British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 1685–1687 1685

LETTER TO THE EDITOR

Amiloride treatment and increased risk of pressure ulcers in hospitalized patients

Correspondence Dr Matthieu Roustit, Unité de Pharmacologie Clinique, Centre d'Investigation Clinique de Grenoble – Inserm CIC1406, CHU de Grenoble, 38043 Grenoble Cedex 09, France. Tel.: +33 4 7676 9260; Fax: +33 4 7676 9262; E-mail: mroustit@chu-grenoble.fr

Received 15 April 2016; **Revised** 18 July 2016; **Accepted** 4 August 2016

Matthieu Roustit[1,2,3], Céline Genty[4,5], Marion Lepelley[6], Sophie Blaise[2,7], Bérengère Fromy[8,9], Jean-Luc Cracowski[1,2,3] and Jean-Luc Bosson[4,5,6]

[1]Université Grenoble-Alpes, HP2 UMR 1042, F-38000 Grenoble, France, [2]Inserm, HP2 UMR 1042, F-38000 Grenoble, France, [3]CHU Grenoble-Alpes, Pôle Recherche, Inserm CIC1406, F-38000 Grenoble, France, [4]Université Grenoble-Alpes, TIMC-IMAG, F-38000 Grenoble, France, [5]CNRS, TIMC-IMAG, F-38000 Grenoble, France, [6]CHU Grenoble-Alpes, Pôle Santé Publique, F-38000 Grenoble, France, [7]CHU Grenoble-Alpes, Pôle Pluridisciplinaire de Médecine, F-38000 Grenoble, France, [8]CNRS, Laboratoire de Biologie Tissulaire et Ingénierie thérapeutique (LBTI), UMR 5301, Lyon, France, and [9]UCBL1, Université Lyon, France

Keywords acid-sensing ion channels (ASICs), amiloride, microcirculation, pressure ulcers

Tables of Links

TARGETS
Ligand gated ion channels [2]
ASIC

LIGANDS
Amiloride

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Acid-sensing ion channels (ASICs) are voltage-insensitive cation channels primarily activated by acidosis, with various pharmacological effects [3]. More specifically, ASIC3 has been shown to be a neuronal sensor for appropriate adjustment to pressure in the cutaneous microcirculation, protecting healthy skin against pressure ulcers (PUs) in animal model [4].

Besides its diuretic properties, the potassium-sparing diuretic amiloride was the first described inhibitor of ASICs. In both rodents and humans, the blockade of ASIC with amiloride blunted pressure-induced vasodilation (PIV) [4], an early microvascular response to low pressure that reflects cutaneous vascular fragility when altered [5, 6].

In patients treated with amiloride, the physiological protection of the skin against pressure might therefore be impaired though ASIC blockade. However, whether treatment with amiloride is associated with an increased risk of PUs is unknown. We tested this hypothesis in a large database of hospitalized patients.

The Premier Perspective™ database is a clinical and financial information system from about 600 hospitals in the United States. It meets the HIPAA requirements of de-identification. Institutional Review Board approval was obtained on 29 January 2016 (CECIC-Rhone-Alpes-Auvergne, IRB5891). We limited our search to the calendar year 2006, producing a population of approximately 33 million patients. Drug and target nomenclature conforms to the Concise Guide to Pharmacology 2015/16 [1].

Inclusion criteria were patients ≥15 years old who underwent prolonged hospitalization (≥10 days) and exposed to one or more of the following diuretics for ≥5 days: amiloride, triamterene, hyrdrochlorothiazide (HCTZ), spironolactone + HCTZ. Patients with loop diuretics or spironolactone alone were excluded due to different indications (e.g. acute heart failure or primary hyperaldosteronism, respectively) that may increase heterogeneity in the population. Patients who received amiloride alone or combined to

DOI:10.1111/bcp.13084

another diuretic were in the amiloride group, whereas patients treated with the other diuretics were in the control group. Population characteristics (age, gender), clinical data according to the International Classification of Diseases 9th edition, Clinical Modification (ICD9), and length of stay were collected. The outcome was non-admitting PUs (code 707.0).

Continuous data were expressed as mean ± standard deviation or as the median (first–third quartiles) when the distribution was not normal. Comparisons were analysed with the *t*-test or the Mann–Whitney test, as appropriate. Univariate and adjusted odds ratio (OR) for the risk of PU between groups were calculated using logistic regression. We considered *P*-values < 0.05 as significant. Statistical analysis was performed using STATA software (version 13.0 StatCorp College Station, TX, USA).

We identified 424 597 patients undergoing prolonged hospitalization without admitting PUs. Among them, 340 (0.08%) received amiloride and 20 653 (4.86%) had another diuretic for ≥5 days, mostly HCTZ (17 250, 4.06%) or a combination of HCTZ + triamterene (3216, 0.76%). In the whole population, 27 295 patients (6.43%) developed a PU during hospital stay.

The prevalence of PUs was 7.06% and 3.89% in the amiloride and the control groups, respectively ($P = 0.003$). Patients in the amiloride group were younger (63.1 ± 15.6 *vs.* 67.6 ± 14.1; $P < 0.001$) and 52.3% were females (*vs.* 59.7% for controls; $P = 0.006$). Median length of stay was 16 (12–25.5) days in the amiloride *vs.* 14 (11–19) days in the control groups ($P < 0.001$). Malnutrition, acute renal failure and heart failure were all significantly more frequent in the amiloride group, whereas diabetes and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which are known to inhibit ASICs [7], were more frequent in the control group. When adjusting for confounders, amiloride remains significantly associated with an increased risk of PU, with an adjusted OR = 1.57 [1.02; 2.44] ($P = 0.042$) (Table 1). Interestingly, there is a significant interaction with the factor heart failure, amiloride being a significant risk factor only in patients with heart failure (Table 1).

These results suggest that amiloride increases the risk of incident PU in hospitalized patients. This hypothesis relies on a strong theoretical background: PIV, which delays the decrease in cutaneous blood flow produced by local low pressure, is decreased by amiloride through ASIC blockade. Deprived of this physiological protection, diabetic and aged patients show an early decrease in cutaneous blood flow in response to pressure, that reflects microvascular fragility [5, 6]. Such an inability of the skin to resist pressure could explain the higher risk of developing PUs in these patients. This study further strengthens that ASIC blockade contributes to the development of PUs, likely via inability of the cutaneous microcirculation to adapt to local pressure, as previously shown in mice [4].

However, our results need to be interpreted with caution due to limitations. First, despite the use of a large database, our inclusion criteria restricted the number of cases to 827. For this reason, a limited number of potential confounders to adjust for were considered, and we focused on those that we considered to be the most relevant to our population [8, 9]. Another limitation of this study is that the chronology of events (i.e. onset of PU regarding drug intake) is not known precisely. Indeed, we could not identify patients receiving amiloride as a chronic treatment before hospitalization. In order to limit this bias, we considered only non-admitting PUs in patients treated for ≥5 days. However, the duration of treatment that increases the risk of ulcer is unknown. Finally, we did not have reliable data regarding tobacco use, and therefore were not able to take into account this possible confounder.

In conclusion, our study suggests that treatment with amiloride is an independent risk factor for PU in hospitalized patients with heart failure. Other diuretics may therefore be preferred in patients at risk.

Table 1

Risk factors for pressure ulcers in hospitalized patients

	OR [95% CI]	*P*-value	aOR [95% CI]	*P*-value
Amiloride	1.88 [1.23–2.86]	0.003	1.57 [1.02–2.44]	0.042
Age	1.018 [1.013–1.024]	<0.001	1.023 [1.017–1.029]	<0.001
Length of stay	1.024 [1.022–1.028]	<0.001	1.025 [1.022–1.028]	<0.001
Malnutrition	2.28 [1.57–3.31]	<0.001	1.76 [1.17–2.65]	0.006
Acute renal failure	2.04 [1.72–2.41]	<0.001	1.42 [1.19–1.71]	<0.001
Heart failure[a]	1.91 [1.63–2.23]	<0.001	1.44 [1.22–1.70]	<0.001
Diabetes	1.45 [1.26–1.67]	<0.001	1.44 [1.25–1.67]	<0.001
NSAIDs	0.94 [0.82–1.08]	0.41		
Gender (male)	0.97 [0.84–1.12]	0.71		
Surgery unit	1.05 [0.91–1.22]	0.47		

aOR: odds ratio for the risk of PU between groups adjusted for age, length of stay, diabetes, congestive heart failure, malnutrition and acute renal failure

[a]In this model there is a significant interaction between the group and the factor Heart failure ($P = 0.028$): among patients without heart failure, amiloride did not increase the risk of pressure ulcers (OR = 0.88 [0.43–1.83], $P = 0.737$), while it has a significant effect in patients with heart failure (OR = 2.59 [1.44–4.65], $P = 0.001$). NSAIDs: nonsteroidal anti-inflammatory drugs

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. JLB had support from Sanofi who provided us with the Premier Perspective™ database. Sanofi had no relationship with the content of the Premier Perspective™ database, and did not have any involvement in the design and analysis of this study; nor in the preparation, review or approval of the present manuscript.

We thank Dr Alison Foote (Grenoble Clinical Research Center) for editing the manuscript.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054–D1068.

2 Alexander SPH, Peters JA, Kelly E, Marrion N, Benson HE, Faccenda E, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: Ligand-gated ion channels. Br J Pharmacol 2015; 172: 5870–903.

3 Baron A, Lingueglia E. Pharmacology of acid-sensing ion channels – physiological and therapeutical perspectives. Neuropharmacology 2015; 94: 19–35.

4 Fromy B, Lingueglia E, Sigaudo-Roussel D, Saumet JL, Lazdunski M. Asic 3 is a neuronal mechanosensor for pressure-induced vasodilation that protects against pressure ulcers. Nat Med 2012; 18: 1205–7.

5 Fromy B, Abraham P, Bouvet C, Bouhanick B, Fressinaud P, Saumet JL. Early decrease of skin blood flow in response to locally applied pressure in diabetic subjects. Diabetes 2002; 51: 1214–7.

6 Fromy B, Sigaudo-Roussel D, Gaubert-Dahan M-L, Rousseau P, Abraham P, Benzoni D, *et al*. Aging-associated sensory neuropathy alters pressure-induced vasodilation in humans. J Invest Dermatol 2010; 130: 849–55.

7 Voilley N, de Weille J, Mamet J, Lazdunski M. Nonsteroid anti-inflammatory drugs inhibit both the activity and the inflammation-induced expression of acid-sensing ion channels in nociceptors. J Neurosci Off J Soc Neurosci 2001; 21: 8026–33.

8 Grey JE, Harding KG, Enoch S. Pressure ulcers. BMJ 2006; 332: 472–5.

9 Fogerty MD, Abumrad NN, Nanney L, Arbogast PG, Poulose B, Barbul A. Risk factors for pressure ulcers in acute care hospitals. Wound Repair Regen 2008; 16: 11–18.