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Full Review

Drug adherence in chronic kidney diseases and dialysis

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ABSTRACT

Poor long-term adherence and persistence to drug therapy is universally recognized as one of the major clinical issues in the management of chronic diseases, and patients with renal diseases are also concerned by this important phenomenon. Chronic kidney disease (CKD) patients belong to the group of subjects with one of the highest burdens of daily pill intake with up to >20 pills per day depending on the severity of their disease. The purpose of the present review is to discuss the difficulties encountered by nephrologists in diagnosing and managing poor adherence and persistence in CKD patients including in patients receiving maintenance dialysis. Our review will also attempt to provide some clues and new perspectives on how drug adherence could actually be addressed and possibly improved. Working on drug adherence may look like a long and tedious path, but physicians and healthcare providers should always be aware that drug adherence is in general much lower than what they may think and that there are many ways to improve and support drug adherence and persistence so that renal patients obtain the full benefits of their treatments.

Keywords: chronic kidney diseases, drugs, hyperparathyroidism, hypertension

INTRODUCTION

The main objectives of the management of patients with chronic kidney diseases (CKD) are as follows: (1) to slow the progression toward end-stage renal disease (ESRD) by controlling the underlying renal disease but also factors contributing to the deterioration of renal function such as hypertension, (2) to manage common complications of CKD such as hyperphosphataemia, acidosis or anaemia, which may also participate in the degradation of kidney function and (3) to identify and manage comorbidities (diabetes, coronary heart disease, heart failure, etc.) that lead to the increased risk of mortality and hospitalization of CKD patients [1]. Once on dialysis, the goals are changing slightly being mainly focused on treating complications (anemia and hyperparathyroidism) and preventing the high morbidity and mortality associated with maintenance dialysis [2].

These therapeutic goals can hardly be achieved without lifestyle measures and substantial drug treatments dedicated to each of these medical problems which add to one another along the course of the patient's disease starting most frequently with hypertension and followed later on by anaemia, acidosis and phosphocalcic disorders [3]. Thus, patients with CKD and those receiving dialysis belong to the group of chronic patients with the highest daily pill burden, comparable with patients with HIV or severe cardiac diseases [4, 5]. Thus, a recent survey of patients on maintenance dialysis in the USA reported a median number of 19 pills with one-quarter of them taking >25 medications daily [6]. In earlier stages of CKD, patients are treated with a mean of 6–12 medications [7]. As expected, such a high pill burden is inevitably associated with major problems of drug adherence, the number of drugs being an important determinant of long-term drug adherence in chronic diseases [6]. Thus, as in many other chronic diseases, a low adherence to drug treatments (down to 3%) as well as a low adherence to nutritional recommendations has been reported in CKD and dialysis patients [8].

The purpose of the present review is to discuss drug adherence issues in patients with CKD Stage 1–5 in view of the most recent literature. Although adherence is also a major concern in renal transplantation, this topic will not be addressed and readers are referred to some recent reviews on the topic [9, 10].

DEFINITION OF ADHERENCE

Drug adherence is commonly defined as the extent to which a patient's behaviour, with respect to taking medication, corresponds with agreed recommendations from healthcare providers. Adherence can be divided into two main components: persistence and execution. Persistence is defined as the time from initiation to discontinuation of therapy whereas the execution refers to the comparison between the prescribed drug dosing regimen and the patient's drug history while on treatment. The latter definition includes dose omissions (missed doses) and the so-called drug holidays (three or more days without drug intake). The minimal percentage of adherence necessary to obtain the full benefits of a drug is generally unknown and often set arbitrarily at 80%.

FREQUENCY OF POOR ADHERENCE IN CKD PATIENTS: THE DIFFICULTY TO OBTAIN RELIABLE DATA

Numerous studies have analysed the adherence rates to drug therapies in patients with CKD or on maintenance dialysis. The general conclusion of these studies is that poor drug adherence is frequent among CKD patients but there is always a wide range of figures depending on which aspect of drug therapy is investigated. Thus, in a large survey of quantitative studies exploring predictors of non-adherence to phosphate-binding medications in maintenance dialysis, Karamanidou *et al.* reported a range of non-adherence to phosphate binders from 21 to 74% in 34 studies addressing specifically this issue [11]. In two large studies evaluating hypertension management in CKD, ~30% of patients were considered as having a poor adherence leading to uncontrolled blood pressure (BP) [12,13].

There are several reasons for the wide variations in estimations of low adherence. First, the definition of drug adherence is often inconsistent. Second, the methods used to measure drug adherence are not very reliable and tend to overestimate drug adherence. This is the case for example for the Morisky questionnaire that was used in many studies including the REGARDS study [13]. Interestingly, when different methods are used in the same study, large variations in adherence are observed. Besides being a major cause of ignoring drug adherence in clinical practice, the lack of simple and reliable methods to measure drug adherence also remains a major limitation to any effective improvement in adherence-related medication problems. As discussed recently [14], the ideal method should provide a reliable capture, storage, analysis and communication of dosing history data in ways that make it difficult or impossible for patients or trial staff to censor or otherwise manipulate the data. Methods that meet these criteria today include the following: retrospective analysis of prescription refill records [1], analysis of chemical markers of drug exposure [2] and automatic electronic time-stamping and compilation of events more or less strongly linked to the act of taking medication (e.g. package opening, dosage form dissolution) [3]. Other methods, such as questionnaires, interviews and periodic counts of patients' returned, untaken doses, are subject to many uncertainties and easy manipulation by patients. Today, electronic monitoring of drug adherence is probably the most reliable method to assess the patients' behaviour toward drug therapy. Using this method, we learned that drug adherence is a dynamic process and that there is no clear and well-defined cutoff below which a patient can be considered non-adherent as this may change depending on the type of therapy. Finally, white-coat adherence (e.g. the phenomenon that medication adherence tends to improve around the time of a scheduled clinical visit but declines thereafter) is a crucial phenomenon that affects our evaluation of adherence [14]. Unfortunately, in CKD patients, the complexity of drug therapies often limits the use of electronic monitors because several treatments should be monitored simultaneously, which is due to financial and practical reasons often not feasible. Nevertheless, physicians and healthcare professionals should be aware that drug adherence is probably much lower than what has been measured in clinical studies. At last, as in other chronic diseases, the major issue of poor adherence is related to the absence of long-term persistence of therapy rather than occasional forgetfulness [14].

HYPERTENSION MANAGEMENT AND ADHERENCE IN CKD PATIENTS

Hypertension develops early in CKD patients and is an important determinant of the progression of CKD toward end-stage renal diesease (ESRD). An adequate control of BP results in a slower decline in renal function [15]. Therefore, a strict control of blood pressure (BP) is recommended in all CKD patients with a target BP of <130/80 mmHg and more recently <140/90 mmHg according to the last European Society of Hypertension (ESH) guidelines [16].

As reported recently in the KEEP study (Kidney Early Evaluation Program) involving 10 813 CKD patients, the BP control rate remains low in CKD patients with 13.2% of patients having <130/80 mmHg [17]. In a study of 7227 CKD patients followed at a Veterans Administration Medical Centre, BP targets were achieved only in 35% of patients [12], and in the reasons for geographic and racial differences in stroke (REGARDS) study, 36.2% of patients had a BP of >140/90 mmHg but 61.6% had a BP of >130/80 mmHg [13]. Drug adherence was assessed using the medication possession ratio in the VA study [12] and using the Morisky questionnaire in the REGARDS study [13]. Not surprisingly, >30% of patients were poorly adherent, a percentage that might well be even greater in reality. Of note, a Brazilian study, which measured drug adherence longitudinally in CKD patients, has shown that drug adherence (measured by self-report) tends to improve as renal function deteriorates, suggesting that with the progression of the kidney disease both physicians and patients become more concerned by the quality of BP control [18].

In patients on maintenance dialysis, the BP control rate does not appear to be better although patients adequately dialysed tend to normalize their BP, suggesting an important role of the duration and quality of dialysis [19]. The evaluation of BP control in maintenance dialysis is further complicated by

measurement issues and by the absence of a clear definition of BP targets that should be obtained in these patients [20]. However, the results of meta-analyses suggest that antihypertensive therapy leads to significant benefits in dialysed patients [21]. Nonetheless, poor adherence to antihypertensive therapy is also common in dialysis. In an Italian survey involving 1238 haemodialysis patients in 54 centres, only 47% of patients were adherent to their treatment [22]. Several factors are associated with poor adherence in dialysis. The most common are as follows: younger age, male gender, poor quality of social support, an elevated number of comorbidities, health beliefs and mood disorders—predominantly depression—a frequent complication in patients on maintenance dialysis [23].

HYPERPHOSPHATAEMIA AND HYPERPARATHYROIDISM MANAGEMENT AND ADHERENCE IN CKD PATIENTS

Hyperphosphataemia and secondary hyperparathyroidism develop relatively late in the course of renal diseases and concern essentially patients on maintenance dialysis [3]. High plasma phosphorus is recognized as a significant independent risk factor for cardiovascular morbidity and mortality by promoting vascular calcifications [24]. Phosphate binders and drugs prescribed for controlling serum parathyroid hormone (vitamin D analogues and calcimimetics) are main contributors and account for about one-half of the daily pill burden in dialysed patients [6]. Indeed, patients are generally prescribed 1–2 tablets of phosphate binders at each meal. It is no surprise that adherence to phosphate binders is low under these circumstances. According to the international Dialysis Outcome and Practice Pattern Study, <50% of dialysis patients have controlled phosphorus, suggesting a poor adherence to phosphate binders as well as to dietary recommendations [25]. As stated earlier, in a recent review of 34 published studies, drug adherence to phosphate binders ranged between 22 and 74% (mean 51%), depending on the method used to assess drug adherence [11]. This can be explained by the facts that most phosphate binders are still of large size, difficult to swallow or to chew with a minimum of water and not particularly tasty. In fact, the prescription of phosphate binders is an excellent example of the negative feedback on drug adherence when increasing the dose and number of pills in patients whose serum phosphorus is not on target. If serum phosphorus remains high, physicians tend to increase the prescription of phosphate binders without considering the possibility of a low drug adherence. Consequently, the new prescription only aggravates the situation and deteriorates drug adherence further.

Drug adherence seems to be also a concern with the administration of vitamin D or its analogues and with calcimimetics. Indeed, the prevalence of 25-OH vitamin D deficiency remains high in patients with CKD with or without dialysis [26,27] whereas some clinical benefits of vitamin D supplementation have been demonstrated clinically [28]. The high prevalence of vitamin D deficiency among CKD 5 patients strongly suggests major problems of drug adherence and/or prescribing strategies. In recent years, calcimimetics have been developed to improve the management of secondary hyperparathyroidism in dialysis patients. These drugs are effective but their use is sometimes limited by a low tolerability profile due to gastrointestinal discomfort [29]. A large survey of 4923 dialysis patients has recently demonstrated that drug adherence to cinacalcet is relatively low with 46% non-adherent, 27% of low adherence and only 28% highly adherent patients at 12 months, an observation which may have a high economic impact [30]. In a recent controlled study, drug adherence to cinacalcet could actually be improved by using an electronic drug adherence monitoring-based approach. In brief, cinacalcet adherence was monitored using an electronic system for 6 months. Drug prescription was adapted according to the results of drug adherence, and results were discussed with the patients in motivational interviews [31]. This so-called integrated care approach enabled the unmasking and improvement of drug adherence problems, to transiently achieve better PTH control, at a lower dose of cinacalcet (Figure 1). Patients with poor adherence at baseline benefited mostly, suggesting that in this patient group the integrated care approach should be proposed before increasing cinacalcet dose.

ADHERENCE TO OTHER CONCOMITANT THERAPIES IN CKD PATIENTS

In addition to hypertension and mineral metabolism, CKD patients often receive treatments to reduce their cardiovascular risk including aspirin and statins. In addition, >25% of patients are treated for type 2 diabetes. At last anaemia management represents another burden in CKD Stage 5 patients but the management of anaemia is now increasingly performed through intravenous infusions of iron and subcutaneous erythropoietin injections.

In the general population, drug adherence to primary and secondary prevention of cardiovascular diseases is rather low and decreases with time to reach ~50% at 1 year [32]. This is probably also the case in CKD and dialysis patients. Thus, in a French survey on quality of care in CKD patients [33], only

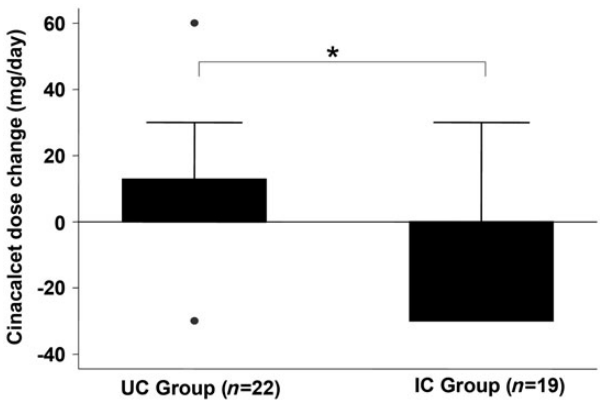

FIGURE 1: Effect of adherence monitoring on the 6-month dose of cinacalcet necessary to control parathyroid hormone in dialysis patients. UC, usual care; IC, intervention (electronic monitoring of drug adherence + counseling), from ref. [31]. *P < 0.03. Note that the dose of cinacalcet was reduced by almost 30% in monitored patients.

one-third of the patients were on statins, which is rather low if one considers the high cardiovascular risk and recent cardiology guidelines recommending treatment in all patients with a high risk of cardiovascular event whatever the level of cholesterol [34]. Moreover, the use of statins was found to be effective in reducing cardiovascular events in non-dialyzed CKD patients [35]. In maintenance dialysis, no clear benefit of statins has been observed so far in controlled studies. In the MASTERPLAN study, in which 788 patients with CKD 2 to 5 were enrolled with a follow-up of 4.6 years, 60% of patients were prescribed a statin, 40% received aspirin and 20% glucose-lowering drugs [36]. A modest increase in these percentages was observed using multifactorial intervention with nurse practitioners [36].

CAUSES AND POTENTIAL STRATEGIES TO IMPROVE DRUG ADHERENCE IN CKD PATIENTS

In order to develop rational strategies to improve drug adherence in CKD patients, it appears important to identify the reasons why these patients decide at any time not to take their drugs, decisions that may well differ depending on their health conditions and complexity of their treatments. This was actually explored in a recent study using structured interviews of adult patients with CKD 3 to 5 [37]. As expected, reasons for deciding to withhold some treatments were as follows: concerns about polypharmacy (pill burden), the fear of drug interactions, pill size and frequency, cost of drugs, and doubts on the real efficacy of some of the prescribed drugs, lack of understanding and poor communication with physicians [37]. Interestingly, patients tend to rank the importance of their treatments based on the expected benefits (reduction of symptoms) and/or side-effects. Thus, strategies to improve drug adherence in CKD patients should primarily focus on the patient's (and physician's) motivations as well as on developing trust and empathy providing as much information as possible on the necessity of taking all of these drugs. In dialysis patients, Neri *et al.* have actually illustrated the relationship between the adherence probability and the number of tablets per day according to the perception of the patient's burden of therapy. As shown in Figure 2, not only the number of tablets but also the perception of the patient plays an important role in reducing the probability of an adequate adherence (Figure 2) [11].

When evaluating drug therapies themselves, the focus should be on simplifying drug regimens for example using fixed-dose combinations enabling once daily dosing for hypertension or drugs with longer duration of action to prevent the effect of missed doses [38]. The pill burden can also be reduced by using newer drugs administered less frequently. This is the case for example of iron therapy, which can now be administered safely intravenously at higher doses with newer forms of iv iron. Another example is the monthly administration of erythropoietin-stimulating agents available in many countries. Regarding phosphate binders, new compounds are being developed, which can normalize serum phosphorus with only three pills a day [39]. In maintenance dialysis

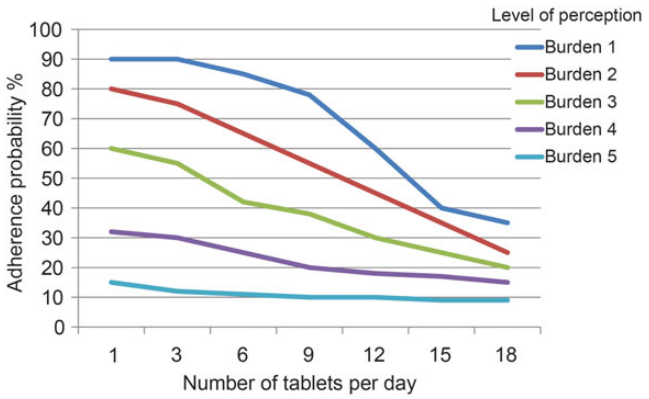

FIGURE 2: Relationship between the number of tablets per day and the probability of adherence according to the perception of the burden of therapy in dialysis patients (from ref. [22]).

patient, one strategy could be to administer a maximum of drugs intravenously at the end of the dialysis session or orally under direct supervision. In this context, new vitamin D analogues such as paracalcitol have been developed, which can be administered intravenously for the management of secondary hyperparathyroidism [40]. With the same idea in mind, a new form of intravenous calcimimetic is now being developed.

Among all strategies investigated to improve drug adherence which were more or less successful [41], one interesting approach is the development of a team-based strategy involving specialized nurses and/or pharmacists in order to enhance the control rates of the various risk factors (hypertension, diabetes, dyslipidaemia, etc.) [36,42–44]. Several such programmes have been initiated in North America and Europe and demonstrated some clear improvements in the percentage of patients adequately treated and reaching therapeutic goals in CKD [42–44]. Thus, in Canada, the participation of community pharmacists in a multidisciplinary team including nephrologists, nurses and pharmacists enabled the improvement of the control of BP in participants with stage 2–4 CKD [44]. In the multifactorial approach and superior treatment efficacy in renal patients with the aid of nurse practitioners (MASTERPLAN) study conducted in the Netherlands, specialized nursing care clearly improved the management of cardiovascular risk factors at 1 and 2 years in patients with stage 3–4 CKD randomized to the intervention arm as compared with the control group [36]. A recent systematic review and meta-analysis of team-based randomized studies has actually confirmed the potential benefits of such interventions [45]. However, some doubts remain on the economical aspects of these interventions [46] and whether the team-based approach really reduces cardiovascular end points as well as the progression toward ESRD remains uncertain [36].

CONCLUSIONS

The goal of the present review was to re-emphasize the crucial role of drug adherence in the management of CKD patients at any stage of the disease including on maintenance

haemodialysis. Poor adherence should be taken into consideration in all clinical situations in which targets are not reached despite substantial efforts to prescribe the most adequate therapies. Because of the complexity of treatment and the high pill burden, CKD patients are at very high risk of poor adherence and should definitively be supported in their efforts to maintain a good persistence. Physicians and all other healthcare professionals should be aware of the different strategies available to help their patients and should join their efforts to alleviate the barriers to good adherence by improving the communication, reducing the pill burden and if possible by monitoring drug adherence occasionally when there is suspicion of poor adherence.

CONFLICT OF INTEREST STATEMENT

None declared.

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