ACTA FACULTATIS MEDICAE NAISSENSIS

UDC: 612.17:616.12-008.331.1

Scientific Journal of the Faculty of Medicine in Niš 2010;27(4):221-224

Case report ■

Recurrent Malignant Hypertension Treated with Angiotensin II Receptor Blocker (ARB) and ACE Inhibitor

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SUMMARY

The prognosis of malignant hypertension without treatment is poor, with more than 80% mortality in two years. It is unusual to see it on more than one occasion in the same patient. We demonstrated clinical course, response to treatment and outcome of a patient presenting with recurrent malignant hypertension. In this patient, we did not see high renin as expected, but hypotensive effect of ARB and ACE inhibitor with normal salt diet was good. This is not surprising, since it has been shown that dual renin-aldosteron system blockade is more effective than doubling the usual dose of an ARB. Dual renin-angiotensin system blockade was effective in controlling blood pressure and restoring organ damage with regression of left ventricular hypertrophy and restoring renal function.

Key words: **malignant hypertension, angiotensin II receptor blockers, inhibitors of angiotensin converting enzyme, renin-angiotensin-aldosterone system**

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INTRODUCTION

Malignant hypertension by definition is a rare and life-threatening condition, clinically defined as severe hypertension accompanied by bilateral retinal hemorrhages and/or hard exudates, with or without papilloedema. Histologically, it is characterized by fibrinoid necrosis of arterioles. If untreated, the prognosis is poor with more than 80% mortality in two years (1). The incidence of malignant hypertension is diminishing and the outcome is more favorable with recent advances in therapy, with a five-year survival until death or dialysis of 74% (2). At the Department Of Hypertension in University Medical Center in Ljubljana we did not treat patients with malignant hypertension for the last few years. With malignant hypertension being a relatively rare condition, it would be unusual to see it on more than one occasion in the same patient. Early detection, treatment and careful follow-up of patients with malignant hypertension are therefore essential, and lack of compliance may have serious consequences.

It has been suggested that factors other than the level of BP, particularly activation of the renin-angiotensin system, may contribute to the development of fibrinoid necrosis. The level at which fibrinoid necrosis occurs is dependent upon the baseline BP (3). Patients with chronic hypertension have arteriolar hypertrophy that minimizes the transmission of pressure to the capillary circulation. As a result, malignant hypertension is usually associated with a diastolic pressure above 130 mmHg.

The plasma renin activity is typically increased in patients with malignant hypertension, a response that may be mediated by both an initial natriuresis induced by the high pressure and renal vascular injury. In addition, activation of tissue renin-angiotensin systems may be important as shown in an animal model of angiotensin II-mediated malignant hypertension (4). It seems reasonable to treat patient with malignant hypertension with blocking renina-angiotensin-aldosteron system with ACE inhibitors and angiotensin II receptor blockers.

Case of recurrent malignant hypertension

We demonstrate clinical course, response to treatment and outcome of a patient presenting with malignant hypertension.

A young woman, with a family history of hypertension had been registered as mild hypertensive patient four years before. She stopped taking prescribed antihypertensive drugs apparently due to side effects. She was admitted to hospital because of headache, vomiting and nausea and disturbances of vision. In the previous six months she had lost 15 kg. Her blood pressure was 230/150 mmHg and retinal features of malignant hypertension (hemorrhages, exudates and papilloedema) bilaterally were seen. Hypertensive encephalopathy was diagnosed on the basis of clinical symptoms and CAT scan.

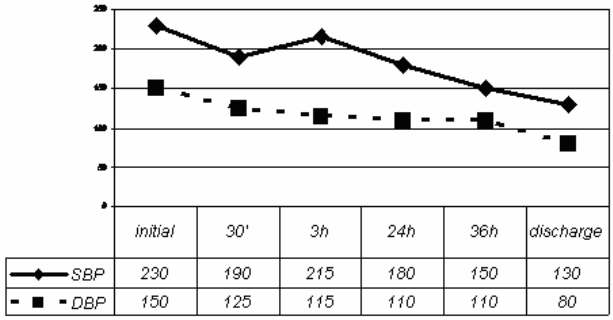
In urine, there were proteinuria end eritrocituria. Serum creatinin was elevated, as expected potassium was lower than normal, but plasma rennin activity and concentration of aldosteron in serum were normal (Table 1). Screening tests for secondary hypertension were negative, left ventricular hypertrophy was found.

Table 1. *Laboratory data*

Creatinin 252 μmol/l
Serum potassium 2,9 mmol/l
Proteinuria 3
Plasma renin activity 1,65 nmol/l/h (normal)
Aldosteron 0,17 nmol/l (normal)

Initially, in the first six hours blood pressure was reduced by 13% with Captopril 25 mg and after 24 hour by 25%, and after 36 hours her blood pressure was 150/110 mmHg. Symptoms of hypertensive encephalopathy disappeared and we treated her with losartan 50 mg, ramipril 10 mg, and metoprolol 100 mg. The major risk with excessive and uncontrolled hypotensive response is ischemic symptoms (e.g., angina pectoris, myocardial infarction, or stroke) due to an excessive therapy (5).

Her blood pressure at discharge was 130/82 mmHg (Figure 1), there were no retinal hemorrhages, exudates nor papilloedema. Laboratory tests showed increase of serum creatinin to 300 μmol/l, serum potassi - um was normal.



	initial	30'	3h	24h	36h	discharge
SBP	230	190	215	180	150	130
DBP	150	125	115	110	110	80

Figure 1. *Patients blood pressure*

Two months later vision disturbances, retinal features of malignant hypertension (hemorrhages, exudates and papilloedema) bilaterally reappeared again. Despite these findings, her office blood pressure at the examination was 125/73 mmHg. During the next two weeks, her blood pressure was well controlled, retinal changes of malignant hypertension disappeared. She told us that she stopped taking drugs and she started with therapy just two days prior to hospitalization.

Two years later her blood pressure was well controlled and there were no malignant fundi and renal function was restored (Table 2). Left ventricular mass index was normal at first diagnosis of mild hypertension, high at malignant phase and normal again after two years of effective treatment (Figure 2).

Table 2. *Laboratory data two years later*

Therapy: losartan 50 mg, ramipril 5 mg, metoprolol 100 mg, amlodipine 5 mg
BP 120/84 mmHg
Creatinin 125 μmol/l
Potassium 4,1 mmol/l
Proteinuria 2
Plasma renin activity 26,96 nmol/l/h (n. 1,15-4,16 nmol/l/h)
Retinopathy grade II

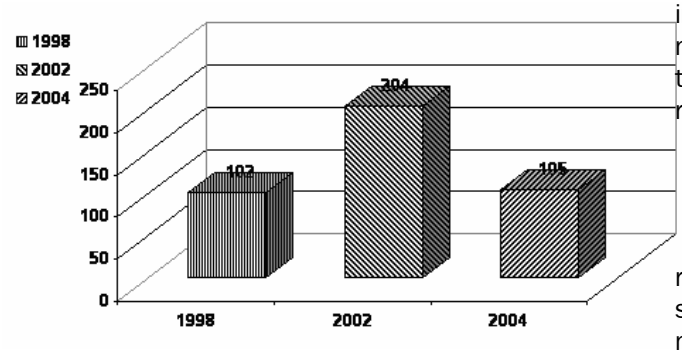


Figure 2 . *Left ventricular mass index*

DISCUSSION

Malignant hypertension is usually mediated by activation of renin-angiotensin-aldosteron axis. In our patient, we did not see high renin, although hypotensive effect of ARB and ACE inhibitor with normal salt diet was good. This is not surprising, since it has been shown that dual RAS blockade is more effective than doubling the usual dose of an ARB (6-8).

Indeed, we saw elevated renin activity in our patient as a consequence of the treatment. Administration of an ACE inhibitor initially reduces both circulating and tissue concentration of angiotensin II by blocking the enzymatic conversion of angiotensin I to angiotensin II via ACE. Long - term treatment with ACE inhibitor is accompanied by a gradual return of circulating and tissue angiotensin II to pretreatment level, a phenomenon termed “angiotensin II escape” (9). Strong evidence in support of the concept of angiotensin II escape was demonstrated only in chronic heart failure (10). We suppose that in malignant hypertension angiotensin II escape is possible and combination of ACE inhibitor and ARB therapy may be effective not only for reducing blood pressure but as a consequence of suboptimal tissue protection.

ACE inhibitors and angiotensin II receptors blockers have been shown to be effective in the treatment of congestive heart failure, high-cardiac-risk profile patients and proteinuric chronic kidney disease (11). Hypertension trial results (12,13) clearly show that restoring renal function could be due to lowering proteinuria with combination therapy beyond good control of blood pressure.

Recent data (14,15) have suggested that angiotensin II may act as a proinflamatory stimulus beyond its vasoconstrictor effects. Agents that completely block renin-angiotensin system may limit arterial inflammation. Malignant arterial hypertension is a chronic inflammatory disease (arterioloitis) that is in part treatable with current medication. New methods of interfering with inflammatory pathways are required to further improve the prognosis and prevent also an atherosclerotic process. This may offer an alternative strategy for treating patients with a range of renin concentrations, and may potentially increase the cardio- and nephroprotective benefits through a more complete blockade of the renin-angiotensin.

CONCLUSION

We concluded that poor drug compliance was responsible for the recurrence of malignant hypertension, illustrating the difficulty of persuading asymptomatic patient to adhere to take several drugs over prolonged period of time.

The initial reduction to a diastolic pressure of approximately 100 mmHg in patients with malignant hypertension is often associated with a modest worsening of renal function. Antihypertensive therapy should not be withheld in this setting unless there has been an excessive reduction in blood pressure. Dual renin-angiotensin system blockade was effective in controlling blood pressure and restoring organ damage (LV hypertrophy, renal failure).

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REKURENTNA MALIGNA HIPERTENZIJA LEČENA BLOKATOROM RECEPTORA ANGIOTENZINA II (ARB) I ACE INHIBITOROM

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Sažetak

Prognoza maligne hipertenzije bez lečenja je loša, sa više od 80% mortaliteta u periodu od dve godine. Nije uobičajeno da se vidi više od jednog puta kod istog bolesnika. U radu su predstavljeni klinički tok, odgovor na tretman i ishod kod bolesnika sa rekurentnom malignom hipertenzijom. Kod ove bolesnice renin nije bio povećan, što je bilo očekivano, dok je hipotenzivni efekat ARB-a i ACE inhibitora uz dijetu sa normalnim unosom soli bio dobar. Ovo nije iznenađujuće jer je pokazano da je dvostruka blokada sistema renin-angiotenzin efektivnija od dupliranja uobičajene doze blokatora receptora angiotenzina II. Dvostruka blokada sistema renin-angiotenzin bila je efikasna u kontroli krvnog pritiska i uspostavljanju funkcije organa nakon oštećenja uz regresiju hipertrofije leve komore i obnavljanje bubrežne funkcije.

Ključne reči: **maligna hipertenzija, blokatori angiotenzin II receptora, inhibitori angiotenzin konvertujućeg enzima, sistem renin-angiotenzin-aldosteron**