

Postmortem serum tryptase levels in anaphylactic and non-anaphylactic deaths

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ABSTRACT

Background The postmortem diagnosis of anaphylaxis remains difficult due to the lack of specific biomarkers. Mast cell tryptase (MCT) levels are used as a marker of mast cell degranulation in living patients and elevated levels have also been described in postmortem serum samples in anaphylaxis-associated deaths, although elevated levels may also be seen in non-anaphylaxis-associated deaths.

Objective To investigate the effects of cause of death, site of blood sampling, degree of sample haemolysis and the presence of opiates on postmortem MCT levels.

Method We obtained sera from three collection sites from 189 non-suspicious coronial postmortems and aortic samples from 10 anaphylactic deaths to characterise postmortem MCT.

Results MCT were elevated ($>11.4 \mu\text{g/L}$) in 57% of aortic samples, 58% of femoral samples and 30% of subclavian samples. In aortic samples, there were significantly higher levels of MCT in anaphylaxis-associated deaths compared with other causes of death. Aortic MCT levels $>110 \mu\text{g/L}$ had a sensitivity of 80% and specificity of 92.1% for anaphylaxis-associated deaths. There was a significant correlation between MCT and degree of sample haemolysis but no correlation with the presence of opiates.

Conclusions Moderately elevated MCT levels are common in postmortem sera. Aortic values $>110 \mu\text{g/L}$ may support a diagnosis of anaphylaxis-associated death, although the diagnosis should not be based on this test alone. There was significant variation between sample sites and reference ranges for individual sample sites should be established.

INTRODUCTION

Anaphylaxis is a severe, life-threatening systemic reaction and typically has a rapid onset with multi-organ involvement. The essential underlying mechanism is the presence of biologically active chemical mediators released from mast cells or basophils.^{1–2} Anaphylaxis occurs in an acute and unexpected manner and may be fatal. Given its rarity and unpredictable nature, the true incidence of fatal anaphylaxis is not known precisely, but is estimated to cause death in 0.65–2% of cases of anaphylaxis (0.5–3 per million people per annum).^{3–7}

The postmortem diagnosis of anaphylaxis remains a significant challenge. Morphologic changes may be non-specific or absent and the diagnosis is typically based on investigational, clinical, laboratory and autopsy data after exclusion of other possible causes.⁸ There are currently no specific biomarkers for anaphylaxis-associated death. The most commonly used serum biomarker for

anaphylaxis is mast cell tryptase (MCT). Tryptase is selectively and abundantly produced by mast cells. When these cells are activated and degranulate, the preformed mediators stored in cytoplasmic granules are released. These mediators include histamine, carboxypeptidase A, proteoglycans, serine proteases chymase and tryptase.⁹ In living patients, MCT levels can be used as markers of mast cell numbers and mast cell activation.^{10–12} In comparison with other markers, tryptase has been shown to be relatively stable with a long half-life and therefore can also be measured days postmortem.^{13–14}

Recent investigations have focused on the utility of elevated postmortem MCT levels in serum as an indicator for anaphylaxis-associated deaths. Initial studies had suggested consistent elevations of MCT in postmortem samples from patients with suspected anaphylaxis.¹⁵ However, elevated MCT have also been seen in situations where patients have died of documented non-anaphylactic causes, including atherosclerotic cardiovascular disease,¹⁴ asphyxia,¹⁶ trauma¹⁷ and heroin overdose.¹⁸ Furthermore, some studies suggested variability according to sampling site, possibly in part due to postmortem diffusion from mast cell rich tissues such as the heart.^{13–16}

In this study, we obtained sera from 189 non-suspicious coronial postmortems and 10 anaphylactic deaths to assess the diagnostic value of postmortem MCT levels. Additionally, we investigated whether the cause of death, site of blood sampling, sample haemolysis or the presence of opiates affected tryptase levels.

METHODS

Blood samples

Blood samples were collected between September and October 2009 and February–April 2010 from cadavers undergoing a coronial postmortem. Cases of suspicious death were excluded. There were 189 cases where blood was available from all three specified collection sites. Fifty-five (29.1%) were women and 134 (70.9%) were men with a mean age of 58 years (range 16–94 years). Blood samples were collected from the subclavian artery via a transcutaneous approach on arrival to the morgue. Further samples were collected from the aorta and femoral arteries at the time of the postmortem. No patients were identified with anaphylaxis during this time period. These results were compared with aortic samples from 10 patients with known anaphylaxis-associated deaths identified between 2006 and 2011. Serum tryptase was measured using an immunofluorescent enzyme assay (ImmunoCAP Phadia now Thermo Fisher Scientific, Sweden)

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measuring both α and β tryptase levels. Sample haemolysis was measured and expressed as a Haemolysis Index (Architect, Abbott Diagnostics, USA). Ethical approval for this study was granted by the West Australian Coronial Ethics Committee.

Cause of death

The cause of death was identified by a forensic pathologist. The causes of death in the non-anaphylactic deaths were divided into eight groups: (1) trauma $n=25$, (2) cardiac $n=74$ (68 cardiac ischaemia, 6 cardiac arrhythmia), (3) vascular $n=9$ (seven pulmonary embolus, two aortic aneurysm rupture), (4) asphyxia $n=31$ (1 asthma, 24 suicidal hanging or asphyxia, 2 drowning, 2 carbon monoxide poisoning, 2 choking on food bolus), (5) sepsis $n=13$, (6) drug overdose $n=13$, (7) intracranial haemorrhage $n=5$ and (8) other causes $n=19$. Of the 10 anaphylaxis-associated deaths, five occurred due to insect stings (four bees, one ant), two occurred due to medications (amoxicillin and iodine), one occurred due to food allergy (peanut), one case occurred due to hydatid cyst rupture and the cause of death in one case was not identified.

Statistical analysis

Comparison between cause of death groups was performed using a Kruskal–Wallis one-way analysis of variance. Comparison between sampling sites was performed using the Wilcoxon signed-rank test. Correlation analysis was performed using the Spearman correlation coefficient. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using Medcalc V.11.6.1.0 (Mariakerke, Belgium).

RESULTS

Tryptase levels

One patient who died from acute butane toxicity was excluded from analysis due to undetectable levels of MCT in samples from all three sites (all <1.0 $\mu\text{g/L}$). No other patient had an undetectable MCT level from any site. There was no association between MCT and body mass index or gender. Using the assay normal range in living patients of <11.5 $\mu\text{g/L}$, 107 (57%) of aortic samples, 109 (58%) of femoral samples and 57 (30%) of subclavian samples displayed an elevated MCT. There was significant correlation between MCT in samples from aortic, subclavian and femoral collection sites for all non-anaphylactic deaths (all $p<0.001$) (see online supplementary figure S1). However, there could be significant variability between sampling sites for individual cases (see online supplementary figure S2). Across all non-anaphylactic death groups, there were significantly higher tryptase values in aorta (median 13.2 $\mu\text{g/L}$) and femoral (median 12.5 $\mu\text{g/L}$) compared with subclavian site (median 9.1 $\mu\text{g/L}$) (both $p<0.0001$). There was no significant difference between aorta and femoral sites ($p=0.15$) (figure 1).

Median tryptase levels according to cause of death and site of sampling are shown in table 1. There were no significant differences in tryptase levels according to non-anaphylactic causes of death from the femoral site ($p=0.13$). In the subclavian samples, there were significantly higher levels in patients who died from trauma when compared with asphyxia, vascular deaths and drug overdoses only (all $p<0.05$), and higher levels in cardiac deaths compared with asphyxia and vascular deaths only (both $p<0.05$). In the aortic group, there was a significantly lower level of tryptase in patients who died from asphyxia compared with the trauma, cardiac and sepsis groups ($p<0.05$). The anaphylaxis-associated deaths had significantly higher MCT in aortic samples compared with all other causes of death ($p<0.002$) (figure 2).

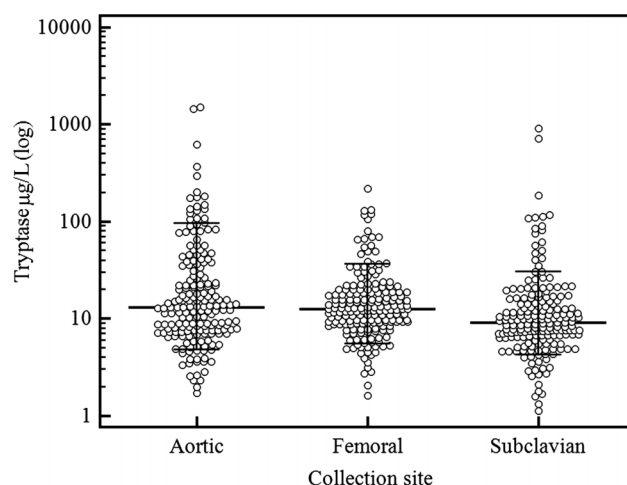


Figure 1 Serum tryptase levels from post-mortem samples in non-anaphylactic deaths from aortic, femoral and subclavian collection sites. The bars on the graph represent the 10th, 50th and 90th centiles.

Using the data available for aortic samples, a receiver operating characteristic curve analysis was performed (figure 3). The area under the curve was $0.92 (\pm 0.03)$. Table 2 shows the sensitivity and specificity for aortic tryptase levels at varying concentrations of tryptase. The MCT test performed best at a cut-off of around 110 $\mu\text{g/L}$. Setting a cut-off at this level would be associated with four (31%) false positives in the sepsis group, one case (8%) in the drug overdose group, four cases (5%) in the cardiac group, one case (4%) in the trauma group, zero cases in the vascular and asphyxia groups and four cases (21%) in other causes of death group. At the prevalence of anaphylaxis in this study (5.3%), the positive predictive value of an aortic MCT >110 $\mu\text{g/L}$ was 34.9% with a negative predictive value of 98.9%.

Tryptase and haemolysis

There was significant correlation between levels of haemolysis in samples taken from aortic, subclavian and femoral collection

Table 1 Mast cell tryptase levels from the three collection sites according to cause of death

Cause of death	Aortic	Femoral	Subclavian
Anaphylaxis ($n=10$)	174.0 (31.6–3875.0)	NA	NA
Asphyxia ($n=31$)	10.4 (2.6–80.8)	10.9 (1.6–57.2)	7.8 (2.7–21.7)
Cardiac ($n=74$)	10.1 (1.6–918.0)	13.6 (1.7–1453)	13.3 (3.1–221.0)
Drug overdose ($n=13$)	13.1 (2.0–148.4)	13.5 (3.9–36.3)	7.5 (1.8–187.2)
ICH ($n=5$)	25.0 (5.2–1522.0)	14.9 (9.8–107.0)	7.6 (5.2–40.6)
Other ($n=19$)	15.7 (3.6–373.0)	12.8 (2.9–130.9)	8.5 (1.1–116.6)
Sepsis ($n=13$)	39.3 (2.3–628.0)	9.6 (2.1–18.0)	7.5 (1.3–713.0)
Trauma ($n=25$)	16.9 (3.6–201.0)	13.7 (2.7–131.2)	12.6 (3.6–112.5)
Vascular ($n=9$)	8.8 (2.3–45.5)	10.9 (3.6–30.4)	7.6 (1.7–8.8)
Total ($n=199$)			
Median	13.2*	12.5	9.1
90th centile	96.7*	36.8	30.6
95th centile	149.8*	67.6	81.1

Median values for tryptase ($\mu\text{g/L}$) are displayed with minimum and maximum values for the group in parentheses.

*Excluding anaphylaxis cases.

ICH, intracranial haemorrhage; NA, not available.

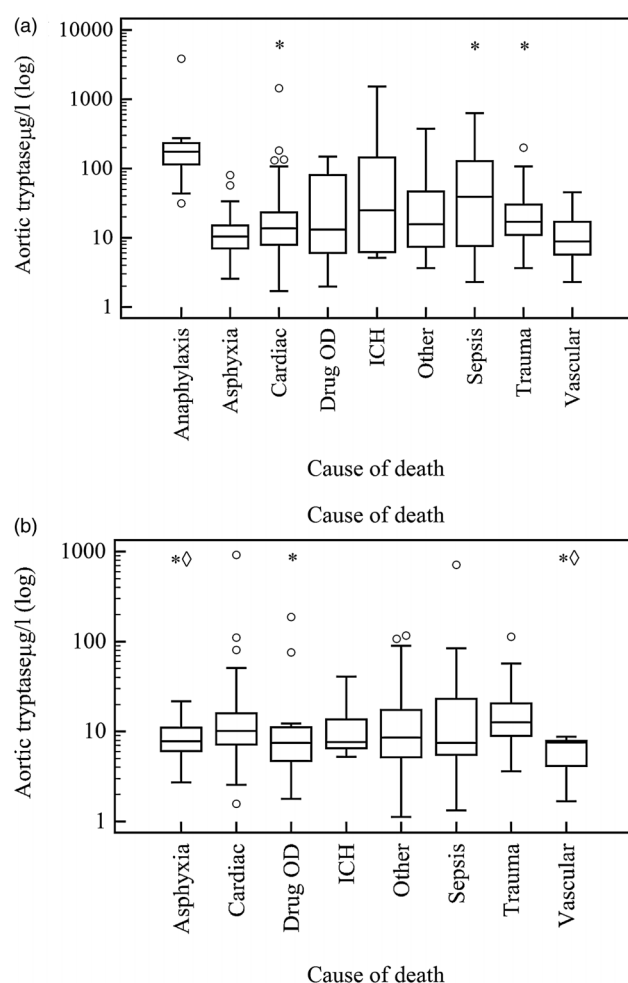


Figure 2 Box plot showing tryptase values according to cause of death from aortic artery (A) and subclavian artery (B). Bottom, median and top of the lines of box mark the 25th, 50th and 75th centiles; vertical from bottom and top represent 10th and 90th centiles. For aortic samples, the anaphylaxis group was significantly higher than all other causes of death and * represents significantly different from asphyxia. For subclavian samples, * represents significantly different from cardiac deaths. ICH, intracranial haemorrhage; OD, overdose.

sites for all non-anaphylactic deaths (all $p < 0.001$). However, there were significantly higher levels of haemolysis in the aortic samples compared with both subclavian and femoral samples (both $p < 0.001$) but no significant difference between subclavian and femoral samples ($p = 0.40$). There was no correlation of haemolysis with cause of death for aortic, femoral or subclavian samples ($p = 0.30$, $p = 0.11$ and $p = 0.45$, respectively). There was a significant positive correlation between the level of haemolysis and the MCT levels for aortic, femoral and subclavian samples ($p < 0.001$) (figure 4).

Tryptase and opiates

Toxicology data were available for 125 cases (66.1%). Of these, opiates were detected in 32 cases (16.4%), including morphine ($n = 14$), codeine ($n = 3$), morphine + codeine ($n = 9$), tramadol ($n = 2$), oxycodone ($n = 1$), morphine + codeine + methadone ($n = 1$), methadone + tramadol ($n = 1$) and oxycodone + tramadol ($n = 1$). Nine out of 13 cases of drug overdose had detectable opiates in postmortem blood samples. There was no

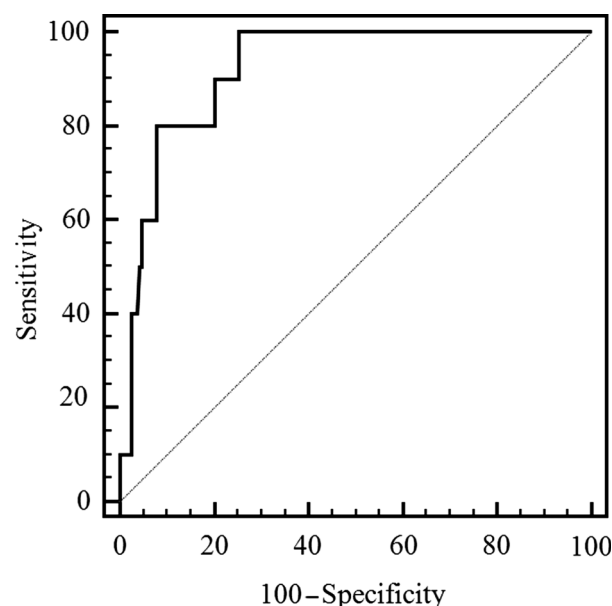


Figure 3 Receiver operating characteristic curve showing discrimination power of postmortem aortic tryptase values for diagnosis of anaphylaxis-associated death.

difference in tryptase levels between patients with and without detectable opiates (all $p \geq 0.18$).

DISCUSSION

Previous studies have suggested elevated postmortem levels of MCT may indicate premortem anaphylaxis.¹⁵ However, elevated MCT levels have also been found in a large number of patients who died from non-allergic causes. In this study, non-anaphylactic postmortem samples showed significant numbers of samples with results above the normal range for living patients, irrespective of sampling site or cause of death. Previous studies have shown higher tryptase levels in non-anaphylaxis postmortem control samples than the upper limit for living patients, suggesting moderate tryptase elevations are more frequent than initially thought in postmortem sera.^{16 17 19} This may reflect passive diffusion of mast cell contents following autolysis of mast cells in vessel walls and tissue. A previous study showing a positive correlation between tryptase levels in heart blood and pericardial fluid suggested postmortem diffusion of tryptase may also occur between compartments.¹³

Tryptase levels from the subclavian artery were significantly lower than femoral or aortic samples. Lower subclavian sample

Table 2 Sensitivity, specificity and likelihood ratios of postmortem aortic tryptase for anaphylaxis-associated death according to tryptase level

Tryptase level (µg/L)	Sensitivity (%)	Specificity (%)	Likelihood ratio
>11.4	100	43.4	1.8
>20	100	65.6	2.9
>50	80	83.0	4.7
>100	80	90.5	8.4
>110	80	92.1	10.1
>150	60	95.2	12.5
>200	40	96.8	12.5

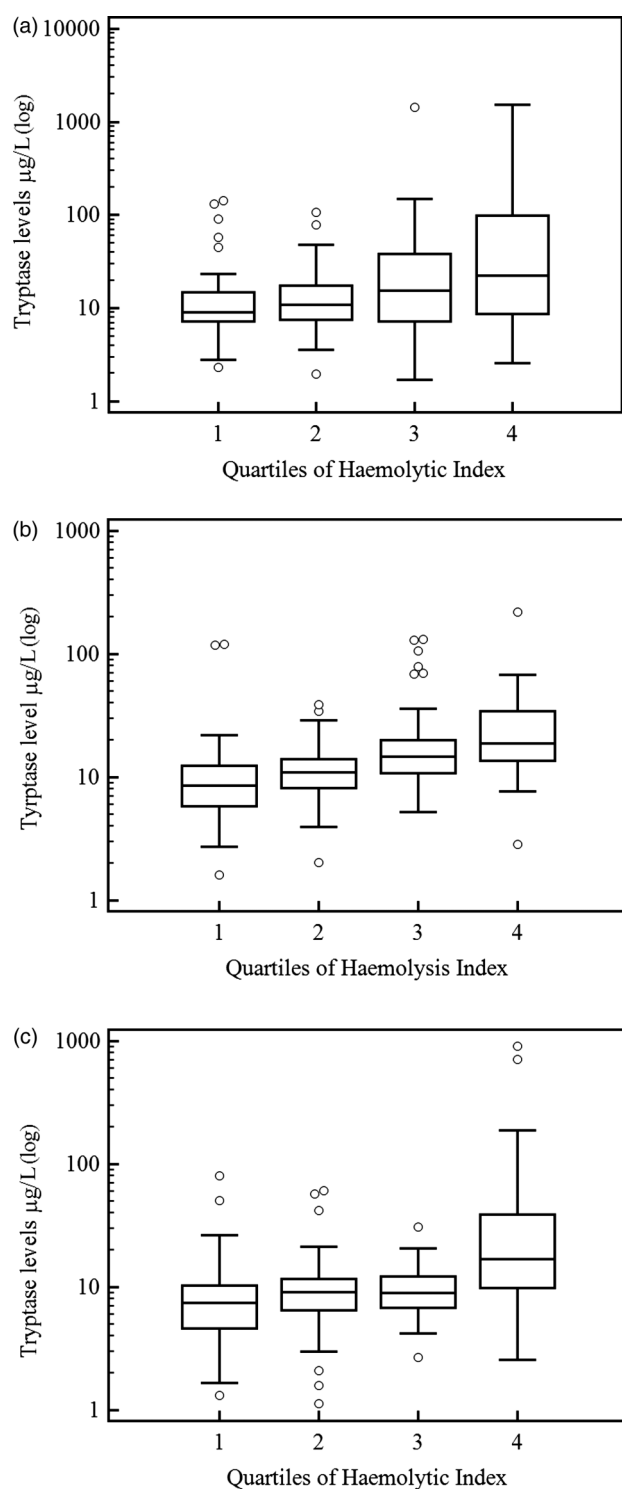


Figure 4 Mast cell tryptase levels in aortic (A), femoral (B) and subclavian (C) samples in non-anaphylaxis deaths divided into quartiles according to sample haemolysis (Haemolytic Index).

levels could in part reflect timing of the sample collection since subclavian samples were collected on arrival of the body to the morgue, whereas aortic and femoral samples were collected at the time of necropsy. The influence of time interval between death and sample collection on tryptase levels is unclear. It had no effect on tryptase levels in one study²⁰ but was associated in another study with a gradual increase in tryptase levels with increasing interval following death, which was only significant

after greater than 50 h interval.²¹ As there was not usually a significant delay between arrival at morgue and postmortem being performed, this is unlikely to explain the significant differences between sites, although further analysis of samples collected at the same time would need to be performed to confirm this.

Previous studies had suggested higher tryptase levels in femoral samples in patients who died of asphyxia¹⁶ and trauma.¹⁷ However, we did not find any difference in femoral tryptase levels according to cause of death, and in aortic samples the levels seen in asphyxia were significantly lower than those seen in trauma, cardiac death and sepsis. Subclavian samples showed slightly higher levels in trauma compared with asphyxia, vascular deaths and overdose only. While the level of haemolysis did positively correlate with MCT level, there was no difference in levels of haemolysis according to cause of death. Haemolysis therefore could not explain the relationships between MCT and cause of death. Although artificially induced haemolysis in vitro was not associated with elevated MCT (data not shown), in vivo postmortem haemolysis did have a significant effect on MCT levels. These data differ from the findings of Edston *et al*¹⁷ who did not see an association between haemolysis and tryptase levels in 27 non-trauma control patients, but did see a significant association between tryptase levels and haemolysis in 27 patients who died of trauma. Given the larger numbers in this study and the significant association with tryptase levels and haemolysis from all collection sites, our data suggest that postmortem haemolysis does need to be considered when interpreting samples. The lack of tryptase rise on artificial haemolysis in our study and others¹⁷ may suggest that the haemolysis per se is not the cause of the rise of tryptase but may act as a surrogate marker for other postmortem processes which may be associated with higher tryptase levels such as clotting, liquefaction and tissue necrosis. Aortic samples did show higher levels of haemolysis compared with subclavian or femoral sites, although the reason for this is unclear.

Analysis of aortic samples from anaphylactic deaths showed significantly higher MCT levels than all other causes of death with a level of 110 μg/L giving the best sensitivity and specificity in this group. Given the observed differences in MCT between the sampling sites, the suggested cut-off of 110 μg/L from this study should only be considered appropriate to aortic samples. A previous study had suggested the use of a higher upper clinical reference limit of 45 μg/L in femoral samples for the post-mortem diagnosis of anaphylaxis.¹⁶ Applying this to femoral samples from our study population would result in 16 (8%) false-positive results in the non-anaphylactic deaths. In comparison, using our suggested cut-off of 110 μg/L for aortic samples would result in 15 (8%) false positives in the non-anaphylactic deaths. It is, however, important to note that an aortic cut-off of 110 μg/L would also have missed two cases of anaphylaxis (one peanut allergy 43.3 μg/mL, one cause unknown 31.6 μg/mL). Low MCT levels have been well described in patients with food-induced anaphylaxis and MCT levels below the cut-off cannot fully exclude anaphylaxis as the cause of death.^{22–24}

One of the major issues identified in this study was that although there was a strong correlation between MCT levels from the three collection sites, there could sometimes be significant variation in levels between the sites for individual patients, such that samples from one site had a very low level whereas another site from the same patient had a very high level. It was not possible to assess in this study whether samples from one specific site or even sampling from multiple sites would be better to allow distinguishing of anaphylaxis-associated deaths versus non-anaphylactic deaths as only aortic samples were

available from the anaphylaxis-associated death patients. Further studies comparing MCT levels from multiple sites in both anaphylaxis-associated and non-anaphylaxis-associated deaths are needed to address this question.

Previous studies have suggested opiates may be associated with increased MCT levels in postmortem samples following the identification of elevated MCT in a number of cases of drug overdoses.¹⁸ It is well known that opiates cause non-Immunoglobulin E-mediated mast cell activation.²⁵ We found no relationship between the presence of opiates in blood and MCT levels in this study. Furthermore, there were no differences in drug-related deaths associated with opiates when compared with patients dying of other causes who had opiates detected in their system to suggest a dose-related effect.

Interestingly one patient who died from butane toxicity had undetectable MCT in all samples. The precise mechanism of sudden death associated with butane inhalation is yet to be determined, although in suicidal butane poisoning is most likely to be related to asphyxia.²⁶ Assessment of MCT on similar patients is needed to assess if this is a consistent and perhaps clinically useful finding.

In summary, moderate MCT elevations in postmortem samples are common. Aortic samples showed significantly higher levels in anaphylaxis-associated deaths compared with other causes of death. Although levels from the sample sites correlated in most cases, there could be significant variation in levels between sites for some individual cases. Together these data show that although MCT are high in anaphylaxis-associated deaths, they may also be significantly elevated in non-anaphylaxis-associated deaths. A number of factors should be considered when interpreting the MCT result, including the clinical history, site of sample draw and degree of sample haemolysis, and a diagnosis of anaphylaxis-associated death cannot be made on the MCT level alone. This study is limited by not having anaphylaxis samples from all collection sites. Further studies are required to assess whether samples from multiple sites or a single site are more accurate for the postmortem diagnosis of anaphylaxis-associated death.

Take home messages

- Elevated tryptase levels are relatively common in postmortem sera
- Tryptase levels >110 µg/L in samples taken from the aorta may support the diagnosis of anaphylaxis in postmortem samples

Contributors MG conceived the original concept for the study. MG, CB, JW and PH contributed to study design, obtained funding and critically revised the manuscript for important intellectual content. MG and CB carried out the experimental work. AMT performed statistical analysis, interpreted the data, wrote and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests None.

Ethics approval West Australian Coronial Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure E1. Serum tryptase levels from post-mortem samples from non-anaphylactic deaths for (A) aortic versus femoral collection site, (B) aortic versus subclavian site and (C) femoral versus subclavian collection site. Correlation coefficients $\rho=0.474$ (A), $\rho=0.546$ (B) and $\rho=0.570$ (C). Solid line represents line of equivalence.

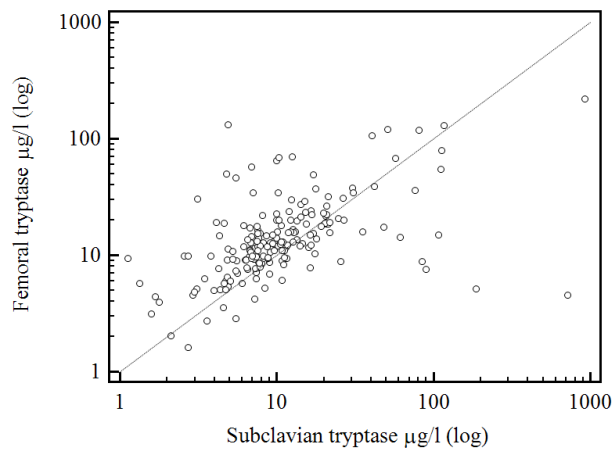
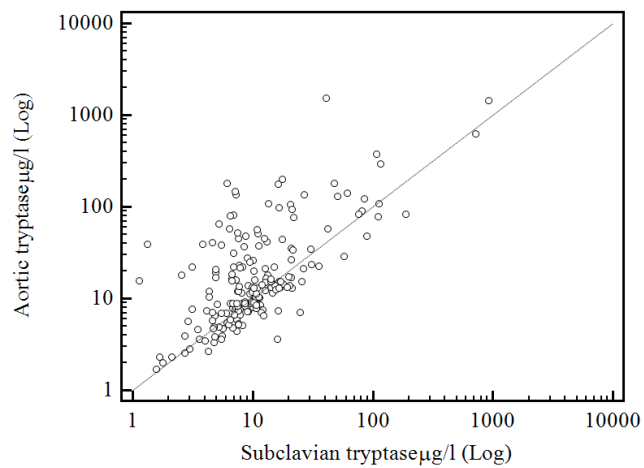
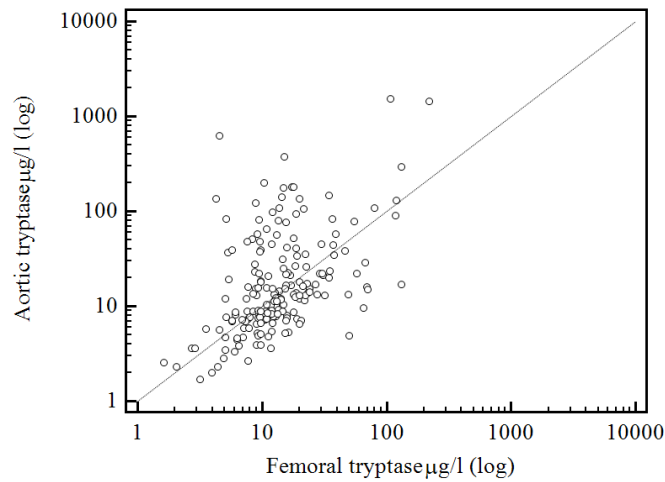


Figure E2. Graphs showing variation in tryptase results from each of three collection sites according to cause of death. Results from aortic (O), femoral (Δ) and ($\square$) subclavian collection sites with lines showing results for individual cases. For patients with a tryptase level greater than 210 $\mu\text{g/l}$ ($\dagger$) aortic sample was 294 $\mu\text{g/l}$, ($*$) aortic sample was 373 $\mu\text{g/l}$, ($\cdot$) subclavian sample was 713 $\mu\text{g/l}$ and aortic sample was 628 $\mu\text{g/l}$, and ($\ddagger$) aortic sample 1522 $\mu\text{g/l}$

