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Moxonidine: Clinical Profile

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Several haemodynamic, humoral, and metabolic changes develop in patients with hypertension. Antihypertensive drugs inhibiting or reversing these alterations are of clinical value in the therapy of hypertension. Among these agents, most recently the imidazoline I_1 receptor agonists can also be considered as the first therapeutic option. Moxonidine is a selective I_1 receptor agonist with a pharmacokinetic profile that enables it to be used once daily. It inhibits the consequences of the increased sympathetic tone, it increases natriuresis, and therefore effectively decreases blood pressure in a wide variety of hypertensive patients. The particular advantage of moxonidine is that it can increase the insulin sensitivity of those patients where it is decreased, therefore it is useful in hypertensive patients with insulin resistance. Moxonidine can be combined with many other antihypertensive drugs such as thiazides, ACE-inhibitors, calcium antagonists, but it can be potentially useful in combinations with alpha$_1$-blockers, angiotensin AT_1 blockers, and, in a particular group of patients, with beta-blockers (patients with exaggerated sympathetic tone, or in those with hyperthyroidism). *J Clin Basic Cardiol 2001; 4: 197–200.*

Key words: moxonidine, imidazoline agonists, I_1 receptors, hypertension

Hypertension is a multifactorial disease involving several genetic and environmental factors, resulting in a complex disturbance of circulatory regulation. At the first stage of the disease it is characterised by an increase in sympathetic and a decrease in parasympathetic tone, at first by an increase in cardiac output and later on by increased total peripheral vascular resistance (TPR) [1, 2]. High blood pressure is frequently associated with metabolic alterations such as insulin resistance (IR), impaired glucose tolerance (IGT), dyslipidaemia, and also with concomitant risk factors, obesity and left ventricular hyperthrophy (LVH). The so-called metabolic syndrome – Syndrome X or multimetabolic syndrome first described by Reaven [3] – is characterised by the increased sympathetic activity [4].

Properly individualised antihypertensive treatment is a necessity because the goal of the therapy is not merely to decrease blood pressure but to reverse metabolic alterations and improve quality of life. The classic centrally acting antihypertensive drugs (clonidine, methyldopa, guanfacine) stimulate pre- or postsynaptic alpha$_2$-adrenoceptors, mainly in the NTS, reduce sympathetic efferentation, decrease TPR and heart rate, and thereby systolic (SBP) and diastolic (DBP) blood pressure. Unfavourable effects of these drugs (dry mouth, decreased alertness, sleepiness, sedation, impotence, constipation) limited their use, so these agents are not considered as first-line antihypertensive drugs [5, 6].

Receptors attracting substances with imidazoline structure have been identified and characterised [7]. By now, three different subclasses of imidazoline receptors can be distinguished: I_1, I_2, and nonI_1-nonI_2 receptors. Mainly the I_1 receptors are involved in the cardiovascular regulatory processes, we believe that the I_2 receptors are connected to the monoamino-oxidase enzyme, and the nonI_1-nonI_2 receptors were identified on the presynaptic membrane modulating neurotransmission [8]. Development of specific imidazoline I_1 receptor agonists, rilmenidine [9] and moxonidine [10, 11], made it possible to affect more selectively the CNS centres participating in the regulation of blood pressure. During the last few years promising data became available showing beneficial effects of imidazoline I_1 receptor agonists, not only on blood pressure, but on other concomitant risk factors such as LVH, IR and IGT [12].

Cardiovascular effects

I_1 receptors are an integral part of physiological and pathological cardiovascular regulation [13–15]. I_1 agonists influence blood pressure while having no or very little effect on heart rate or alertness. Their central site of action was localised in the *nucleus reticularis* of the rostral ventrolateral medulla [7, 16]. These drugs decrease here the neuronal activity, suppress the efferent sympathetic activity, and as a consequence, the TPR and blood pressure [17].

Renal effects

Peripheral I_1 receptors in the renal proximal tubuli may also contribute to the long-term control of blood pressure, as stimulation of I_1 receptors increases osmotic clearance [18], diuresis and natriuresis [19]. This may be a direct renal effect [20] or a combined, central plus peripheral one [18, 21].

Metabolic effects

I_1 receptors may play a role in regulation of glucose metabolism as agmatin, the possible endogenous ligand for I_1 receptors, and moxonidine have an antihyperglycaemic effect [22]. Furthermore, moxonidine increased insulin secretion and improved glucose tolerance in obese spontaneously hypertensive rats, where it also decreased the food consumption and prevented the increase of body weight [23]. On isolated pancreatic beta-cells moxonidine acutely inhibited but chronically stimulated the release of insulin [24]. These effects may be the consequence of the inhibition of ATP-sensitive K-channels [25]. Furthermore, insulin receptor autophosphorilation with increased expression of insulin receptor substrate-1 suggest direct effects on insulin action at cellular level [23, 26].

Other antihyperglycaemic effects of moxonidine could be due to the reduction of sympathetic tone and thereby decreased stimulation of peripheral alpha$_1$, alpha$_2$, beta$_1$ and beta$_2$-adrenergic receptors. The reduced activation of alpha$_1$-adrenoceptors causes vasodilation and increases delivery of insulin and glucose to the skeletal muscles, the decreased alpha$_2$ stimulation enhances glucose-mediated insulin release. The decreased stimulation of beta$_1$-receptors reduces lipolytic activity in the fat cells while that of beta$_2$-receptors results in a reduction of glycogenolysis in the liver, and also in an increased activity of glucose transporters [27].

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Clinical Profile of Moxonidine

Pharmacokinetics

Moxonidine is readily absorbed from the gastrointestinal tract, the absorption rate is at least 90 % of the ingested dose, and the bioavailability is around 88 %. The maximum plasma concentration is achieved 1 hour after ingestion, the area under concentration-time curve (AUC) is 5.4 ng/ml × hr. Volume distribution is 1.8 L/kg, plasma protein binding is 7 %. No hepatic first-pass metabolism occurs. The kidney eliminates 90 % of moxonidine, the elimination half-life in the plasma is 2.6 hours, the total renal clearance is 1150 ml/min. Its antihypertensive effect lasts longer than 24 hours, because moxonidine tightly binds to the I_1 receptors which enables us to use it once daily. The pharmacokinetic profile of moxonidine is similar in hypertensive and normotensive individuals and it is not changed by repeated administration. The renal clearance of moxonidine is only slightly reduced in the elderly. Impaired renal function (glomerular filtration rate < 60 ml/min) decreases the clearance of moxonidine therefore the dose should be titrated accordingly [28–30].

Effects of moxonidine in essential hypertension

Analysis of the dose-response relationship of moxonidine revealed that a daily dose of 0.2–0.6 mg induces satisfactory blood pressure reduction in patients with mild-to-moderate essential hypertension. The higher the baseline blood pressure, the larger the antihypertensive effect, which lasted for at least 24 hours, and it did not change in the elderly [30].

In a placebo-controlled, 6-week study of patients with mild-to-moderate hypertension moxonidine (0.2–0.4 mg o.d.) significantly decreased blood pressure by 19.5/11.6 mmHg (SBP/DBP, respectively) [31, 32]. In another, 8-week, double-blind, randomised study involving 47 hypertensive patients (stage I or II) the effect of moxonidine (0.2–0.4 mg o.d.) was compared with that of enalapril (5–10 mg o.d.) and placebo by conventional measurements and also by ambulatory blood pressure monitoring (ABPM). As compared to placebo, both moxonidine and enalapril significantly decreased blood pressure: moxonidine by 19.5/12.3 mmHg, enalapril by 18.9/11.8 mmHg, and placebo by 4.6/4.7 mmHg; the difference between moxonidine and enalapril was statistically not significant. The trough/peak ratio for moxonidine was 0.74, that for enalapril was 0.70 [33]. Further double-blind studies revealed that the antihypertensive effect of moxonidine is comparable with that of captopril (25 mg b.i.d.), clonidine (0.3 mg daily), nifedipine sustained release (20–40 mg daily), atenolol (50–100 mg o.d.), or hydrochlorothiazide (25 mg o.d.) [32].

Moxonidine (0.2–0.6 mg o.d.) was also effective in patients with mild-to-moderate essential hypertension on long-term – one or two years – treatment. After stopping the treatment blood pressure gradually increased, so no rebound hypertension was noted [34].

In a 6-month study of 20 hypertensive patients with left ventricular hyperthrophy (LVH), moxonidine significantly reduced left ventricular mass. Septum thickness was also reduced and end-diastolic left ventricular internal diameter increased, while ejection fraction was not affected [32]. In a recent transthoracic echocardiography study the effects of different doses of moxonidine were compared: 20 patients were given 0.6 mg o.d., 8 patients 0.4 mg o.d., and 4 patients: 0.2 mg o.d. After 9 months of treatment blood pressure, left ventricular mass and interventricular septum thickness significantly decreased while the posterior wall end-diastolic thickness and left ventricular end-diastolic diameter did not change. Significant dose-related changes were not found but a tendency to an association between the dose of moxonidine and the degree of left ventricular mass reduction was shown [35].

Moxonidine effectively decreases TPR either at rest or during physical exercise [31, 36] while cardiac output and stroke volume are not affected [36]. Heart rate usually does not change but tachycardiac episodes are often suppressed on moxonidine treatment [37]. These effects are clearly caused by sympathoinhibition, as plasma noradrenaline level and plasma renin activity are decreased [31, 36], and a microneurography study shows a direct reduction in sympathetic efferentation [38]. Besides the TPR, coronary resistance also decreased, coronary flow and coronary arterial reserve significantly increased on long-term (6–9 month) moxonidine treatment of hypertensive patients while exercise tolerance capacity increased and patients had less angina pectoris symptoms. Authors suggested that these beneficial effects of moxonidine were due to the regression of structural microvascular alterations and interstitial collagen of coronary vessels [39]. This finding might give an impetus for further studies with moxonidine in patients with hypertensive microvascular angina.

Metabolic effects of moxonidine

In patients with hypertension and coexisting metabolic diseases or abnormalities (diabetes mellitus, dyslipidaemia) it is important to apply a treatment which can improve or at least be neutral to the metabolic state. In clinical studies moxonidine not only did not worsen dyslipidaemia or diabetes mellitus [31], but it was beneficial on glucose metabolism. A retrospective analysis showed that moxonidine dose-dependently decreased fasting glucose levels in hypertensive patients [22]. In an extensive, double-blind, placebo-controlled study of 77 obese hypertensive patients moxonidine significantly increased insulin sensitivity (euglycaemic clamp-test) by 11 %, and in a glucose resistant subgroup by 21 %, but it had no significant effect in insulin-sensitive patients. The insulin secretion in response to glucose stimulation was not changed [40]. More studies are required to establish whether this beneficial metabolic effect of moxonidine could prevent development of insulin resistance or diabetes mellitus in hypertensive patients and if it could also improve the cardiovascular morbidity-mortality outcomes.

Moxonidine in antihypertensive combinations

In a randomised, double-blind trial the antihypertensive effect in hypertensive patients with the combination of moxonidine (0.4 mg o.d.) and hydrochlorothiazide (25 mg o.d.) was greater and the number of responders was higher than in those with monotherapies [41]. In the open phase of the TOPIC study, moxonidine monotherapy (0.2–0.4 mg o.d.) was effective (DBP < 90 mmHg or the decrease in DBP > 10 mmHg) in 52 % of hypertensive (stage I or II) patients. In the double-blind, randomized phase of this study, in those patients where the moxonidine alone was not sufficiently effective, its combination with amlodipine (5 mg o.d.) was effective in 46.9 %, with enalapril in 26.8 %, with hydrochlorothiazide in 21.1 % of patients [42].

Safety and tolerability of moxonidine

Analysis of long-term studies of moxonidine shows that use of moxonidine is safe and well tolerated. It has no unfavourable effects on neurohumoral or metabolic functions, it can safely be administered to hypertensive patients with concomitant diseases (diabetes mellitus, gout, bronchial asthma, depression, ischaemic heart disease). Side effects were significantly less frequent and less serious as compared with the so-

called centrally acting drugs (reserpine, clonidine, guanfacine, methyldopa, guanabenz). On short-term studies the most frequently reported side effects were dry mouth (10 %), fatigue and dizziness (6–7 %), but headache was less frequent (–4 %) than in placebo-treated patients [30]. On long-term administration of moxonidine the frequency of side effects gradually decreases. Analysis of data from 9295 patients revealed that the dry mouth occurs in 2.7 %, dizziness in 1.5 %, faintness in 1.3 %, fatigue in 1.3 %, sleep disorders in 0.2 %, while depression and impotence were not reported [5, 7, 12, 13, 15, 30, 31, 32, 37]. The safety and tolerability of moxonidine was reviewed over an 8-year period – 1989 to 1997 – including 74 clinical trials and an estimated 370,000 patient-years of exposure. Dry mouth and somnolence were the most frequently reported adverse events, followed by headache and dizziness. In phase II to IV controlled studies in 1460 hypertensive patients the incidence of dry mouth was 8 to 9 %, somnolence 5 to 8 % and headache 6 % on spontaneous reporting. Treatment discontinuation, because of adverse events, was < 4 % [43].

Car driving is an important factor to be considered when choosing an antihypertensive agent. The classical centrally acting hypertensives – clonidine, guanfacine, methyldopa – are usually not indicated for drivers because they impair driving ability by slowing the reflex responses. In contrast to these agents, moxonidine did not affect driving performance and it suppressed critical blood pressure peaks in stress situations and stabilised blood pressure [44].

When Should We Use Moxonidine?

Main goals in the synthesis of new drugs are listed by Mancia et al. [45] as follows:

1. Drugs that interfere with the mechanisms involved in the initiation and maintenance of high blood pressure;
2. Those reducing blood pressure in an effective and well balanced (over 24 hours) way;
3. Couple effectiveness with no harmful consequences and side effects, thus making long-term drug administration both safe and well tolerated;
4. Drugs should not have any negative effect on other cardiovascular risk factors (eg increase in serum cholesterol, serum glucose, and insulin resistance);
5. Achieve protection against the organ damage associated with hypertension, ultimately leading to more effective prevention of cardiovascular disease.

For moxonidine the following evidence has been obtained:

1. It suppresses sympathetic tone, which is involved in the development and maintenance of hypertension.
2. It effectively reduces blood pressure on a long-term basis and in a well-balanced way, eg the effect lasts for at least 24 hrs, and therefore it can be administered once daily. Its effectiveness is comparable with that of the so called 'first-line' antihypertensive agents.
3. It has no harmful adverse effects, it is safe and well tolerated.
4. It has favourable effects on adverse metabolic concomitants of hypertension (insulin resistance) that depend at least in part on sympathetic activity.

More evidence is needed on possible protection by imidazoline receptor modulation against target organ damage [44].

Moxonidine is potentially useful in patients with metabolic syndrome (hypertension, obesity, impaired glucose tolerance or type-2 diabetes mellitus, dyslipidaemia), and in this case its use is advised by the Guidelines of the Hungarian Society of Hypertension [46].

In combination with thiazide-type diuretics it may be useful in hypertensive patients with congestive heart failure, but this indication needs further confirmation.

With dihydropyridine-type calcium antagonists it can be indicated in hypertensive patients with ischaemic heart disease (particularly with microvascular angina), with obliterative atherosclerosis, with chronic parenchymal renal disease, or with bronchial asthma.

With ACE-inhibitors or with *angiotensin AT_1 antagonists* it can be indicated for hypertensive patients with type-2 diabetes mellitus, with chronic parenchymal renal disease, with congestive heart failure, and also for elderly patients.

With alpha$_1$-adrenoceptor antagonists it may be useful in hypertensive patients with type-2 diabetes mellitus, with dyslipidaemia, with benign prostatic hyperthrophy.

With beta-blockers moxonidine is probably beneficial in patients with hyperthyroidism or in those with exaggerated sympathetic tone.

The antihypertensive effectiveness of some of these combinations (with thiazides, dihydropyridine-type calcium antagonists, ACE-inhibitors) has been proven [30, 31, 41] while others (with AT_1 antagonists, with alpha$_1$-blockers, with beta-blockers) are to be elucidated. Mortality and morbidity outcome studies are also needed in this special patient population to evaluate the potentially beneficial effects on cardiovascular target organ damage of hypertension.

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