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Relation between patients' variable drug dosing histories and office blood pressure in treatment-resistant hypertension

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OBJECTIVES

Suboptimal compliance with prescribed therapy results in variable exposure to the treatment and is recognized as a potential cause for non- or poor-response to prescribed anti-hypertensive drug regimens. Burnier et al. has shown that objective monitoring of compliance may be useful in the management of hypertensive patients [1]. Nevertheless, in clinical practice, non-compliance is often overlooked and simply ignored. The primary objective of this study is to assess the impact of variable dosing histories on blood pressure in unresponsive hypertensive patients treated with multiple drugs.

METHODS

The study involved 89 patients coming from two different settings:

- 44 resistant hypertensive patients treated with at least three anti-hypertensive drugs and recruited in a clinical trial aiming at improving patients' compliance and clinical outcome.
- 45 uncontrolled patients followed by general practitioners in a clinical practice and who were included in a compliance enhancement program.

Office blood pressures were measured at each clinic visit. Antihypertensive drug dosing histories were compiled electronically by medication event monitors (MEMS®). A separate monitor was used for each prescribed antihypertensive drug. Patients involved in this study were usually treated with multiple therapies that could also change over time. For this reason, daily compliance with treatments was summarised by a binary variable indicating whether the patient took at least one of the drugs as prescribed by the physician. Nonlinear mixed effect models were used to analyse the impact of variable dosing histories on systolic blood pressures (SBP). A sigmoid E_{max} model was identified to describe the relation between SBP collected over time and drug exposure.

RESULTS

Figure 1 shows the evolution of SBP over time. In this plot, the day of the introduction of the MEMS monitor has been defined as day zero. Broken green lines correspond to individual patient SBP profiles. A red dot is used to indicate each patient's baseline SBP; i.e. the last SBP available before day 0. A loess curve has been plotted in dark green to highlight the average SBP evolution over time. The average SBP at baseline is 160 mmHG. A decrease in SBP appears quickly after the start of the intervention and seems to reach a plateau after 200 days. The corresponding average decrease in SBP after the compliance intervention is 15 mmHG and has been previsouly reported [2]. The association between compliance and SBP decrease is however hard to establish because before baseline, compliance with prescribed therapy was not monitored.

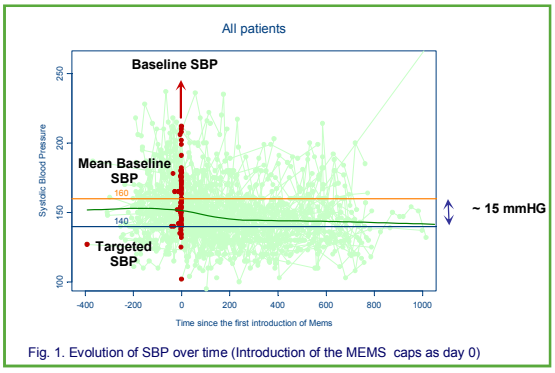

Fig. 1. Evolution of SBP over time (Introduction of the MEMS caps as day 0)

After baseline, compliance with prescribed treatments was summarised by a binary variable indicating for each consecutive day whether or not the patient took at least one of the drugs as prescribed by the physician. Figure 2 shows the evolution over time of the daily percentage of compliers in both groups. The average proportion of patients who complied with at least one of the prescribed dosing regimens was stable over time and significantly higher in the clinical trial setting (92% vs 81%,p=0.0004). A weekend affect was also observed (p=0.0007): the odds of taking at least one prescribed medication was 26% higher during a week day compared to a weekend day. In the next section we study the association between drug exposure and SBP decrease observed after baseline.

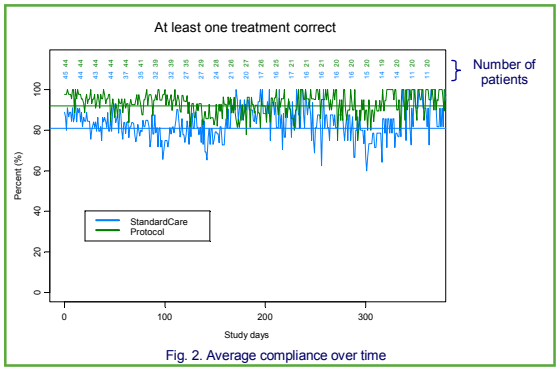

Fig. 2. Average compliance over time

The daily indicators were used to define the average number of days with correct dosing in a window of 10 days prior to the measurement of blood pressure. Figure 3 shows difference in SBP from baseline against compliance. A loess curve has been drawn in green to highlight the association between both variables. Most of the observations correspond to a high level of compliance but this plot suggests that the response improves in a non-linear way when compliance increases. Figures 4 shows the individual SBP profiles: observations associated with a compliance of less than 50% over the 10 days prior to the measurement have been represented by plain dots. An individual profile illustrates a potential relation between low compliance level and uncontrolled SBP.

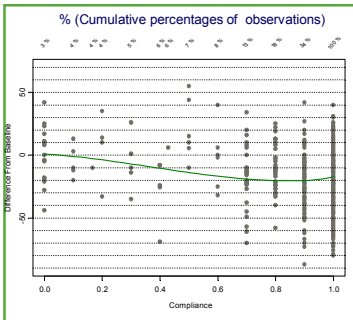

Fig. 3. Difference in SBP from baseline versus compliance

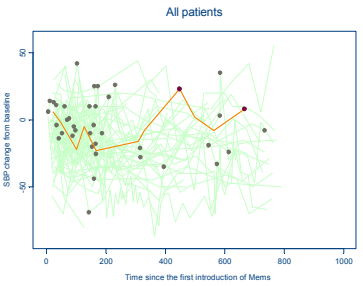

Fig. 4. Difference in SBP overtime

First, a random intercept longitudinal model was implemented to assess SBP over time. The model was adjusted for baseline blood pressures (linear relation, p<0.0001). Compliance was initially introduced as a factor with 10 levels indicating the number of days with at least one drug intake over the 10 days previous to the SBP measurement. Figure 5 shows the estimated effect related to the different levels of compliance: each dot corresponds to the estimated effect. Grey dots have been used to represent non significant effects whereas a green dot corresponds to a significant difference compared to the 0-level. Those estimates suggest a sigmoid relationship between compliance and SBP. Therefore a sigmoid E_{max} model was used to fit the data. The association between SBP reduction and compliance estimated through the sigmoid E_{max} model has been drawn in green in Figure 5. The model estimates a 24 mmHg [11-37] decrease in SBP for a typical patient achieving a 100% drug exposure. Fifty percent of the maximal reduction in SBP was achieved at a drug exposure level of 51 % [26-76].

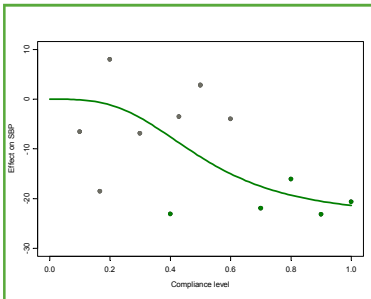

Table 1 Parameter Estimates

Param	Estimate	Standard Error	Pr > |t|	Lower	Upper
i_0	156.210	4.050	<.0001	148.160	164.270
alpha	0.488	0.067	<.0001	0.355	0.622
imax	23.839	6.607	0.0005	10.705	36.974
ic50	0.508	0.126	0.0001	0.257	0.759
n	3.192	2.471	0.2000	-1.721	8.104

$$sbp_{ij} = i_0 + b_i + \alpha \cdot (sbp_{i0} - 140) - i_{max} \cdot compl_{ij}^{n} \Big/ (ic_{50}^{n} + compl_{ij}^{n})$$

Fig. 5. Estimated relation between SBP and compliance

This model shows that a treated hypertensive patient, with a baseline SBP of 140 mmHg is expected to present a SBP of 156 mmHg [CI95: 149-164] with a 10% compliance and of 136 mmHg [CI: 132-140] with a 90% compliance.

A sensitivity analysis was performed to check the shape of the selected model. Both subsets of patients supported separately the sigmoid E_{max} shape.

CONCLUSIONS

This analysis shows a statistically and clinically significant association between SBP and electronically compiled dosing histories. It allows one to estimate the expected SBP over the entire spectrum of compliance observed with the prescribed antihypertensive drugs. Nevertheless, the changes of treatment during the course of the study were so complex that it was impossible to model this aspect in the current setting. Consequently, an improvement of SBP apparently related to a change of compliance could also be the result of a change of treatment. Moreover, the fact that the monitoring of compliance in the standard care was not mandatory may also induce a selection bias blurring the relation between SBP and compliance. A well controlled study should be set up to confirm the findings reported in this poster.

References :

[1] Burnier M, Schneider MP, Chiolero A, Stubi CL, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. Journal of hypertension 2001, 19:335-341.

[2] Figueiredo H., Bugnon O., Burnier M., Favre M., Avenati T., Schneider M.P. Poster CPS-P-081, FIP Congress Cairo 2005