Chapter 2

Mortality Reduction by Vitamin D Receptor Activation in End Stage Renal Disease: A commentary on the robustness of current data.

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Nephrol Dial Transplant 2009; 24: 703-706

For decades the role of VDRA in ameliorating hyperparathyroidism and hypocalcemia in severe kidney failure and end stage renal disease has been acknowledged. Because of reduced renal 1α-hydroxylase activity an activated VDRA analogue is prescribed (calcitriol, doxercalciferol, paricalcitol or alfacalcidol). Recently, an analysis of a large cohort of hemodialysis patients from the US demonstrated that the use of a vitamin D receptor activator (VDRA) was associated with a reduced mortality when compared with non-users of any VDRA[1]. Most intriguing was the fact that, using complex statistical methodology in an attempt to dissect the causes of this improved mortality, the favourable outcome of patients on VDRA, could only partly be attributed to improvements in biochemical markers of mineral and bone disease. This has set the field on fire and has led to an increased scientific interest in assumed biological and physiological mechanisms of VDRA, beyond its well-defined effects on bone and mineral metabolism. On top of that, in several other cohorts, comparable results were achieved, using comparable methods[2-5]. Very recent meta-analyses on the question of mortality effects of VDRA either questioned[11] or confirmed[12] its favourable effect. This leaves the practicing nephrologist with the question: Is the currently available level of evidence enough to change clinical practice, i.e. should a VDRA be prescribed to ESRD patients, regardless of their level of PTH, calcium or phosphate level? Doubt arises from the well-recognised limitation of these studies: They compared groups that were not randomised, and therefore leaves the potential for unrecognised differences between groups that accounted for observed differences in outcome.

A definite answer to this question should ideally come from prospective randomized controlled trials (RCT). These trials with regard on mortality effects of VDRA in ESRD patients are lacking, and therefore currents knowledge and opinion are based on observational data. Although there is an ever-increasing amount of data demonstrating potential mechanisms that might contribute to the observed improved patient outcome[6], the vast majority of these data come from animal studies or in vitro experiments. For these reasons, the potential benefit of VDRA is debated, the indications for its use have become more vague, and the probability of VDRA use in the presence of a relative contra-indication like hypercalcemia, has increased. However, a meticulous appreciation of available data from observational studies, instead of a complete dismissal of it, might prevent loss of important clues to clinical nephrology or delay its application for years. Therefore, in the current commentary we

attempt to critically consider the large observational studies, that examined the role of VDRA on mortality in patients with ESRD on dialysis form a epidemiological view.

Historical cohort study versus retrospective cohort study

One of the major points in the discussion regarding the possible positive effects VDRA, is the fact that the most important data comes from a historical cohort study[1,7]. The problem is that a historical cohort study is often confused with a retrospective cohort study. In a retrospective cohort study, the information is gathered retrospectively, which means that the obtained information is fairly unreliable. In a historical cohort on the other hand, the information is not gathered retrospectively, but prospectively. In other words, in a historical cohort study information is used that is gathered some time ago. Because of this, the information used in a historical cohort study is much more reliable than the information of a retrospective cohort study. One of the problems of a historical cohort study on the other hand is that the information to be used is the information that is available at the time of measurement and sometimes that information is not complete. Therefore, it is possible that there are unknown differences between groups that are responsible for the observed effects. With a retrospective cohort study the problem of non-complete information is less prominent, because the researchers are able to get all the relevant information, however, as mentioned before, in a fairly unreliable way. All the currently large observational studies on VDRA in ESRD[1-5], that are the focus of this commentary, are historical cohort analyses. So the positive effects of VDRA use on both cardiovascular and all-cause mortality reported in the historical cohort study by any of these can be partly caused by unobserved difference between groups. One of the possibilities to deal with the potential problem is the use of sensitivity analyses.

Sensitivity analyses

With sensitivity analyses, the data are reanalysed to explore the robustness of the results. This can be done by changing data, relaxing assumptions or by analysis of subgroups. When all analyses lead to more or less the same result, the results of the primary analysis are robust and therefore reliable. In the study by Teng et al.[1] for instance, sensitivity analyses were performed on subgroups with a different initial survival time. Because all results were

more or less comparable, the positive effects of VDRA that has been found in this particular study seems to be quite robust.

The use of complicated statistical analyses

One of the problems that arise when many sensitivity analysis are done is that the majority of researcher or clinician does not understand it anymore. When the statistics becomes complicated and difficult to understand, the results of the particular study are not trusted anymore; especially when the results of the study are somewhat controversial. This is one of the main methodological issues in the VDRA discussion; the statistics used in the studies that show a positive effect of VDRA is complicated. In most observational studies, due to the longitudinal nature of the studies, the effect of time-varying covariates is investigated[1-5,7] different weights in marginal structural models are used[1], generalised estimating equations are used[2]. All these techniques are quite relevant, but because they are complicated and sometimes not interpreted in the proper way[2] it leads to suspicion.

The use of propensity scores

One of these complicated issues is for instance the use of propensity scores. In a propensity score the information of several potential confounders is combined into one score. Propensity scores are therefore mostly used in small observational studies (or in large studies with not many events) to decrease the number of potential confounders. In the study of Teng et al.[1], propensity scores were used, even though the study population was huge and the number of events was rather high. In other words, although it was not wrong, it was not necessary to use propensity scores in this study. Again, because many researchers and clinicians do not really understand what a propensity score is, the use of it leads to suspicion regarding the results of the study.

Confounding and mediation

In many of the observational studies that show a positive effect of VDRA use, time-varying covariates are used[1,2,4,5]. The use of time-varying covariates is important to investigate possible mediating effects of these covariates. In light of this, a strong distinction must be made between confounding and mediation. Both a confounder and a mediator are related to the central determinant (i.e. VDRA use) and they are also related to the outcome of the

study (in this respect mostly death). The difference between the two is whether or not the particular variable is in the causal pathway. Age, for instance is a typical confounder, because is it mostly related to VDRA use, it is certainly related to mortality, and it is not in the causal pathway. A way to deal with confounders is to adjust for them and in none of the large observed cohorts[1-5], this changed conclusions from unadjusted results.

PTH on the other hand is a typical mediator; PTH is related to VDRA use, it is related to mortality and it is probably in the causal pathway[8,9]. Also calcium and phosphate might be in the causal pathway and might in itself influence mortality[5,10]. It is possible that due to VDRA use, PTH levels decrease and therefore the probability of dying is lower. The problem with confounding and mediation is that within regression analysis it is investigated in exactly the same way. First a 'crude' effect is estimated (an analysis with only the use of VDRA as determinant) and secondly an 'adjusted' effect is estimated (an analysis where the potential confounder or mediator is added to the regression model). In both adjusted analysis, the effect of VDRA (for instance the HR when Cox regression analysis is performed) has to be compared with the effect of VDRA from the 'crude' analysis. It is crucial that both differences in effect between the 'crude' and adjusted analysis have to be interpreted differently. When the age adjusted effect of VDRA is much lower than the 'crude' effect of VDRA, it means that part of the effect of VDRA is caused by age (VDRA being more prescribed to younger patients). The 'real' effect of VDRA is therefore the age-adjusted effect. When the PTH adjusted effect of VDRA is (much) lower than the 'crude' effect of VDRA, it means that part of the effect of VDRA goes through PTH. In this situation, the 'real' effect of VDRA is the 'crude' effect and there is some additional information about the part of the effect that goes through the mediator. The difference between confounding and mediation is often difficult, which complicates the interpretation of adjusted/multiple regression analysis. To investigate possible mediation, the use of time varying covariates is very useful, because when a variable is in the causal pathway, there has to be some time-lag between the determinant and the mediator. Surprisingly however, in the study of Teng et al.[1] there was no mediating effect of either PTH, phosphorus or calcium. So there must be another mechanism that is responsible for the positive effects of VDRA use. In many studies[2,4,5] possible confounding variables and mediation variables are analysed together, which makes it even more difficult to obtain the 'real' effect of VDRA use.

Effect modification

Both mediation and confounding should be further distinguished from effect modification. Effect modification means that the effect of VDRA is different for, for instance males versus females, older versus younger patients, etc. Effect modification can be investigated by adding interaction terms (i.e. multiplication between the central determinant and the potential effect modifier) to the multiple regression models. When there is significant effect modification, the results should be presented subgroup specific. Another way to examine possible effect modification is to perform stratified analysis. This was performed by Teng et al.[1], but again, when comparing only *matched* age groups, *same* gender, *same* race, or any other potential confounder of which information was available, the favourable effects of VDRA displayed a remarkable consistency, so no convincing effect modification of any of the examined covariates could be established.

Association versus prediction models

Another issue in multiple regression analysis is the difference between association models and prediction models. With an association model, the researcher is interested in the effect of one central determinant (such as VDRA use) and the effect of the central determinant is estimated in the best possible way (i.e. by investigating confounding, effect modification and mediation). With a prediction model, however, the researcher is interested in the best (and most simple) combination of variables that can predict the outcome. In that situation, the researcher is not specifically interested in one central determinant such as VDRA, but in all possible predictor variables. The problem is that the statistical modelling process is totally different for building an association model than for building a prediction model. In the latter, for instance, backward and/or forward selection procedures can play a role. It should be obvious that in studies where the effect of VDRA is investigated, an association modelling procedure should be used. Unfortunately, this is not always the case. For instance, in the study of Shoji et al.[3] a prediction modelling procedure is used in a situation where the authors should have used an association modelling procedure, and although VDRA use was still present in the final prediction model, the results should be interpreted with caution.

Conclusion

In conclusion, the results of the observational studies that show a positive effect of VDRA in dialysis patients seems to be quite robust and therefore reliable. The biggest problem is the possibility of unknown differences between compared groups, which is due to the historical cohort design used. In the absence of prospective randomised trials, two other important pieces of information are important for the clinician to decide whether or not changing every day practice. The first is the presence of a plausible mechanism that might explain the observed benefit of VDRA use in patients on dialysis and the second is to address the potential of doing harm by VDRA.

Several studies found effects of VDRA beyond its "traditional" role in bone and mineral metabolism. The renin biosynthesis can be inhibited[13,14], possibly explaining part of observed effects of vitamin D metabolites on arterial function[15]. VDRA has a positive impact on left ventricular abnormalities in rats[16] and myocardial hypertrophy in hemodialysis patients[17]. In young hemodialysis patients it was shown that calcitriol attenuates insulin resistance, improved insulin secretion on an oral glucose load and improved hypertriglyceridemia[18]. These and other potential mechanism, as recently been reviewed[19] all suggest mechanisms for improved cardiovascular outcome in patients on dialysis. Besides its potential beneficial effects on cardiovascular events, VDRA has a potential positive impact on immune function[20,21], and it is suggested that supplementation of vitamin D is associated with reduced incidence of colorectal cancer[22]. These and even several other mechanisms[6] all could explain part of the beneficial effects of VDRA, beyond its traditional effects on bone and mineral metabolism.

When considering potential toxicity when prescribing VDRA, it is important to realize that the safe upper dose level of calcidiol has not been established[23]. In renal failure usually active vitamin D is used, instead of calcidiol, so one must be cautious interpreting data about safe doses. However, for any metabolite or analogue of vitamin D, hypercalcemia is the hallmark of toxicity. There is some concern that calcitriol, *via* induction of hypercalcemia might contribute to vascular or cardiac calcifications[24]. There are no data that currently used doses of VDRA in itself contributes to the process of vascular calcification, but the hypercalcemia or positive calcium balance induced by vitamin D supplementation probably does[25].

Although all data considering mortality effects of VDRA in hemodialysis patients come from historical cohort analyses, it is inconsiderate to dismiss these results entirely. As discussed, within each of these observational studies[1-5], methods used are robust, sensitivity analysis, including subgroup analysis all point to the same conclusion. The results between studies, in different populations, are consistent. There are numerous studies that provide rational explanations for observed improved outcome for dialysis patients treated with VDRA. It is prudent to prevent hypercalcemia, but there are no known levels above which VDRA has to be interrupted. It is probably also prudent to avoid excessive intake of calcium, because the serum calcium concentration does not necessarily reflect calcium balance. For these reasons, one might argue that it is reasonable to prescribe a VDR activator to all dialysis patients, while restriction calcium intake, unless a hypercalcemia develops. However, the ultimate answer to the discussion whether or not VDRA has beneficial effects in hemodialysis patients has to be obtained from a randomised controlled trial.

Disclosure:

MV has participated in advisory boards and has received research-funding from Abbott. JT reports no conflicts of interest

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