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ORIGINAL ARTICLE

Assessment of postoperative changes in antihypertensive drug consumption in patients with primary aldosteronism using the defined daily dose

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Summary *Background:* The number of antihypertensive drug classes cannot accurately reflect the total consumption of antihypertensive drugs used to control blood pressure. The defined daily dose has been adopted to permit consumption analysis of many prescribed drugs. The aim of the present study was to assess postoperative changes in antihypertensive drug consumption in patients with primary aldosteronism using the defined daily dose as the unit of measurement.
Methods: This retrospective study included 110 Japanese patients who underwent unilateral laparoscopic adrenalectomy between 1995 and 2012. Antihypertensive drug doses were calculated according to the standard of the defined daily dose recommended by the World Health Organization to compare drug use. After assessing postoperative changes in antihypertensive drug consumption, univariate and multivariate analyses were performed to identify clinical predictors for a 75% or greater decrease in the defined daily dose.
Results: Consumption of antihypertensive drugs decreased postoperatively in 95.4% of patients. The median decrease in the defined daily dose was 76.8%. A postoperative decrease

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of 75% or greater in the defined daily dose was confirmed in 52.7% of patients. Multivariate analysis identified no medical history of cardiovascular disease, low body mass index, and short duration of hypertension as independent predictors of a postoperative decrease of 75% or greater in the defined daily dose.
Conclusion: The defined daily dose is a useful tool for assessing total changes in the consumption of antihypertensive drugs in patients with primary aldosteronism. Using the defined daily dose, clinicians could explain in detail to patients with primary aldosteronism the predicted postoperative change in antihypertensive drug consumption.

1. Introduction

Primary aldosteronism (PA) is caused by the autonomous secretion of aldosterone from adrenocortical lesions, and it is associated with hypertension due to sodium retention and hypokalemia due to increased potassium excretion.[1–3] Aldosterone excess leads to cardiovascular damage, independent of its effects on blood pressure (BP).[1–3] Primary aldosteronism is primarily caused by an aldosterone-producing adenoma (APA) or by bilateral adrenal hyperplasia (also known as idiopathic hyperaldosteronism).[1–3]

Laparoscopic adrenalectomy is the preferred approach to treat patients with unilateral PA such as APA.[4–6] Despite normalization of the endocrine abnormalities, not all patients with PA have their hypertension cured completely by laparoscopic adrenalectomy.[1–3] Many predictors of hypertension cure in PA patients have been reported.[7] The number of antihypertensive drug classes can be a robust predictor for postoperative hypertension cure in PA patients.[7–11] However, it cannot reflect the total consumption of antihypertensive drugs to control BP accurately.

Using the number of antihypertensive drug classes as a unit of measurement, the following two types of patients can be regarded as taking an equivalent amount of antihypertensive drugs: (1) patients who take 50 mg of eplerenone and 5 mg of amlodipine and (2) patients who take 100 mg of eplerenone and 10 mg of amlodipine. However, the second type of patient apparently has more severe hypertension, despite taking the equivalent two classes of antihypertensive drugs.

The defined daily dose (DDD) has been adopted to assess the consumption of many prescribed drugs.[12,13] The doses of diverse drugs were calculated in accordance with the standard of the DDD recommended by the World Health Organization (WHO) to compare drug use.[14] At present, clinicians can search each drug's DDD at the web address http://www.whocc.no/atc_ddd_index. The DDD system is often applied at the population level; however, in many studies, it can be used to compare individual drug utilization as a unit of measurement.[12–18]

The aim of this study was to assess postoperative changes in antihypertensive drug consumption in PA patients, using the DDD as the measurement unit, and to identify clinical predictors for decreased antihypertensive drug consumption.

2. Methods

2.1. Patient selection

The clinical variables associated with a postoperative decrease in antihypertensive drug consumption were surveyed retrospectively among PA patients seen at the Chiba University Hospital Chiba, Japan. One hundred and ten patients with PA who underwent unilateral laparoscopic adrenalectomy between 1995 and 2012 were analyzed. The criteria used to establish the diagnosis of PA were a history of hypertension resistant to antihypertensive drugs with or without hypokalemia, and increased plasma aldosterone concentration (PAC) and suppressed plasma renin activity (PRA). In this study, patients had a confirmed PAC:PRA ratio of at least 20.0 ng/dL per ng/mL/hour as a biochemical screen for PA.[1–3] Additional confirmation of the diagnosis was obtained using the saline-loading test, the captopril-challenge test, and/or the upright furosemide-loading test.[1–3] Differentiation between APA and idiopathic hyperaldosteronism was obtained by computed tomography or by magnetic resonance imaging. Furthermore, lateralization of aldosterone overproduction was demonstrated through adrenal vein sampling (AVS) and/or adrenal dexamethasone-suppression scintigraphy with ^{131}iodine (^{131}I) cholesterol in all patients.[1–3,5] The result of AVS was used to identify unilateral hypersecretion. When the finding of scintigraphy was equivocal or contrary to that of AVS, the AVS results were given precedence over the results of scintigraphy.

Postoperative normalization of plasma aldosterone levels was defined as decreased concentration of plasma aldosterone (<15.0 ng/dL). In this study, all patients were confirmed to have normalized plasma aldosterone levels after laparoscopic adrenalectomy. Hypokalemia cure was achieved after surgery in all patients with preoperative hypokalemia. The underlying adrenocortical lesion was pathologically identified in all patients after surgery. Pathological findings revealed cortical adenoma in 95 patients and nodular hyperplasia in 15 patients.

2.2. Definitions

The BP of each patient was classified in accordance with WHO 1999 guidelines as normal BP (<140/90 mmHg) or

hypertension.[19] Clinicians prescribed antihypertensive drugs to the patients to maintain a normal BP when the patients were hypertensive without antihypertensive drugs after surgery.

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.[14] The DDD provides a fixed unit of measurement, independent of price and dosage form, thereby enabling researchers to assess and compare drug consumption.[14] Using the DDD, consumption of antihypertensive drugs in PA patients was assessed preoperatively and at 6 months postoperatively.[14] Table 1 shows an example of calculating individual DDDs of antihypertensive drugs. A change in the DDD was defined as follows: change in the DDD% = (preoperative total DDD − postoperative total DDD)/preoperative total DDD × 100. Using the example in Table 1, the decrease in the DDD was consequently 75.0%.

2.3. Data collection

The following were collected from the patients' medical records: age, sex, body mass index (BMI), family history of hypertension in first-degree relatives, comorbidities, duration of hypertension, the DDD of antihypertensive drugs, the systolic BP and diastolic BP, and clinical laboratory data. Comorbidities included cardiovascular disease, diabetes mellitus, and subclinical Cushing syndrome. The laboratory data included serum potassium, PAC, PRA, and estimated glomerular filtration rate (eGFR). We calculated the eGFR using a new equation that has been developed and validated in a Japanese population.[20]

2.4. Statistical analysis

The results are reported as the median (range) or as the mean ± the standard deviation, as appropriate. First, each patient's DDD was calculated, and the change was compared using the Wilcoxon signed rank test. Second, the patients were divided into two groups, according to whether a decrease in the DDD was 75% or greater at the 6-month follow-up assessment. The cutoff value of 75% was based on the median change in the DDD. Third, univariate analyses were performed to estimate the association between a postoperative decrease of 75% or greater in the DDD and the preoperative variables. Continuous parametric variables were compared using *t* tests. Nonparametric variables were compared using Mann-Whitney *U* tests. Categorical variables were compared using χ^2 tests or Fisher's exact test. After significant candidate variables were selected on the basis of univariate analyses, multivariate logistic regression analysis was used to identify clinical predictors associated with a postoperative decrease of 75% or greater in the DDD. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using SAS version 9.2 software (SAS Institute, Cary, NC, USA).

Table 1 Calculation example for the individual defined daily dose.

	Preop daily consumption (mg/day)	DDD (mg/day)	DDD
Eplerenone	100	50	100/50 = 2.0
Amlodipine	10	5	10/5 = 2.0
		Total DDD	4.0
	Postop daily consumption (mg/day)	DDD (mg/day)	DDD
Cilnidipine	10	10	10/10 = 1.0
		Total DDD	1.0

DDD = defined daily dose; Postop = postoperative; Preop = preoperative.

3. Results

Table 2 shows the DDDs of each antihypertensive drug class used before and after surgery and the number of patients who took each antihypertensive drug class. No patient in this study took combination products such as an angiotensin receptor blocker with diuretics. In this study, the DDDs decreased significantly from 2.4 ± 1.2 preoperatively to 1.0 ± 1.2 postoperatively ($p < 0.01$). At the 6-month follow up, the DDD decreased in 101 patients. By contrast, the DDD increased in five patients and did not change in four patients.

The median change in the DDD was −76.8%. The proportion of patients with a postoperative decrease of 75% or greater in the DDD was 52.7%. Table 3 shows the predictors associated with a postoperative decrease of 75% or greater in the DDD on univariate analyses. The following variables were significantly associated with a postoperative decrease in the DDD of 75% or greater: age, sex, BMI, medical history of cardiovascular disease, duration of hypertension, preoperative DDD of antihypertensive drugs, preoperative systolic BP, PRA, and eGFR ($p < 0.05$). These significant variables were examined by multivariate logistic regression analysis, which identified no medical history of cardiovascular disease [odds ratio (OR) 5.44, $p = 0.02$], low BMI (OR

Table 2 Defined daily doses of each antihypertensive drug class the patients used before and after surgery.

Antihypertensive drug class	Preop DDD	Postop DDD
Aldosterone antagonist	1.0 ± 0.5	1.1 ± 0.7
N	106	4
Calcium channel blocker	1.3 ± 0.5	1.2 ± 0.6
N	98	61
α-blocker	0.6 ± 0.3	0.6 ± 0.2
N	19	8
Angiotensin receptor blocker	1.2 ± 0.5	1.1 ± 0.4
N	15	15
β-blocker	0.5 ± 0.4	0.3 ± 0.2
N	6	5
Other antihypertensive drugs	0.9 ± 0.4	1.1 ± 0.1
N	5	4

Data are presented as mean ± SD, unless otherwise indicated. DDD = defined daily dose; *N* = number of patients; Postop = postoperative; Preop = preoperative.

1.23, $p = 0.03$), and short duration of hypertension (OR 1.12, $p < 0.01$) as independent predictors of a postoperative decrease of 75% or greater in the DDD (Table 4).

4. Discussion

This study is the first to use the DDD as the unit of measurement to assess postoperative changes in antihypertensive drug consumption in PA patients. The DDD is suitable for therapeutic analyses and at the individual level.[12–18] The DDD has been used to measure antihypertensive drug utilization in individual patients and to assess the effects of invasive treatment for renal artery stenosis.[17] The DDD can assess postoperative changes in antihypertensive drug consumption, even though the antihypertensive drug classes changed after treatment.[12,17]

Despite a decreased DDD in most patients, nine patients could not postoperatively reduce their antihypertensive drug use to control their BP. Based on the number of antihypertensive drug classes, some patients were postoperatively categorized into the hypertension improvement group (i.e., they had a lower BP and took a fewer number of antihypertensive drug classes). This was first revealed by using the DDD because it can reflect the total consumption of antihypertensive drugs. Assessing postoperative changes in antihypertensive drug consumption by the number of antihypertensive drug classes alone may mislead clinicians.

Multivariate analysis identified no medical history of cardiovascular disease, low BMI, and short duration of hypertension as independent predictors of a postoperative decrease in the DDD of 75% or more (Table 4). Cardiovascular disease was a robust predictor for decreased antihypertensive drug consumption in the present study, although it was not significantly associated with hypertension cure in our previous study.[21] The total consumption of antihypertensive drugs depends on patient-related factors such as the severity of the disease. Thus, in patients with a medical history of cardiovascular disease, antihypertensive drug consumption was not markedly decreased after surgery. Clinicians would hesitate to decrease antihypertensive drugs to control BP postoperatively because of the medical history of cardiovascular disease.

The excessive production of aldosterone in PA patients leads to a higher frequency of cardiovascular events, compared to essential hypertension patients.[8] In view of the postoperative decrease of antihypertensive drug consumption and prevention of cardiovascular disease, early diagnosis and treatment of PA are the most important tasks to maximize the benefits of laparoscopic adrenalectomy and to minimize the progression of hypertension-mediated vascular damage.[21,22]

The present study had some limitations. First, the retrospective nature of this study may have affected the quality of the data. This study included patients over a long period (between 1995 and 2012), and the initial diagnostic criteria for PA varied because of the lack of a generally accepted diagnostic algorithm for PA throughout this period. However, each patient was uniformly reviewed before being included in the study. Second, some drugs such as benidipine have not been assigned DDDs. Thus, it was not possible to assess antihypertensive drug consumption in patients taking the drugs that have not been assigned DDDs. Third, the assigned DDD is based on the recommended dose with reference to a 70-kg person. The assigned DDDs may be slightly higher for Japanese people because a Japanese person's weight is generally lower than

Table 3 Univariate analyses of candidate predictors for a postoperative decrease of 75% or greater in the defined daily dose.

Variable	≥75% decrease ($N = 58$)	<75% decrease ($N = 52$)	p
Age (y)	48 ± 13	55 ± 10	<0.01
Sex (female)	66	44	0.04
BMI (kg/m^2)	22 ± 2.7	24 ± 3.4	<0.01
Family history of hypertension, %	50	48	0.99
Comorbidities			
Cardiovascular disease	9	29	0.01
Diabetes mellitus	10	19	0.29
Subclinical Cushing syndrome	12	21	0.30
Duration of hypertension (y)	(0–30)	(1–35)	<0.01
Preop DDD of antihypertensive drugs	2.1 ± 1.1	2.8 ± 1.1	<0.01
Preop systolic BP (mmHg)	147 ± 22	158 ± 22	<0.01
Preop diastolic BP (mmHg)	87 ± 14	94 ± 14	0.24
Preop clinical laboratory values			
Serum potassium (mmol/L)	2.9 ± 0.5	3.0 ± 0.6	0.33
PAC (ng/dL)	31.8 (2.3–92.1)	29.9 (3.0–160.0)	0.95
PRA (ng/mL/h)	0.1 (0.0–1.2)	0.2 (0.0–4.1)	0.04
eGFR (mL/min/1.73 m^2)	76.3 ± 19.2	63.0 ± 17.3	<0.01

Data are presented as mean ± SD or median (range), unless otherwise indicated.
BMI = body mass index; BP = blood pressure; DDD = defined daily dose; eGFR = estimated glomerular filtration rate; PAC = plasma aldosterone concentration; PRA = plasma renin activity; Preop = preoperative.

Table 4 Multivariate logistic regression analysis of significant candidate predictors for a postoperative decrease of 75% or greater in the defined daily dose.

Variable	Odds ratio (95% CI)	p
No medical history of cardiovascular disease	5.44 (1.27–23.28)	0.02
Low BMI	1.23 (1.02–1.47)	0.03
Short duration of hypertension	1.12 (1.04–1.22)	<0.01

BMI = body mass index; CI = confidence interval.

a Western person's weight. However, using DDD as a unit of measurement is not an issue when comparing drug consumption in one person.

In many PA patients, laparoscopic adrenalectomy could induce a significant fall in antihypertensive drug consumption. However, the total consumption of antihypertensive drugs may not be decreased as much in PA patients with a medical history of cardiovascular disease. Furthermore, even though the preoperative number of antihypertensive drug classes decreased, attention should be paid to the total consumption of antihypertensive drugs to control BP in PA patients. The DDD is a useful tool for assessing the total change in the consumption of antihypertensive drugs in PA patients. Clinicians could use the DDD to explain in detail to PA patients the postoperative change in antihypertensive drug consumption.

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