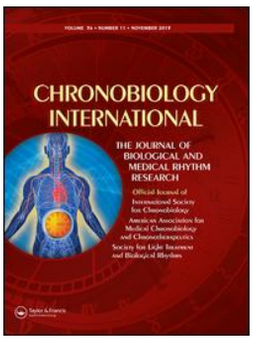

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CHRONOBIOLOGY DISCUSSION FORUM

A commentary on the Spanish hypertension studies MAPEC and HYGIA

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ABSTRACT

The recently published chronotherapeutic Spanish papers MAPEC and HYGIA proposing that antihypertensive drug treatment should be given at bedtime suffers from obvious deficiencies in study design and are not a valid basis for drug treatment of hypertension.

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In medical journals as well as in the lay press there is an ongoing discussion on the chronotherapeutic papers MAPEC and HYGIA from Spain. MAPEC results in the "novel therapeutic goal" that ingestion at least one tablet of the entire daily dose of ≥1 conventional hypertension medication at bedtime best decreases cardiovascular morbidity and mortality (Hermida et al. 2010, 2014). The HYGIA project extends the recommendation in that all antihypertensive medications – independent from the group of the antihypertensive and including fixed combinations – should be taken at bedtime (Hermida et al. 2019; Hermida 2016). Having in mind to best treat hypertensive patients these publications need a critical commentary:

The relevant blood pressure data obtained at baseline and after treatment in MAPEC and HYGIA are compiled in Table 1. The table shows that the study design is rather questionable in many ways. In HYGIA both treated and untreated patients are described who were monitored over a 48 h (!) period. Then, these patients were asked to take the drugs either in the morning or at bedtime, surprisingly both groups consisted of treated and untreated patients with no distinction between both groups. Next point of criticism: Having in mind that the daytime mean blood pressure value at baseline was 136/81 mmHg (nighttime 123/70 mmHg) and the inclusion criteria was a daytime mean of t least 135/85 mmHg only mild hypertensives (grade 1) or patients with high-normal blood pressure values and very well-controlled hypertensives could have been included. In the light of the low blood pressure values, it is not surprising that a high percentage of subjects showed a non-dipping pattern taking into account a nocturnal fall of <10% (Table 1). In general, this definition of non-dipping and the associated risk refers only to untreated hypertensives. In treated hypertensives in whom a decrease or normalization of a high blood pressure during daytime by morning dosing will result in a decrease of the day-night blood pressure difference.

There are additional restrictions: Many chronopharmacological studies with different antihypertensives were performed already in the 1990 s in a cross-over design morning versus evening dosing, both in dippers and non-dippers (Lemmer 2007). These studies gave clear-cut evidence that different antihypertensives quite differently affected the 24-h BP profile, especially the nightly fall: Most important, ACE-inhibitors – in contrast to CCB and AT_1Antagonists – resulted in super-dipping on evening dosing in dippers, leading to increased cardiovascular side effects, whereas CCB normalized the non-dipping by evening dosing (Lemmer 2007). Unfortunately, such cross-over studies are not available for combination compounds of antihypertensives. Nevertheless, the Spanish authors conclude from the HYGIA data that also the combination of antihypertensives should be dosed entirely at bedtime (Hermida et al. 2019; Hermida 2016; Hermida et al. 2010, 2014). This recommendation completely

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Table 1. Blood pressure values (mean ± SD) in SBP and DBP during 48-h of ABPM in the MAPEC and in the HYGIA studies. In the MAPEC study all medication was either dosed after awakening or at least one dose was given at bedtime (Hermida et al. 2010, 2014) (1 medication 43.3%, 2 medications 16.3%, ≥3 medications 40.3%), in the HYGIA study all medications (≥1) were either dosed after awakening or at bedtime; both groups contained treated and untreated patients (Hermida et al. 2019; Hermida 2016).

MAPEC	Awakening (n = 1084)	Bedtime (n = 1072)
Baseline values		
48-h SBP mmHg	130.7 ± 15.5	130.5 ± 13.6
48-h DBP mmHg	78.2 ± 10.4	78.7 ± 10.0
Treatment		
48-h SBP mmHg	124.9 ± 15.1	125.3 ± 12.9
48-h DBP mmHg	71.6 ± 9.8	71.9 ± 9.5
% Non-Dipper	61.6	34.4
HYGIA	**Awakening (n = 9552)**	**Bedtime (n = 9532)**
Baseline values		
48-h SBP	131.4 ± 14.4	131.7 ± 13.3
48-h DBP	77.2 ± 10.6	77.5 ± 10.3
% Non-Dipper	49	49.5
Treatment		
48-h SBP	125.6 ± 14.5	124.4 ± 12.9
48-h DBP	73.1 ± 9.9	72.2 ±. 9.2
% Non-Dipper	50.3	37.5

ignores the risks of an increased nocturnal fall in selected hypertensives, especially under combination therapy. In epidemiological studies, a more pronounced fall of the blood pressure at night (over-dipping, extreme dipping) is well documented with an increased risk of ischemia and disturbance of retinal perfusion, mainly in older patients (Kario et al. 1996; Pierdomenico et al. 1998, 2016; Pillunat et al. 2015; Suzuki et al. 2000).

Thus, the results of the HYGIA study and its implication for the treatment of hypertensive patients have to be seen in the light of obvious deficiencies:

- Both treated and untreated patients are included within the same group, not separated by statistics.
- The degree of hypertension is not reported.
- The unusual high percentage of non-dippers might be due to the calculation of data over 48 hours of ambulatory blood pressure monitoring (ABPM).
- A comparison to 24 h data means and percentage of nocturnal fall – as usually used in ABPM studies – is not presented. Therefore, the difference between awaking and bedtime SBP (3.3 mm Hg) and DBP (1.6 mmHg) though significant can hardly be taken as an index of preference in evening dosing.
- The dipping pattern is not considered as an important criteria for treatment.
- The reported 1:1 randomization describes no further criteria in the study protocol.
- An evaluation of end points in the study protocol is missing

In conclusion, the introduction of 24-h ABPM greatly contributed to a better diagnosis and treatment of hypertensive patients. Both the HYGIA and the earlier published MAPEC study are criticized by international experts (Carlberg and Brunström 2020). Whereas MAPEC recommends to dose at least one antihypertensive at night, the HYGIA study recommends that all compounds including combination therapy should be given at bedtime. Both studies suffer from severe deficiencies and are not reported according to CONSORT standards. The scientific basis for evening dosing, in general, is not presented. This recommendation could be dangerous for several hypertensive patients resulting in silent ischemia at night. Finally, according to the Spanish studies 24-h blood pressure monitoring would not further be necessary to decide which drug and at what time would be best to treat the elevated blood pressure of an individual patient. It is the great advantage of the introduction of the 24 h blood pressure monitoring that patient-dependent individualized treatment is possible according to the respective 24-h blood pressure profile obtained. Twenty-four hour-ABPM is even a prerequisite for possible evening dosing of an antihypertensive drug. Finally, it is a pity that sounds chronopharmacological recommendations available of how and when to treat are not considered in the Spanish studies.

Disclosure of interest

The authors have no conflict of interest.

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