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Postmortem serum catecholamine levels in relation to the cause of death

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Abstract

Catecholamines are major humoral factors and neurotransmitters that contribute to various stress responses. However, they have been considered unstable due to agony, terminal medical care and postmortem interference. The present study was a comprehensive investigation of postmortem serum levels of adrenaline (Adr), noradrenaline (Nad) and dopamine (DA) with regard to the cause of death in serial medicolegal autopsy cases ($n = 542$) including fatalities from various traumas and diseases. There was a slight tendency toward postmortem increases of Nad and DA in cardiac blood as well as Adr and Nad in peripheral blood, a slight age-dependent decrease in Adr and DA in right heart blood, and a marked increase in serum DA due to administration during critical medical care. When these factors were taken into consideration, significantly higher cardiac blood levels were observed for Adr and Nad in injury and asphyxiation cases and for Adr in fatal methamphetamine (MA) abuse and other poisoning cases, whereas those levels were lower in fatal hypothermia. Drowning, fire fatality, acute cardiac death and cerebrovascular disease showed intermediate Adr and Nad levels. The DA level was elevated in cases of injury, hyperthermia, MA fatality and other poisoning. Topographical analyses suggested that the major sources of increased serum catecholamines in cases of injury was abdominal viscera including adrenal glands, and that in cases of asphyxiation, drowning, fire fatality, hyperthermia, MA fatality, other poisoning, acute cardiac death and cerebrovascular disease was the extremities in addition to abdominal viscera. However, there was in part a large case-to-case difference in each marker related to individual causes of death. These findings differed markedly from clinical observations and suggest that the postmortem serum catecholamine levels may reflect the magnitude of physical stress responses during the process of death in individual cases.

Keywords: Catecholamine; Blood biochemistry; Trauma; Stress

1. Introduction

In medicolegal autopsy, systematic investigations to assess the cause and process of death are necessary to meet social requirements through reliable interpretation of medicolegal issues, especially for cases of traumatic and unexpected sudden death. With respect to biochemical analyses, catecholamines may be useful markers for investigating various stress responses in the process of death involving bleeding, burns, cold exposure, physical hyperactivity or drug abuse, when these markers can be used in combination with other chemical and immunohistochemical markers [1–11]. Previous studies suggested increases in serum or urinary catecholamines in fatal hypothermia and in deaths involving a longer agony period [12–16]. In postmortem investigation, however, catecholamines have been considered rather unstable markers for investigating the cause or process of death due to agony, terminal medical care and postmortem interference [16–18]. Thus, a systematic study is necessary to establish the applicability of these markers for postmortem investigation of death.

In the present study, we performed a comprehensive analysis of postmortem serum levels of adrenaline (Adr), noradrenaline (Nad) and dopamine (DA) with regard to the cause of death in serial routine medicolegal casework.

2. Materials and methods

2.1. Materials

Serial medicolegal autopsy cases within 48 h postmortem at our institute were examined: total, $n = 542$; 386 males and 156 females; 15–97 years of age (median, 60.0 years of age); postmortem interval, 3–47 h. For this

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purpose used were cases where witnessed and/or circumstantial evidence has been well established to confirm survival and postmortem times estimated based on their pathological findings. Postmortem time is shown by the middle of estimated period, for which the deviation was within about 1 h in cases of <18 h postmortem and within about 4 h in cases of 18–48 h postmortem [19]. The specimens were collected aseptically using syringes: blood from the left and right heart chambers, subclavian and external iliac vein ($n = 531$, $n = 542$, $n = 421$ and $n = 300$, respectively), The blood samples were centrifuged immediately to separate the sera, and samples were subsequently stored at −20 °C until use. The causes of death were classified on routine macromorphological, micropathological and toxicological bases, as shown in Table 1. For all groups, clearly accountable cases were cellected.

2.2. Methods

Serum catecholamines were measured using high performance liquid chromatography [20]. The ranges of measurements were 2.0–10,500 pg/ml for Adr, 1.8–19,500 pg/ml for Nad and 2.1–18,750 pg/ml for DA. Samples were diluted with saline before measurement (10 to 1,000-fold for cardiac and subclavian venous serum, and up to 100-fold for external iliac venous serum). The accuracy and reliablity were checked for reproducibility following serial 10-fold dilutions, and nonreproducible data were not used.

Blood %COHb saturation was analyzed on a CO-oximeter system (Ciba-Corning 270, New York) [21,22]. Blood cyanide and alcohol levels were determined by head-space gas chromatography/mass spectrometry [23]. Drug analyses were performed by gas chromatography/mass spectrometry.

2.3. Statistical analyses

Fisher exact test was used to compare two parameters including catecholamine levels, gender and age of subjects, survival time and postmortem interval. For comparison between groups, the nonparametric test (Mann-Whitney *U* test) and Scheffe or Games-Howell test were used for analyses involving multiple comparisons. These analyses were performed using Microsoft Excel and Statview (version 5.0, SAS Institute Inc. SAS Campus Drive Cary). A *P*-value less than 0.05 was considered significant. In Figs. 1–3, the results of data analyses are shown in box-plots, in which 50% of the data are summarized in the box, the line represents the median and the lines outside of the box represent the 90% confidence interval. The sensitivity and specificity in distinguishing two groups using cut-off Adr, Nad and DA values were estimated by receiver-operating characteristics (ROC) analysis [24,25]. The area under the curves were calculated and analyzed by one-tailed test. The optimal compromise between sensitivity and specificity was determined graphically.

3. Results

3.1. Topographical distribution and influence of critical medical care

Serum catecholamine levels were markedly higher in cadavaric sera compared with their clinical reference intervals (Adr, <100 pg/ml; Nad, 100–450 pg/ml; DA, <20 pg/ml) at each site, showing a very large case-to-case variation. For all

Table 1
Case profiles ($n = 542$)

Cause of death	*n*	Cardiopulmonary resuscitation	Male/female	Age (years)		Survival time (h)	Postmortem interval (h)	
				Range	Median	Range	Range	Median
Blunt injury								
Head injury	68	44	51/17	17–96	54	0–36	3–35	17.0
Others	73	23	53/20	16–94	57	0–44	4–44	18.0
Sharp instrument injury	41	7	31/10	19–81	47	<0.5–2.5	6–47	15.5
Asphyxia								
Hanging	7	0	7/0	35–78	58	<0.5	12-44	22.5
Strangulation	15	0	8/7	15–93	44	<0.5	7-33	19.5
Aspiration	9	2	3/6	53–94	76	<0.5	9–42	19.0
Drowning								
Freshwater	17	0	9/8	46–79	60	<0.5	8–37	20.0
Saltwater	10	0	8/2	34–67	51	<0.5	8–47	16.0
Fire fatalities								
COHb < 60%	38	4	21/17	18–93	72	<0.5–2	8–35	14.5
COHb > 60%	36	0	26/10	25–87	63	<0.5	5–42	12.0
Hyperthermia	8	2	6/2	15–80	69	1–5	9–40	20.0
Hypothermia	12	1	10/2	44–80	63	3–10	9–45	15.0
Fatal poisoning								
Methamphetamine	8	1	7/1	30–52	39	3–32	19–34	26.5
Others[a]	17	2	12/5	23–71	38	<0.5–10	6–38	27.0
Myocardial infarction	87	15	61/26	44–93	67	<0.5–36	6–35	16.5
Ischemic heart diseases	33	9	27/6	17–97	68	<0.5–1.5	5–35	13.0
Congestive heart diseases	22	10	18/4	39–87	68	unknown	4–38	21.0
Cerebrovascular diseases[b]	28	4	19/9	39–94	61	<0.5–14	5–39	24.0
Protracted death[c]	13	5	10/3	19–84	71	days-unknown	13–42	22.5
Total	542	129	386/156	15–97	60	0-unknown	3–47	17.5

[a] Sedative-hypnotics ($n = 12$) and carbon monoxide ($n = 5$).
[b] Spontaneous cerebral hemorrhage ($n = 22$) and subarachnoid hemorrhage ($n = 6$).
[c] Bacterial pneumonia ($n = 7$) and chronic renal failure ($n = 6$).
COHb, carboxyhemoglobin.