Drug Safety 1998 Sep; 19 (3): 191-203
0114-5916/98/0009-0191/$06.50/0

Safety and Tolerability of Moxonidine in the Treatment of Hypertension

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Contents

Abstract

Classical centrally acting antihypertensive agents lower blood pressure by reducing excessive sympathetic tone; however, their clinical use is limited by an adverse effect profile resulting from α_2-adrenoceptor agonism. Moxonidine is a new centrally acting agent showing selective agonism of imidazoline I_1 receptors, but very little α_2-adrenoceptor agonism.

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 patients with hypertension (n = 1460), the incidence of dry mouth was 8 to 9%, somnolence 5 to 8% and headache 6%, as recorded by spontaneous reporting; the percentage of patients discontinuing treatment because of adverse events did not exceed 4%. Subgroup analyses revealed no differences in adverse events related to age or gender. Moxonidine did not exacerbate concomitant

conditions such as diabetes mellitus or chronic obstructive pulmonary disease, or interact pharmacokinetically with concurrent medications such as hydrochlorothiazide, digoxin and glibenclamide (glyburide). Coadministration of moxonidine with lorazepam resulted in small additional impairments in tasks requiring attention.

A similar distribution of adverse events was observed in uncontrolled studies (n = 1058). The incidence and severity of dry mouth and somnolence were found to decrease with increasing exposure to moxonidine over a period of up to 2 years. Serious adverse events were rare in all trials and could not be attributed to administration of moxonidine. Post-marketing surveillance of the adverse effect profile of moxonidine detected 2 additional adverse effects: nausea and allergic skin reactions. The safety profile of moxonidine, combined with proven antihypertensive efficacy, suggests that it may have an important role to play in the management of mild-to-moderate hypertension.

Cardiovascular disease is the largest single contributor to mortality in Westernised countries. The causes are multifactorial, but essential hypertension is significant among the risk factors. Hypertension is an increasingly significant public health and medical problem: it is estimated that half of the population of the world aged over 65 years has elevated blood pressure.[1,2]

Genetic predisposition to hypertension and a number of environmental factors are known to interact to differing degrees to raise blood pressure.[3] In the last 10 years, evidence has accumulated to suggest that hypertension can form part of a syndrome linking raised blood pressure and coronary heart disease with metabolic disorders such as dyslipidaemia, glucose intolerance and insulin resistance.[4,5] The metabolic syndrome is believed to arise, in part, from neurohormonal overactivity of the sympathetic nervous system.[6] This has driven the development of new concepts in inhibition of the sympathetic nervous system as a means not only of controlling raised blood pressure *per se*, but also of modulating the hypertension syndrome.

Centrally acting antihypertensive agents have been available since the 1950s,[7] but are no longer first-line agents for the treatment of hypertension. Methyldopa has a high affinity for α_2-adrenoceptors in the CNS and reduces elevated blood pressure by sympatho-inhibition;[8] however, the α_2-adrenoceptor agonism of this agent is associated with an unfavourable adverse effect profile. Clonidine has affinity for α_2-adrenoceptors and imidazoline I_1 receptors.[8] The discovery of distinct I_1 receptors in the rostral ventrolateral medulla[9,10] presented a new therapeutic target and a potential means of dissociating antihypertensive effects from adverse effects. First generation centrally acting antihypertensive drugs (e.g. reserpine and methyldopa) have been shown to be effective in limiting the complications of hypertension.[8]

Moxonidine and rilmenidine represent a new generation of centrally acting antihypertensive agents.[8,11] Moxonidine is a selective I_1 receptor agonist with low affinity for α_2-adrenoceptors. It was introduced for clinical use in the treatment of hypertension in 1991. Moxonidine lowers blood pressure by reducing systemic vascular resistance without reducing cardiac output. Oral administration of moxonidine 0.2 to 0.4 mg/day has been shown to reduce systolic blood pressure by 20 to 30mm Hg and diastolic blood pressure by 10 to 20mm Hg (these figures are not placebo-corrected).[12] Achievement of blood pressure control by moxonidine is similar to that of antihypertensive agents from other classes such as diuretics, α- and β-blockers, calcium antagonists and ACE inhibitors.

Early clinical trials showed that moxonidine was not associated with a high incidence of adverse effects. Webster and Koch[13] reviewed data reported from controlled and uncontrolled clinical trials and from post-marketing surveillance to December 1994, and found that moxonidine was well

Table I. Demographic data from clinical trials (moxonidine-treated patients only)

	Type of trial			
	phase I	phase II/III: placebo-controlled	phase II/IV: active-controlled	uncontrolled
Total no. of patients	302	742	957	1058[a]
Age (y)				
Minimum	18	21	18	16
Maximum	81	77	89	91
Mean ± SD	32	54.2 ± 10.7	55.5 ± 10.4	58
≤50 (%)		264 (35.6)	296 (30.9)	
51-60 (%)		252 (34.0)	352 (36.8)	
≥61 (%)[b]	14 (4.6)	226 (30.5)	309 (32.3)	274 (26)
Gender of patients (%)				
Male	253 (83.8)	376 (50.7)	570 (59.6)	585 (55.3)
Female	49 (16.2)	366 (49.3)	387 (40.4)	473 (44.7)

a Including 13 patients with severe hypertension.

b ≥65 years in phase I and uncontrolled studies.

SD = standard deviation.

tolerated and showed no evidence of inducing severe adverse effects during that period.

This article reviews and updates all safety information received on moxonidine over an 8-year period from 1989 to December 1997. The safety data are from 2 main sources – clinical trials and periodic drug safety update reports (PDSUR). The PDSUR data have been collated by Solvay Pharmaceuticals and refer to the Solvay product only, whereas the reviewed clinical trials were conducted by Solvay Pharmaceuticals and some by Beiersdorf-Lilly. The clinical trial data include safety assessments from phase I and phase II to IV studies conducted in 9 countries and entered onto a database by Solvay Pharmaceuticals; these data form the basis of this report.[14]

1. Patient Characteristics and Moxonidine Administration

1.1 Phase I Clinical Pharmacology Trials

A total of 302 patients were exposed to moxonidine in 20 clinical pharmacology studies conducted between 1981 and 1994. Safety data from these studies were analysed. The study participants included 274 healthy volunteers and 28 patients with diagnosed conditions, including congestive heart failure (n = 10), asthma (n = 12), hypertension (n = 5) or anxiety disorders (n = 1). The mean age of the patients was 32 years and the majority (84%) were men (table I). 16 of the studies were crossover in design; 4 were double-blind, controlled with clonidine or placebo, and 4 were open and uncontrolled. The trials tested single oral and intravenous doses of moxonidine, as well as multiple dose regimens that lasted for up to 3 weeks in 1 trial. Moxonidine was administered as a single oral dose of 0.1 to 1mg, a single intravenous dose of 0.2 to 1mg, or multiple oral and intravenous doses of 0.2 to 0.4 mg/day.

1.2 Phase II to IV Controlled Trials

30 controlled trials have been carried out since 1983 and results concerning safety recorded in a database. Of those trials, 8 were placebo-controlled and 22 were active-controlled. The demographic data are shown in table I. In the placebo-controlled trials, approximately half of the 742 patients treated with moxonidine were men (50.7%) and the average age was 54.2 ± 10.7 years. A slightly higher proportion of the 957 patients in the active-controlled studies were men (59.6%, pooled over all studies) and the mean age was 55.5 ± 10.4

years. The frequency of concomitant diseases was similar among all moxonidine-treated patients in the placebo-controlled and active-controlled studies (table II), and in each case the occurrence of concomitant diseases in the moxonidine groups was similar to that in the parallel placebo or active control groups.

The doses of moxonidine administered in the placebo-controlled trials were fixed in all but 47 (6%) patients in whom the dose was titrated according to efficacy criteria. The majority of the patients received oral moxonidine 0.4 mg/day, but some trials tested 0.2, 0.6 and 0.8 mg/day. A similar pattern of moxonidine testing was seen in the active-controlled trials, except for 2 early comparative trials with clonidine in which a dosage range of 0.1 to 1 mg/day was used. Over 90% of patients in the placebo-controlled trials received moxonidine for 1 to 3 months, as did 62% of patients in the active-controlled studies. 96 patients (10%) received moxonidine for a period exceeding 6 months; most of these patients were taking part in a double-blind trial of moxonidine versus sustained-release nifedipine. Table II lists the reference drugs used in the active-controlled trials.

1.3 Uncontrolled Trials

16 short term (up to 3 months) and 8 long term (6 to 24 months) uncontrolled trials have been reported since 1982. Of these, 3 investigated moxonidine in combination with hydrochlorothiazide, xipamide/triamterene or a β-blocker. In the trials, a total of 1058 patients (55.3% men; mean age 58 years) were exposed to moxonidine; 1045 had mild-to-moderate hypertension and 13 had severe hypertension (table I). Of these patients, 515 received moxonidine for more than 6 months. The dosage of moxonidine used ranged from 0.1 to 2.0 mg/day (average dosage 0.2 to 0.4mg) and was either fixed (5 trials) or titrated to achieve optimal regulation of blood pressure (19 trials). The most frequently administered dosage was 0.2 mg/day.

Table II. Reference antihypertensive drugs used in phase II to IV clinical trials

No. of studies	Class	Drug(s)
2	α_2-Adrenoceptor agonists	Clonidine
9	ACE inhibitors	Captopril, enalapril, cilazapril, ramipril
3	β-Blockers	Atenolol
6	Calcium antagonists	Nifedipine, nitrendipine
2	Diuretics	Hydrochlorothiazide
1	Imidazoline receptor agonists	Rilmenidine
4	Combination regimens	Moxonidine + hydrochlorothiazide, moxonidine + β-blocker, moxonidine + xipamide/triamterene

1.4 Periodic Drug Safety Update Reports (PDSUR)

Four PDSUR on oral moxonidine 0.2mg, 0.3mg and 0.4mg have been issued between 1989 and 1997 and the data from these reports are included in this review.[15-18] The first 3 were compiled in the format proposed by the Council for International Organizations of Medical Sciences (CIOMS) Working Group II,[19] and the fourth according to the recommendations of the International Conference on Harmonisation.[20,21] The PDSURs reviewed all adverse events associated with moxonidine produced by Solvay, including events reported spontaneously from the market, reports from health authorities and published case reports, irrespective of any causality assessment. In addition, the PDSURs included serious adverse drug reaction reports from clinical studies. In line with international guidelines, clinical study reports without a reasonable possibility of a causal relationship between the drug and the adverse event, as assessed by both the company and the reporter, were not considered as reactions and were therefore excluded from the reports. The worldwide exposure to moxonidine is estimated to be over 370 000 patient-years.

2. Data Collection and Analysis

The clinical pharmacology studies encompassed a wide range of aims and methodologies. Adverse events seen with moxonidine treatment were pooled across trials according to the route of administration and dosage regimen. In the placebo-controlled phase II and III trials, the method of choice for collecting adverse event data was to record spontaneous reports at each study visit. This method was also used in the majority of the active-controlled studies, but in 4 trials a checklist method was used. The checklist comprised 21 items which were graded as 'not present', 'mild' or 'severe' at each study visit and the connection of each item, if present, with the study medication was judged 'improbable', 'possible' or 'probable'. In all the controlled trials, the proportion of patients discontinuing treatment was noted. Haematology and clinical chemistry parameters were measured and compared across the groups. For serious adverse events, the relationship to the study drug was assessed by the investigators. In the trials using spontaneous reporting of adverse events, the data were also analysed according to gender and age subgroups. In the uncontrolled trials, the majority of adverse event data were collected by spontaneous reporting, but the checklist method was used in 7 trials.

Analysis of safety data from the pharmacological and uncontrolled studies was based on individual medical and statistical reports, while data from the controlled studies were derived solely from information on case record forms entered into a database. For each type of clinical study, safety data were pooled to simulate a single protocol, single-centre approach, to derive overall frequencies and simple mean values. By this method, data from each patient had the same weight in the overall outcome. A potential disadvantage of this approach was that the effects of study size and design and treatment interactions were not taken into account. Nevertheless, this method of data pooling was felt to be appropriate to this stage in development, since only studies with intraindividual comparisons were performed. Safety was evaluated on the basis of adverse event reporting and laboratory findings. Analysis was generally performed on the intention-to-treat population, i.e. all patients who received at least 1 dose of trial medication, and was based on all adverse events, treatment-emergent adverse events (adverse events not present before treatment or worsened during treatment), serious adverse events and patients discontinuing treatment because of adverse events. Serious adverse events

Table III. Most common adverse events occurring in patients exposed to moxonidine in 20 phase I clinical pharmacology trials

	Route of administration				All trials[a]	Placebo[b]
	intravenous	oral				
		single dose	rising dose[c]	multiple dose		
No. of patients evaluable for safety data	31	105	10	153	289	78
Total no. of patients with adverse events (%)	15 (48.4)	64 (61.0)	10 (100)	94 (61.4)	173 (59.9)	
No. of adverse events (%):						
somnolence	11 (35.4)	45 (42.9)	10 (100)	52 (34.0)	108 (40)	23 (29.5)
headache	4 (12.9)	20 (19)	6 (60)	19 (12.4)	43 (15.9)	5 (5.7)
dry mouth	6 (19.4)	13 (12.4)	10 (100)	17 (11.1)	36 (13.3)	7 (8.9)
dizziness	6 (19.4)	10 (9.5)	2 (20)	14 (9.2)	30 (11.1)	3 (3.4)
abnormal thinking		12 (11.4)		2 (1.3)	14 (5.2)	5 (5.7)
asthenia	4 (12.9)		6 (60)	5 (3.3)	9 (3.3)	2 (2.3)

a Spontaneously reported adverse events only.

b Spontaneous reporting from 6 studies.

c Data collected by checklist.

were defined as any event requiring hospitalisation or prolongation of hospitalisation, that was potentially disabling, life-threatening, fatal or contributing to death. Congenital anomaly, cancer and overdose were also considered as serious adverse events. Specifically, dose-dependency, long term exposure, drug-drug and drug-disease interactions were examined. A large number of patients in phase II and III received other medications.

3. Results

3.1 Phase I Clinical Pharmacology Trials

Despite the fact that these studies had differing aims and used a variety of methodologies, when data were pooled according to the route of administration of moxonidine, the type of adverse event seen was found to be independent of the route and frequency of dosage (table III).

All but 10 of the 289 evaluable study participants were in trials in which adverse events were collected by spontaneous reporting and, of these participants, 59.9% reported adverse events. Somnolence was the most common spontaneously reported event, occurring with an overall frequency of 40% across all the trials. In 2 trials where dose-dependence was evaluable, somnolence showed a clear relationship with dose over the range of moxonidine doses used in the trials. Somnolence was also reported by 29.5% of volunteers in the placebo groups, indicating the generally high frequency of reporting of this event in phase I trials.

Headache was the next most commonly reported adverse event, with an overall frequency of 16% (table III). However, this figure is put into perspective by comparing the frequency of headache seen in individuals taking moxonidine (n = 83) or placebo (n = 78) in the 6 placebo-controlled phase I trials; headache was reported by 7.2 and 5.7% of moxonidine and placebo recipients, respectively.

Dry mouth occurred following moxonidine treatment with an overall frequency of 13% in all phase I studies. In the placebo-controlled trials, the incidence of this event was 22.9% (19 of 83) and 8.9% (7 of 78) in the moxonidine and placebo groups, respectively. The occurrence of dizziness, 'abnormal thinking' (Coding Symbols for Thesaurus of Adverse Drug Reaction Terms definition) and asthenia may have been related to the pharma-

Table IV. Spontaneously reported adverse events in patients exposed to moxonidine in 8 phase II and III placebo-controlled clinical trials

	All patients	Moxonidine					Placebo
		gender subgroups		age subgroups (y)			
		male	female	≤50	51-60	≥61	
No. of patients	742	376	366	264	252	226	399
No. of patients with treatment-emergent adverse events (%)	287 (38.7)	143 (38.0)	144 (39.3)	106 (40.2)	96 (38.1)	85 (37.6)	123 (30.8)
No. of patients withdrawing from treatment because of adverse events (%)	30 (4.0)						8 (2.0)
No. adverse effects by body system (%):							
Body as a whole	133 (17.9)	71 (18.9)	62 (16.9)	60 (22.7)	43 (17.1)	30 (13.3)	59 (14.8)
somnolence	54 (7.3)						15 (3.8)
headache	44 (5.9)						28 (7.0)
Nervous system	120 (16.2)	53 (14.1)	67 (18.3)	43 (16.3)	42 (16.7)	35 (15.5)	33 (8.3)
dry mouth	66 (8.9)						9 (2.3)
Respiratory	41 (5.5)	19 (5.1)	22 (6.0)	16 (6.1)	13 (5.2)	12 (5.3)	28 (7.0)
Digestive	38 (5.1)	21 (5.6)	17 (4.6)	11 (4.2)	14 (5.6)	13 (5.8)	24 (6.0)
Metabolic/endocrine	36 (4.9)	14 (3.7)	22 (6.0)	15 (5.7)	9 (3.6)	12 (5.3)	12 (3.0)
Cardiovascular	24 (3.2)	11 (2.9)	13 (3.6)	9 (3.4)	9 (3.6)	6 (2.7)	10 (2.5)

Table V. Treatment-emergent adverse events occurring most commonly in patients exposed to moxonidine in 22 phase II to IV active-controlled clinical trials

	Moxonidine		Reference antihypertensive drug	
	spontaneous reporting	checklist	spontaneous reporting	checklist
No. of patients	718	239	776	112
No. of patients with adverse events (%)	210 (29.2)	175 (73.2)	240 (30.9)	88 (78.6)
No. of patients withdrawing from treatment because of adverse events (%)	24 (2.5)	25 (2.8)		
No. of adverse events by body system (%)				
Nervous system	94 (13.1)	109 (45.6)	83 (10.7)	42 (37.5)
dry mouth	56 (7.8)	105 (43.9)	26 (3.4)	56 (50.0)
Body as a whole	93 (13.0)	137 (57.3)	93 (12.0)	52 (46.4)
somnolence	38 (5.3)	106 (44.4)	31 (4.0)	41 (36.6)
headache	43 (6.0)	87 (36.4)	46 (5.9)	34 (30.4)
Digestive	25 (3.5)	123 (51.5)	35 (4.5)	67 (59.8)
Cardiovascular	19 (2.6)	39 (16.3)	25 (3.2)	27 (24.1)
Metabolic/endocrine	18 (2.5)	4 (1.7)	19 (2.4)	12 (10.7)

cological effects of moxonidine. Abnormal thinking in particular was frequently reported in 1 trial employing psychometric evaluation of vigilance.

Two serious adverse events were reported in phase I trials, both of whom were judged to be unrelated to moxonidine treatment. For all the studies, a total of 10 patients discontinued treatment, of which 2 were withdrawn because of drug-related adverse events (a pronounced fall in blood pressure after administration of intravenous moxonidine 0.6mg in 1 case, and an accidental injury which resulted in an overnight stay in hospital in the other case). No clinically significant trends in laboratory parameters were observed.

3.2 Phase II and III Placebo-Controlled Clinical Trials

Safety data were collected by spontaneous reporting in all 8 studies, in which 287 (38.7%) of 742 moxonidine-treated patients reported treatment-emergent adverse events (table IV). The most frequently reported events were dry mouth (8.9%), somnolence (7.3%) and headache (5.9%). When the data were corrected for placebo effect, dry mouth showed dose-dependency, whereas headache fell within or below the placebo range. No clear tendency for somnolence could be shown.

The incidence of spontaneously reported adverse events showed no relationship with gender or age (table IV). 67 moxonidine-treated patients withdrew from the placebo-controlled trials; 30 of these patients withdrew because of adverse events. Three serious adverse events were reported in the moxonidine arm of the placebo-controlled trials. These events were acute cardiac failure after 38 days of moxonidine treatment, sudden death due to cerebral embolism after 40 days of treatment, and unstable angina pectoris after 77 days of treatment. All of these events were considered to be unrelated or unlikely to be related to treatment. Of the 287 patients receiving moxonidine who reported treatment-emergent adverse events, 274 events (95.1%) were mild or moderate in severity.

3.3 Phase II to IV Active-Controlled Clinical Trials

22 trials compared moxonidine with standard reference antihypertensive agents of different classes. The nature and frequency of adverse events in these trials varied according to which of the 2 methods of collecting safety data was used.

In 18 trials in which spontaneous reporting was used, 210 (29.2%) of 718 evaluable patients reported adverse events with moxonidine, as did 240 (30.9%) of 776 patients in the reference antihypertensive drug control group (table V). The events most frequently reported with moxonidine were dry mouth, headache, somnolence and dizziness (table V). The pooled data showed that 114 (25.7%) of 444 male patients and 96 (35.0%) of 274 female patients reported adverse events (table VI). When evaluated according to age, the frequency of adverse events decreased slightly with age. In the subgroup aged ≤50 years, 72 (31.2%) of 231 patients reported adverse events, compared with 77 (29.1%) of 265 and 61 (27.5%) of 222 patients in the 51 to 60 years and ≥61 years groups (table VI). Among the spontaneously reported adverse events with moxonidine, 194 of 210 (92.4%) were mild or moderate in severity and the distribution of severity was similar in the reference antihypertensive drug-treated patients.

The incidence of adverse events was greater when the adverse event reports were documented by the checklist method, which is known to elicit a higher frequency of reporting than spontaneous reporting. In 4 controlled parallel-group trials, 73% of 239 moxonidine-treated patients reported treatment-emergent adverse events, as did 79% of 112 patients in the control group (table V). Using the checklist method, somnolence, dry mouth and headache were recorded in 44, 44 and 36%, respectively, of moxonidine-treated patients and in 37, 50 and 30%, respectively, of controls (table V). In a fifth checklist-monitored trial, the results of which have not yet been included on the database, 6 of 25 (24%) of moxonidine-treated patients reported 'undesired effects of medication'. Across all the reference antihypertensive drug-controlled trials, 63 of 957 patients receiving moxonidine withdrew from treatment; 24 (2.5%) because of adverse events (table V). Among patients treated with moxonidine in these trials, 8 serious adverse events were reported. These were bone fracture (n = 3), myocardial infarction (2), syncope (1), renal tumour (1) and atrial fibrillation (1), all of which were judged to be either unrelated or unlikely to be related to treatment. Laboratory haematology data revealed no trends in the moxonidine-treated pa-

Table VI. Treatment-emergent adverse events by gender and age occurring most commonly in patients exposed to moxonidine in 22 phase II-IV active-controlled clinical trials (spontaneous reporting)

	Moxonidine					Reference antihypertensive drug				
	gender subgroups		age subgroups			gender subgroups		age subgroups		
	male	female	≤50 years	51-60 years	≥61 years	male	female	≤50 years	51-60 years	≥61 years
No. of patients	444	274	231	265	222	448	328	251	301	224
No. of patients with treatment-emergent adverse events (%)	114 (25.7)	96 (35.0)	72 (31.2)	77 (29.1)	61 (27.5)	142 (31.7)	98 (29.9)	79 (31.5)	90 (29.9)	71 (31.7)
No. of adverse events (%)										
Body as a whole	49 (11.0)	44 (16.1)	29 (12.0)	32 (12.1)	32 (14.4)	57 (12.7)	36 (11.0)	29 (11.6)	35 (11.6)	29 (12.9)
somnolence	22 (5.0)	16 (5.8)	13 (5.6)	9 (3.4)	16 (7.2)	22 (4.9)	9 (2.7)	4 (1.6)	13 (4.3)	14 (6.3)
headache	22 (5.0)	21 (7.7)	12 (5.2)	16 (6.0)	15 (6.8)	27 (6.0)	19 (5.8)	19 (7.6)	16 (5.3)	11 (4.9)
Nervous system	44 (9.9)	50 (18.2)	31 (13.4)	37 (14.0)	26 (11.7)	46 (10.3)	37 (11.3)	27 (10.8)	26 (8.6)	30 (13.4)
dry mouth	25 (5.6)	31 (11.3)	17 (7.4)	25 (9.4)	14 (6.3)	13 (2.9)	13 (4.0)	6 (2.4)	10 (3.3)	10 (4.5)
Respiratory	9 (2.0)	7 (2.6)	6 (2.6)	6 (2.3)	4 (1.8)	17 (3.8)	10 (3.0)	7 (2.8)	14 (4.7)	6 (2.7)
Digestive	14 (3.2)	11 (4.0)	11 (4.8)	7 (2.6)	7 (3.2)	16 (3.6)	19 (5.8)	8 (3.2)	15 (5.0)	12 (5.4)
Metabolic/ endocrine	7 (1.6)	12 (4.4)	5 (2.2)	8 (3.0)	6 (2.8)	14 (3.1)	6 (1.8)	6 (2.4)	9 (3.0)	4 (1.8)
Cardiovascular	8 (1.8)	11 (4.0)	8 (3.5)	4 (1.5)	7 (3.2)	15 (3.3)	10 (3.0)	13 (5.2)	8 (2.7)	4 (1.8)

Table VII. Adverse events occurring most commonly in patients exposed to moxonidine in 24 uncontrolled clinical trials

	Duration of moxonidine treatment				
	all trials	<1 week	1-4 weeks	>4 weeks–6 months	>6 months
No. of patients	1043	15	121	377	530
No. of patients reporting adverse events (%)	376 (36.0)	6 (40.0)	64 (52.9)	117 (31.0)	189 (35.7)
No. of patients withdrawing from treatment because of adverse events (%)	28 (2.7)		2 (1.6)	10 (2.7)	16 (3.0)
No. of adverse events (%):					
Dry mouth	152 (14.5)	5 (33.3)	38 (31.4)	54 (14.3)	55 (10.4)
Somnolence	86 (8.2)		29 (24.0)	38 (10.1)	19 (3.6)
Headache	82 (7.8)		20 (16.5)	26 (6.9)	36 (6.8)
Dizziness	61 (5.8)		15 (12.4)	18 (4.8)	28 (5.3)
Insomnia	28 (2.7)		9 (7.4)	6 (1.6)	13 (2.5)
Asthenia	21 (2.0)		10 (8.3)	4 (1.1)	7 (1.3)
Nausea	19 (1.8)		6 (5.0)	6 (1.6)	7 (1.3)

tients. Likewise, although several statistically significant differences were found in blood chemistry parameters in individual trials, none of the changes from baseline to post-study were considered to be of clinical relevance.

3.4 Uncontrolled Trials

A total of 1043 patients with mild-to-moderate hypertension received moxonidine and were evaluated in 24 short term and long term uncontrolled trials. Of these patients, 376 (36.0%) reported adverse events (table VII). In 7 of the studies, a checklist was used. Dry mouth, somnolence, headache and dizziness were the most commonly reported events across all trials.

When the adverse event data were pooled according to duration of moxonidine treatment, the frequency of adverse events in patients receiving the drug in the long term trials was found to be lower than that among patients exposed to moxonidine for 1 to 4 weeks (table VII). Specifically, the incidence of dry mouth fell from 33.3% during short (<1 week) treatment to 10.4% in patients exposed to moxonidine for >6 months. Likewise, somnolence occurred less frequently in the long term group (3.6%) compared with the short term group (24% for 1 to 4 weeks' exposure). There were 22 serious adverse events recorded among moxonidine-treated patients in uncontrolled trials, of which 2 (9.0%) were considered probably related to moxonidine treatment. These events were orthostatic hypotension and transient ischaemic attack with vertigo; both patients recovered fully. 28 patients (2.7%) withdrew from 10 uncontrolled studies due to adverse events.

3.5 PDSUR

Table VIII shows the distribution of adverse drug reaction reports included in PDSURs for the last 5 years. In total, 231 adverse drug reactions were reported between 1993 and 1997, of which the principal source (90%) was spontaneous reports from the market. Cumulative experience for the period covered by all reports has confirmed that moxonidine has not been associated with any serious long term adverse effects and is well tolerated. Through the system of pharmacovigilance, which is sufficiently powerful to detect rare adverse events, 'nausea' and 'allergic skin reactions' have been added to the adverse effects described in the core data sheet for moxonidine. No other adverse effects not previously reported have been seen to date. Moreover, there has been no increase in the reporting of adverse effects despite the increase in numbers of patients surveyed in the PDSURs during this period.

After completion of the most recent PDSUR, a case of cholestatic hepatitis was reported in an

Table VIII. Number and distribution of adverse drug reaction reports included in periodic drug safety update reports (PDSURs) between 1993 and 1997

Period	Reports received (n)		Report source (n)						
			market		health authority		literature		clinical study[a]
	all	serious	all	serious	all	serious	all	serious	
1993	8	4	8	4	0	0	0	0	0
1994	73	4	72	3	0	0	0	0	1
1995	41	1	39	0	1	0	0	0	1
1996	19	6	16	3	1	1	0	0	2
1997	90	21	74	11	9	3	1	1	6
Total	231	36	209	21	11	4	1	1	10

a Serious cases only.

82-year-old man. The effect was reported to be drug related. The patient recovered after supportive treatment including phytomenadione (vitamin K_1), albumin and diuretics.[22]

3.6 CNS Effects

The sedating effects of moxonidine on the CNS were examined by electroencephalogram (EEG) and psychometric testing, and were found to be small and clinically insignificant when compared with the sedating effects of clonidine.[23,24] The minimal CNS effects of moxonidine were further evident in a study by Schmidt and colleagues[25] who found no impairment in driving ability in patients taking moxonidine for hypertension, and that the substantial increases in blood pressure occurring in individuals with hypertension during the test drive were abolished by moxonidine treatment. Two double-blind, placebo-controlled, crossover studies showed that moxonidine did not interact with moclobemide following coadministration to healthy volunteers, but some impairment of tasks requiring a high level of attention was noted when moxonidine was coadministered with lorazepam.[26]

3.7 Pharmacokinetic and/or Pharmacodynamic Studies

Following oral administration of moxonidine, 80 to 90% of the dose is absorbed. Peak plasma concentrations are reached between 0.6 to 0.7 hours after administration. The elimination half-life of moxonidine is 2 to 2.5 hours and food intake does not influence the oral bioavailability.[27] There is no pharmacokinetic interaction between moxonidine and hydrochlorothiazide, digoxin or glibenclamide (glyburide).[28-30] A double-blind, placebo-controlled, crossover study showed that moxonidine did not interact with moclobemide following coadministration to healthy volunteers.[26] Kirch and colleagues[31,32] reported that, in patients with impaired renal function, moxonidine did not lead to further deterioration of the condition, and the increased elimination half-life and area under the curve $(AUC)_{0\text{-}24h}$ resulting from renal dysfunction affected neither the blood pressure response nor the nature, frequency or severity of adverse events. Moxonidine does not alter hepatic enzymatic systems as it is not metabolised by the cytochrome P450 enzymatic system.

3.8 Patients with Chronic Obstructive Pulmonary Diseases

A completed double-blind, randomised, parallel-group study comparing moxonidine with ramipril in 106 patients with chronic obstructive pulmonary disease (COPD) and hypertension showed that moxonidine did not impair pulmonary function while producing sufficient blood pressure reduction. A slight but insignificant increase in forced expiratory volume in 1 second (FEV_1) of 12ml was noted in moxonidine-treated patients from day 0 to day 56 of treatment ($p = 0.713$), as was an increase in oxygen partial pressure (PO_2) of 0.60mm Hg ($p = 0.599$). Likewise, insignificant decreases in FEV_1 (58ml, $p = 0.180$) and PO_2 (0.5mm Hg, $p =$

0.623) were recorded in ramipril-treated patients over the same period.[33]

3.9 Overdose

Three case reports of moxonidine overdoses have been received to date. Two of the events occurred in the children of 2 patients taking moxonidine, following accidental ingestion of the agent. Both children, aged 2 and 3 years, recovered fully without signs of cardiovascular disorder. The third case was intentional ingestion of moxonidine, ranitidine and alcohol (ethanol) during a suicide attempt by a 23-year-old man. The plasma concentration measured was at least 70-fold higher than that which would be expected after ingestion of a recommended dose. The patient developed bradycardia, somnolence and hypotension. He was treated and recovered without sequelae.

The recommended treatment for an overdose involves a number of measures aimed at supporting the circulatory system. Tolazoline, an α-blocker, may reverse part of the symptoms.

3.10 Combination Therapy

Frei et al.[34] compared the efficacy and safety of moxonidine alone, hydrochlorothiazide alone, the combination of both drugs and placebo. The combination of both active drugs improved efficacy without additive effects on the adverse effect profile. Other studies combining moxonidine with representatives of other major classes of antihypertensive drugs are presently being evaluated.

4. Discussion

This review of data from clinical trials involving over 3000 patients and post-marketing surveillance covering an estimated 370 000 patient-years of exposure confirms previous observations, and highlights 2 key features. First, moxonidine has a good safety profile over a wide dose-range. Neither serious adverse events nor changes in laboratory parameters have been associated with moxonidine administration to date. Secondly, to date moxonidine has been well tolerated. In placebo-controlled studies the only adverse effects clearly attributable to moxonidine have been dry mouth, affecting 9% of individuals, and somnolence, affecting 7% of patients. The dry mouth is likely to be caused by moxonidine reducing salivary flow as a result of its weak α_2-receptor agonist activity. Post-marketing surveillance has since supported these clinical trial findings.[35]

The low frequency of somnolence reported in clinical trials (5 to 8%) is noteworthy and bears out the prediction that moxonidine should result in a low incidence of sedation because of its reduced α_2-adrenoceptor agonist activity. The practical implications of the low degree of sedation induced by moxonidine were shown in the nonimpairment of driving skills.[25] Phase II/III placebo-controlled trials have shown that the frequency of symptoms, such as headache and disorders of the respiratory and digestive systems, were higher in the placebo groups than in the moxonidine arms of the studies (table IV). Long term treatment, which is essential for the ongoing control of hypertension, did not reveal any unexpected adverse effects with moxonidine, and the incidence and severity of dry mouth and somnolence decreased with increasing exposure for up to 2 years. The adverse event profile of moxonidine failed to show any trends linked to age or gender.

The majority of the adverse effects of moxonidine were mild-to-moderate in severity, an important feature in compliance with antihypertensive treatment.[36] Antihypertensive agents of different classes, for example thiazides and β-blockers, can be associated with potentially severe adverse effects that are cardiovascular and metabolic in nature. This can lead to the development or worsening of certain conditions. By contrast, moxonidine has no apparent adverse effects on glucose and lipid metabolism.

Early clinical experience has shown that moxonidine was as effective as either atenolol or nifedipine in reducing blood pressure in patients with mild-to-moderate hypertension.[37,38] However, in addition, this efficacy was accompanied by a lower incidence of adverse effects than with

either the β-blocker or the calcium antagonist.[37,38] β-blockers in particular are contraindicated in patients with a history of bronchial asthma or wheezing. There are concerns that calcium antagonists may increase mortality when used in heart failure or post–myocardial infarction and may worsen survival in hypertensive patients, but this has been vigorously debated.[39,40] Moxonidine has been found to have no deleterious effects on haemodynamic indices in patients with mild-to-moderate heart failure.[41]

5. Conclusions

Overall, the reference antihypertensive drug-controlled studies showed that the incidence of adverse events with moxonidine did not exceed that for the reference antihypertensive drug. No exacerbation of concomitant diseases has been reported and moxonidine does not appear to induce any cardiovascular or metabolic disorders.[42,43] Furthermore, there is no evidence for adverse interaction between moxonidine and concurrent medications. Safety data from diverse sources collected using a variety of methods were included in this review. Despite this heterogeneity, particularly with regard to differences in adverse event frequency elicited by spontaneous reporting and checklist recording, clinical trial data and post-marketing surveillance have provided similar impressions of the safety profile of moxonidine over an 8-year period.

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