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Antihypertensive Drug Procurement Trends from 1995 to 2004: Transition over a Decade

Khalid AJ Al Khaja, PhD*

Objective: To evaluate antihypertensive procurement trends in Bahrain from 1995 to 2004.

Setting: Pharmacology and Therapeutics, Arabian Gulf University/Directorate of Material Management, Ministry of Health.

Design: A retrospective audit study based on the data from the Directorate of Material Management, Ministry of Health (MOH), Bahrain.

Method: A review of the annual antihypertensive drug procurement data from 1995 to 2004 was performed.

Result: The procurement rate of angiotensin converting enzyme inhibitors (ACEIs), diuretics and alpha-blockers, significantly increased while the rate of calcium channel blockers (CCBs), methyldopa and hydralazine declined during this decade. Beta-blockers were the top-ranked agents in both 1995 and 2004. Significant interclass changes were evident: increase in procurement of long-acting ACEIs, CCBs and indapamide associated with a decline in short-acting ACEIs, CCBs and thiazide and thiazide-like diuretics in 2004. Angiotensin-II receptor blocker (ARB) – valsartan was introduced in 1999.

The procurement of fixed-dose combinations (FDCs) increased from 0.9% in 1995 to 3.4% in 2004, associated with a significant decline in Moduretic and Brinerdin and by introduction of Co-Diovan, Preterax and Bi-Preterax. High cost due to renin-angiotensin-aldosterone inhibitors (ACEIs and ARBs) accounted for approximately half of the total antihypertensive drugs budget. According to Ministry of Health budget, the annual drug budget for antihypertensive drugs increased from 6.7% in 1995 to 14.1% in 2004. During that decade, there was a rapid annual growth rate for diuretics, CCBs and FDCs.

Conclusion: The antihypertensive procurement strategy has qualitatively improved; there is a shift towards selection of more rational long-acting antihypertensives and FDC products. Analysis of drug procurement trend should be a critical component of national drug policy.

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Drugs have made an important contribution to global reductions in morbidity and mortality[1]. An effective national drug policy requires legislation, rational drug selection, registration and

* Professor of Pharmacology
Department of Pharmacology & Therapeutics
Arabian Gulf University
Kingdom of Bahrain
Email: khlidj@agu.edu.bh

quality assurance, procurement and distribution, education and training, information for public and research[2]. In drug selection and procurement, health and economic related objectives should be considered[3]. Procurement objectives include preparation of a list of essential, safe, effective and of good quality drugs. Cost-effectiveness consideration is the economic goal during selection[3]. Based on evidence-based clinical guidelines, the use of a limited number of rationally selected drugs is the core concept of essential drugs program.

Several guidelines for management of hypertension have been published between 1990s and 2004 by the World Health Organization (WHO)/International Society of Hypertension (ISH)/Joint National Committee (JNC) on Detection, Evaluation and Treatment of High Blood Pressure[4-9]. Analysis of antihypertensive drug prescribing pattern, either as monotherapy or in combination has been evaluated in several studies[10-12]. Based on PubMed database search (up to 2005) using MeSH terms "antihypertensive drugs/procurement/trends/purchasing", not a single study has been reported, which dealt with antihypertensive procurement either in Bahrain or in other Middle Eastern countries.

The aim of this study is to evaluate the antihypertensive drug procurement trends in Bahrain from 1995 to 2004.

METHOD

New medications are purchased by the Directorate of Material Management/Procurement Management section based on drug policy recommendations and allocated drug budget[13].

Analysis of annual purchases of antihypertensives was based on the reports obtained from the Directorate of Material Management/Inventory Management section. These reports included units, quantity of medications purchased, unit price and total cost. The data for 10-year period from 1995 to 2004 was compiled. The procurement rate and annual growth rate were calculated based on published reports[14].

Data were analyzed using SPSS/PC+, version 12. Chi-square test and Fisher's exact test, as appropriate were used to test the differences. A p-value <0.05 was considered statistically significant.

RESULT

The procurement rate from 1995 to 2004 of various antihypertensive drug classes and fixed-dose combinations are presented in table 1. During this period, the procurement rate of antihypertensive single drug classes significantly declined from 99.04% to 96.52%, whereas fixed-dose combinations increased from 0.92% to 3.44%. The procurement rate of angiotensin converting enzyme inhibitors (ACEIs), diuretics and α-blockers significantly increased while the rate of calcium channel blockers (CCBs), methyldopa and hydralazine declined during this decade. In 1995, the most common antihypertensive drugs purchased, in descending order were β-blockers (29.31%), CCBs (25.22%), methyldopa (18.68%), ACEIs (13.65%) and diuretics (10.41%). Compared to drug purchased in 2004, β-blockers (28.29%), ACEIs (25.06%), CCBs (20.57%), diuretics (16.14%) and methyldopa (3.06%) were the most common. Angiotensin-II receptor blockers (ARBs) such as valsartan were introduced in 1999.

Table 1: Single Drugs and Fixed-Dose Combinations of Antihypertensives 1995 and 2004

Classes of Antihypertensive Agents	Procurement (%)				Difference in Proportion[a]	95% CI[b]
	1995	1998	2001	2004		
Single Drugs						
α-adrenoceptor blockers	0.31	0.89	1.5	1.39	1.08	(1.071, 1.084)[c]
Angiotensin converting enzyme inhibitors	13.65	19.21	24.01	25.06	11.41	(11.37, 11.43)[c]
Angiotensin-II receptor blockers[d]	-	-	1.22	1.78	-	-
β-blockers	29.31	30.61	29.04	28.29	-1.02	(-1.06, -0.98)[c]
Calcium channel blockers	25.22	24.56	23.05	20.57	-4.65	(-4.68, -4.61)[c]
Diuretics	10.41	10.75	13.89	16.14	5.73	(5.70, 5.73)[c]
Sympatholytics (Methyldopa)	18.68	10.92	5.63	3.06	-15.62	(-15.65, -15.59)[c]
Vasodilators (Hydralazine)	1.46	0.45	0.34	0.23	-1.23	(-1.24, -1.22)[c]
Subtotal	**99.04**	**97.39**	**98.68**	**96.52**		
Fixed Dose Preparations						
Amiloride + hydrochlorothiazide (Moduretic)	0.01	-	-	-	-	
Clopamide + dihydroergocristine + reserpine (Brinerdin)	0.91	0.57	0.27	0.11	-0.79	(-0.80, -0.78)[c]
Triamterene + hydrochlorothiazide (Dyazide)	-	2.0	0.99	0.71	-	-
Perindopril + indapamide (Bi-Preterax and Preterax)[e]	-	-	-	0.84	-	-
Valsartan + hydrochlorothiazide (Co-Diovan)[f]	-	-	-	1.78	-	-
Subtotal	**0.92**	**2.57**	**1.26**	**3.44**		
Total Percentage	**99.96**	**99.96**	**99.94**	**99.96**		

[a] Difference in proportions between 1995 and 2004; [b] confidence interval; [c] $p<0.05$; [d] introduced in 1999; [e] introduced in 2003; [f] introduced in 2002

Moduretic (amiloride 5mg+hydrochlorothiazide [HCTZ] 50 mg) was substituted with Dyazide (triamterene 50 mg+HCTZ 25 mg) in 1996. The procurement of Brinerdin (a fixed-dose of clopamide 5 mg+dihydroergocristine 0.5 mg + reserpine 0.1 mg) significantly declined by 87.9% in 2004 ($p<0.0001$). Co-Diovan (valsartan 80 mg + HCTZ 12.5 mg) was introduced in 2002 and accounted for 51.7% of overall fixed-dose products procured in 2004. In 2003, Preterax (indapamide 0.625 mg + perindopril 2 mg) and Bi-Preterax (indapamide 1.25 mg + perindopril 4 mg) were introduced and accounted for 24.4% of overall fixed-dose products procured in 2004.

Variations in procurement of antihypertensives drug classes between 1995 and 2004 is shown in table 2. The procurement of ACEIs – cilazapril, perindopril and lisinopril significantly increased by 3905%, 675% and 30.9%, respectively, whereas captopril declined by 65% ($p<0.0001$). Cilazapril, perindopril and lisinopril accounted for 60.3% of overall ACEIs purchased in 2004. On the other hand, the purchase of captopril and enalapril, which accounted for 79.9% of overall ACEIs in 1995 significantly declined to 38.3% in 2004. A significant shift in procurement of long-acting amlodipine and felodipine from 0.49% in 1995 to 24.2% in 2004 was evident; compared to short-acting nifedipine, which significantly declined by 25% (77.52% to 58.12%) in 2004. Procurement of thiazide-like diuretic indapamide significantly increased from 23.09% in 1995 to 63.68% in 2004, whereas, furosemide, chlorthalidone and HTCZ significantly declined.

Table 2: Variation in Procurement of Antihypertensive Drugs 1995-2004

Classes of Antihypertensives	1995	2004	Difference in Proportion	95% CI[a]
ACE Inhibitors				
Benazepril	0.95	1.39	0.44	(0.42, 0.46)[b]
Captopril	61.47	21.51	-39.95	(-40.05, -39.85)[b]
Cilazapril	0.22	8.81	8.59	(8.56, 8.62)[b]
Enalapril	18.39	16.78	-1.61	(-1.69, -1.53)[b]
Lisinopril	14.80	19.39	4.58	(4.50, 4.66)[b]
Perindopril	4.14	32.09	27.94	(27.88, 28.00)[b]
Total Percentage	**99.97**	**99.97**		
β-blockers				
Acebutolol	0.65	0.10	-0.55	(-0.56, -0.53)[b]
Atenolol	78.06	81.59	3.53	(3.46, 3.59)[b]
Carvedilol	-	4.55	-	-
Metoprolol	0.58	0.20	-0.37	(-0.38, -0.36)[b]
Propranolol	20.70	13.54	-7.15	(-7.21, -7.09)[b]
Total Percentage	**99.99**	**99.98**		
Calcium Channel Blockers				
Amlodipine	0.49	19.01	18.51	(18.47, 18.55)[b]
Diltiazem	14.63	13.69	-0.93	(-0.99, -0.87)[b]
Felodipine	-	5.19	-	-
Nifedipine	77.52	58.12	-19.40	(-19.47, -19.32)[b]
Verapamil	7.34	3.96	-3.37	(-3.41, -3.33)[b]
Total Percentage	**99.98**	**99.97**		
Diuretics				
Chlorthalidone	6.39	0.99	-5.39	(-5.45, -5.34)[b]
Furosemide	37.75	21.20	-16.32	(-16.43, -16.20)[b]
Hydrochlorothiazide	32.97	14.10	-18.87	(-18.98, -18.76)[b]
Indapamide	23.09	63.68	40.59	(40.48, 40.69)[b]
Total Percentage	**99.98**	**99.97**		

[a] CI = confidence interval; [b] $P < 0.05$

From 1995 to 2004, the antihypertensive drug expenditure increased at an annual growth rate of 41.1% for fixed dose combination products, 27.5% for CCBs, 19.1% for diuretics, 15.1% for ACEIs, 11.9% for ARBs and 10.5% for β-blockers, see table 3. The expenditures on methyldopa and hydralazine had declined at an annual rate of 10.5% and 8%, respectively. In 2004, the expenditure on renin-angiotensin-aldosterone system (RAAS) inhibitors accounted for 46.9% of the overall expenditure on antihypertensive drugs, see table 3. Per capita antihypertensive expenditure increased from $1.068 in 1995 to $4.55 in 2004, an annual growth rate of 15.6%, see table 4. The total medication/related expenditure from 1995 to 2004 did not exceed 10% of the total Ministry of Health's budget.

Table 3: Antihypertensive Drug Expenditure (US $) 1995–2004

Antihypertensive Drugs	1995	1998	2001	2004	Change (%)[a]	Annual Growth Rate
	Expenditure (%)					
ACEIs	320,773 (51.2)	652,765 (59.3)	1,017,920 (51.1)	1,303.827 (40.5)	306.5	15.1

ARBs	-	-	130,976 (6.6)	205,237 (6.4)	56.7	11.9
β-blockers	94,317 (15.1)	128,143 (11.6)	175,051 (8.8)	255,531 (7.9)	170.9	10.5
CCBs	64,659 (10.3)	139,046 (12.6)	411,170 (20.7)	735,173 (22.8)	1037	27.5
Diuretics	65,162 (10.4)	105,23 (9.6)	202,498 (10.2)	375,711 (11.7)	476.5	19.1
Hydralazine	3,729 (0.6)	1,584 (0.1)	1,597 (0.08)	1,623 (0.05)	-56.5	-8.0
Methyldopa	65,364 (10.4)	48,927 (4.4)	33,716 (1.7)	21,480 (0.7)	-67.1	-10.5
α-blockers	2,143 (0.3)	6,312 (0.6)	5,520 (0.3)	9,438 (0.3)	340	16.0
Fixed-dose combinations	10,005 (1.6)	18,887 (1.7)	12,564 (0.6)	312,792 (9.7)	3026	41.1

ACEIs = Angiotensin converting enzymes; ARBs = Angiotensin-II receptor blockers; CCBs = Calcium channel blockers; [a] Difference between 1995 and 2004

Table 4: Population Growth and per Capita Expenditure on Antihypertensives 1995-2004

	1995	1998	2001	2004	Absolute Change (%)[a]	Annual Growth Rate
Population	586,110	642,972	654,619	707,160	20.7	1.9
% population 45-64 years[b]	9.2	9.5	12.6	12.5	35.9	3.1
% population ≥ 65 years[b]	2.2	2.2	2.5	2.5	13.6	1.3
MOH budget (US $)	145,430,463	-	170,596,026	243,172,185	61.0	4.9
Total medication expenditures (US $)	9,329,801	12,662,781	17,012,521	22,839,578	144	9.4
Proportion of medication expenditures	6.4	-	10.0	9.6	50.0	4.1
Total antihypertensive expenditures(US $)	626,152	1,100,901	1,991,012	3,220,812	414	17.8
Proportion of antihypertensive expenditures	6.7	8.7	11.7	14.1	110.4	7.7
Per capita expenditure of antihypertensive medications (US $)	1.068	1.712	3.041	4.55	326	15.6

[a] Difference between 1995 and 2004; [b] both Bahrainis and expatriates; MOH=Ministry of Health

DISCUSSION

The current study provides insight into antihypertensive drug procurement pattern from 1995 to 2004, a decade during which three revised guidelines by WHO and JNC have been published[4-9].

Several significant changes were evident of antihypertensive procurement strategy from 1995 to 2004, see table 1. β-blockers were the top ranked antihypertensive drug class in both 1995 and 2004 despite a modest decline in 2004. CCBs gradually declined from second rank in 1995 to third in 2004 and were superseded by ACEIs from fourth rank in 1995 to second in 2004. Diuretics did not rank among the top three antihypertensive drug classes in 1995 and 2004. Methyldopa shifted from the top third in 1995 to fifth rank by 2004.

The procurement of both methyldopa and hydralazine significantly declined between 1995 and 2004. These antihypertensives are inappropriate for initial monotherapy and their use is often associated with annoying adverse effects[5,8]. Methyldopa is no longer recommended as first-line antihypertensive therapy except in hypertension of pregnant women; it is reserved as second or third line add-on drug, particularly for resistant cases of hypertension[5,8]. A marked decline in

procurement of both methyldopa and hydralazine may explain how the policy of drug procurement process in Bahrain is somewhat influenced by international guidelines and clinical practice standards.

It is increasingly recognized that in many cases of hypertension the recommended BP target is achieved only by multi-drug therapy. Multi-drug regimen can be fixed-dose combinations or concurrent therapy with different antihypertensives[5,8]. Fixed-dose antihypertensive preparations are combination of at least two antihypertensives from different pharmacologic classes designed to provide enhanced efficacy, minimize the likelihood of dose-dependent adverse effects and to enhance drug compliance by once-daily dosing. This study revealed that procurement of fixed-dose combination products had increased and are characterized by a shift towards the newer expensive brands such as Bi-Preterax, Preterax and Co-Diovan surpassing Moduretic, Dyazide and Brinerdin. Nevertheless, such trends also has contributed to a further escalation of total antihypertensive expenditure observed during the study period, see table 3.

Significant dynamic changes were observed for ACEIs, CCBs and diuretics between 1995 and 2004, see table 2. A key concept of antihypertensive drug therapy is to lower BP with longer-acting drugs, which provides 24 hours efficacy once-daily[5,8]. Significant increase in procurement of long-acting ACEIs (cilazapril, lisinopril and perindopril), CCBs (amlodipine and felodipine) and diuretics (indapamide) with substantial concurrent declines in short-acting ACEIs (captopril), CCBs (nifedipine) and thiazide diuretics in 2004 was evident, see table 2. Pharmaceutical promotion practices and advertisements could have influenced the observed shifts in antihypertensive drug procurement trends[10,11].

The per capita antihypertensive drug expenditure was found to be marginally affected by demographic changes such as the annual population growth rate, especially by the proportion of middle-aged and elderly populations, see table 4. This observation is similar for what was found in other studies[15,16]. Drug expenditure can be affected by price inflation and drug volume changes. However, the primary reason for escalation of drug expenditures is increased drug consumption driven by needs, innovation and demand[17].

There are several price and non-price related factors that underpin changes in overall antihypertensive expenditure. Preference for antihypertensive combination therapy, multiple indications for antihypertensives, particularly RAAS inhibitors, shifts in doctors' preference for new medications, population growth and demographic shifts (expatriates in Bahrain) would have contributed to the overall expenditure, see table 2 and 4.

In most developing countries, drug expenditures for ministries of health are second only to staff salaries and benefits, accounting for 45–90% of non-personnel costs[18]. Unlike most other developing countries, the expenditure on medications in Bahrain did not exceed 10% of the total ministry of health's budget, see table 4.

CONCLUSION

Drug policy decisions and national procurement strategy for antihypertensives in Bahrain have been qualitatively improved between 1995-2004. Expenditures due to antihypertensive procurement had increased steadily over the decade although the drug procurement policy has been governed by joint bulk purchasing program on drugs and medical supplies among GCC countries and by generic substitution policy. Further steps towards achieving cost

containment of superfluous drug-related expenditure should be considered. Drug procurement analysis should be a critical component of national drug policy.

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