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ORIGINAL ARTICLE

Basic Study

Mast cell tryptase and carboxypeptidase A expression in body fluid and gastrointestinal tract associated with drug-related fatal anaphylaxis

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Abstract

AIM: To investigate the expression of mast cell tryptase and carboxypeptidase A in drug-related fatal anaphylaxis.

METHODS: The expression of mast cell tryptase and carboxypeptidase A in 15 autopsy cases of drug-related fatal anaphylaxis and 20 normal autopsy cases were detected. First, the expression of mast cell tryptase was determined in stomach, jejunum, lung, heart, and larynx by immunofluorescence. Different tissues were removed and fixed in paraformaldehyde solution, then paraffin sections were prepared for immunofluorescence. Using specific mast cell tryptase and carboxypeptidase A antibodies, the expression of tryptase and carboxypeptidase A in gastroenterology tract and other tissues were observed using fluorescent microscopy. The postmortem serum and pericardial fluid were collected from drug-related fatal anaphylaxis and normal autopsy cases. The level of mast cell tryptase and carboxypeptidase A in postmortem serum and pericardial fluid were measured using fluor enzyme linked immunosorbent assay (FEIA) and enzyme linked immunosorbent assay (ELISA) assay. The expression of mast cell tryptase and carboxypeptidase A was analyzed in drug-related fatal anaphylaxis cases and compared to normal autopsy cases.

RESULTS: The expression of carboxypeptidase A was less in the gastroenterology tract and other tissues from anaphylaxis-related death cadavers than

normal controls. Immunofluorescence revealed that tryptase expression was significantly increased in multiple organs, especially the gastrointestinal tract, from anaphylaxis-related death cadavers compared to normal autopsy cases (46.67 ± 11.11 *vs* 4.88 ± 1.56 in stomach, 48.89 ± 11.02 *vs* 5.21 ± 1.34 in jejunum, 33.72 ± 5.76 *vs* 1.30 ± 1.02 in lung, 40.08 ± 7.56 *vs* 1.67 ± 1.03 in larynx, 7.11 ± 5.67 *vs* 1.10 ± 0.77 in heart, $P < 0.05$). Tryptase levels, as measured with FEIA, were significantly increased in both sera (43.50 ± 0.48 μg/L *vs* 5.40 ± 0.36 μg/L, $P < 0.05$) and pericardial fluid (28.64 ± 0.32 μg/L *vs* 4.60 ± 0.48 μg/L, $P < 0.05$) from the anaphylaxis group in comparison with the control group. As measured by ELISA, the concentration of carboxypeptidase A was also increased more than 2-fold in the anaphylaxis group compared to control (8.99 ± 3.91 ng/mL *vs* 3.25 ± 2.30 ng/mL in serum, 4.34 ± 2.41 ng/mL *vs* 1.43 ± 0.58 ng/mL in pericardial fluid, $P < 0.05$).

CONCLUSION: Detection of both mast cell tryptase and carboxypeptidase A could improve the forensic identification of drug-related fatal anaphylaxis.

Key words: Gastrointestinal tract; Drug-related fatal anaphylaxis; Forensic Pathology; Mast cell carboxypeptidase A; Mast cell tryptase

Core tip: Drug-related fatal anaphylaxis is occasionally encountered in forensic pathology routine. However, markers in the identification of drug-related fatal anaphylaxis still need further exploration. This study identified two important markers in drug-related fatal anaphylaxis, tryptase and carboxypeptidase A, which may improve postmortem diagnosis of anaphylaxis in medicolegal expertise.

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INTRODUCTION

Drug-induced anaphylaxis, also called allergic shock, is an immunologically mediated event that occurs after drug exposure in sensitized individuals and could lead to death[1-3]. However, postmortem diagnosis of anaphylaxis is difficult in medicolegal expertise. There was less different clinical symptom and pathological morphologic change between fatal anaphylaxis and general sudden death[4,5]. In current autopsy cases, general disease, intoxication, and violent death should be excluded first, and then exposure to allergen and clinical symptoms are evaluated in combination to identify anaphylaxis[2,6]. Therefore, exploration of novel, precise methods for anaphylaxis identification could be important in routine forensic pathology.

Drug-induced anaphylaxis can be initiated by binding of foreign drugs to specific immunoglobulin E (IgE) on mast cells[7,8]. Subsequently, various kinds of mediators are secreted from the mast cells, thereby inducing anaphylaxis[7,9,10]. Tryptase is a serine protease mainly stored in the granules of mast cells that is released at the onset of anaphylaxis[11]. Several studies have reported that serum tryptase levels may be a reliable indicator of anaphylaxis because of its long serum half-life compared to other secreted mediators[11-13]. However, the normal value of tryptase varies in different countries. Thus, more a more precise standard should be determined. Another chemical mediator, mast cell carboxypeptidase A, has been the focus of postmortem diagnosis of anaphylaxis. Carboxypeptidase A is a secreted protease that may be released following activation of mast cells to mediate acute anaphylaxis[14,15].

Therefore, we determined whether the level of carboxypeptidase A or a combination of carboxypeptidase A and tryptase could be meaningful in the postmortem diagnosis of anaphylaxis. In this study, the expression of tryptase and carboxypeptidase A in multiple organs of cadavers was detected by immunofluorescence. Fluor enzyme linked immunosorbent assay (FEIA) and enzyme linked immunosorbent assay (ELISA) were used to measure the level of tryptase and carboxypeptidase A in postmortem serum and pericardial fluid, respectively.

MATERIALS AND METHODS

Immunofluorescence of tryptase in different tissues

During autopsy, the stomach, jejunum, lung, heart, and larynx were removed, fixed, and embedded in paraffin for preparation of sections. Immunofluorescence was performed as previously described with minor alterations[16]. Briefly, mouse anti-human mast cell tryptase, mouse anti-human carboxypeptidase A, and rabbit anti-mouse IgG-TRITC (Santa Cruz, Dallas, TX, United States) were used to detect tryptase in different organs. The sections were observed using fluorescence microscopy (BX61, Olympus, Tokyo, Japan). Ten random visual fields were imaged per section and the number of tryptase-positive cells was counted. All experiments were approved by the Ethics Committee of Shanxi Medical University.

Quantification of tryptase and carboxypeptidase A levels in serum and pericardial fluid

Blood was collected from the right cardiac cavity and

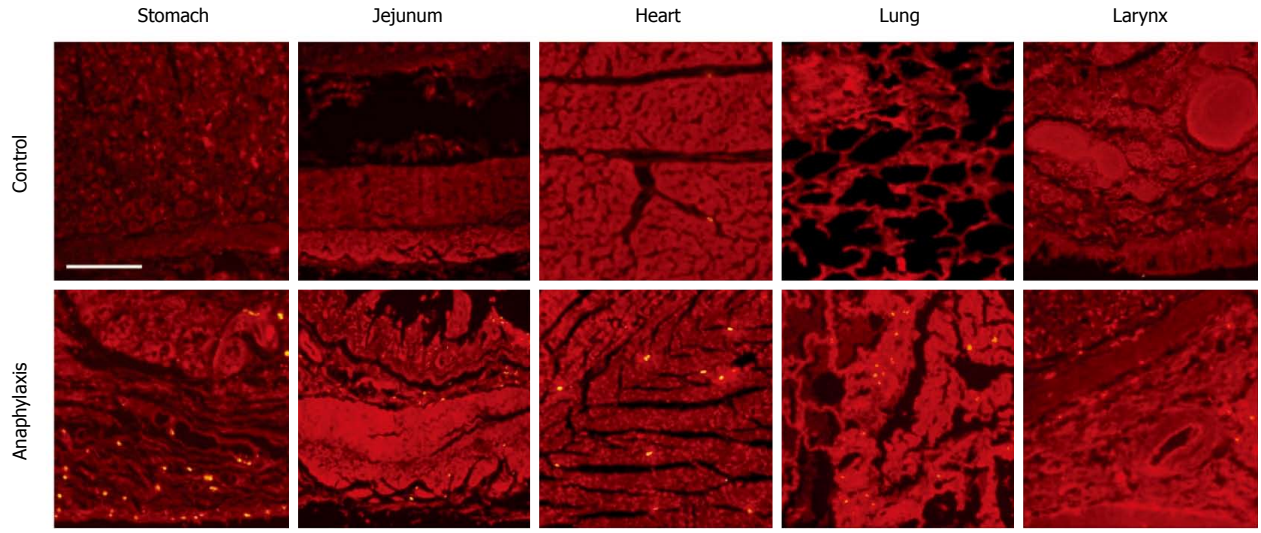

Figure 1 Immunofluorescence staining of tryptase in different organs. Scale bar = 200 μm.

Table 1 Number of tryptase-positive particles in the anaphylaxis and control groups

	Control (× 100)	Anaphylaxis (× 100)
Stomach	4.88 ± 1.56	46.67 ± 11.11[1]
Jejunum	5.21 ± 1.34	48.89 ± 11.02[1]
Lung	1.30 ± 1.02	33.72 ± 5.76[1]
Larynx	1.67 ± 1.03	40.08 ± 7.56[1]
Heart	1.10 ± 0.77	7.11 ± 5.67[1]

[1]Denotes significant difference *vs* control, $P < 0.05$, $n = 10$.

centrifuged. The serum and pericardial fluid were stored at -80 ℃ until use. Samples from 35 autopsy cases were measured. The causes of death in the anaphylaxis group (15 cases, 10 male, five female) included three of penicillin, three of ceftriaxone, three of levofloxacin, five of lomefloxacin *via* intravenous drip, and one of ibuprofen *via* oral administration. Anaphylaxis was diagnosed by clinical features, where the anaphylaxis symptoms occurred in all cases within 30 min. All postmortem autopsies were performed within 72 h. For the control group, 20 cases without allergic reaction, craniocerebral injury, coronary heart disease, and recreational drug use were selected. The level of tryptase in serum and pericardial fluid was measured by a commercial FEIA kit (Pharmacia Diagnostics, Uppsala, Sweden). Carboxypeptidase A levels were determined using an ELISA kit (Huamei Bio, Wuhan, China) according to the manufacturer's instructions.

Statistical analysis

Data were expressed as mean ± SE, and a student't test was used to compare differences between groups. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 17.0 software (Palo Alto, California, United States).

RESULTS

The expression of tryptase in different organs of anaphylaxis cadaver

Immunofluorescence was performed to detect the expression of carboxypeptidase A and tryptase in different organs. Less carboxypeptidase A was expressed in tissues from anaphylaxis cadaver than control (data not shown). Next, the expression of tryptase was detected in different organs. As shown in Figure 1, multiple tryptase-positive particles were observed in the mucous layer, with less in the muscular layer of the stomach and jejunum, from anaphylaxis cadaver. In contrast, the expression of tryptase was less in tissues from the control group. We also detected the expression of tryptase in some other tissues. Tryptase was observed in the bronchia wall and the small vessel wall in the lung, the small vessel wall in the submucosa of the larynx, and the periphery mesenchyme of the small vessels in the heart (Figure 1 and Table 1).

Determination of tryptase and carboxypeptidase A in postmortem serum and pericardial fluid

We examined tryptase in the sera and pericardial fluid from 15 autopsy cases who died of anaphylaxis and 20 control cases. The levels of tryptase were significantly increased in both sera and pericardial fluid from the anaphylaxis group in comparison with control group (Table 2). The concentrations of carboxypeptidase A were increased more than 2-fold in the anaphylaxis group compared to the control group (Table 3). Taken together, our results suggested that both tryptase and carboxypeptidase A were increased in drug-related fatal anaphylaxis.

Table 2 Expression of tryptase in serum and pericardial fluid

	n	Serum (μg/L)	Pericardial fluid (μg/L)
Control	20	5.40 ± 0.36	4.60 ± 0.48
Anaphylaxis	15	43.50 ± 0.48[1]	28.64 ± 0.32[1]

[1]Denotes significant difference *vs* control, $P < 0.05$.

Table 3 Expression of carboxypeptidase A in serum and pericardial fluid

	n	Serum (ng/mL)	Pericardial fluid (ng/mL)
Control	20	3.25 ± 2.30	1.43 ± 0.58
Anaphylaxis	15	8.99 ± 3.91[1]	4.34 ± 2.41[1]

[1]Denotes significant difference *vs* control, $P < 0.05$.

DISCUSSION

Drug-induced fatal anaphylaxis is frequently encountered in medicolegal expertise. Some current indicators of anaphylaxis, including IgE and histamine, lack specify or stability[17-19]. Compared to other secreted mediators, tryptase and carboxypeptidase A have a long half-life *in vivo*, which led to the speculation that these two proteases may be superior indicators for the postmortem diagnosis of anaphylaxis[20,21]. In the present study, we measured the levels of mast cell tryptase and carboxypeptidase A in postmortem serum and pericardial fluid. Schwartz *et al*[22] had reported that the concentration of tryptase increased rapidly after allergic shock and that it could be detected up to 4 d in autopsy. Moreover, the severity of the allergic reaction was shown to be highly related to tryptase level[13,23,24]. Although the standard of serum tryptase is different in normal adults among countries, a tryptase value greater than 10 μg/L can be considered abnormal[25,26]. We found that the level of tryptase in the serum from the anaphylaxis group was 8-fold higher than control. Meanwhile, this value in the pericardial fluid was 6-fold greater in the anaphylaxis group than control. These results were consistent with previous findings suggesting that tryptase may be a specific marker in the postmortem diagnosis of anaphylaxis. However, it has also been reported that serum tryptase levels are increased in patients with coronary heart disease, mastocytosis patients, and some drug abusers[27-30]. Therefore, these causes of mortality should be excluded before making a diagnosis of anaphylaxis.

Another chemical mediator secreted from mast cells, carboxypeptidase A (also known as carboxypeptide A3, CPA3), was increased in allergic reactions, which was positively correlated to chymases[31,32]. As shown for tryptase, carboxypeptide was also highly expressed in the epithelium of asthma patients[33,34]. We confirmed that the level of carboxypeptidase A increased significantly in both postmortem serum and pericardial fluid from anaphylaxis cadavers compared with control. Although there was less in depth investigation of carboxypeptide levels in the postmortem serum from anaphylaxis cases, we speculate that the alteration of carboxypeptide was also meaningful. Measuring both carboxypeptide and tryptase could improve the postmortem diagnosis of anaphylaxis. Furthermore, determining levels of these mediators from the pericardial fluid in the closed serous cavity would help to avoid possible contamination after death.

During medicolegal expertise, the detection of indicators often occurs long after death, making it increasing difficult to obtain the serum or pericardial fluid samples. Therefore, determining the expression of chemical markers in different organs from the cadavers is important. Although carboxypeptidase A was expressed less in tissues from both normal and anaphylaxis cadaver, the expression of tryptase in stomach, jejunum, lung, heart, and larynx from the drug-induced anaphylaxis group was significantly greater than the control group.

In conclusion, the expression of mast cell tryptase and carboxypeptidase A in body fluid and postmortem organs, especially gastrointestinal tract, could be meaningful in the identification of drug-related fatal anaphylaxis. Taken together with immunofluorescent identification, measurement of serum mast cell-specific tryptase and carboxypeptidase A levels might be a novel precise method that could improve postmortem diagnosis of anaphylaxis in medicolegal expertise. In addition, the detection of tryptase level in postmortem organs could also be meaningful in cases where it is difficult to collect serum/pericardial fluid due to the advanced state of decay during medicolegal expertise.

COMMENTS

Background

Drug-related fatal anaphylaxis could be occasionally encountered in routine forensic pathology. However, additional markers for the identification of drug-related fatal anaphylaxis are still needed.

Research frontiers

The exploration of novel markers and methods for the identification of drug-related fatal anaphylaxis could be important in the forensic identification of anaphylaxis.

Innovations and breakthroughs

This article provides new evidence for the use of mast cell tryptase and carboxypeptidase A as biomarkers to identify drug-related fatal anaphylaxis. It is suggested that the expression of tryptase and carboxypeptidase A in the gastroenterology tract and other tissues might be important markers in the case that it is difficult to collect serum/pericardial fluid because of the advanced state of decay during medicolegal expertise.

Applications

Combination of mast cell tryptase and carboxypeptidase A detection could improve the forensic identification of drug-related fatal anaphylaxis.

Peer-review

This is an interesting study about drug-related fatal anaphylaxis. The expression

of mast cell tryptase and carboxypeptidase A in drug-related fatal anaphylaxis are investigated. And the expression of mast cell tryptase and carboxypeptidase A in 15 autopsy cases of drug-related fatal anaphylaxis and 20 normal autopsy cases were detected. The authors concluded that combination of mast cell tryptase and carboxypeptidase A detection could improve the forensic identification of drug-related fatal anaphylaxis. And the detection of tryptase level in postmortem organs could also be meaningful in the case that hard to collect serum/pericardial fluid and advanced state of decay during medicolegal expertise.

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