

Renin Angiotensin Aldosterone System and Drug Allergies Complicated with Hypotension

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Acute anaphylaxis is a potentially life-threatening reaction. Besides immunologic factors, it has been shown that non-immunologic factors may also play a prominent role in the pathophysiology of anaphylaxis.¹ Renin angiotensin aldosterone system (RAAS) dysfunction has been proposed as one of the most important non-immunologic factors in the development of anaphylaxis, and it is strongly considered to play a role in anaphylactic reactions due to hymenoptera venom. In several studies, it has been shown that the dysfunction of this system is prominent, especially in anaphylactic reactions complicated with hypotension.^{1,2,3} The RAAS acts systemically and locally to influence vascular tone, blood volume and myocardial contractility. It is also an important mechanism for maintaining arterial blood pressure during circulatory changes.⁴

In the present study, we investigated RAAS in patients who had experienced anaphylaxis with

SUMMARY It has been discussed in several studies that non-immunologic factors, such as renin angiotensin aldosterone system (RAAS) may play a role in the pathophysiology of anaphylaxis. This study aimed to determine whether RAAS plays a part in the fall in blood pressure during drug reactions or not. Twenty patients who experienced hypotension during drug reaction and 15 healthy volunteers were enrolled in this study. None of the patients in the study or control groups were under treatment with any drug that was capable of influencing to RAAS. Serum levels of angiotensin-I (A-I), angiotensin-II (A-II), angiotensin converting enzyme (ACE) and aldosterone were measured in both study and control groups. The Mann-Whitney U test was used to compare the results of the groups. There were no statistically significant differences between the groups with respect to A-I, A-II, ACE and aldosterone levels. It was concluded that a fall in blood pressure during drug reaction must be the result of mast cell mediator effects on the vascular wall rather than RAAS impairment.

hypotension due to drugs, to reveal whether this system plays a part in the fall of blood pressure during drug reactions or not.

PATIENTS AND METHODS

Twenty patients (12 females, 8 males) who experienced hypotension during drug reaction were enrolled in this study (study group). The control group consisted of 15 healthy age and sex matched volunteers (5 females, 10 males) without experience of anaphylaxis. None of the individuals in the study

and control groups was under treatment with any drug that was capable of influencing RAAS.

Venous blood samples were withdrawn within 1-2 minutes after the anaphylaxis from a cubital vein directly into a plain glass tube. Serum levels of angiotensin-I (A-I), angiotensin-II (A-II), angiotensin converting enzyme (ACE) and aldosterone were measured in both

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study and control groups. Measurements were performed by radioimmunoassay method using commercially available kits (SORIN Biomedica, Saluggia-Vercelli, Italy for A-I; EURO Diagnostic B.V., Arhem, Holland for A-II and ACE, Diagnostic System Laboratories Inc., Texas, USA for aldosterone). The assays were performed according to the manufacturers' recommendations.

The data processed by computer and Mann-Whitney U test was used to compare the results of the groups. A *p* value less than 0.05 was considered statistically significant.

RESULTS

The mean age was 31 ± 8.2 years in the study group (range 19 to 50 years) and 29.2 ± 8.6 years in the control group (range 15 to 43 years). Mean values and a comparison of the variables of interest are presented in Table 1. There were no statistically significant differences between the groups with respect to A-I, A-II, ACE and aldosterone levels, and the *p* value was higher than 0.05 for each parameter.

DISCUSSION

Circulation has several protective mechanisms that maintain perfusion of vital organs during acute hypotensive episodes. Regulation of circulatory responses is provided by the integrated effects of both neural and hormonal systems. The sympathetic nervous system and the RAAS are the most extensively studied systems. The RAAS was first recognised as a classical endocrine system with effects mediated entirely by circulating hormones. However, it has been demonstrated that all components of the system are present in many tissues.⁵

Impaired RAAS activity may contribute to the dramatic fall in blood pressure in anaphylactic reactions.⁶ In anaphylaxis due to hymenoptera stings, the absence of a relation between the severity of clinical findings and prick test and/or specific IgE levels, leads to consideration of the presence of some non-immunologic factors in these reactions. As a matter of fact, significantly decreased A-I and A-II levels have been shown during hypotensive episodes due to hymenoptera sting-induced anaphylax-

is.^{1,2,3} Cross-reactivity between antibody to hymenoptera venom and angiotensin has been suggested. After making a decision on the relationship between the RAAS and anaphylactic reactions to hymenoptera venom, the relationship among other anaphylactic reactions and the RAAS becomes more important in explaining the pathophysiology of these types of reactions. The RAAS is activated in acute severe asthma, although not in all asthmatics. The mechanism of this activation is unclear, but recent evidence has shown elevation of renin and angiotensin II in response to nebulized and intravenous salbutamol.⁶

A fall in blood pressure is not an uncommonly encountered finding in drug allergies. Estimation of severity of hypotension is almost always impossible in such reactions. Furthermore, while some patients experience hypotension during drug allergy, others do not. The relation of RAAS dysfunction to hypotensive episodes occurring in drug reaction has not been clearly established.

In the present study, our goal was to dispute this possible relationship, but we could not show

Table 1 Comparison of A-I, A-II, ACE and aldosterone levels of the patients with hypotensive drug reactions and healthy controls

	N	A-I (ng/ml)	A-II (pg/ml)	ACE (U/l)	Aldosterone (pg/ml)
Study Group	20	1.2 ± 3.13	11.5 ± 17.44	6.4 ± 9.84	219 ± 138.64
Control Group	15	1.1 ± 1.94	11.1 ± 14.72	6.1 ± 5.81	213 ± 147.17
		<i>p</i> > 0.05	<i>p</i> > 0.05	<i>p</i> > 0.05	<i>p</i> > 0.05

1. Values are given as means \pm S.D.

2. Reference values: Angiotensin I: < 5.7 ng/ml; Angiotensin II: 5-15 pg/ml; ACE: 5-10 U/l; Aldosterone: 30-200 pg/ml.

any relationship. RAAS components were similar in patients who experienced hypotensive drug reactions and healthy controls. Similarly, in our previously reported study, we investigated RAAS in anaphylactic reactions due to aeroallergen immunotherapy, and revealed the absence of RAAS dysfunction.⁷

In conclusion, RAAS dysfunction seems to be specific only to hymenoptera venom anaphylaxis, since the relationship between RAAS and anaphylaxis triggered by other factors has not been shown with respect to current knowledge. Depending on our results, it may be concluded that a fall in blood pressure during drug reactions must be related to excessive and consecutive mediator

released from the mast cells and its effects on the vascular wall, rather than RAAS impairment. On the other hand, it may also be concluded that normal levels of RAAS components soon after a hypotensive episode may be evidence for "a partial failure" or "impairment" of this RAAS system, however. So, further detailed studies are necessary to expose the performance and current role of RAAS in unopposed hypotensive reactions.

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