Port J Nephrol Hypert 2015; 29(3): 187-191
Advance Access publication 07 August 2015

Paracelso's prediction and today's dilemma: how to treat atrial fibrillation in patients on haemodialysis?

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Received for publication: 10/07/2015
Accepted in revised form: 14/07/2015

Paracelso, a famous ancient Swiss physician, pointed out in the 16th century that: "only the dose makes a poison" ("dosis sola facit venenum"[1]), meaning that the right dose distinguishes a poison from a medicine. However, would he ever guess that one of the most commonly used rat poisons, the dicumarinic compounds, would save so many lives? Indeed, these drugs were instrumental to handle severe situations like deep vein thrombosis/pulmonary embolism and enabled us the implantation of highly thrombogenic mechanic prosthetic cardiac valves. The recognition that arterial embolism associated with atrial fibrillation (AF) is a major cause of thrombotic strokes (CVAs) and systemic arterial embolism (e.g., mesenteric), prompted cardiologists and neurologists to initiate a bold effort to prevent these disabling events. The vitamin K antagonists (VKA), which tackle numerous coagulation factors, were the first drugs that proved useful in this prevention. Despite the efficacy of VKA, they have a narrow therapeutic window, easily changing from life-saving drug to dangerous poison, reviving Paracelso's citation in our memory...

The use of VKA requires frequent monitoring by international normalized ratio (INR) measurements and are subject to numerous food-drug and drug--drug interactions (with drugs as commonly used as omeprazole, which may trigger dramatic increases in INR in patients medicated with VKAs). Therefore, new alternatives, the so called "new oral anticoagulants" (NOACs) targeting specific factors (thus, also denominated Target-Specific Oral Anticoagulants or TSOACs), namely thrombin (dabigatran) or factor Xa (Xa-bans, like rivaroxaban, apixaban and endoxaban), were a breakthrough in the therapeutic armamentarium; several new points in the coagulation cascade are also being investigated as potential targets, like factors V, VII, VIII, IX, XI and XII. The use of a "guided missile"-like attack towards specific targets, rather than a broader widespread attack to the coagulation cascade has theoretical advantages. First, cumbersome INR monitoring is not necessary, due to a more predictable and less variable pharmacokinetic profile, as well as the fact that NOACs display fewer clinically relevant drug interactions. On the other hand, the lack of specific, broadly available tests to evaluate the effect of these drugs, limits both our ability to be sure if the right dose is being delivered, as well as to monitor adherence to therapy. Lack of specific antidotes is another bothersome problem, although dialytic removal of the NOAC (limited to dabigatran) or the use of activated and non-activated Protrombin Complex Concentrates (aPCC and PCC), FEIBA (Factor eight inhibitor bypassing agent) as well as antifibrinolytic agents (tranexamic acid or ε-aminocaproic acid) have been used with success in life-threatening cases of bleeding associated with these drugs[2]. In addition, several specific antidotes to NOACs are under study[2].

One potential advantage of the NOACs over VKAs is that the latter interfere with the carboxylation of other important proteins, like, matrix-Gla protein, critical to prevent vascular and valvular calcifications (vitamin K). This is not only a theoretical problem, as half of the patients with calciphylaxis are treated with VKA and this ominous condition is present in less than 5% of dialysis patients[3]. Furthermore, supplementation of vitamin K attenuates the development of vascular calcification in a murine model[4]. Prevention of vascular and valvular calcifications has been one of the areas where nephrologists have invested more effort to reduce the unacceptable cardiovascular morbidity and mortality observed in patients with all stages of chronic kidney disease (CKD)[5,6]. However, whether the treatment with NOACs will be associated with less vascular or valvular calcification than the one observed in patients under VKAs is still unproven both in patients with CKD and with normal kidney function. Needless to say that if less coronary, peripheral vascular and valvular calcification develops less under treatment with these new drugs even in patients with normal or minimally reduced renal function, it will mean a significant advantage over the VKAs. One limitation to prospectively follow this issue, irrespective of kidney function (e.g., the rate of progression of aortic stenosis) is the fact that NOACs are not currently recommended to be used in AF in the context of valvular disease. The finding that dabigatran was inferior to warfarin in the treatment of valvular AF in the RE-ALIGN trial reduced the enthusiasm in studying patients with valvular pathology[7]. It also is worth noting that there has been an inherent ambiguity in the unfortunate terminology of "valvular" and "non-valvular" atrial fibrillation – as noted above, NOAC's are not recommended for the treatment of AF in the context of valvular disease. However, the term "valvular AF" really is derived from Framingham data published three decades ago – and it was used contextually in patients with rheumatic mitral stenosis. Although there have been recent attempts to resolve this linguistic issue, clinicians likely still puzzle over what exactly is meant by "non-valvular" AF.

Large trials demonstrated non-inferiority[8,9] or superiority[10] of NOACs relative to VKA in CVA prevention in patients with AF, with reduction of severe bleeding, particularly, haemorrhagic CVAs (RE-LY[8], ROCKET-AF[9], ARISTOTLE[10]). Conversely, some authors point to possible increase in gastrointestinal bleeding events with the use of NOACs in comparison to the use of warfarin[11], particularly in patients more than 75 years old[12].

Subgroup analysis of these large trials in patients with reduction of the glomerular filtration rate (GFR) – CKD in stages II and III – showed very interesting results[13,14]. It is important to mention that patients with stage III CKD have AF more frequently than age-matched patients with normal renal function and have a much increased risk for stroke[15]. In this group of patients, both VKAs and NOACs are well established as valid therapies to reduce the risk of strokes[15].

General practitioners, internists, cardiologists take care of the majority of patients with less advanced kidney disease (Stages II, III and, sometimes, stage IV CKD). Sometimes orthopaedists and other specialists may also prescribe NOACs or other anticoagulants to these patients, not always being aware of a reduced renal function. Nephrologists may be involved in the care of these patients as consultants and should be aware of the pharmacokinetic and pharmacodynamic characteristics of these drugs at different degrees of renal dysfunction, keeping also in mind predictable drug interactions and proactively instructing patients on the potential risks of these drugs. Nephrologists may also be an invaluable help to other clinicians in the adjustment of doses, keeping always in mind 3 important points:

1) Estimated creatinine clearances (Cockroft and Gault, MDRD and CKD-EPI) may be misleading, as the formulas assume a serum creatinine in steady state; if the creatinine is raising, as in acute kidney injury, they may drastically overestimate the true GFR. This is a frequent problem when pharmacokinetic programmes to adjust drug prescriptions (usually with the MDRD formula incorporated to the calculation) assume a steady state serum creatinine and it is actually rising.

2) Most major trials and subgroup analyses were based on Cockroft-Gault estimates, not the most accurate and expressed in ml/min rather than mls/min/1.73 m2 (the latter expressed both in the MDRD and CKD-EPI formulas).

3) If GFR drops suddenly (ex.: gastrointestinal haemorrhage, dehydration, concomitant use of

NSAIDs/Coxibes, the use of intravenous radiological contrast), bioaccumulation and toxicity is very likely to occur, particularly with dabigatran, due to its predominant route of excretion by renal clearance. In this situation, the NOAC may change "from friend to foe" and the lack of specific antidotes, reminds us again of Paracelso's thought!

Moving to the treatment of AF in more advanced renal disease, our knowledge is almost exclusively based in retrospective data. Therefore, despite the fact that patients with advanced renal disease have significantly more frequent AF and CVAs than the age-matched population with normal renal function[16], there is not a single randomized clinical trial (RCT) to guide us on whether or not should these patients be treated either with VKAs or with any NOACs. Prevalence of AF is also age-dependent in the dialysis population reaching 17% in the 51-60 years group and as high as 37% in patients aged 71-80 in one study[16]. It is important to appreciate that Stage 5 CKD patients display a paradox of simultaneously suffering more haemorrhagic[17] and thrombotic events[18]. Some retrospective studies report that patients on haemodialysis have more haemorrhagic events when under VKA[19], while another study shows an increase of both haemorrhagic and thrombotic events in patients under VKA[20]; however, one prospective, non-randomized, Italian study points that VKAs are safe and efficacious in dialysis patients[21]. To note that is this study, only a minority of patients under VKA, aspirin or neither had CVAs; death was very frequent in patients on HD with AF, but mostly from cachexia, sudden death, sepsis or neoplasia[21]. The information on the use of VKAs or NOACs is even more limited in the peritoneal dialysis population and no specific study addresses this group of patients.

Not surprisingly, the DOPPS study group unveils a very heterogeneous pattern of VKA prescription in patients with Stage 5 CKD presenting with AF in different countries and regions[22]. Many studies point to the importance of the percentage of time within the therapeutic target range (TTR) both for the efficacy in CVA prevention as well as for the haemorrhagic risk[15,19-22]; patients on haemodialysis seen to be particularly challenging to be kept within the TTR and have an added haemorrhagic risk as they receive heparin during the dialysis sessions. Many of these patients are also treated with antiplatelet medications (aspirin, clopidogrel) due to concomitant coronary or peripheral artery disease, raising the haemorrhagic risk if anticoagulated. The limited use of VKAs in the dialysis population occurs despite many of the patients with stage 5 CKD who present with AF qualify for the indication to receive anticoagulation if the CHA2DS2VASc score is applied[23]. Anyway, the decision to anticoagulate patients with stage V CKD on haemodialysis is controversial and several factors need to be taken in consideration, including the possibility of INR monitoring at the dialysis facility, previous haemorrhagic events and whether we deal with primary or secondary prevention (i.e., if the patient presented with a previous CVA or transient ischaemic attack).

Of course, the above discussion is related to the "prophylactic use" of VKAs in the setting of AF and does not apply to situations when there is no alternative to oral anticoagulation, like after the placement of a prosthetic mechanic valve or in a hypercoagulable state associated with pulmonary embolism or other thrombotic problems. However, the avoidance of chronic anticoagulation with VKAs is an additional reason for the preferential placement of biologic cardiac valves in stage V CKD patients, which is stressed by several authors[24,25].

If VKAs are controversial in stage V CKD, what about NOACs? Again, it is important to keep in mind that stages IV and V CKD were always exclusion criteria for patient recruitment in the major NOAC trials[8-10] and no RCT data is available on this issue to guide nephrologists, cardiologists or neurologists... Despite the contraindication, which is highlighted in the drug information of all the NOACs against the use of these drugs on patients undergoing haemodialysis, the search of prescription data bases of a large dialysis supplier in the USA, revealed that NOACs are being used in haemodialysis patients; and, sometimes, with unadjusted doses...[26]. Not surprisingly, the incidence of problems was larger than that observed in patients on warfarin[26] in this crude retrospective analysis. The US FDA (Food and Drug Administration) actually approved the use of apixaban in US dialysis patients in January 2014 – not based on clinical data, but on limited pharmacokinetic data[27]. It is important to emphasize that different drugs have very distinct patterns of renal excretion, being particularly high with dabigatran (85%)[28], while the Xa-bans have between 25 and 33% of renal

excretion. One Xa-ban in study, betrixaban, is particularly interesting as only 5% is excreted by the kidneys[29]. However, the Xa-bans are tightly protein-bound and, as such, not dialyzable, unlike the thrombin antagonist[15,29].

One additional area of great interest, is the use of NOACs in recipients of organ allografts, namely, kidney transplants with different thromboembolic conditions, including AF, deep vein thrombosis and orthopaedic post-operative periods (remember, they are more prone to fractures...). The same alerts on dose adjustment according to GFR applies as in patients with stages III and IV CKD, as many renal transplant recipients have reduced kidney function but, in addition, the risk of bidirectional interaction between immunosuppression (IS), particularly calcineurin inhibitors (tacrolimus, cyclosporine) and mTOR inhibitors (sirolimus and everolimus) is significant and studies are very scant. Conversely, steroids, like prednisone, may increase NOAC metabolism according to some drug interaction softwares, like Micromedex. Although the IS drug levels can and should be very closely monitored in this setting, as CYP 3A4 metabolism is shared by both groups of drugs, the monitoring of NOAC drug levels is still not generally available. Some limited studies or case reports point to some of these risks and potential interactions[30,31]. Even the evaluation of biological effect of these drugs in the coagulation cascade is not widespread, although easier tests are being developed. Finally, as previously mentioned, antidotes are still undergoing trials[2]. The potential risk of at least moderate degree of interaction is highlighted in the individual drug information and can easily be displayed using interaction softwares like Micromedex or Uptodate/Lexicomp®.

One point of paramount importance is that the NOACs are much more expensive than VKAs, what may limit their compliance, particularly in elderly and disadvantaged patients, conditions often observed within the dialysis population.

As a conclusion, NOACs were a major advance in therapeutics and nephrologists wait eagerly RCTs involving haemodialysis, peritoneal dialysis and in kidney transplantation, as the currently available information on the use of these drugs in these populations of patients is very limited. In addition, VKAs also need to be studied in patients on haemodialysis and peritoneal dialyss as information is contradictory on the risks and benefits.

Conflict of interest statement: None declared

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