



## LETTERS TO THE EDITOR

# The sum of defined daily doses does not represent the potency of an antihypertensive drug regimen

Dear Editor,

Takanobu Utsumi and colleagues underline the difficulty to account for medication changes when comparing blood pressure (BP) before and after adrenalectomy in patients with primary aldosteronism (PA) [1]. This is a common concern when assessing the effect of any BP lowering intervention while the background pharmacological treatment is amenable to changes.

The authors rightly indicate that simply summing the number of antihypertensive drug classes neglects the dose of each drug. They propose to add the number of daily-defined doses (DDD) of each drug to better reflect the antihypertensive potency of a drug regimen. Three underlying assumptions must be questioned: first, that all drugs prescribed at one DDD have the same antihypertensive potency; second, that the potency of any drug is proportional to the number of DDD; third, that the potency of multiple drugs is the sum of their individual potency.

The first assumption is supported by strong evidence in the context of essential hypertension [2]. However, all drug classes are not equal in patients with PA. For instance, one DDD of an aldosterone antagonist is much more effective than one DDD of an angiotensin converting enzyme inhibitor in these patients. The second assumption is false, even in the context of essential hypertension: when the dose of an antihypertensive drug is doubled, its antihypertensive effect is only increased by 20% [2]. The third assumption is again supported by strong evidence in essential hypertension [2], and I see no reason to think that it is false in patients with PA.

Let us go back to the example taken in the paper: eplerenone 100 mg + amlodipine 10 mg preoperatively and cilnidipine 10 mg postoperatively. We must first assume that 2 DDD of eplerenone have 1.2 times the potency of 1 DDD. Likewise, 2 DDD of amlodipine have 1.2 times the potency of 1 DDD. Taken together, 2 DDD of eplerenone + 2

DDD of amlodipine have 2.4 times the potency of 1 DDD of a single drug. From this preoperative regimen, a single postoperative drug at one DDD represents a -58% decrease in antihypertensive potency. This is far from the -75% decrease in the sum of DDD.

By contrast, we always use the number of drug classes as a proxy for the antihypertensive potency of a regimen [3–5]. Going from a 2 drugs regimen to a 1 drug regimen, as in the example from the paper, represents a -50% decrease in the number of antihypertensive drug classes. While simpler, this approximation (-50%) is also closer to the real drop in antihypertensive potency (-58%) than the decrease in the sum of DDD (-75%).

To conclude, Takanobu Utsumi and colleagues are right: the number of drug classes is a biased estimate of the potency of an antihypertensive regimen. However, it is less so than the total number of DDD, because the impact of combining drug classes largely prevails over increasing their doses.

## References

1. Utsumi T, Kawamura K, Imamoto T, et al. Assessment of postoperative changes in antihypertensive drug consumption in patients with primary aldosteronism using the defined daily dose. *Asian J Surg*. 2014 [epub ahead of print].
2. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ*. 2003;326:1427.
3. Steichen O, Zinzindohoué F, Plouin PF, Amar L. Outcomes of adrenalectomy in patients with unilateral primary aldosteronism: a review. *Horm Metab Res*. 2012;44:221–227.
4. Küpers EM, Amar L, Raynaud A, Plouin PF, Steichen O. A clinical prediction score to diagnose unilateral primary aldosteronism. *J Clin Endocrinol Metab*. 2012;97:3530–3537.
5. van der Linden P, Steichen O, Zinzindohoué F, Plouin PF. Blood pressure and medication changes following adrenalectomy for unilateral primary aldosteronism: a follow-up study. *J Hypertens*. 2012;30:761–769.

Olivier Steichen\*  
AP-HP, Hôpital Tenon, Service de Médecine Interne,  
F-75020, Paris, France

Sorbonne Universités, UPMC Univ Paris 06, Faculté de  
médecine, F-75006, Paris, France

INSERM, U1142, LIMICS, F-75006, Paris, France

\*Service de médecine interne, hôpital Tenon, 4 rue de la  
Chine, F-75020 Paris, France. Tel +33 1 56 01 78 31;  
Fax +33 1 56 01 70 82.

E-mail address: [olivier.steichen@tnn.aphp.fr](mailto:olivier.steichen@tnn.aphp.fr)

Copyright © 2015, Asian Surgical Association. Published by Elsevier  
Taiwan LLC. All rights reserved.

<http://dx.doi.org/10.1016/j.asjsur.2015.02.001>

## The defined daily dose is a simple tool to assess total drug consumption as a measurement unit

We previously reported that the defined daily dose (DDD) is a useful tool to assess the total consumption of antihypertensive drugs in patients with primary aldosteronism (PA). Thus, DDD can be used as a substitute for the number of antihypertensive drug classes.<sup>1</sup> Oliver Steichen<sup>2</sup> agreed that the number of antihypertensive drug classes cannot accurately reflect the total consumption of antihypertensive drugs in PA patients.

Furthermore, he politely indicated some limitations in our previous study.<sup>2</sup> He assumed that all antihypertensive drugs at one DDD do not necessarily have the same potency, because one DDD of an aldosterone antagonist is much more effective than one DDD of the other classes of antihypertensive drugs in PA patients. However, even aldosterone antagonists, such as spironolactone and eplerenone, are not equally effective in each PA patient because of different background factors. Some investigators reported different responses to spironolactone in each PA patient, which was suggested to be a primary drug in postoperative hypertension cure.<sup>3,4</sup> Proye et al<sup>4</sup> suggested that PA patients who did not respond to spironolactone had coexisting essential hypertension. Prolonged hyperaldosteronism induces detrimental and irreversible effects on the cardiovascular system, which could result in resistant hypertension despite normalizing plasma aldosterone levels after surgery.<sup>5</sup>

Oliver Steichen<sup>2</sup> presented a calculation example for the antihypertensive potency in his own way. However, his calculation method neglects each patient's different background factors. Patients with PA who had accumulated vascular damage, such as longer duration of hypertension and older age, are thought to be considerably influenced by coexisting essential hypertension.

We emphasize again that the DDD is a simple tool to assess and compare drug consumption, not to be confused with the therapeutic dose or with the dose actually prescribed by a physician for an individual patient. The pri-

mary goal of our previous study was to assess postoperative changes in antihypertensive drug consumption, not antihypertensive drug potency.<sup>1</sup> We did not assess the antihypertensive potency of a drug regimen in our study.<sup>1</sup> If clinicians would like to assess the antihypertensive potency of a drug regimen, a prospective study that includes preoperative and postoperative blood pressure (BP) data for each patient should be conducted after adjustment of each used drug and background factor.

Oliver Steichen is right: the DDD might not be able to reflect the antihypertensive potency of a drug regimen completely. A prospective study that includes complete analysis of BP data after adjustment of each used drug and background factor will be needed to assess the potency of antihypertensive drugs, because the degree of coexisting essential hypertension differs in each PA patient. At present, the DDD is an irreplaceable tool to assess and compare total drug consumption as a measurement unit in a person.

### References

1. Utsumi T, Kawamura K, Imamoto T, et al. Assessment of postoperative changes in antihypertensive drug consumption in patients with primary aldosteronism using the defined daily dose. *Asian J Surg.* 2014;37:190–194.
2. Steichen O. The sum of defined daily doses does not represent the potency of an antihypertensive drug regimen. *Asian J Surg.* 2014 [Epub ahead of print].
3. Zarnegar R, Lee J, Brunaud L, et al. Good blood pressure control on antihypertensives, not only response to spironolactone, predicts improved outcome after adrenalectomy for aldosteronoma. *Surgery.* 2007;142:921–929.
4. Proye CA, Mulliez EA, Carnaille BM, et al. Essential hypertension: first reason for persistent hypertension after unilateral adrenalectomy for primary aldosteronism? *Surgery.* 1998;124:1128–1133.
5. Utsumi T, Kamiya N, Endo T, et al. Development of a novel nomogram to predict hypertension cure after laparoscopic adrenalectomy in patients with primary aldosteronism. *World J Surg.* 2014;38:2640–2644.

Takanobu Utsumi\*  
Hiroyoshi Suzuki  
*Department of Urology, Toho University Sakura Medical  
Center, Sakura, Japan*

Tomohiko Ichikawa  
*Department of Urology, Graduate School of Medicine,  
Chiba University, Chiba, Japan*

\*Corresponding author. Department of Urology, Toho University Sakura Medical Center, 564-1 Shimoshizu, Sakura-shi, Chiba 285-8741, Japan.  
*E-mail address: [p-cats@pd6.so-net.ne.jp](mailto:p-cats@pd6.so-net.ne.jp) (T. Utsumi)*  
22 January 2015

Copyright © 2014, Asian Surgical Association. Published by Elsevier Taiwan LLC. All rights reserved.

<http://dx.doi.org/10.1016/j.asjsur.2015.02.001>