

# Postmortem Redistribution of Lidocaine after Epidural Anesthesia Accidental Death

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## Abstract

Epidural anesthesia is often used form in Chinese primary hospitals and lidocaine is the most favorite anesthetic. Fatalities due to epidural anesthesia accident and lidocaine overdose are often happened, but there still have not obvious evidence to indicate the real reason of death according to the concentration of lidocaine in postmortem blood because the postmortem redistribution (PMR). An animal models using dogs has been developed, whereby the dogs received an intravenous, subarachnoid, and epidural injection of lidocaine (75 mg/kg body weight). The dogs were placed at room temperature after sacrifice. The cardiac blood, inferior vena cava blood, liver and cerebrum samples were collected at 0 h, 1 h, 4 h, 8 h, 24 h, 48 h and 72 h postmortem with the same animal's corpse. The lidocaine is easier diffusion from canalisvertebralis to cardiac blood in subarachnoid administration. The level commonly has a great change from 48 h after death in cardiac blood, from 35.7 mg/L to 1421.9 mg/L, and then decreasing 50% at 72 h. The inferior vena cava blood concentration was stabilized in postmortem time. The cerebrum concentration of subarachnoid administration decreased by 50% and was observed at 72 h after death. The changes were observed in cardiac blood in intravenous and epidural administration groups, but no changes were observed in cerebrum. Lidocaine concentrations did not change significantly in the liver in any of the three groups. This study can assist toxicologists to determine which specimens should be the most appropriately during the interpretation of lidocaine concentrations in epidural accidents.

**Keywords:** Lidocaine; Postmortem redistribution; Epidural anesthesia; Accident

## Introduction

Epidural anesthesia is the most commonly used forms of central neuraxial blockade. It can be used as an analgesic adjuvant to general anesthesia, the sole anesthetic for procedures involving the lower limbs, pelvis, perineum, lower abdomen or thorax and it is the most popular method of pain relief during surgery, obstetrics and pain control. Epidurals block nerve impulses from the lower spinal segments, it results in decreased sensation in the lower half of the body. Epidural medications often use local anesthesia which blocks pain in a particular region of the body, including lidocaine, bupivacaine, or procaine. As the first aminoamide-type local anesthetic, it was synthesized in 1943 as xylocaine. Lidocaine is a drug commonly used as a local anesthetic and as an antiarrhythmic and it also used as an epidural anesthesia or combined spinal-epidural (CSE). Meanwhile, Epidural anesthesia remains a fundamental part of China primary hospital of anesthesia, because of its success, predictability, and low complication rate.

At recent years, fatalities due to epidural anesthesia accident are often happened [1-4], and many cases of poisoning resulting from its overdose have been reported [5-8]. As far as forensic toxicological identification, analytical methods for lidocaine are well developed and documented [9-11]. However, there is no obvious evidence indicated the cause of death in anesthesia, difficult to distinguish the cause of death between accident and natural. Single injection and catheter

techniques are the two basic methods during epidural anesthesia. The most common cause of epidural anesthesia faults occurred during placement. There have many reasons caused accident, anesthetist's malpractice, complicated canalisvertebralis structure etc. General risks include dual puncture by the spinal needle or incorrect catheter placement during epidural anesthesia, the local anesthetic may be injected into the vein for canalisvertebralis rich vasculature, the catheter may be misplaced to the subarachnoid space, anesthetist did not found fault or the catheter was placed correctly into the epidural space but the anesthetic dose exceeded the maximum permissible doses. The detection of toxicants in postmortem cases is more difficult than in clinically derived specimens. Because many reasons influenced the concentration of toxicants in blood, which included postmortem redistribution, the stability of toxicants in different biological samples etc. Therefore, interpreting the test results remain a challenge for forensic toxicologists due to the lack of postmortem redistribution data for the lidocaine before autopsy. The aim of this study was to investigate the postmortem redistribution of lidocaine in epidural anesthesia accident, to compare the changes in concentrations in these three different path poisoning death, intravenous, subarachnoid space and epidural injection, along with the samples collected times during the ambient temperature.

## Materials and Methods

### Animals

Animals were Chinese male dogs weighing 18 kg to 21 kg and provided by the laboratory animal center of Shanxi Medical University.

Nine dogs were used during the experiments and divided into three groups and three dogs for each group. All experiments were performed in accordance with the Regulations of Shanxi province laboratory animal management governing animal studies. The dogs were administered 2% lidocaine hydrochloride solution. A single dose of 75 mg of lidocaine per kilogram body weight was administered to each dog. Group 1 was given by intravenous injection. Group 2 was given by subarachnoid space and Group 3 was given by epidural. Before the experiments, dogs were emptied stomach 12 h, but water was allowed ad libitum.

### Chemicals

Lidocaine was obtained from the Institute of Forensic Science Ministry of Public Security PRC and was prepared 1 mg/ml in ethanol. Lidocaine hydrochloride injection was purchased from the Hospital of Shanxi Medical University (H31021071, China). All solvents used were analytic grade.

### Experiments

Dogs were administered lidocaine injections at a constant rate during five minutes by intravenous, subarachnoid, or epidural injections, respectively. Electrocardiograms, Heart rate, blood pressure and respiration were measured at experiments from pre-administration to death with a biological function system. After sacrifice, dogs were placed in a left recumbent position at ambient temperature (19°C to 23°C). The cardiac blood, inferior vena cava blood, liver, and cerebrum samples were collected at 0 h, 1 h, 4 h, 8 h, 24 h, 48 h, and 72 h postmortem (three dogs for each experimental group). The inferior vena cava blood was limited to 2 mL in order to

prevent drawing blood from the upper cardiac blood. After samples had been collected at each postmortem interval (PMI), the dogs were completely sutured. All fluid samples were stored at 4°C, and solid samples were kept at -20°C until analysis.

### Analytical method

The matrices were extracted using liquid-liquid extraction and the concentration of lidocaine was determined using gas chromatography-mass spectrometry (Thermo fisher, TRACE DSQ). The GCMS was operated with a transfer line temperature of 250°C and a source temperature of 250°C. The GC was equipped with a 30-m TRACE TR-5MS capillary column with helium as the carrier gas set at a flow rate of 1.0 ml/min. 1 µL of the extractive was injected into the GCMS. The GC was equipped with a splitless injection port operated at 280°C in the split mode with a purge time of two minutes. The oven temperature profile was established as follows: 150°C hold time 1 min to 280°C at 10°C/min and a final hold time of 2 min, resulting in a total run time of 16 min. The MS was operated in the selected ion-monitoring mode and the following ions were monitored: quantitating ion 86 and qualifier ions 58 and 86.

### Results

#### The variation of vital signs

The changes of heart rate, blood pressure and respiration from antemortem to death in intravenous, subarachnoid, and epidural administration are given in Tables 1-3 respectively.

Time	Electrocardiogram	Respiratory	Blood pressure
Before the injection	Regular	Regular	Regular
In injection process	Accelerated	Accelerated	Elevated
4 min after injection	Slow	Long, fast	The highest
6 min after injection	Bradycardia, irregular	Cheyne-Stokes breath	Disappearance
8 min after injection	Atrial flutter, Ventricular Fibrillation	Slower and disappearance	Disappearance
Mean disappear time	8(6-10) min	7.2(4-9) min	6.5(5-8) min

**Table 1:** Variation of vital signs in intravenous administration dogs.

Time	Electrocardiogram	Respiratory	Blood pressure
Before the injection	Regular	Regular	Regular
2 min after injection	Slow	Accelerate	Elevate
Injection finished	Accelerate, Ventricular Fibrillation	Long, fast	Lower
2 min after injection finished	Bradycardia, irregular	Cheyne-Stokes breath	Lower
7~47 min after injection finished	Atrial flutter, Ventricular Fibrillation	Slower and disappearance	Disappearance
Mean disappear time	23.8(7~42) min	18.6(10~47) min	16.4(7~35) min

**Table 2:** Variation of vital signs in subarachnoid administration dogs.

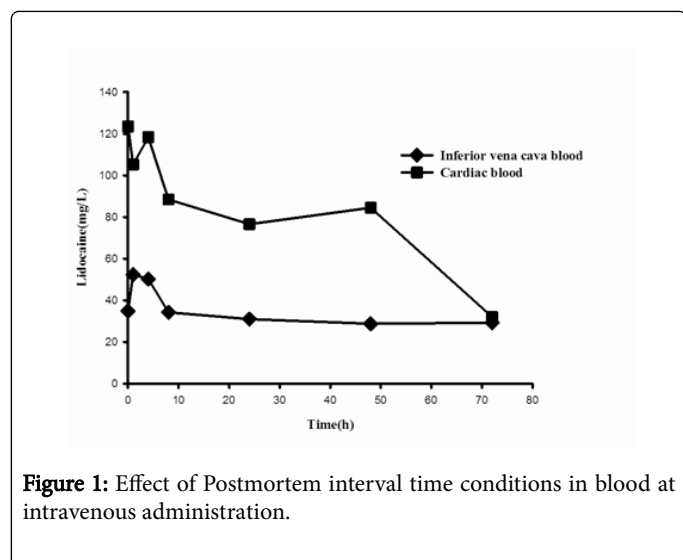
Time	Electrocardiogram	Respiratory	Blood pressure
Before the injection	Regular	Regular	Regular
2 min after injection	Accelerate	Accelerate	Elevate
Injection finished	Accelerate	Long, fast	Lower
18 min after injection finished	Bradyarrhythmia, irregular	Cheyne-Stokes breath	Lower
23~30 min after injection finished	Atrial flutter, Ventricular Fibrillation/disappearance	Slower and disappearance	Disappearance
Mean disappear time	23.6 min	21.4 min	23.6 min

**Table 3:** Variation of vital signs in epidural administration dogs.

The respiration and blood pressure mean disappear time by intravenous injection was also the fastest disappeared time of the three groups. They were 18.6 min and 16.4 min by subarachnoid administration, 21.4 min and 23.6 min by epidural administration. The heart rate disappeared time was 8 min after intravenous injection. It was the fastest of the three groups compared to 23.8 min by subarachnoid injection and 23.6 min by epidural administration.

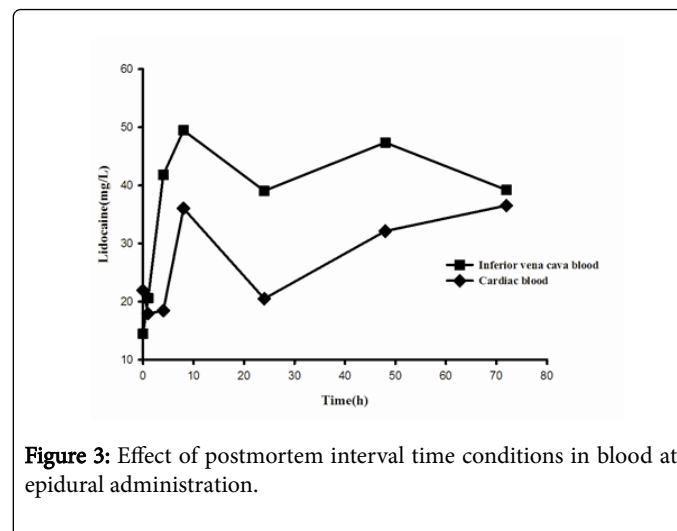
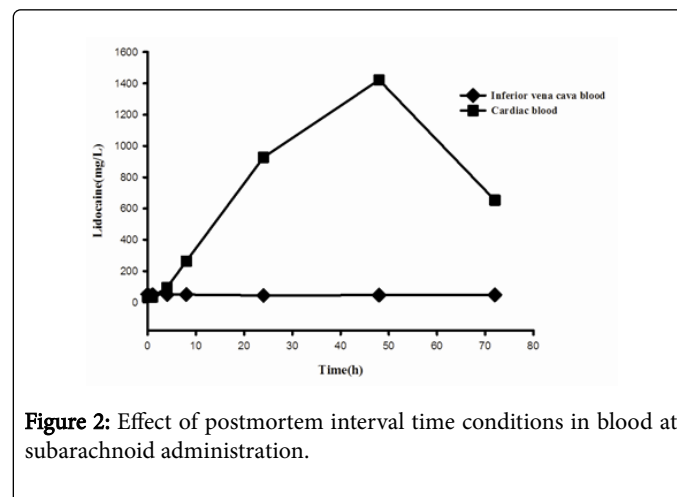
### The changes of lidocaine concentrations in postmortem blood samples

Postmortem blood lidocaine concentration by intravenous injections ranged from 34.9 mg/L to 29.3 mg/L in the inferior vena cava blood, and from 123.5 mg/L to 32.1 mg/L in cardiac blood. Results are shown in Figure 1. The inferior vena cava blood increased 1 h postmortem after death and then decreased slightly. In cardiac blood, drug concentrations decreased fourfold at 72 h. Figure 2 shows the postmortem changes in blood observed for lidocaine concentration by subarachnoid administration.



The lidocaine concentration did not change significantly in the inferior vena cava blood. On the other hand, the cardiac blood concentration increased significantly at 48 h postmortem from 35.7 mg/L to 1421.9 mg/L, it was about fortyfold, then decreased of 50% was observed between 48 h to 72 h postmortem. Figure 3 presents the postmortem changes in blood observed for lidocaine concentration by

epidural administration. The inferior vena cava blood and cardiac blood concentrations were increased in the first 8 h, decreased from 8 h to 24 h after death and then increased from 24 h to 72 h after death. The change of lidocaine concentration in inferior vena cava blood and cardiac blood was consistent after death.



### Times varying of lidocaine concentration in different tissues

Figures 4-6 present the postmortem changes observed for lidocaine concentration by different administration pathways. For three administration pathways (intravenous, subarachnoid and epidural), the lidocaine concentrations did not change significantly in the liver. The cerebrum concentration by subarachnoid (Figure 5) decreased by 50% and was observed at 72 h after death. For the intravenous and epidural administration, the cerebrum concentrations did not change.

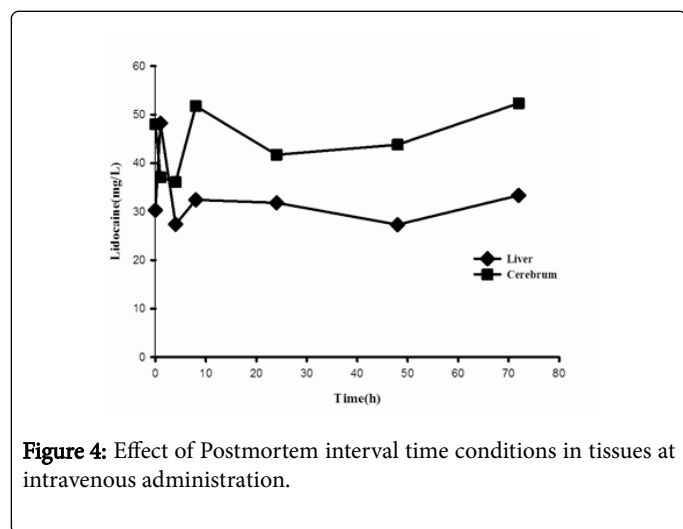


Figure 4: Effect of Postmortem interval time conditions in tissues at intravenous administration.

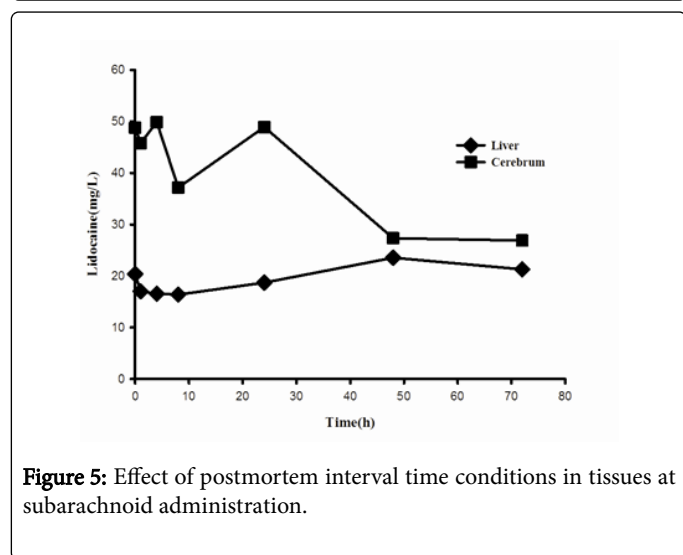


Figure 5: Effect of postmortem interval time conditions in tissues at subarachnoid administration.

### Discussion

Postmortem redistribution processes potentially affect the concentration of all toxicants in postmortem cases as a result of diffusion of toxicant from higher to lower concentrations following disruption of cellular membranes [12-18]. In particular, the concentration of heart blood is influenced by this process. It is particularly significant for toxicants with high lipid solubility, high apparent volume of distribution ( $V_d$ ) greater than 3 L/kg, or high tissue concentrations relative to blood taken from the heart. It had been proved by many examples include the tricyclic antidepressants [17-22], dioxin [19-24] and the amphetamines [25]. To the best of our knowledge, there is a few study investigated the postmortem

redistribution of lidocaine. The volume distribution of lidocaine is 1.1 L/kg to 2.1 L/kg, and the structure includes hydrophilic and lipophilic groups. Along with pH, it expresses different functions. Some studies have investigated the postmortem diffusion of basic drugs into cardiac blood from surrounding tissues and tracheal and lidocaine could diffusion into the blood after intubation by cardiopulmonary resuscitation [25,26].

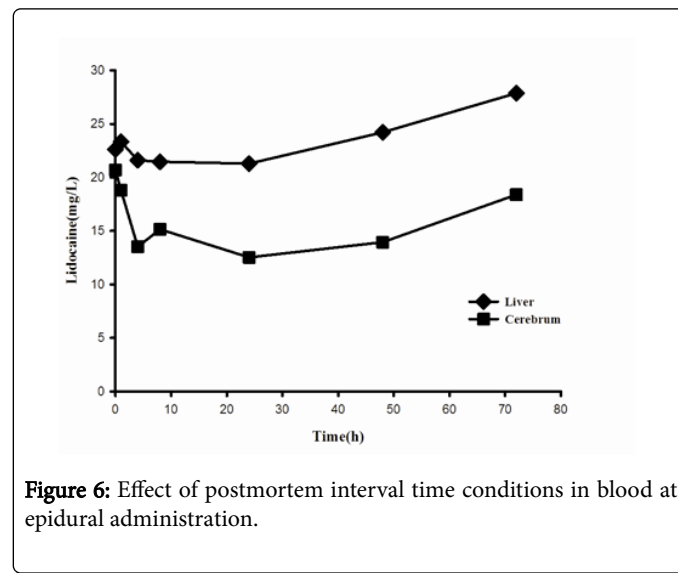


Figure 6: Effect of postmortem interval time conditions in blood at epidural administration.

The animal models by intravenous, subarachnoid and epidural administration lidocaine have been developed. In three groups of different administration pathways, the concentration of lidocaine in postmortem cardiac blood was influenced by PMR phenomenon. The cardiac blood concentration in subarachnoid space was more significant changed along with postmortem interval. In particular, there was a significant change in autopsy and 48 h after death postmortem cardiac blood (35.7 mg/L versus 1421.9 mg/L), and then decreased 50% at 72 h. A slightly larger change in intravenous and epidural postmortem cardiac blood from autopsy to 72 h after death (123.5 mg/L versus 32.1 mg/L, 21.9 mg/L versus 36.5 mg/L, respectively), it was obvious different to observed in subarachnoid administration. The inferior vena cava blood concentration was not changed significantly in each group. For overdose lidocaine, there is a reservoir of unabsorbed lidocaine in canalisvertebralis. The subarachnoid administration group was easily diffused from canalisvertebralis to cardiac blood. The epidural space is the airtight area of space that surrounds the dural sac and is bounded by the posterior longitudinal ligament anteriorly, the ligamentum flavum, and the periosteum of the laminae posteriorly. The lidocaine was closed in the space could hardly diffusion from the epidural space.

Human cases often relied on experimental animal studies, such as rats [27-33] to study postmortem toxicant redistribution, these animal models were dissected corpses in postmortem different interval time. About three to six animals were autopsied at each postmortem time. The greater individual difference would cause unstable experimental data, and it will influence the study of postmortem redistribution. This study established the whole animal models to study the postmortem lidocaine redistribution. The sacrificial animals were placed along with unified position (left lateral position). The samples were collected with the same animal's organ at different postmortem interval time. The situation of sample collected and detected is similar with actual cases. It can effectively avoid the influence of individual difference.

## Conclusion

The present study reported that lidocaine concentration changes in samples depending on the way of lidocaine intake and postmortem interval times. The subarachnoid administration is easier diffusion from canalisvertebralis to cardiac blood. The lidocaine concentration commonly has a great change from 48 h after death in cardiac blood. The inferior vena cava blood concentration was stabilized in postmortem time. Finally, the whole animal models are the better way to study postmortem redistribution. To interpret the results of toxicological, if specimens are available, analysis of both blood cerebrum and liver is recommended, especially the cardiac and inferior vena cava blood. Meanwhile, this study can assist toxicologists to determine which specimens should be the most appropriately in epidural accidents.

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