Difficult blood pressure control: watch out for non-compliance!

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Introduction

Blood pressure control remains an essential therapeutic approach to prevent the occurrence of coronary heart disease, heart failure, stroke and premature death [1]. It is also one of the most effective ways to retard the progression of diabetic and non-diabetic renal diseases [1]. Even though every practising physician readily

recognizes the need to lower blood pressure in hypertensive patients, numerous reports from developed and developing countries show that hypertensive patients with well-controlled blood pressure represent only a small percentage of the hypertensive population [2–8]. Thus, there is clearly a need to develop effective strategies to improve the management of hypertension.

The small percentage of patients with a well-controlled blood pressure in epidemiological surveys contrasts with the rather high response rate obtained in clinical trials investigating new antihypertensive drugs or therapeutic strategies. Thus, in the Hypertension Optimal Treatment (HOT) study, 88% of patients assigned to a target diastolic blood pressure ≤90 mmHg achieved this goal after 12 months of antihypertensive treatment [9]. In the ALLHAT study, > 60% of the enrolled patients achieved a blood pressure goal < 140/90 mmHg at 5 years [10]. This apparent discrepancy is perhaps explained by the experimental conditions in which clinical trials are conducted and by the selection of patients and physicians both being more motivated or willing to achieve target blood pressure levels when engaged in clinical studies. Nevertheless, it strongly suggests that it should be possible to increase the overall percentage of patients reaching a satisfactory blood pressure control.

Partial blood pressure control: what is today’s attitude?

There are several potential reasons why hypertension could be difficult to control with a standard antihypertensive treatment: these include an incorrect diagnosis, secondary forms of hypertension, inadequate antihypertensive therapy, associated factors or diseases, such as the use of non-steroidal anti-inflammatory drugs, or non-compliance with antihypertensive drug regimens. Besides these factors, Berlowitz et al. [11] have emphasized the role of physicians who may not be aggressive enough in their management of hypertension. Thus, these investigators have found that physicians often were reluctant to intensify treatment in patients with uncontrolled blood pressure [12]. The most frequent reason for not adapting therapy is that physicians were satisfied with the blood pressures achieved, although these were not those recommended by their national guidelines. Similarly, Hyman et al. [13] have found that 25% of primary care physicians would not intensify the treatment in hypertensive patients with a diastolic blood pressure of 94 mmHg or a systolic blood pressure of 158 mmHg unless patients had cardiovascular complications. In a recent Belgian survey, many patients with mild hypertension and a high or very high cardiovascular risk were actually not treated for hypertension [14]. These results clearly indicate that the physicians’ attitude represents one part of the answer.

Today, if the patient fails to respond to treatment, the most common medical response is to increase the dose of the antihypertensive agent, to add another drug or eventually to change the therapeutic agent. In some cases, clinical investigations looking for a secondary form of hypertension will be conducted. Thus, when facing an apparent resistance to drug therapy, physicians have a systematic bias considering that the patient is basically a non-responder or that the pharmacological regimen is inadequate. This ‘pharmacological’ attitude leads either to the use of high doses of antihypertensive agents which are very likely to produce side effects, or to the prescription of several antihypertensive compounds according to the step-care therapy scheme. However, both the occurrence of side effects and the increased complexity of the regimen have been shown to reduce drug adherence and the persistence of treatment [15]. This is perhaps one reason why physicians are reluctant to intensify drug therapy in hypertensive patients and are satisfied with a partially controlled blood pressure.

Why not consider compliance?

For many patients in whom treatment proves ineffective, the explanation is not poor drug efficacy but inadequate patient adherence to therapy. Patient compliance with drug therapy has been recognized as one of the major reasons why antihypertensive therapy fails in the USA [16]. In a German survey, non-compliance was responsible for ~17% of treatment interruptions [15]. Thus, when the blood pressure response to therapy is not the one expected, there is also a probability that the patient is a non-complier rather than a non-responder, even though non-compliance is also common among patients with a well-controlled blood pressure [17]. Unfortunately, compliance is a difficult parameter to assess clinically. Therefore, it is easier to label the failure incorrectly as a non-response. As discussed previously, not detecting non-compliance as a contributor to insufficient response is likely to result in wrong measures being taken. A simpler and perhaps a more accurate approach would be to consider non-compliance—but how can we make the diagnosis?

The detection and quantitative assessment of non-compliance is a particularly difficult task. The difficulty is inherent in the characteristics of non-compliance. Indeed, the most frequent profile of non-compliance is the repeated occasional omission of therapeutic doses which may sometimes lead to a treatment interruption. Thus, compliance is a very dynamic process; patients may adhere completely to their drug regimen for some periods of time and suddenly become non-compliant because of problems interfering with their treatments. Therefore, the ideal compliance monitoring system should integrate this dynamic component and provide reliable data covering long periods of treatment. Today, most of the available techniques do not fulfill this criterion.

As shown in Table 1, there are several ways to monitor compliance, including self-reported compliance, counting pills or biological markers. All these methods have their limitations. Counting pills, for example, is
easily manipulated by the patient and may not detect even major deviations from the drug dosing regimen. Although this approach is used commonly in clinical trials, the pill count is known to overestimate the number of tablets really taken [18]. Clinical pharmacologists would certainly recommend measuring either blood or urinary concentrations of the prescribed drug using sensitive assays. This is indeed the only way to ascertain that a drug has been taken. However, this approach requires repeated blood or urine sampling, and will certainly fail to detect poor long-term compliance in patients whose compliance improves shortly before a physician’s appointment (‘white coat’ compliance).

Interestingly, most physicians claim that they do not need any monitoring system because they can easily detect non-compliance in their patients. Studies have demonstrated, however, that clinicians’ estimates of non-compliance are very poor [19,20]. Thus, Gilbert et al. [19] have demonstrated that physicians could not predict compliance with any more accuracy than if they were guessing. By assessing compliance using a pill count and an arbitrary threshold of 80% to define good or poor compliance, Gilbert et al. showed that the sensitivity and specificity of the clinical judgment were 10 and 86%, respectively. Using an electronic monitoring system as the gold standard, we have found recently that the positive predictive value of the physician’s estimate of compliance is only ~30% [20]. Our results indicate that physicians are good at detecting a good compliance but they are poor at detecting patients with a low compliance, i.e. those patients who need to be identified. Thus, in contrast to the general belief of many physicians, detecting non-compliance in clinical practice is almost impossible without the use of a monitoring system. A reliable assessment of compliance could have a great impact on clinical practice and help to reduce unnecessary prescriptions, investigations and hospitalizations.

Microelectronic ‘real-time’ monitors are available that record each time the container holding the medication is opened [21]. Although the fact that the container has been opened is recorded and when it was done, this does not determine whether the removed medication was swallowed. This may be a problem with short-term monitoring but rarely when the patient is monitored for several months. Moreover, if the pill box has not been opened, drug compliance is very unlikely. The main advantage of these devices is that they provide objective measurements of drug adherence that can be discussed with the patient. Thus, they are helpful in identifying and correcting compliance problems. Electronic monitoring is also helpful in identifying another aspect of poor compliance—deviation from the recommended dose timing.

Is there a place for the electronic monitoring of compliance in the management of hypertensive patients?

As mentioned above, poor adherence to treatment can be observed in patients with well-controlled blood pressure as well as in patients with uncontrolled hypertension [17]. Nevertheless, it is mainly in uncontrolled patients that non-compliance becomes a real clinical issue because it represents a potential cause of resistant hypertension or treatment failures. When occurring in well-controlled patients, low compliance may only reflect the fact that these patients are perhaps being overtreated since they do not need the complete treatment to lower their blood pressure.

We have evaluated whether monitoring compliance electronically may identify and improve compliance in patients with resistant hypertension (average blood pressure 156/106 mmHg with treatment) [22]. A total of 41 patients who were resistant to a regimen of three drugs were studied prospectively. Patients were informed that their currently prescribed drugs were to be provided in electronic monitors for the following 2 months. We found that monitoring compliance alone significantly improved blood pressure at 2 months (145/97 mmHg). In a third of patients, blood pressure was normalized (<140/90 mmHg) and a further 20% of patients were observed to have poor compliance. Patients with the lowest compliance showed significantly higher achieved diastolic blood pressures. In 30 patients whose compliance was monitored for up to 4 months and drug treatment adapted whenever necessary, blood pressure was significantly reduced even further (from 150/100 to 143/94 mmHg). Electronic monitoring of compliance was effective in improving both compliance and blood pressure control. These results therefore emphasize the potential clinical

### Table 1. Methods available to assess compliance to drug therapy in clinical practice

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Respect of consultations</td>
<td>Easy</td>
<td>Only indicative, not reliable</td>
</tr>
<tr>
<td>Physicians’ impression</td>
<td>Easy</td>
<td>Poorly reliable, subjective</td>
</tr>
<tr>
<td>Patient interview</td>
<td>Easy</td>
<td>Underestimate, subjective, limited by memory</td>
</tr>
<tr>
<td>Clinical response</td>
<td>Easy</td>
<td>Punctual, non-specific, only indicative</td>
</tr>
<tr>
<td>Occurrence of side effects</td>
<td>Relatively easy, objective</td>
<td>Not reliable</td>
</tr>
<tr>
<td>Prescription renewal</td>
<td>Relatively easy, objective</td>
<td>Overestimates compliance, punctual</td>
</tr>
<tr>
<td>Pill count</td>
<td>Proves ingestion</td>
<td>Costly, punctual, invasive (blood or urine)</td>
</tr>
<tr>
<td>Drug monitoring</td>
<td>Dynamic measurement, reports enable discussion</td>
<td>Does not prove ingestion, cost</td>
</tr>
<tr>
<td>Electronic monitors</td>
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benefits of using electronic monitoring of compliance in the management of patients with refractory hypertension.

We extended this study to our entire out-patient department and showed that monitoring of compliance itself reduced blood pressure in all 69 patients with resistant hypertension (from 159/104 to 143/92 mmHg) [23]. During the monitoring period, blood pressure was normalized (<140/90 mmHg) in a third of patients, significantly improved in a third, and remained unchanged in the other third (Figure 1). Interestingly, electronic monitoring of compliance enabled us to identify patients who were either overtreated, had poor compliance or needed to change their treatment. These results suggest that electronic monitoring of compliance can improve the efficacy of antihypertensive drug treatment in patients with resistant hypertension, probably because drugs are taken more consistently during the monitoring period. Moreover, the information obtained from electronic monitoring can help physicians to make more rational therapeutic decisions. Improvements in blood pressure control with the compliance monitoring have also been found in patients with mild to moderate hypertension [24,25].

Conclusions

Electronic monitoring of compliance should not be performed in all patients. It is, however, a very useful tool in patients who do not respond to treatment as expected, or in high-risk patients for whom omitting one or several doses of their treatment may lead to major complications. This may be the case, for example, in hypertensive patients with congestive heart failure for whom omitting several doses of their diuretic may lead to an immediate hospitalization. Since the probability of poor adherence increases in parallel with the number of daily doses, patients receiving a multiple therapy would represent a good target group. Additional studies should now be conducted in order to define more precisely the patient populations which are the most likely to benefit from monitoring. Such equipment may seem expensive to purchase (~$US50 per capita). However, the newer devices can be used for up to 4 years. One should also take into account that non-compliance has a cost as it leads to an increase in medical expenses and it decreases the cost-effectiveness of the interventions. At present, we are convinced that compliance monitoring is clinically useful and that a pertinent monitoring of compliance should have a positive effect on health care costs. Yet, whether it is economically worthwhile remains to be demonstrated in carefully conducted clinical studies [26,27].

Conflict of interest statement. None declared.

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Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what to do if the serum creatinine and/or serum potassium concentration rises

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Keywords: angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; hyperkalaemia; hypertension; serum creatinine

Introduction
Guidelines governing the optimal treatment of blood pressure in patients with chronic renal failure emphasize the need for more stringent blood pressure control and the use of drugs that interfere with the renin–angiotensin system [1,2]. As this approach is adopted, physicians will commonly encounter patients where blood pressure control is accompanied by an increase in