

BLOOD PRESSURE: NON-INVASIVE METHOD TO MONITOR DRUG ACTION

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SUMMARY

This pilot study investigated whether the daily measurement of a non-invasive parameter such as blood pressure using a mercury sphygmomanometer monitors drug action and interaction. The blood pressure of six patients aged 68 to 87 years (one male and five females) treated with cardiovascular drugs was monitored for up to forty one days together with changes in the treatment or patients' condition. Some patients have periods of larger variations in the blood pressure than others and are probably related to episodes of increased worry due to a worsening condition such as pain. The establishment of a baseline profile of the blood pressure helps to detect trends of changes in blood pressure. The sudden increase of the diastolic blood pressure to 100mmHg followed by a drop to 65mmHg over a five day period preceded a fall, dizziness and postural hypotension. Withdrawal of the diuretic brought an improvement while the blood pressure returned to pre-crisis values. In another case, diuretic withdrawal caused no deterioration of the blood pressure. Blood pressure monitoring indicated that drugs could be safely withdrawn from a polypharmacy treatment. In one case the blood pressure was controlled by increasing the dose of nifedipine and withdrawing the diuretic and atenolol. In an 82 year old the withdrawal of cimetidine which was combined with nifedipine brought no change in the blood pressure, an interaction expected in younger subjects. The graphical representation of the

observations should promote a more rational drug use and trigger the sequence for investigations at the right time.

INTRODUCTION

Drug monitoring is important to check drug action especially in the elderly who usually have altered pharmacokinetic and pharmacodynamic parameters when compared to young healthy adults in whom *in vivo* studies are usually carried out. Extrapolation of data generated in the young healthy adult to the elderly patient requires great care. The awareness to this problem is indicated by the increase in the studies which are being carried in the age group older than 60 to 65 years. The occurrence of therapeutic accidents when data generated in the middle-aged white man has been extrapolated to the elderly using criteria which is not valid¹ to the age group being applied to, makes monitoring of drug action in the elderly of great importance. This monitoring can either be invasive or non-invasive.

For the elderly patient on chronic treatment, the invasive method may not be appropriate. This usually involves skin puncturing and therefore specialised personnel would be required. In many cases the number of skin punctures need to be quite large, especially if the patient's condition is not stable. For routine monitoring on a daily basis, the invasive methods would drain the already limited sources of the specialised personnel² and would be a cause of discomfort for the patient. Many invasive methods require analysis of the samples taken and therefore it takes some time before a result could be obtained.

Although the invasive procedures are important to give data on the pharmacokinetic parameters of drugs, correlation between the pharmacokinetic data and the pharmacodynamic results may be difficult in the elderly. The main reasons are that in the elderly there is on one hand an altered sensitivity of the organs to a drug and on the other hand there are changes in the pharmacokinetic parameters. One would find changes in drug absorption, distribution, metabolism and excretion. These changes are not linear with age but are dynamic. On an individual basis these changes could have an alteration in the direction of change. With advancing age the amount of body fat increases^{3,4,5}. As a corollary, the ratio of the total body water decreases with age. At ages

over 60 years, body fat percentage decreases^{4,5,6}. In females this is rapid after the age of 60 years while for the males this starts in middle age and continues throughout most of the lifespan⁷. These observations indicate that the fat to lean mass ratio would increase and then decrease as one ages with the genders having a different rate of change.

The situation would be worse if a number of drugs are administered together especially if they are involved in the same pharmacodynamic and pharmacokinetic mechanisms. A recent study at St Vincent de Paule Residence for the Elderly on 104 patients showed that 32.7 per cent of the elderly take a drug combination consisting of more than one drug with action directed towards the cardiovascular system⁸. This makes monitoring of the drug action rather difficult. The invasive methods would require to determine the pharmacokinetic parameters such as the drug blood levels for all the drugs that could interact with the cardiovascular system. This would not indicate how the target organs of the cardiovascular system would respond to the number of drugs acting on this system at the same time.

As happens in a lot of consultations at the general practitioners' surgery, many people view the blood pressure determination as an occasional, if not an after thought, method to check if one is hypertensive or not. The routine determination of the blood pressure, as it is non invasive method, could be a valuable tool to evaluate drug efficacy. The aim of this pilot study is that since it is a pharmacodynamic end point in itself, blood pressure could be a useful parameter to monitor drug action and interaction in patients taking cardiovascular drugs whether the patient is normotensive or not.

METHOD

The systolic and diastolic blood pressures were determined for six elderly patients aged 68 to 87 years (Table 1) at St Vincent de Paule Residence for the Elderly. These patients consisted of one male and five females and the observation period lasted up to forty one days. The blood pressure was measured by the ward nurses using a mercury sphygmomanometer with the patient in a sitting position except for one determination for patient JA who could not sit up. In this case, the blood pressure was taken with the patient in the supine position. At the same

time, any changes in the drug treatment and other observations of the patient were noted.

Statistical analysis was carried out using the Student's paired *t*-test.

Table 1
Patients who participated in the monitoring of the blood pressure

| Code | Age (Years) | Sex |
|------|-------------|--------|
| MS | 68 | Female |
| FT | 69 | Male |
| RB | 74 | Female |
| AA | 79 | Female |
| CA | 82 | Female |
| JA | 87 | Female |

RESULTS AND DISCUSSION

A common problem when evaluating blood pressure is the fluctuations that may occur for no apparent reason. However, the blood pressure could be influenced by emotional factors that vary from day to day or from moment to moment. These factors may include not so friendly relationships with the relatives that had visited them recently or other patients on the same ward or the actual procedure that is carried out to determine the blood pressure. Worry about the deterioration of some function could also be the source of tension that causes daily fluctuations of the blood pressure.

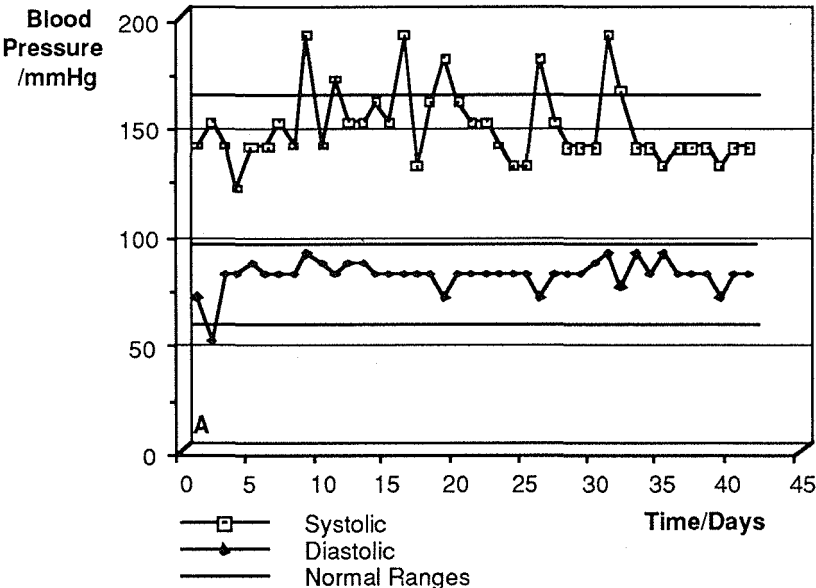
At the start of the observation period, the treatment regimen of patient AA (Table 2) is indicated by event A. In the study, event A describes the treatment already being received by the patient at the start of the observation period. For patient AA, although there was no change in the treatment, large variations in the systolic blood pressure were observed (Figure 1). These could be described as fluctuating between the hypertensive borderline and the normotensive values. The diastolic blood pressure was relatively more stable except for a single reading of 50 mm of mercury on the second day of the observation period. None

of the readings of the diastolic blood pressure were above the threshold where one would consider treatment for hypertension. The systolic blood pressure was more stable during the first 8 days and the last 9 days of observation period indicating that the causative stimulus was transient. This could be related to the presence on a when required basis.

Table 2
 Events that occurred during monitoring of blood pressure - elderly female patient AA aged 79

| Day | Event | Description of event |
|-----|-------|---|
| 1 | A | Nifedipine 10 mg every 8 hours Vitamins B and C compound 1 tablet every 12 hours Pacacetamol 500 mg 1 every 8 hours when needed |

Fig. 1. Monitoring of an elderly female patient AA aged 79 with a poor control of blood pressure



The large fluctuation in the systolic blood pressure indicate that the use of this parameter in evaluating the blood pressure of a patient should not be based on a single, occasional determination. A series of determinations taken at least once daily for a long enough period and considering the overall condition of the patient would be necessary to evaluate a response of the subject to drug therapy. This therapy may not be primarily aimed to control the blood pressure but some other function of the cardiovascular system. Drugs used for activity in the cardiovascular system may also have some action on the blood pressure control.

The residents at St Vincent de Paule Residence for the Elderly are encouraged to go home and live with their relatives periodically (Table 3). The change of environment could be deleterious or otherwise to the general condition of the patient. The large number of drugs that the patient is taking could also cause the problem of compliance.

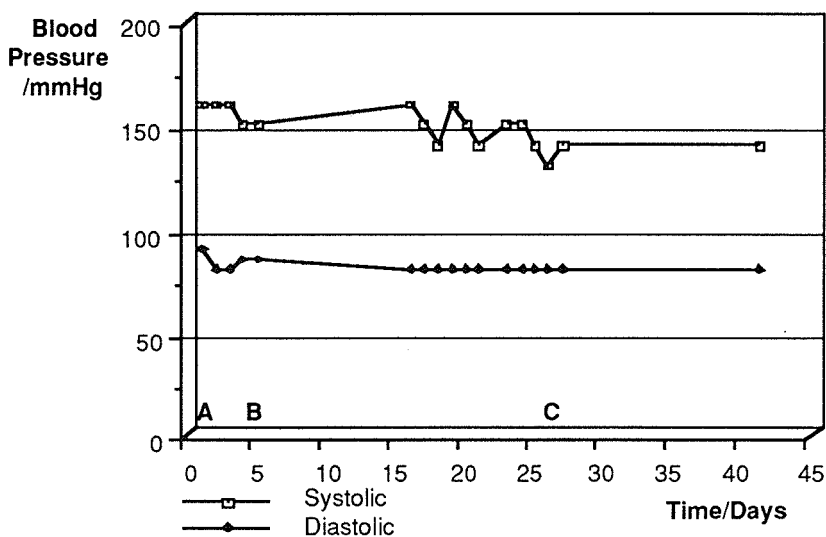
Table 3
Events that occurred during monitoring of blood pressure - elderly female patient MS aged 68

| Day | Event | Description of Event |
|-----|-------|--|
| 1 | A | Nifedipine 10 mg every 8 hours Digoxin 0.0625 mg daily Aspirin 150 mg daily Frusemide 80 mg daily Slow release potassium chloride 600 mg every 12 hours |
| 6 | B | Ten days at home |
| 28 | C | Thirteen days at home |

The establishment of the baseline values of a non-invasive parameter and repeating the tests each time the patient is under hospital care would indicate if the patient is benefitting from his stays with the relatives or not (Figure 2). Patient MS stayed at his home on events B and C for periods of 10 and 13 days respectively. Returning to St Vincent de

Paule Residence for the Elderly and repeating the blood pressure determination, the values obtained indicate that there was no deterioration in her condition if not a slight improvement of the systolic blood pressure. This reflects a good compliance by the patient when she is away from the care of the Residence and therefore she should not be discouraged in continuing with the periodic stays with her relatives.

Fig. 2. Effect of drugs - Elderly female patient MS aged 68 with periods at home



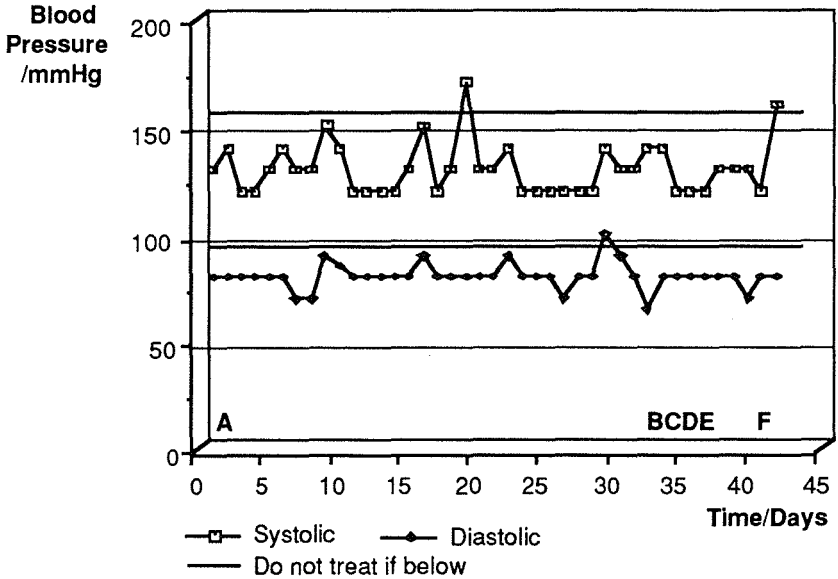
The use of diuretics leads to the lowering of the plasma electrolytes. Hypokalaemia has been implicated in muscle fatigue⁹, giddiness¹⁰, postural hypotension and episodic cerebral ischaemia with falls and funny turns¹¹. These symptoms could be identified in events B, C and D (Table 4). Hypokalaemia may be the reason for these events because the general condition of patient JA improved as soon as the diuretic was stopped (events D and E).

Table 4
 Events that occurred during monitoring of blood pressure - elderly
 female JA patient aged 87

| Day | Event | Description of Event |
|-----|-------|--|
| 1 | A | Aspirin 300 mg $\frac{1}{4}$ daily Nifedipine 10 mg daily Hydrochlorothiazide/ Amiloride HCl 50/5 mg $\frac{1}{2}$ tablet daily |
| 34 | B | Patient fell sweating unresponsive to name |
| 35 | C | Patient lying motionless in bed Dizziness on raising head Weakness |
| 36 | D | Stop: Hydrochlorothiazide/amiloride Patient lethargic |
| 37 | E | Patient better but dizzy |
| 41 | F | Patient probably had myocardial infarction |

Hypokalaemia has also been implicated in cardiac arrhythmias^{9,12} which could have predisposed to the myocardial infarction as seen by the drop in diastolic blood pressure prior to event B (Figure 3). The blood pressure determined during event D was measured with the patient in the lying position so that the real value is lower than that actually recorded when compared to the other readings. Stopping the diuretic on day 36, that is event D, brought an improvement in the blood pressure because of the decreased diuresis.

Fig. 3. Effect of drugs and condition of elderly female patient JA aged 87 indicated by events A to F



In a patient who could be considered to be on the higher side of the normotensive range of the blood pressure and then experience a sharp drop in the diastolic blood pressure that culminated in events B, C and D such as falls and weakness, one would have recommended the determination of the plasma electrolytes, especially the plasma potassium, the enzyme levels of, for example, creatinine phosphokinase and an electrocardiogram prior to day 34 (event B), when the first symptoms appeared.

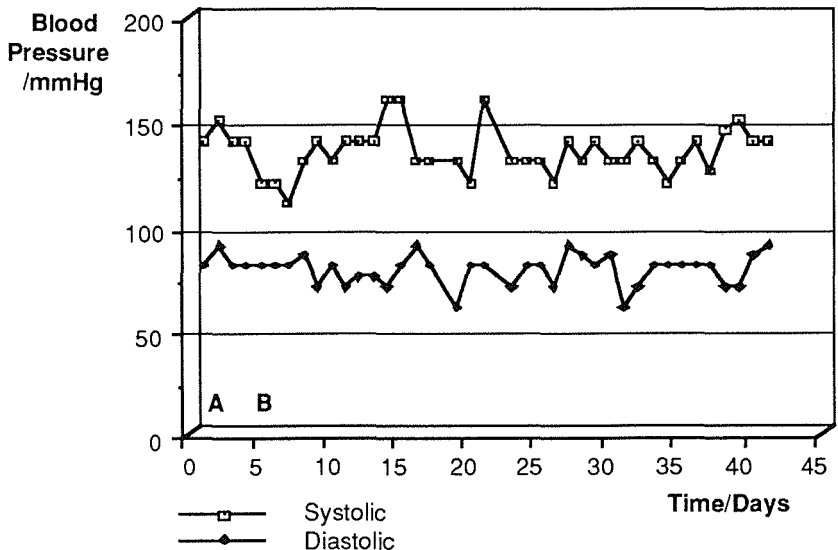
In this case the daily monitoring of the blood pressure could have triggered the sequence of tests that resulted in a more positive diagnosis. This could have been earlier than day 41 (event F) when the note of probably a myocardial infarction was entered in the patient record.

For the diabetic patient who requires treatment with the diuretics, namely of the thiazide group and the loop diuretics, there is the problem of the impairment of the glucose tolerance. This problem occurred in patient RB (Table 5) after six days of observation and the thiazide diuretic was withdrawn from the treatment.

Table 5
 Events that occurred during monitoring of blood pressure - elderly female patient RB aged 74

| Day | Event | Description of Event |
|-----|-------|--|
| 1 | A | Nifedipine 10 mg every 8 hours Digoxin 0.0625 mg daily Hydrochlorothiazide/Amiloride HCl 50/5 mg - one daily Insulin: morning Lente 40 units Actrapid 20 units evening Lente 10 units Actrapid 10 units |
| 6 | B | Stop: Hydrochlorothiazide/Amiloride Sugar blood levels out of control |

Fig. 4. Effect of drugs in diabetic elderly female patient RB aged 74 - blood sugar control poor. Events A and B



Although the systolic and diastolic blood pressure (Figure 4) fluctuated over a wide range, especially during the first ten days after the diuretic was stopped (Event B) these values remained within the normal ranges of the blood pressure. This indicates that the withdrawal of the diuretic did not affect the blood pressure during the observation period of this case although the patient history said that she was hypertensive.

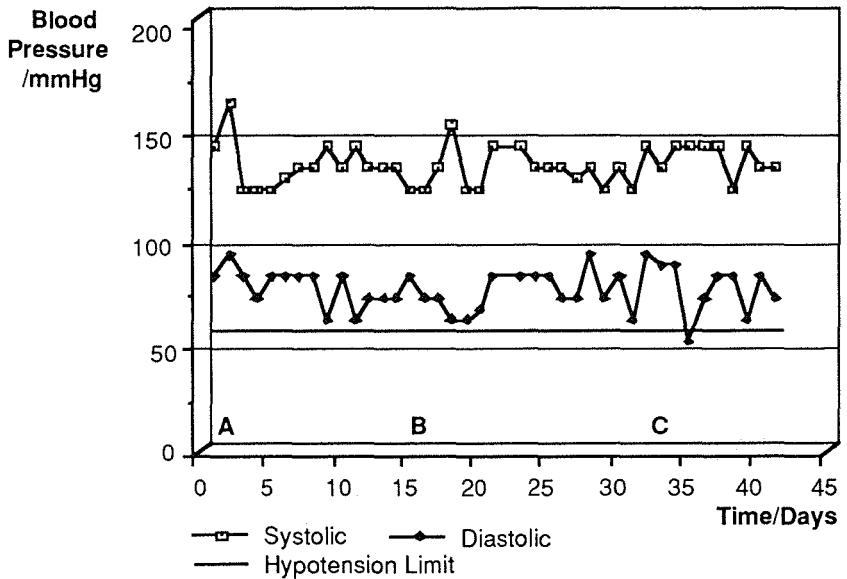
Studies on the effect of the co-administration of drugs on their metabolic disposition have shown that cimetidine decreases the metabolism of various cardiovascular drugs such as propranolol¹³, metoprolol¹⁴, nifedipine¹⁵, lignocaine¹⁶, and quinidine¹⁷. The efficiency of N-demethylation of theophylline falls with age but the fall is not affected by phenytoin induction or cigarette smoking¹⁸ or by inhibition with cimetidine^{19,20}. A similar problem could also occur in elderly patients taking nifedipine in combination with cimetidine. Patient CA (Table 6) had cimetidine added to the treatment with nifedipine because of a peptic ulcer. Nausea and vomiting made it necessary to reduce the dose of cimetidine after 17 days (Event B) and the course of treatment with the H2 antagonist was stopped after 34 days (Event C). Various studies indicated that cimetidine is expected to decrease the metabolism of nifedipine thus increasing blood levels of the calcium antagonist. One of the end effects of this would be a decrease of the blood pressure.

Table 6
Events that occurred during monitoring of blood pressure - elderly female patient CA aged 82

| Day | Event | Description of Event |
|-----|-------|--|
| 1 | A | Nifedipine 10 mg every 8 hours Cimetidine 400 mg every 12 hours |
| 17 | B | Cimetidine 200 mg morning 400 mg evening |
| 34 | C | Stop: Cimetidine |

Monitoring of the blood pressure during the course of treatment with these drugs (Figure 5) did not indicate any changes in the blood pressure although the treatment was changed. As far as the blood pressure is concerned, this indicated that cimetidine apparently did not inhibit the metabolism of nifedipine since changing the amount of cimetidine from 400 mg twice daily to none (Events A to C) did not bring any significant changes in the blood pressure. Confirmation of this observation requires the use of invasive methods to determine the blood levels of the drugs and their metabolites. However, the monitoring with the non-invasive, end point method would be enough for a rational dose adjustment, if required.

Fig. 5. Effect of drugs in elderly female patient CA aged 82 as indicated by events A, B and C



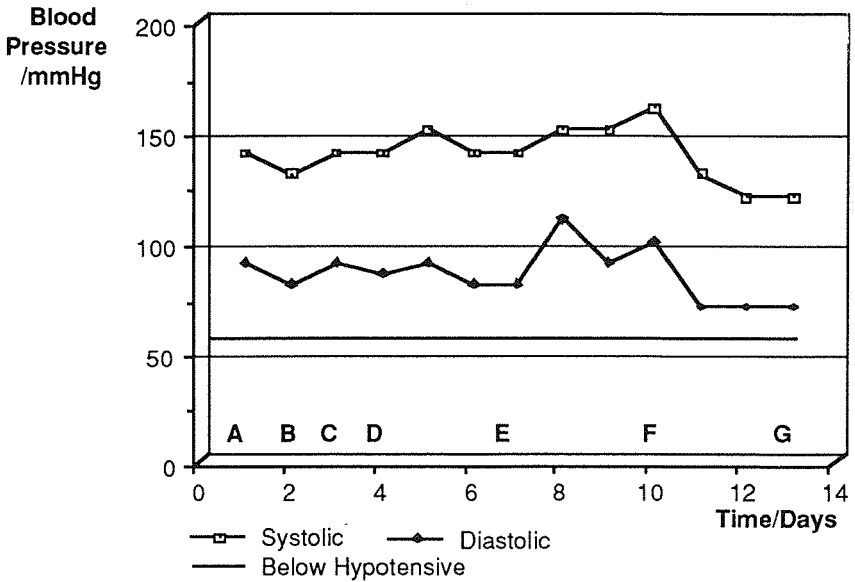
Patient FT (Table 7) has a typical treatment schedule one might find in the elderly. In spite of the polypharmacy (Event A), the patient had to be admitted to hospital.

Table 7
 Events that occurred during monitoring of blood pressure of elderly
 male patient FT aged 69

| Day | Event | Description of Event |
|-----|-------|---|
| 1 | A | Atenolol 50 mg daily Nifedipine 10 mg daily Hydrochlorothiazide/ Amiloride HCl 50/5 mg, 1/2 tablet daily Digoxin 0.125 mg daily Mianserin HCl 10 mg at night Paracetamol 2 every 6 hours Ibuprofen 2 every 8 hours |
| 2 | B | Added: Disopyramide 100 mg 1 every 8 hours Slow release KCl 600 mg 8 hourly Bendrofluazide 5 mg 1 daily |
| 3 | C | Stop: Hydrochlorothiazide/ Amiloride |
| 4 | D | Stop: Atenolol - KCl - Bendrofluazide |
| 7 | E | Stop: Paracetamol |
| 10 | F | Increased Nifedipine to 20 mg 8 hourly |
| 13 | G | Decreased Digoxin to 0.0625 mg daily |

Changing of the diuretic (Figure 6) brought no change in the blood pressure and was withdrawn (Events B, C and D). Stopping the diuretics and atenolol (Events C and D) caused a gradual increase of the diastolic and systolic blood pressure which was counteracted by an increase of the dose of nifedipine (Event F). The overall effect is that the patient was admitted to hospital having seven drugs and not under control. Reducing the number of drugs to five and an adjustment of the dosages of some of the other drugs brought an improvement of the blood pressure of the patient.

Fig. 6. Effect of drugs in male elderly patient FT aged 69 as indicated by events A to G



CONCLUSION

Although the sample is small and the subjects were randomly selected this gave a spectrum of the type of interactions that I expected in this group of patients. This pilot study points out the need to monitor patients at risk such as the elderly being treated with cardiovascular drugs on a regular and daily basis and not leave the determination of the blood pressure until a crisis had occurred. One would need a larger sample to confirm the observations that emerged from this study. These observations indicated that the daily monitoring of the blood pressure would give information on a deteriorating condition earlier, opens the possibility of decreasing the number of drugs while keeping the patients' condition under control and indicate whether there is a drug interaction or not on an individual basis.

The ward pharmacist could play an important role in analysing the non-

invasive parameters to help the health care team in understanding how the treatment is affecting the patient with respect to the overall drugs' pharmacodynamic activity. The daily monitoring of such parameters should help in a more rational drug therapy and could be the trigger to initiate a sequence of tests to understand more the condition of the patient before a crisis occurs.

Since pharmacodynamic parameters such as the blood pressure, frequency of anginal episodes or the quantity of nitrates required and pulse rate are non-invasive, their measurements could be repeated as frequently as necessary without increasing the distress of the patient. These could be monitored by the patient himself or by a junior member of the health care team such as a pharmacy or nursing student under supervision. During the monitoring exercise, the pharmacist would also have the chance to discuss the treatment with the patient. This would help to promote a better understanding between the patient and the health care team to the benefit of a better drug therapy to the elderly patient.

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