality

Introduction

Charles Mackay (1814–89) was a 19th century Scottish poet, journalist, chronicler and song writer. In 1841, he published a book entitled 'Memoirs of Extraordinary Popular Delusions and the Madness of Crowds' [1] which was one of the first, if not the first, attempts to describe and understand market or social psychology. It 'debunked' events like the South Sea Bubble of 1720, astrology, tulipomania, prophecies and 'the love of the marvellous and the disbelief of the true'. With the world economy still reeling from (yet) another example of financial mass delusion, it is reassuring to report that this book is still in print, and perhaps, now would be the good time to ensure that it is more widely read. It might also be good material for nephrologists to study.

The introduction to this book includes this section: 'We find that whole communities suddenly fix their minds upon one object, and go mad in its pursuit; that millions of people become simultaneously impressed with one delusion, and run after it, till their attention is caught by some new folly more captivating than the first. We see one nation suddenly seized, from its highest to its lowest members, with a fierce desire of military glory; another as suddenly becoming crazed upon a religious scruple, and neither of them recovering its senses until it has shed rivers of blood and sowed a harvest of groans and tears, to be reaped by its posterity [1].

The South Sea Company experience is salutary. In 1720, in return for a loan of £7 million to finance the war of the Spanish Succession (against France), the House of Lords passed the South Sea Bill, which allowed the South Sea Company a monopoly in trade with South America. The company underwrote the English National Debt, which stood at £30 million, on a promise of (perpetual) 6% interest from the government. Shares immediately rose to 10 times their value, speculation ran wild, and all sorts of companies, some lunatic, some fraudulent or some just optimistic, were launched. Then, the 'bubble' in London burst!

The stocks promptly crashed, and the people lost all of their investments. The whole country suffered a catastrophic loss of money, property and confidence. The gullible mob, whose innate greed had fuelled this mass hysteria for wealth, demanded vengeance. The South Sea Company directors were arrested, and their estates forfeited' [1].

I think, in 2010, we now need to seriously address the question of whether we, as a renal community, have allowed ourselves collectively to become seized by the notion that a higher haemoglobin equates with a healthier patient, and that we will automatically confer better clinical outcomes. It is at least possible that, as a result of optimism triumphing over evidence, we have not always best served our patient population. Two events have changed my opinion on this. The first event was one of my young symptomatic epoetin-resistant dialysis patients having an unexpected stroke as I took his haemoglobin from 9.3 g/dL to 10.8 g/dL over 10 weeks by increasing his epoetin dose (done exactly as recommended by all Best Practice Guidelines), with a deterioration in his blood pressure control. Recovery in his health was complete soon after, but my confidence in this strategy was not so quickly restored. The second 'event' was the publication of the TREAT study [2].

In this short, personal commentary, I shall elaborate on this theme, citing examples and evidence, developing my arguments still further beyond those articulated in a similar publication in 2010 [3].

The state of play in 2010—haemoglobin and health in chronic kidney disease patients

As I have previously recounted [3], epoetins were first used in 1986 in man to effect an increase in haematocrit [4]. At that time, patients on renal dialysis (renal replacement therapy) were routinely very anaemic (with typical haemoglobin levels of 4–8 g/dL), often transfused (with the attendant chronic dangers of iron overload, viral infections and allosensitization), and symptomatic (tiredness, lack of stamina and easy fatigue). The epoetins, one of the earliest successfully-deployed biopharmaceuticals, must have seemed to be a huge advance in the clinical management of patients with chronic kidney disease—which indeed was (and remains) the case.

In those early days, the dramatic reduction in (but never abolition of) the need for regular blood transfusions, and the ability to manage patients with a significantly higher haematocrit, made a great difference to patients and all those involved with their chronic care. The initial enthusiasm for this new approach rested almost entirely on demonstrating transfusion avoidance, and on limited data sets showing improvements in exercise tolerance, walking distance, quality of life, and improvements in left ventricular size and performance (see [3]). The side effect profile of artificially engineering a higher haematocrit using epoetin was just as evident from the outset [3,4]. This early, and justified, enthusiasm for epoetin use was bolstered by many epidemiological associations between higher haematocrit values and better outcomes, by practice pattern surveys and registries, which routinely reported 'compliance' with the still nascent and untested guidelines statements, and by seditious financial considerations which distorted clinical decision making and practice [5,6].

So, nearly 25 years later, after the seminal paper was first published in 1986 [4], what do we now know, or still do not know, about this complex therapeutic area in 2010? We can frame our present state of knowledge using the now infamous Rumsfeld dialectic of 'known knowns, known unknowns, and unknown unknowns' [7]. The first thing we do know is that it is indeed a complex matter. One of the early lessons, not yet completely absorbed, is that chronic kidney disease is not a state of absolute lack of circulating erythropoietin, but is often a state of continuous, and very variable, erythropoietin resistance [8]. The chief reason for this is iron deficiency (*ab initio* or consequent upon stimulated erythropoiesis), though there are many other potential reasons for resistance to endogenous erythropoietin, or epoetins, as well [8]. The first thing we do not know in 2010 is how best to deploy these biologically powerful and pleiotropic synthetic hormones—the epoetins—in clinical practice.

Much has now been written about the rise and fall in the fortunes of epoetins [3,9]. The recent excellent paper by

McFarland and colleagues, using long-term data derived from the DOPPS [10], tells a remarkable story of the rapid uptake in the use of epoetins, the rapid increase in subjects' haemoglobin levels over the period 1996–2009, and the huge increase in the doses of the various epoetins and erythropoiesis-stimulating agents (ESAs) used (and of course by extension, in the cost of their healthcare unless offset by improved clinical outcomes).

These data were derived from 11 countries (representative of the global dialysis practice of advanced healthcare economies). It can be seen that in 1996–2001, or thereabouts, at the start of the epoetin era, in the seven countries reporting then to DOPPS, in only two was the mean haemoglobin concentration in dialysis patients >11 g/dL, or to put another way, only 20–25% of dialysis patients had a haemoglobin concentration >12 g/dL. By the third DOPPS era, 2005–present, out of the 11 reporting countries, no fewer than 10 had dialysis patients' mean haemoglobin concentrations >11.5 g/dL, or to put another way, 4 countries had more patients with a haemoglobin concentration >12 g/dL than <12 g/dL. Epoetin doses had also increased over this same period, from ~5000–8000 to 13 000–18 000 IU/week [the USA being an exception in having markedly higher epoetin dosage (but not achieved haemoglobin) from the outset, which rose still higher].

The normal haematocrit trial by Besarab and colleagues published in 1998 [11] was the first major 'shot across the bows' for higher haemoglobin outcomes, coming 1 year after the first guidelines statements were published enshrining a target haemoglobin value of 11–12 g/dL [12]. The publication and slow understanding of the next three large studies—CREATE [13], CHOIR [14] and TREAT [2,15]—have now confirmed, in many if not all minds, the suspicion that all is not well with our current understanding of how and when to attempt to alter haematocrit using ESAs in subjects with chronic kidney disease.

In 2010, we saw the publication of an excellent meta-analysis by Strippoli and colleagues [16,17] in which it is now clearer than ever that the risks of embarking on epoetin use in chronic kidney disease patients are significant, and crucially, without patient-level information to guide us, the balance between risk and harm for each patient is blurred, or unknown. In the conclusion of this paper it is stated 'Targeting higher haemoglobin levels in CKD increases risks for stroke, hypertension, and vascular access thrombosis and probably increases risks for death, serious cardiovascular events, and end-stage renal disease'. This conclusion was reached after meticulous analysis of 27 trials involving 10 452 participants. The quality of many of the trials conducted, and now reanalysed, was, by current standards, either poor or suboptimal. The meta-analysis could not find evidence for sustained improvement in quality of life measures (whose metrics are notoriously subjective and, the authors suspected, may have been subject to positive bias reporting). This meta-analysis makes for sobering reading, and its conclusions and recommendations need to be taken very seriously by all of us.

The European Best Practice Guidelines group was the first to address this issue in the post-TREAT era [18], and crucially has now recommended, that, for diabetic or comorbidly challenged patients with chronic kidney disease, a new treatment target of 10–12 g/dL (and not the historical target of 11–12 g/dL) is warranted. This is important as it is a long-overdue acceptance that adoption of 'one size fits all' clinical targets is both inadequate for, and inapplicable to, chronic kidney disease patients. It was the view of this group, however, that the TREAT study findings [2,15], by far the largest and most comprehensive study of the long-term treatment of anaemia in chronic kidney disease, should not be extrapolated beyond chronic kidney disease patients with type II diabetes (itself ~33–50% of chronic kidney disease patients), which some would find a disappointingly conservative view in the light of the many concerns now being raised about these issues [2,3,9,15]. Of course, it is now KDIGO that will opine on this, after a thorough review of all available evidence, later in 2011.

Quo vadis?

In my view, treating patients with chronic kidney disease with epoetins just to 'correct' a haemoglobin level, or to comply with a guideline or practice-pattern group statement, is not good medicine, any more than is deciding to dialyse a patient based purely on eGFR measurements; van Biesen and Vanholder in a recent editorial elegantly 'debunk' this notion of a "numbers-based" decision algorithm, favouring a blend of symptoms and measurements in individual patients, with of course patient involvement in the decision [19]. This is just as true for anaemia management.

In a recent paper, Agarwal strongly extolled the virtues of individualizing the decision about how to manage renal anaemia [20]; provocatively, in the article's title, he chooses to use the phrase 'resurrecting the doctor–patient relationship in the anemia debate'. In this article, he argues that the lower limit for haemoglobin might potentially be set at such a level as does not lead to a detectable increase in transfusion-related allosensitization. Certainly, epoetins do not abolish, but significantly reduce, blood transfusion rates. However, some caveats must be entered. First, the effect of leucodepleted blood on the immunological system is complex [21,22]: donor-specific transfusion, or one HLA-DR-mismatched transfusion, may be either non-harmful or beneficial, and this effect may vary between men and women. Pregnancy/abortion remain the biggest allosensitization risk factor [21,22]. Second, in the UK, only ~50% of dialysis patients ever get on a renal transplant waiting list, and of these, only 25% or thereabouts have had a transplant in a 2-year period after being wait-listed [23], so these arguments may not be relevant to the majority of dialysed patients whose comorbidities, or situations, preclude organ transplantation.

I believe we need now to do many things urgently. There are at least six important issues that we need properly designed and independently funded and managed trials, reanalysis of existing datasets, or patient-level outcome data, to answer:

(1) What is the 'interaction effect between target haemoglobin, achieved haemoglobin and epoetin dose'? This could in part be answered by randomizing patients to

'low-dose' epoetin versus 'high-dose' epoetin (with stringent safety safeguards).

(2) What is the 'ideal anaemia treatment paradigm'? Is this careful repletion of iron stores, and correction of other causes for erythropoietin resistance, and waiting to see what effect this has on haemoglobin concentrations, versus early simultaneous use of iron and epoetins together? Daniel Coyne has recently called for trials of different anaemia strategies, and this must be a priority [24].

(3) What is the 'ideal correction phase duration' and 'maximal rate of haematocrit rise' (using any intervention)? If we take the example of hyponatraemia for a moment, it is more important to avoid rapid rises in plasma sodium over time, than to aim for any particular target plasma sodium level.

(4) What are the pathomechanisms and markers for 'epoetin-induced vascular injury'? We need detailed investigations about the effect of epoetin on vascular endothelium, on specific vascular beds (e.g. the brain and heart) and especially on platelet numbers and function. We also need to understand if the simultaneous use of high-dose intravenous iron supplements with high-dose intravenous epoetin promotes adverse changes in platelet numbers and function, endothelial cell number and function, and measures of oxidative stress.

(5) We urgently need 'nested observational and interventional studies' of a diverse range of 'cardiac and other biomarkers' to see if we can more precisely track clinical and investigative characteristics of cohorts of patients who are more prone to, or immune from, the potential adverse consequences of epoetin use.

(6) We need to be honest enough to state that 'the ideal haematocrit may vary' from patient to patient, and even within the same patient depending on their clinical situation. This might mean that someone who has been treated to one haemoglobin value might need a new target value if their clinical situation alters, e.g. post-stroke or myocardial infarction, or with intercurrent illnesses. What is challenging for us all is that in 2010, we perhaps can only be certain that haemoglobin levels <9 g/dL are harmful, and that haemoglobin levels >13 g/dL can be harmful, but the clinical impact of what lies between—which is where ~75–85% of contemporary chronic kidney disease patients' haemoglobin values lie—is far from clear-cut.

Conclusions

It is clear that clinical use of epoetins in chronic kidney disease, cancer, heart failure and other situations is now falling, at least as expressed in financial terms [25], and is under scrutiny like never before, so it behoves us in the renal community to get this right, or find 'solutions' imposed upon us by others, e.g. regulators. While some may baulk at the implicit agenda of pharmacoeconomic analysis playing a role in clinical decision making, it is surely both irresponsible and naïve not to address the issue of the huge cost of ESAs. If we accept that TREAT [2] was in 'clinical' equipoise [15], it was not in 'economic' equipoise; the 'treatment' arm using a median monthly dose of 176 μg darbepoietin (and IV iron) would involve significantly higher monthly expenditure than the 'placebo' arm. We nephrologists have a responsibility to husband precious healthcare resources and not to squander them unnecessarily. Knowing, as all would surely agree, that raising haemoglobin from 6 to 9 g/dL will be of real benefit to patients in diverse ways, is one thing, but moving upwards another 3 g/dL from a starting haemoglobin of 9 g/dL to one of 12 g/dL (which requires very much more epoetin and iron) yields only modest benefit at best, while increasing risk, and at great financial expense, is another consideration altogether.

We have arrived where we are today more through naivety than through knavery, but it will take novelty—a fresh approach—to arrive at the promised land. One potential avenue is to accept that the randomized controlled trial may not be the only or ideal way we can look for clinical trial guidance; David Mendelssohn (personal communication) has talked about a mal-alignment in nephrology through the strict application of evidence-based medicine (EBM) and comparative evaluative research (CER), which does not lend itself well to the advancement of science and clinical care in our specialty. In the USA, CMS (Medicare) has recently introduced a new programme called 'coverage with evidence development (CED)' that allows for conditional funding, while formal collection of additional patient data continues. We may need to collect real-time patient-level outcome data for newly accepted therapies to try to answer fundamental questions about how, and when, we should use them. These questions are not those always best answered by current regulatory—registration trials.

Such an approach would be controversial, and require compromise from purists and pragmatists alike. We might too have to reconsider the role and utility of guidelines statements, and practice pattern surveys. But by using such an approach, we can also explore comprehensively and objectively the benefits and downsides to treating blood pressure [26], plasma phosphate [27], the use of expensive vitamin D analogues in chronic kidney disease [28], and many other examples. The South Sea bubble of course burst, as pithily chronicled by Charles Mackay [1], when people finally realized (all too late) that when something appears too good to be true, it is indeed too good to be true. I think we have now arrived at this point in nephrology.

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Diabesity: an overview of a rising epidemic

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Abstract

'Diabesity' is the term for diabetes occurring in the context of obesity. In this review, we will overview the latest epidemiological data available describing the rising prevalence, health impact and economic impact of diabesity. We will also outline the measures required to slowdown this newly evolving epidemic. The global prevalence of diabetes in 2010 was 284 million people