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**Original Article**

# A 5 Year Study of Deaths Following Administration of Medically Prescribed Drugs: Diagnostic Dilemma and Challenges at Autopsy

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## ABSTRACT

A significant number of deaths occur worldwide due to medical error which is claimed to be the third leading cause of death after heart disease and cancer. Adverse drug reaction or events (ADR/ADE) which consists of drug toxicity, drug side effects and anaphylactic reactions to drugs are included in such deaths.[1] Concluding that death actually resulted from medical error or adverse drug reaction requires a thorough and detailed autopsy with supportive investigations for delivering justice to the bereaved parties. Deaths due to ADR's is associated with diagnostic difficulties as there are only minimal and subtle morphological changes at autopsy which fade away with passage of time. The analysis of specific biochemical markers are not always possible due to lack of facilities. In such cases, the forensic pathologists rely on the autopsy findings and method of exclusion is used to arrive at a correct conclusion. This study is a retrospective analysis of 16 cases of deaths due to alleged medical negligence following medical administration of prescribed drugs, autopsied during a 5-year period from 2011 to 2015. The cases represented approximately 0.1% of all autopsy cases during that period. Data were analysed with regard to age, sex, alleged exposures, clinical symptoms, survival time, autopsy findings, cause of death and time since death.

**Keywords:** Autopsy, Adverse drug reaction, Anaphylaxis, Death investigation, Mortality, Medical negligence

## INTRODUCTION

In day to day forensic medicine practice, we often encounter deaths occurring soon after medical administration of a drug. Such cases invariably raise allegations of medical negligence in the hands of the treating doctor by the bereaved families. Issues of adverse drug reactions like wrong medication, drug side effects, drug toxicity and anaphylactic reaction needs to be seriously addressed at autopsy. Generally, a medical board is comprised in dealing with such cases considering its seriousness. The role of autopsy is highly significant in such death investigation. A complete autopsy with supportive ancillary investigations is required to definitively conclude the cause of death due to ADR. In reality, unfortunately, deaths actually caused by ADRs are faced with difficulties surrounding its diagnosis due to lack of specific findings at autopsy and lack of supportive diagnostic modalities. Adverse drug reactions is a diagnosis of exclusion therefore any other condition causing similar symptoms need to be completely ruled out before giving an opinion of ADR as the cause of death. One of the rare ADRs is anaphylactic shock which is a medical emergency and a cause of sudden unexpected death. It is an immediate type of hypersensitivity reaction inducing a diffuse organ

hypoperfusion induced by an antigen (allergen)-antibody reaction in already sensitised subjects for a foreign substance.[2] The prevalence and incidence of anaphylaxis are unavailable as it is not a reportable disease. Its diagnosis at autopsy becomes a challenge as there are only minimal and subtle morphological changes that are found viz. visceral congestion, laryngeal and pulmonary oedema, mucus plugging of airways and urticarial rashes.[1–4] These changes can be appreciated only if the autopsy is conducted soon after death as they are expected to fade away with passage of time.[2–5] The supportive microscopic changes include eosinophilia and increased mast cells in the oedematous tissues of upper and lower airway, liver and spleen.

During an anaphylactic reaction, many biochemical mediators are released out of which serum mast cell tryptase enzyme (MCT) is considered to be the most stable with a half-life of 2 hour and thus making it measurable even on postmortem.[2–10]

The facilities for quantitative estimation of these biochemical markers are not available in most hospitals. Hence, it becomes difficult to arrive at a confirmatory diagnosis of anaphylaxis based solely on postmortem findings due to the reasons cited above. Ruling out of other conditions actually causing death rather than the alleged ADRs and ruling out false allegations also becomes a part of the death investigation. This study aims to analyse the data gathered from medical records to study the incidence and prevalence of such cases and to study the role and significance of autopsy in such deaths.

## METHODS AND MATERIAL

Data were obtained from the hospital clinical records and postmortem reports of cases with allegation of medical negligence where death occurred immediately following administration of medically prescribed drugs between the years 2011 and 2015. No other cases of medical negligence were included in the study. The data were analysed with regard to age, sex, type of drugs administered, clinical features, postmortem findings, survival time, time since death, cause of death and ancillary investigations. Statistical analysis of the results was done using appropriate statistical tests.

## RESULTS

A total of 16 cases of deaths with history of allegation of medical negligence causing immediate deaths following prescribed drug administration were identified from the medicolegal records of the Department of Forensic Medicine between 2011 and 2015. The incidence of such autopsies amounted to 0.3% of the total autopsied deaths. There was equal distribution of cases between the sexes. No sexual predominance was found (Table 1). The most common age group was 0–10 years (50%) followed by 21–20 (18.75%) (Table 2). All 16 cases were following treatment by some medication. Nearly 11 of the 16 cases occurred through injection of known drugs and vaccine (68.75%), 5 due to administration of unknown drugs (30.75) (Table 3). The known drugs included amikacin, dexamethasone, ondansetron, ferikind and anti-rabies vaccine. The commonest clinical presentation was sudden loss of consciousness (31.25%) followed by restlessness/agitation (18.75%). Other symptoms included palpitation, itching, breathlessness and seizures (Table 4). The mean survival period was 6.2 hours after the onset of symptoms (Table 5). Death occurred within 1 hour in three cases, within 6 hours in six cases and within 12 hours in seven cases. The minimum time of survival after drug administration was 5 minutes and maximum was 12 hours.

**Table 1: Sex Distribution**

| Sex | No. of cases | Percentage |
|---|---|---|
| Male | 8 | 50 |
| Female | 8 | 50 |

**Table 2: Age Distribution**

| Age group | No. of cases | Percentage |
|---|---|---|
| 0–10 | 8 | 50 |
| 11–20 | 1 | 6.25 |
| 21–30 | 3 | 18.75 |
| 31–40 | 2 | 12.5 |
| 41–50 | 2 | 12.5 |

**Table 3a: Alleged Exposure Prior to Symptoms**

| Exposure | No. of cases | Percentage |
|---|---|---|
| Injection of anti-rabies vaccine | 2 | 12.5 |
| Injection of dexamethasone and amikacin | 1 | 6.25 |
| Injection of voveran | 1 | 6.25 |
| Injection ondansetron and wysolone | 2 | 12.5 |
| Injection Ferikind | 1 | 6.25 |
| Injection Unknown Drug | 3 | 18.75 |
| Injection of unknown vaccine | 1 | 6.25 |
| Ingestion of prescribed unknown medication | 5 | 30.75 |

The mean time since death was 3.28 days (Table 6). About 50% of the cases occurred in private clinics, 37.5% in hospitals and 6.5% cases occurred under care of quacks and alternative medicine practitioners each (Table 7).

The autopsy findings were pulmonary oedema (56.25%) and brain congestion (56.25%), laryngeal congestion (43.75%), subcutaneous oedema (43.75%), pulmonary consolidation and cyanosis (37.5% each), brain oedema (31.25%), rashes and patchy mild subarachnoid haemorrhage (18.75%), laryngeal oedema, vocal cord opposition (6.25%). Specific findings were of meningitis in one case and pericarditis in one case (6.25% each) (Table 8). Toxicological analysis of viscera and histopathology was done in all cases. Analysis of biochemical markers of anaphylaxis had not been done due to lack of facilities. Viscera were negative for chemicals in all cases except two. One showed low levels of alcohol and one showed presence of aluminium phosphide poison. Histopathological examination showed natural disease in three cases and were unremarkable in the rest of the cases with unspecific findings.

The opinion regarding the cause of death was pending in await of ancillary investigation reports in six cases, uncertain in two cases, uncertain with possibility of anaphylaxis in four cases, three cases of due to other pathological natural causes (meningitis in one case, cardiogenic shock due to purulent pericarditis in one case, bilateral pulmonary pneumonitis in one case) and poisoning by aluminium phosphide in one case. Six cases where

**Table 3b: Alleged Histories**

| S.No. | Alleged histories |
|---|---|
| 1. | Unknown IV injection was given for pain abdomen by a private doctor |
| 2. | Death in hospital in half an hour following medication (Government Hospital) |
| 3. | Complaint of Loose stool for which two injections given (Dexamethasone and Amikacin) in Private Clinic |
| 4. | For vomiting Injection ondansetron and wysolone given in private clinic |
| 5. | Unknown Injection was given for excessive crying in private clinic |
| 6. | Injection Ferikind S Injection in private hospital |
| 7. | Injection Voveran and Tablet Rantac for abdominal pain in a charitable hospital |
| 8. | Unknown medicine, complaint of wrong medicine by a private doctor |
| 9. | Third dose of anti-rabies administered in a private hospital |
| 10. | Unknown medicine administered in a charitable clinic |
| 11. | Consumption of unknown medicine for her illness prescribed by quack (hakim) |
| 12. | Vaccination (DPT, Hpet, Polio) in MCD maternity home |
| 13. | Anti-rabies vaccine in government hospital |
| 14. | Unknown Injection by unknown doctor |
| 15. | Unknown Injection and IV fluid for fever and vomiting in a charitable hospital by UNANI doctor |
| 16. | Ingestion of unknown packet of powdered medicine for fever prescribed in a private clinic |

**Table 4: Clinical Presentation/Symptoms**

| Symptoms | No. of cases | Percentage |
|---|---|---|
| Sudden loss of consciousness | 5 | 31.25 |
| Itching | 1 | 6.25 |
| Palpitation | 1 | 6.25 |
| Restlessness | 3 | 18.75 |
| Breathlessness | 2 | 12.5 |

**Table 5: Survival Period (from Incidence till Death)**

| Survival time (hours) | No. of cases | Percentage |
|---|---|---|
| <1 hour | 3 | 18.75 |
| 1–6 | 6 | 37.5 |
| 6–12 | 7 | 43.75 |

**Table 6: Time since Death**

| | |
|---|---|
| Minimum | 12 hours |
| Maximum | 7 days |
| Average | 3.28 days |

**Table 7: Place of Incidence**

| Place of incidence | No. of cases | Percentage |
|---|---|---|
| Hospital | 6 | 37.5 |
| Private clinics | 8 | 50 |
| Quacks | 1 | 6.25 |
| Alternative medical practitioner | 1 | 6.25 |

**Table 8: Autopsy Findings**

| Findings | No. of cases | Percentage |
|---|---|---|
| Rashes | 3 | 18.75 |
| Cyanosis | 6 | 37.5 |
| Subcutaneous oedema | 7 | 43.75 |
| Laryngeal oedema | 1 | 6.25 |
| Laryngeal congestion | 7 | 43.75 |
| Vocal cord opposition | 1 | 6.25 |
| Pulmonary oedema | 9 | 56.25 |
| Pulmonary consolidation | 6 | 37.5 |
| Brain congestion | 9 | 56.25 |
| Brain oedema | 5 | 31.25 |
| Mild Subarachnoid haemorrhage | 3 | 18.75 |
| Heart disease | 1 | 6.25 |
| Meningitis | 1 | 6.25 |

**Table 9: Cause of Death Opined**

| Cause of death | No. of cases | Percentage |
|---|---|---|
| Pending (awaiting reports) | 06 | 37.5 |
| Uncertain but possibility of anaphylactic shock not ruled out | 4 | 25 |
| Other pathological conditions | 03 | 18.75 |
| Uncertain | 02 | 12.5 |
| Aluminium phosphide poisoning | 1 | 6.25 |

the cause of death was pending had findings of pulmonary consolidation and histopathological and toxicological confirmation was awaited (Table 9).

## DISCUSSION

This study was undertaken due to the diagnostic dilemma faced by the forensic experts while dealing with alleged medical negligence cases occurring after administration of drugs. Although medication errors are the most common cause of iatrogenic patient injury, less than 2% result in injuries. ADRs in hospitalised patients are estimated to range from 2% to 20% in the United States. About 0.12–1.06 deaths per million person years occurs due to anaphylaxis thus being very rare.[11] Though rare, such deaths become important for correct diagnosis for justice to both the parties.

In our study, cases of alleged negligence causing immediate death following administration of drugs amounted to 0.3% of the total autopsies conducted in the period.

The cases were equally distributed in both the sexes and did not show any sexual predominance. The commonest clinical presentation was sudden loss of consciousness 5/16 cases (31.25%) followed by restlessness/agitation 3/16 (18.75%). Breathlessness was seen in two cases and palpitation and itching were seen in one case each. In seven cases, documentation of clinical symptoms was not available. Such symptoms are predictable of a wide range of conditions, which also includes ADRs. Various combinations of clinical symptoms have been reported during an anaphylactic reaction like the circulatory symptoms viz. confusion, collapse, unconsciousness and

incontinence are considered to be of severe grade and symptoms like diaphoresis, vomiting, presyncope, dyspnoea, stridor, wheeze, chest/throat tightness, nausea, vomiting and abdominal pain indicate moderate reactions. Reactions limited to the skin like urticaria, erythema, and angioedema indicate mild reaction.[12] The most important point to note is the timeline for development of these symptoms. In ADRs, the symptoms should develop immediately after the exposure and such symptoms should be absent prior to the exposure. This was also seen in the study group; however, the clinical history was not all documented and some appeared to be from the history given by the next of kin. The veracity of such statements becomes doubtful considering the manner of the cases and has to be considered.

The mean survival period was 6.2 hours after the onset of symptoms (Table 5). Death occurred within 1 hour in three cases, within 6 hours in six cases and within 12 hours in seven cases. The minimum time of survival after exposure was 5 minutes and maximum was 12 hours. Most studies on anaphylactic deaths report death occurring within 1 hour of symptoms.[5,13] The longer survival time in our study group goes less in favour of ADRs especially anaphylaxis.

The mean time since death was 3.28 days (Table 6). As the time lapse between death and autopsy becomes crucial for the diagnosis of anaphylaxis contemplating loss of evidence it is pertinent that the autopsy be carried out immediately after death. In this study, autopsy findings were present; however, none could be definitely being attributed to ADRs like anaphylaxis. Loss of autopsy finding like laryngeal oedema and vocal cord opposition within 6 hours of death is well known. However, in one case this finding was present even after 7 days post death. Subjective bias with preconceptions could lead to appreciation of such findings, which is not uncommon in forensic practice.

About 50% of the cases occurred in private clinics, 37.5% in hospitals and 6.5% cases occurred under care of quacks and alternative medicine practitioners each (Table 7). This demography could mean two things, one being a general lack of faith in private doctors in the public or it could also mean false accusations in order to avoid the exorbitant fees charged by private practitioners. Either way, the forensic pathologist will have to deal with all the cases judiciously for justice of both the parties.

The autopsy findings were pulmonary oedema (56.25%) and brain congestion (56.25%). Other findings were laryngeal congestion (43.75%), subcutaneous oedema (43.75%), pulmonary consolidation and cyanosis (37.5% each), brain oedema (31.25%), rashes and subarachnoid haemorrhage (18.75%), laryngeal oedema, vocal cord opposition (6.25%). The findings of organ congestion and oedema are non-specific and are seen in many conditions. It is difficulty to conclude death based solely only on these findings. The presence of pulmonary consolidation is sufficient to cause death on its own and points towards a pre-existing morbid condition. The findings of organ congestion, oedema, subarachnoid haemorrhage overlaps with many conditions but are also sometimes the only findings in anaphylactic deaths. In the presence of a typical clinical history, absence of postmortem findings does not exclude the diagnosis of anaphylaxis.[14] A study by Irene Low found pulmonary oedema and pulmonary congestion commoner than laryngeal oedema and cutaneous oedema in anaphylactic deaths.[13] Yiwen Shen found pharyngeal and laryngeal oedema in 50% of the cases and pulmonary congestion and oedema in all the cases studied.[2] The rapidity of death which occurs during anaphylaxis and also the time since death is said to affect the autopsy findings.[5,13] The only macroscopic finding is multivisceral congestion associated or not with the pete chial haemorrhages if death is rapid.[4,5] Studies have shown appreciation of findings like laryngeal oedema and vocal cord opposition till 6 hours after death.[2]

The histopathological examination in most of the cases was insignificant, but at the same time it confirmed the presence of other pathological conditions. ADRs like anaphylaxis may sometimes reveal findings of eosinophilia in the airways and oedema of the upper airways.[6] Postmortem testing of serum markers was not done solely due lack of facilities. In cases where the

cause of death highly suspected to be an anaphylactic reaction, such tests have to be performed if facilities are available. Studies have shown the usefulness of testing of serum markers like tryptase and IgE levels in diagnosing anaphylaxis.[4–6,8–10,14–16] Serum tryptase levels is shown to be elevated to >11.4 μg/L.[17,18] Toxicology analysis was done in all cases which was negative in all cases except two. One showed low levels of alcohol and one showed surprisingly presence of aluminium phosphide poison. Toxicology does not help in determining drug toxicity as most of the drugs are not detected at autopsy due to degradation in the body.

The opinion regarding the cause of death was pending in await of ancillary investigation reports in six cases, uncertain in two cases, uncertain with possibility of anaphylaxis in four cases, three cases were due to other pathological natural causes (meningitis in one case, cardiogenic shock due to purulent pericarditis in one case, bilateral pulmonary pneumonitis in one case) and poisoning by aluminium phosphide in one case. Six cases where the cause of death was pending had findings of pulmonary consolidation and histopathological confirmation was awaited. In these cases also death is likely to be due to pre-existing co-morbid condition. Therefore it is safe to say that in more than half of such deaths reported (9/16) death was from a natural cause. One case where death was due to poisoning could be marked as false/frivolous complaint. It needs to be highlighted that the difficulties associated with diagnosis of ADE or anaphylactic death is a universal problem.[19]

## CONCLUSION

This study highlights the growing distrust among the general public against the medical profession. It also apprises the health professionals about the power of general public in today's India where a doctor can easily be blamed, rightfully or not. This article also emphasis the huge role of the Forensic experts in such cases of alleged medical negligence in providing unbiased justice to both the parties. For correct interpretation of findings and a correct diagnosis, additional facilities for testing of biomarkers should be developed in future.

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