INTRODUCTION

Hypertension is most common cardiovascular disease leading to morbidity and un-timely death. The World Health Organization describes hypertension as the number one risk factor for mortality, as worldwide annually 7.5 million deaths (13% of all deaths) are attributable to high blood pressure (BP)-related diseases.1 In India, the situation is more alarming as hypertension attributes for nearly 10% of all death.2 Prevalence of hypertension in India is reported to vary from 4-15 % in urban and 2-8% in rural population.3 It is estimated that the worldwide prevalence of hypertension would increase from 26.4% in 2000 to 29.2% in 2025.4 It is a major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease. For that reason, the guidelines of hypertension and cardiology societies emphasize that hypertension treatment should aim at reducing the long-term risk of (cardiovascular) morbidity and Mortality.5,6 Hypertension is often referred to as the ‘silent killer’, as its presence is usually symptomless. Antihypertensive drug once started mostly continued through-out life. Antihypertensive drugs were the second largest therapy area in 2011 with the global sales value of more than USD 40 billion, according to the world preview 2018 report by Evaluate Pharma.7 Despite extensive research over the past several decades, control of blood pressure is suboptimal in general population. It has estimated that less than 20% of hypertensive patient have adequate control of blood pressure.8 Indian pharmaceutical industry being one of the largest pharmaceutical markets in the world has a large number of branded formulations and generic brands of the same drug with a large difference in their selling price.9

ABSTRACT

Background: Cardiovascular diseases are the most prevalent cause of death and disability in developed and developing countries. There is a wide variation in the prices of antihypertensive drugs marketed in India. Thus, a study was planned to find out variation in cost in the ACE Inhibitors available in India either as a single drug or in combination and to evaluate the difference in cost of various brands of the same ACE Inhibitors and ARBs by calculating percentage variation in cost in Indian rupees.

Methods: Minimum and maximum costs in rupees (INR) of antihypertensive agents manufactured by different companies, in the same strength and dosage forms were obtained from “current index of medical specialties” January April 2016 and Drug Today October–December 2016. The cost ratio and percentage cost variation were calculated for each generic antihypertensive agent (ACE Inhibitors and ARBs).

Results: This study shows that there is a wide variation in the prices of different brands of same ACE Inhibitors and ARBs in Indian market. Highest cost variation 400% is for Lisinopril (2.5mg), followed by Enalapril (10mg) 394.16%, Telmisartan (20mg) 322.22%. Construclions: There is a wide difference in the cost of different brands of ACE Inhibitors and ARBs available in India. They have important role in management of hypertension particularly if associated with other morbidities like diabetes. The clinicians prescribing these drugs should be aware of these variations in cost so as to reduce the cost of drug therapy and increase the patient adherence to the therapy.

Keywords: Adherence, Angiotension converting enzyme inhibitors, Angiotensin receptor blockers, Cost analysis, Compliance, Cost variation, Hypertension

Original Research Article

Cost variation analysis of ACE inhibitors in India

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Variations in cost of drugs which are very commonly used have large economic implications. This affects the compliance of the patients who need to take these drugs regularly to maintain good health.\textsuperscript{10} Patient compliance play important role in adequate control of blood pressure.

There are several drug used in treatment of hypertension like diuretics, calcium channel blocker, ACE Inhibitors, ARBs, beta blockers, alfa blocker, vasodilators. National guideline recommended Diuretics as preferred initial therapy for most patients with uncomplicated stages 1 hypertension.\textsuperscript{6} But most of the time patient suffers hypertension along with diabetes and so ACE Inhibitors or ARBs should be the first line drugs. The beneficial effect of ACE inhibitor treatment on all cause mortality for hypertensive patients was well established in a recent meta-analysis.\textsuperscript{11} Captopril, enalapril, lisinopril, ramipril, benazepril, trandolapril, fasinopril, quinopril, imdapril are the different type of ACE Inhibitors. Olmesartan, Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan are the ARBs used in treatment of hypertension.

**METHODS**

The prices of 11 oral antihypertensive drug (ACE inhibitors and ARBs), eleven single and thirteen combinations, available in 49 different formulations were analyzed. Price in Indian rupees (INR) of ACEI and ARBs manufactured by different pharmaceutical companies in India, in the same strength, was obtained from Current Index of Medical Specialities (CIMS), July-October 2016, and DRUG TODAY October-December 2016.

- The drug formulations manufactured by a single company or by different companies, but, in different strengths, were excluded.
- The cost of the oral ACE inhibitors and ARBs drugs was estimated for an average of 10 tablets.
- The difference in the maximum and minimum prices of the same drug formulation manufactured by different pharmaceutical companies and percentage variation in price was calculated.
- Percentage cost variation was calculated as follows:

\[
\% \text{ Price variation} = \frac{\text{Maximum cost} - \text{Minimum cost}}{\text{X 100}}
\]

**RESULTS**

This study shows that there is a wide variation in the prices of different brands of same ACE Inhibitors and ARBs in Indian market.

Table 1: Variation in cost of single drug therapy.

| S. No. | Drugs       | Formulation | Dose (mg) | Min. price | Max. price | Range | Price variation |
|--------|-------------|-------------|-----------|------------|------------|-------|-----------------|
| 1      | Captopril   | 1           | 25mg      | 9.07       | 35.70      | 26.63 | 293.60          |
| 2      | Enalapril   | 3           | 2.5mg     | 6          | 22.6       | 16.6  | 276.6           |
|        |             | 5mg         | 9         | 36.7       | 27.7       | 307.7 |                 |
|        |             | 10mg        | 12        | 59.3       | 47.3       | 394.16|                 |
| 3      | Lisinopril  | 3           | 2.5mg     | 10         | 50.00      | 40    | 400             |
|        |             | 5mg         | 25        | 69         | 44         | 176   |                 |
|        |             | 10mg        | 39        | 122.30     | 83.3       | 213.58|                 |
| 4      | Perindopril | 2           | 2mg       | 56.25      | 37.75      | 87.75 | 67.11           |
|        |             | 4mg         | 85        | 123        | 38         | 44.70 |                 |
| 5      | Ramipril    | 4           | 1.25mg    | 14.9       | 44.30      | 29.4  | 197.3           |
|        |             | 2.5mg       | 25.50     | 79.80      | 54.3       | 212.94|                 |
|        |             | 5mg         | 43.00     | 128.80     | 85.8       | 200   |                 |
|        |             | 10mg        | 63.50     | 179.30     | 115.8      | 182.36|                 |
| 6      | Olmesartan  | 3           | 10mg      | 39         | 53         | 14    | 35.89           |
|        |             | 20mg        | 46        | 87.92      | 41.92      | 91.13 |                 |
|        |             | 40mg        | 75        | 149        | 74         | 98.66 |                 |
| 7      | Losartan    | 2           | 25mg      | 13.20      | 45         | 31.8  | 240.90          |
|        |             | 50mg        | 27.50     | 67         | 39.5       | 143.63|                 |
| 8      | Candesartan | 2           | 4mg       | 27         | 34.95      | 7.95  | 29.44           |
|        |             | 8mg         | 45.27     | 61.80      | 16.53      | 36.51 |                 |
| 9      | Irbesartan  | 2           | 150mg     | 78.56      | 240        | 161.44| 205.49          |
|        |             | 300mg       | 168       | 199.65     | 31.65      | 18.83 |                 |
| 10     | Valsartan   | 2           | 80mg      | 69         | 93.50      | 24.5  | 35.50           |
|        |             | 160mg       | 130       | 163        | 33         | 25.38 |                 |
| 11     | Telmisartan | 3           | 20mg      | 18         | 76         | 58    | 322.22          |
|        |             | 40mg        | 28         | 85.10      | 57.1       | 203.92|                 |
|        |             | 80mg        | 89         | 134        | 45         | 50.56 |                 |
Table 2: Variation in cost of combination therapy.

| S. No | Drugs                           | Formulation | Dose (mg) | Min. price | Max. price | Range | Price variation |
|------|--------------------------------|-------------|-----------|------------|------------|-------|-----------------|
| 1    | Enalapril+ Hydrochlorothiazide  | 2           | 5+12.5    | 25         | 31.40      | 6.4   | 25.6            |
|      |                                 |             | 10+25     | 22.75      | 75.66      | 52.91 | 232.57          |
| 2    | Amlodipine+Enalapril            | 2           | 5+2.5     | 25         | 29         | 4     | 16              |
|      |                                 |             | 5+5       | 31         | 76.50      | 45.5  | 146.77          |
| 3    | Lisinopril+ Hydrochlorothiazide | 2           | 5+12.5    | 10         | 52.10      | 42.1  | 421             |
|      |                                 |             | 10+12.5   | 12.5       | 75.75      | 63.25 | 506             |
| 4    | Amlodipine+Lisinopril           | 1           | 5+5       | 32         | 73.3       | 41.3  | 129.06          |
| 5    | Ramipril+ Hydrochlorothiazide   | 2           | 2.5+12.5  | 34.11      | 84.10      | 49.99 | 146.55          |
|      |                                 |             | 5+12.5    | 43.13      | 136.95     | 93.82 | 217.52          |
| 6    | Amlodipine+Ramipril             | 2           | 5+2.5     | 25.30      | 82         | 56.7  | 224.11          |
|      |                                 |             | 5+5       | 71         | 110        | 39    | 54.92           |
| 7    | Losartan+ Hydrochlorothiazide   | 2           | 25+12.5   | 28.50      | 50         | 21.5  | 75.43           |
|      |                                 |             | 50+12.5   | 34         | 89         | 55    | 161.76          |
| 8    | Amlodipine+Losartan             | 1           | 5+50      | 20.80      | 88.47      | 67.67 | 325.33          |
| 9    | Olmesartan+ Hydrochlorothiazide | 2           | 20+12.5   | 67         | 101.75     | 34.75 | 51.86           |
|      |                                 |             | 40+12.5   | 95         | 182        | 87    | 91.57           |
| 10   | Olmesartan+Amlodipine           | 2           | 20+5      | 69.90      | 90.50      | 20.6  | 29.47           |
|      |                                 |             | 40+5      | 109.90     | 130        | 20.1  | 18.28           |
| 11   | Irbesartan+ Hydrochlorothiazide | 1           | 150+12.5  | 69         | 269        | 200   | 289.85          |
| 12   | Telmisartan+ Hydrochlorothiazide| 2           | 40+12.5   | 38.5       | 85         | 46.5  | 120.77          |
|      |                                 |             | 80+12.5   | 110        | 125        | 15    | 13.63           |
| 13   | Telmisartan+Amlodipine          | 1           | 40+5      | 55         | 101        | 46    | 83.63           |

Table 1 shows single drug percentage price variation for various ACE Inhibitor and ARBs. Highest cost variation 400% is for Lisinopril (2.5mg), followed by Enalapril (10mg) 394.16, Telmisartan (20mg) 322.22%.

Table 2 shows, cost variation of fixed dose combinations of ACE Inhibitors or ARBs.

Lisinopril+ hydrochlorothiazide (10+12.5mg): 506%, (5+12.5mg): 421%, Amlodipine+ Losartan (5+50mg): 325.33%, Irbesartan+ Hydrochlorothiazide (150+12.5mg): 289.85%.

DISCUSSION

The Renin-angiotensin-aldosterone system (RAAS) controls circulating volume and electrolyte balance in the human body and is therefore an important regulator of haemodynamic stability. An overactive RAAS is strongly associated with high BP. Both Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are the first line drugs for hypertension and they effectively reduce the risk of cardiovascular and renal events. With sales of US$358 million on the private market, ACE-inhibitors (excluding fixed combinations with diuretics) represent the second largest therapeutic class in the antihypertensive market, just behind the calcium channel blockers. Some 60% of this revenue is shared between three ACE-inhibitors - Lopril (captopril), Renitec (enalapril) and Coversyl (perindopril) - with others competing for the remaining 40%. As they are very important group for treatment and we didn’t find much studies regarding cost variation analysis related to them, so we conducted this study. Hypertensive patient require long term treatment. Inadequate treatment or poor adherence to treatment can leads to stroke, myocardial infarction, vascular disease, and chronic kidney disease which further increase the economic burden to patient and indirectly increases economic burden of the country. Higher medication costs have been found to be a reason for medication nonadherence. Cost related poor medication adherence has been found to be related to adverse health outcomes. In India, there are many pharmaceutical companies which sell a particular drug under different brand names along with the innovator company. There are large numbers of formulations for the same drugs are available leading to large variation in the price of drugs leading to an unnecessary economic burden on Indian population. No correlation has been found between the quality of the medicine and its corresponding price. DPCO is an effective tool for regulation of drug prices. Very few medicines are under drug prices control order. Government should bring more number of antihypertensive drugs under price control.

Many times it is seen that doctors are unaware or underestimate the price of expensive ones which further increase the economic burden over patient and increases the chances of non-adherence with therapy. Physician’s awareness about the cost differences should be ensured.
by providing a manual of comparative drug prices. Availability of manual has been found to reduce patient’s
drug expense.18

CONCLUSION

This study highlights that there is a wide variation in cost among the antihypertensive drugs manufactured by
different pharmaceutical companies. Hypertension requires long term treatment, compliance being a key
factor for successful treatment. Adherence to the
treatment can be increased by decreasing the cost of
therapy. The Government of India should take strict and
effective measures in bringing uniformity in the cost of
the drug for long term benefit of the health.

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