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CASE REPORT

Refractory Vasodilatory Shock Induced by Irbesartan's Acute Intoxication

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Keywords

Overdose, Irbesartan, ECLS, Outcome

Introduction

Angiotensin II (AII) is a strong physiological vasopressor hormone. Sartans act as antagonists of AT1 receptors of AII, inducing a vasodilatation via an upregulation of AT2 receptors. In July 2017, in the New England Journal of Medicine, efficiency of AII to increase blood pressure and reduce conventional vasopressors's dose in severe vasodilatory shock refractory to high-dose vasopressors were observed [1]. Here, we report the case history of an acute vasodilatory shock due to acute massive medication overdose by sartans treated by extracorporeal life support and high-dose of conventional vasopressors in association with terlipressin due to lack of AII availability.

Case Description

We report the case of a 59-years-old man (85 kg), admitted in the ICU for acute vasodilatory shock due to acute massive medication overdose after a first episode of depression consecutive to family problem (divorce). His medical past history was only marked by high blood pressure and atrial fibrillation since 3 years. A mobile intensive care unit (MICU) was dispatched on scene. According to the empty medication packs found, the drugs involved for the intoxication were: Irbesartan 150 mg (50 tablets missing), Diltiazem 200 mg (15 tablets missing), Lercanidipine 10 mg (50 tablets missing), Flecainide 150 mg (20 tablets missing), Rivaroxaban 20 mg (14 tablets missing), Trimebutine 20 mg (17 tablets missing) and Lormetazepam 2 mg (15 tablets missing). His general practitioner prescribed all these medications, in order to treat cardiovascular disorders and depression.

During the pre-hospital setting, blood pressure was initially stable around 110/90 mmHg and heart rate at 88 beats per minute. During the transfer to hospital, 2 episodes of severe bradycardia occurred, rapidly leading to 2 circulatory arrests. Each one was resolved in few minutes after cardiopulmonary resuscitation and 1 mg epinephrine intravenous injection. Tracheal intubation and mechanical ventilation were instituted in the same time due to coma. To maintain blood pressure, the pre-hospital emergency physician decided to infuse 2000 ml of isotonic serum saline, and to introduce continuous infusion of norepinephrine 1 $\mu g.kg^{-1}.min^{-1}$ and epinephrine 0.8 $\mu g.kg^{-1}.min^{-1}$.

Upon ICU arrival, rapidly an increase in vasopressor requirement was necessary, up to norepinephrine 5 $\mu g.kg^{-1}.min^{-1}$ and epinephrine 8 $\mu g.kg^{-1}.min^{-1}$, but this was inefficient in restoring blood pressure, remaining around 35 to 40 mmHg, and induced cardiac arrhythmia. Transthoracic echocardiography found a normal systolic function, left ventricular fraction ejection of 50%, no diastolic dysfunction (E/A ratio of 1) and no hypovolemia estimated by an inferior vena cava diameter of 18 mm.

Therefore, as the shock was mainly vasoplegic and refractory to high doses of vasopressors leading to ma-

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jor side effects impairing cardiac function, it was decided to resort to a bedside-to-bench process, and the patient received extracorporeal life support (ECLS) (CARDIOHELP, Maquet, Rastatt, Germany), which was achieved through percutaneous femoral venous arterial cannulation, with an initial rate of 5 $l.min^{-1}$, 5300 $rev.min^{-1}$ allowing to maintain a mean blood pressure between 50 and 60 mmHg. Laboratory investigations, blood sample 3 hours after ICU admission, observed a plasma level value of 1504 $ng.ml^{-1}$ (therapeutic dose between 50 and 400 $ng.ml^{-1}$) for Diltiazem, 3.43 $mg.l^{-1}$ (therapeutic dose between 0.2 and 0.6 $mg.l^{-1}$) for Flécaïnide and 1.18 $mg.l^{-1}$ (therapeutic dose between 0.08 and 0.17 $mg.l^{-1}$) for Bromazepam. Quantification of other drugs was not available in our laboratory.

Despite primary care and ECLS, vasopressor support was maintained due to the vasodilatory component of the shock induced by irbesartan.

At day 1, we raised the possibility to use AII. Unfortunately, AII is not available in France yet. Therefore, we decided to use an analogue of vasopressin, terlipressin 0.06 $\mu g.kg^{-1}.min^{-1}$, which rapidly allowed decreasing norepinephrine from 5 $\mu g.kg.min^{-1}$ to 1.25 $\mu g.kg^{-1}.min^{-1}$. Withdrawal of terlipressin was performed at day 3, that of epinephrine at day 4, and that of norepinephrine at day 6. Daily transthoracic echocardiography was performed for 10 days and observed no systolic and diastolic impairment. No ECG modification or troponin plasma level raise during ICU stay were observed.

Finally, ECLS was definitely removed at day 6 and the mechanical ventilator at day 14. An acute renal failure occurred, consecutive acute tubular necrosis resulting from shock and high levels of vasopressors infusion, since day 1 requiring, conventional dialysis for 2 weeks. Mechanical ventilation was removed on day 14. The patient left ICU at day 26 and hospital at day 37 for a psychiatric health disease centre. Before leaving hospital, his cardiovascular treatment was re-evaluated, only Nicardipine 100 $mg.day^{-1}$, Diltiazem 200 $mg.day^{-1}$ and Flecainide 150 $mg.day^{-1}$ were maintained.

Conclusions

There is a poor literature on the effect of irbesartan poisoning and consequently its treatment. A previous case described by McNamee, et al. reported successful terlipressin infusion to treat refractory shock induced by irbesartan massive overdose, without requiring ECLS [2]. From a physio-pathological point of view, intoxication by sartan result in a blunt of sympathetic and renin-angiotensin systems, which could be theoretically reversed by AII administration. While vasopressin stimulates the vascular V1a receptors, its use has been proposed, with success, to restore blood pressure in septic and catecholamine resistant shock [3-5]. Terlipressin, the precursor of vasopressin, has also been reported to be effective in the treatment of vasodilatory shock secondary to calcium-channel blocker overdose [6,7].

Recently, Khanna, et al. observed the efficiency of AII in refractory vasodilatory shock, allowing an increase in blood pressure and a reduction in vasopressor requirement [1]. In our case, use of AII would have been interesting to specifically antagonise vasodilatory effects of irbesartan overdose. Since AII is actually unavailable in France, we decided to use terlipressin to directly stimulate V1a receptors, and this strategy clearly enabled to reduce catecholamine requirements. Nevertheless, from a pharmacological point of view, the most appropriate drug for sartan intoxication should be the natural agonist of AT receptors, i.e. AII.

In our case, the patient has suffered from a polymedication poisoning involving various cardiovascular drugs, responsible for vasodilatory and/or negative inotropic effects through different pathways. Transthoracic echocardiography allowed us to conclude that the shock was mainly due to vasoplegia more than negative inotropic effects. While, high does of vasopressors inducing immediate, cardiac arrythmia [8] and delayed, renal failure [9], side effects, we decided to use a pharmacological drug without cardiac effects to antagonise vasodilatation. Terlipressin was chosen because it has been suggested to be safer on renal function than norepinephrine and AII despite controversy [9,10].

Unfortunately, monitoring of irbesartan plasma level is routinely unavailable, which precludes determining the exact role of this drug in the vasodilatory effect during poly-intoxication. Indeed, such monitoring could be useful to predict the optimal vasopressor drug(s) that should be administered, i.e. catecholamine and/or terlipressin, according to the main pathway of the vasodilation.

In conclusion, for patients with refractory vasodilatory shock due to sartan overdose, angiotensin II should be effective from a pathopharmacological point of view, and there is a need to confirm its efficiency in such poisoning. Since this drug is not yet currently available, vasopressin, or its precursor terlipressin, could be used when conventional catecholamine administration is ineffective. Furthermore, this precocious strategy could theoretically enable to avoid ECLS requirement in some case of sartan poisoning.

The authors report no conflict of interest.

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