Pediatr Nephrol (2009) 24:435–437
DOI 10.1007/s00467-008-0955-2

EDITORIAL COMMENTARY

Erythropoietin dosing in children with chronic kidney disease: based on body size or on hemoglobin deficit?

Ruediger E. Port · Otto Mehls

Received: 25 June 2008 / Revised: 4 July 2008 / Accepted: 8 July 2008 / Published online: 12 August 2008

Abstract There are no investigations demonstrating that body size-adapted doses of erythropoietin (EPO) are as equally effective in children as in adults. A treatment starting with 150 IU/kg body weight per week leads to an insufficient rise in hemoglobin levels in anemic children with chronic kidney disease (CKD). Nevertheless, this strategy is widely used and seems to be the reason for a high percentage of young anemic children in spite of EPO treatment. In children and in adults, 1,000 IU EPO intravenously increases the hemoglobin level equally by 0.04 g/l. This strongly argues for specifying the EPO dose in the treatment of children with CKD in absolute amounts. A prediction model exists which allows the determination of the EPO dose which is expected to raise hemoglobin from a given pretreatment level to a desired steady state level.

Keywords CKD children · CKD adults · Renal anemia · Principle of EPO dosing · Prediction model · EPO resistance

In this issue, Bamgbola et al. [1] report on risk factors for erythropoietin (EPO) resistance in pediatric and adult patients on dialysis treatment. They found that EPO sensitivity was negatively influenced by nutritional deficits, inflammation, low dialysis rate and hyperparathyroidism in children and adolescents, whereas iron and folate deficiency were the major determinants in adults. The most interesting observation is the fact that, at the time of analysis, children and adolescents received a higher absolute EPO dose than adults to maintain the same target level of hemoglobin (Hb), despite the fact that mean body weight was significantly lower in children than in the adults. This finding deserves a comment, because it is a widespread strategy to use the adult standard dose of EPO as the standard for children.

R. E. Port
Genentech Inc.,
South San Francisco, CA, USA

O. Mehls (✉)
Division of Pediatric Nephrology,
University Hospital for Children and Adolescents,
Heidelberg, Germany
e-mail: otto.mehls@med.uni-heidelberg.de

Common practice of EPO dosing in children

As in the study by Bamgbola et al. [1], the starting dose of EPO is usually around 150 IU/kg per week. This dose is based on the investigation by Eschbach et al. [2], who found in 333 adult patients in a phase III clinical trial that 85% of the patients required a maintenance dose of less than 150 IU/kg per week to obtain the hemoglobin target levels of 10 g/l. However, in children, this strategy leads to a slow and insufficient increase of hemoglobin concentration. As a consequence, a significantly higher prevalence of anemia in 1,692 erythropoietin-treated pediatric patients with chronic kidney disease (CKD), compared with adults, was reported in a recent study in the USA [3]. It is of special note that the highest percentage of anemia, amounting to nearly 70%, was observed in the very young children below age 5 years.

The insufficient response to 150 IU EPO/kg body weight per week had already been noted in 1994 by Van Damme-Lombaerts et al. [4, 5] and by Gagnadoux et al. [6], who recommended doses up to 300 IU/kg per week for children with a body weight below 30 kg. Infants weighing less than 10 kg needed blood transfusion, despite EPO treatment [7]. The condition of those without the desired response to EPO is often interpreted as being EPO resistant [8, 9]. This raises

the important question as to whether the condition in children is really resistant to EPO or whether EPO for children is simply under-dosed because dosing was based on wrong assumptions.

EPO dosing based on body size: a correct principle?

For most drugs no special pharmacokinetics or pharmacodynamics studies have been performed in children in the past. As a consequence, many drugs are not approved for infants, while empirical dosing according to body size has become accepted without adequate studies. The rationale for dosing according to body size is based on the assumption that the distribution space in children is proportionally smaller. With this strategy, many drugs, such as antibiotics, could be successfully tailored for children of different sizes.

This strategy does not seem to be successful for EPO. There are no investigations demonstrating that a body size-adapted dose is as equally effective as the index dose for adults. On the contrary, the EPO doses successfully used for children could not be correlated with age or body size, as shown in the study by Bamgbola et al. [1]. Port et al. [10] had already demonstrated earlier that the median hemoglobin response to a standard intravenous (i.v.) dose of EPO is independent of body weight. They analyzed the dose response in 52 stable dialyzed children aged 5 years to 20 years, weighing between 16 kg and 52 kg, who received EPO long-term three times per week intravenously. Notably, body weight also had no influence on hemoglobin response to EPO in 54 adult patients with CKD in whom body weight varied between 45 kg and 86 kg [11].

Hemoglobin response to a standard dose of EPO is similar in children and adults

In the study by Bamgbola et al. [1] the children were started on an EPO dose of 150 IU/kg per week. This dose was increased stepwise every 2 weeks until the target hemoglobin level was reached. Surprisingly, the absolute EPO dose for maintaining the hemoglobin target level between 9 g/l and 12 g/l was higher in children than in adults. The authors feel that the comparison of the maintenance dose for children and adults might be biased by the stepwise increase of the EPO dose in children. As a consequence of this strategy, the very high EPO dose at time of last investigation might not be the true maintenance dose but a peak dose in the course of which the target level was finally obtained. However, the authors also distinctly indicate that dosing per kilogram body weight in children with CKD is not correct and should be replaced by dosing according to hemoglobin deficit.

It has been shown in children [10] and adults [11, 12] with CKD that the same absolute dose of 1,000 IU EPO intravenously is able to increase the hemoglobin level by 0.04 g/dl. The initial EPO dose can be calculated individually, based on the hemoglobin level before treatment, the desired hemoglobin level at steady state, and the estimated survival time of the EPO-induced red blood cells. Based on the prediction model of Port et al. [10], the following formula can be used to calculate the dose (d) which is expected to increase hemoglobin from a pre-treatment level (Hb_0) to a desired steady state level (Hb_{SS}) when given intravenously three times per week:

$$d \approx 2400IU\sqrt{\frac{9.6}{Hb_{ss} - Hb_0} - 1}$$

This formula is based on an estimated time to steady state of 11 weeks (the presumed survival time of the erythropoietin-induced red blood cells), so that steady state and targeted hemoglobin level are expected after 33 doses. A similar formula should be applicable for adults.

Why do children need relatively more EPO than adults?

Whereas it is clear that EPO doses for children should be specified as absolute amounts rather than amounts per kilogram body weight, the question remains to be answered as to why EPO has actions in children and adults that are not related to body weight.

This question cannot be answered completely at this moment. Rarely, but certainly, there are other drugs, mostly hormones, which are not optimally used when dosed per kilogram body weight. One of these hormones seems to be vitamin D3. Surprisingly, no systematic investigation exists for dose response. Nevertheless, in experimental studies and also in clinical studies, vitamin D was applied on the basis of body weight to be "scientific". The scientific value of those studies must be questioned. Clinically, the same dose of vitamin D3 that is used in infants for the treatment of vitamin D deficiency (approximately 1,000–5,000 IU/day) is also used in older children and even in adults [13, 14]. Likewise, the i.v. doses of calcitriol (1.5–4 μg/week) for treatment of secondary hyperparathyroidism do not differ widely in children [15] and adults [16]. Consequently, the recommended oral 'starting dose' of 20–40 ng/kg per day [17] must be questioned.

L-thyroxin is another example. The treatment recommendations for the severe hypothyroid state in newborn babies (approximately 50–25 μg), children (75–200 μg) and adults (approximately 100–200 μg) are obviously not based on differences in kilogram body weight!

Anemic newborn babies and infants born before term need "excessive" doses of approximately 1,500 IU EPO/kg

per week to obtain a small clinical benefit [18, 19]. Only if administered intravenously, and not subcutaneously, is a sizeable amount of EPO lost into the urine [20]. It has not been clarified whether or to what extent insensitivity to EPO indeed exists in this age group and to what extent EPO is needed for non-hematopoietic actions such as brain development [21] and angiogenesis [22]. Thus, non-hematopoietic binding and elimination sites might contribute to the relatively increased EPO demand in the young organism.

One other important factor for an increased EPO demand is body growth. The organism has not only to compensate for a low hemoglobin level at a given circulating blood volume but also for a steady increase of this volume. The dimension of this problem might be illustrated by the observation of Vihervuori et al. [23], who looked for changes in hemoglobin levels during growth hormone treatment of short children. Whereas the hemoglobin level hardly changed in growth hormone responders, e.g. idiopathic short stature, it was significantly raised by approximately 2 g/dl within 6 weeks in non-responders, e.g. short children with skeletal dysplasia. This observation gives evidence that growth hormone interacts with EPO production and that EPO and hemoglobin production are increased during skeletal growth.

Conclusion

Anemic children are not principally resistant to EPO but need almost the absolute doses of EPO within the adult range. EPO should be dosed according to Hb deficit and not according to body weight. Further studies are certainly needed to shed more light on this problem.

References

1. Bamgbola OF, Kaskel FJ, Coco M (2008) Analyses of age, gender and other risk factors of erythropoietin resistance in pediatric and adult dialysis cohorts. Pediatr Nephrol doi:10.1007/s00467-008-0954-3
2. Eschbach JW, Adamson JW (1989) Guidelines for recombinant human erythropoietin therapy. Am J kidney Dis 14(2 Suppl 1):2–8
3. Chavers BM, Roberts TL, Herzog CA, Collins AJ, St Peter WL (2004) Prevalence of anemia in erythropoietin-treated pediatric as compared to adult chronic dialysis patients. Kidney Int 65:266–273
4. Van Damme-Lombaerts R, Broyer M, Businger J, Baldauf C, Stocker H (1994) A study of recombinant human erythropoietin in the treatment of anaemia of chronic renal failure in children on haemodialysis. Pediatr Nephrol 8:338–342
5. Van Damme-Lombaerts R, Herman J (1999) Erythropoietin treatment in children with renal failure. Pediatr Nephrol 13:148–152
6. Gagnadoux MF, Loirat C, Berthélémé JP, Maisin A, Kamoun A, Dabout D, Poisson D, Broyer M (1994) Treatment of anemia in hemodialyzed children using recombinant human erythropoietin (Eprex). Results of a French multicenter clinical trial. Nephrologie 15:207–211
7. Al-Hermi BE, Al-Saran K, Secker D, Geary DF (1999) Hemodialysis for end-stage renal disease in children weighing less than 10 kg. Pediatr Nephrol 13:401–403
8. Seeherunvong W, Rubio L, Abitbol CL, Montané B, Strauss J, Diaz R, Zilleruelo G (2001) Identification of poor responders to erythropoietin among children undergoing hemodialysis. J Pediatr 138:710–714
9. Besarab A (2006) Resolving the paradigm crisis in intravenous iron and erythropoietin management. Kidney Int Suppl 69:S13–S18
10. Port RE, Kiepe D, Van Guilder M, Jelliffe RW, Mehls O (2004) Recombinant human erythropoietin for the treatment of renal anaemia in children: no justification for bodyweight-adjusted dosage. Clin Pharmacokinet 43:57–70
11. Uehlinger DE, Gotch FA, Sheiner LB (1992) A pharmacodynamic model of erythropoietin therapy for uremic anemia. Clin Pharmacol Ther 51:76–89
12. Brockmöller J, Köchling J, Weber W, Looby M, Roots I, Neumayer HH (1992) The pharmacokinetics and pharmacodynamics of recombinant human erythropoietin in haemodialysis patients. Br J Clin Pharmacol 34:499–508
13. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281
14. Hathcock JN, Shao A, Vieth R, Heaney R (2007) Risk assessment for vitamin D. Am J Clin Nutr 85:6–18
15. Greenbaum LA, Benador N, Goldstein SL, Paredes A, Melnick JZ, Mattingly S, Amdahl M, Williams LA, Salusky IB (2007) Intravenous paricalcitol for treatment of secondary hyperparathyroidism in children on hemodialysis. Am J Kidney Dis 49:814–823
16. Rodriguez M, Caravaca F, Fernandez E, Borrego MJ, Lorenzo V, Cubero J, Martin-Malo A, Betriu A, Jimenez A, Torres A, Felsenfeld AJ (1999) Parathyroid function as a determinant of the response to calcitriol treatment in the hemodialysis patient. Kidney Int 56:306–317
17. Klaus G, Watson A, Edefonti A, Fischbach M, Rönnholm K, Schaefer F, Simkova E, Stefanidis CJ, Strazdins V, Vande Walle J, Schröder C, Zurowska A, Ekim M, European Pediatric Dialysis Working Group (EPDWG) (2006) Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol 21:151–159
18. Warwood TL, Ohls RK, Wiedmeier SE, Lambert DK, Jones C, Scoffield SH, Neeraj G, Veng-Pedersen P, Christensen RD (2005) Single-dose darbepoetin administration to anemic preterm neonates. J Perinatol 25:725–730
19. Maier RF, Obladen M, Müller-Hansen I, Kattner E, Merz U, Arlettaz R, Groneck P, Hammer H, Kössel H, Verellen G, Stock GJ, Lacaze-Masmonteil T, Claris O, Wagner M, Matis J, Gilberg F, European Multicenter Erythropoietin Beta Study Group (2002) Early treatment with erythropoietin beta ameliorates anemia and reduces transfusion requirements in infants with birth weights below 1000 g. J Pediatr 141:8–15
20. Bührer C, Obladen M, Maier R, Müller C (2003) Urinary losses of recombinant erythropoietin in preterm infants. J Pediatr 142:452–453
21. Noguchi CT, Asavaritikrai P, Teng R, Jia Y (2007) Role of erythropoietin in the brain. Crit Rev Oncol Hematol 64:159–171
22. Fliser D, Bahlmann FH, Haller H (2006) EPO: renoprotection beyond anemia correction. Pediatr Nephrol 21:1785–1789
23. Vihervuori E, Virtanen M, Koistinen H, Koistinen R, Seppälä M, Siimes MA (1996) Hemoglobin level is linked to growth hormone-dependent proteins in short children. Blood 87:2075–2081