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RESEARCH ARTICLE

Post-mortem distribution of some antiepileptic drugs in adult albino rats

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Abstract

Post-mortem redistribution and changes of drugs present major obstacles to interpretation of drugs concentrations in sudden unexplained death of epilepsy. The study aims to investigate the postmortem changes of carbamazepine and phenytoin concentrations in blood and tissue samples of rats. Sixty adult albino rats divided into equal three groups, first group received 250 mg/kg of carbamazepine and second group received 36 mg/kg of phenytoin. The third group received 250 mg/kg of carbamazepine and 36 mg/kg of phenytoin. Heart blood samples were collected from all groups after two hours of drugs administration. Samples of liver, kidney, brain and blood were collected at 2, 24, 48 hrs after sacrifice of all animals. Detection of phenytoin and carbamazepine in serum and tissues was done by enzyme multiplied immunoassay technique. Postmortem blood concentration of carbamazepine and phenytoin decreased after 24, 48 hours in comparison to its antemortem blood and 2 hrs postmortem while it increased with time in brain, liver and kidney when its administration was individual or concurrent. Postmortem distribution of carbamazepine and phenytoin was different in blood and organs according to the time.

Introduction

Post-mortem redistribution of drug represents major problem for interpretation of its concentrations in the dead. Major changes of many drugs concentrations occur after the death. Redistribution of drugs from organs into the blood leads to some concentrations increase, others fall and some do not change (Pélissier et al., 2003).

Process of post-mortem drugs redistribution is a toxicological nightmare although many published lists of therapeutic, toxic and lethal concentrations. Forensic toxicologists should be aware of postmortem drug redistribution for correlation ante-mortem history with laboratory post-mortem drug concentration to conduct the true drug concentration and cause of the death (Kennedy, 2010).

Toxicological studies are difficult in autopsy of sudden unexpected death cases owing to degraded nature of the specimens and wide range of specimens available for analysis. Toxic postmortem drug concentrations can lead to wrong conclusions with resulting liability claims, insurance denials and significant emotional turmoil for all involved. Quantitative analysis leads to error results because of post-mortem redistribution phenomenon while Qualitative tests detect substances that were not present in life and fail to detect substances that led to death (Yarema and Becker, 2005).

Immunoassay is the most widely practiced method of screening samples for drugs. It is a flexible technique that can provide a rapid, inexpensive and convenient method to screen large numbers of samples in a variety of matrices.

Based on the principle of antibody-antigen reaction, immunoassay can detect the presence of drugs and its metabolites in a biological sample thus preventing the need for further confirmatory testing (Stimpfl and Vvcudilik, 2004).

Sudden unexplained death in epilepsy (SUDEP) is an important cause of epilepsy related death, with an annual incidence among patients with epilepsy of 1–2 per 1000. It accounts for approximately 2% of deaths in population-based cohorts of epilepsy and up to 25% of deaths in cohorts of more severe epilepsy. Some studies have reported that frequent, rapid changes in carbamazepine levels may be associated with SUDEP. However, other studies have not found an association between the use of carbamazepine or any other individual antiepileptic drug and SUDEP. There is a little information regarding antiepileptic drugs such as phenytoin and carbamazepine. Further researches are needed to explain the potential role of individual antiepileptic drugs in SUDEP (Walczak, 2003).

All currently available antiepileptic drugs (AEDs) have been associated with SUDEP and current opinion assumes that the relative proportion of patients suffering SUDEP is representative of average antiepileptic drug usage type for a particular time and locality. However, recently analyzed data suggest a strong bias towards carbamazepine. A review of Cardiff Epilepsy Unit data shows that carbamazepine was disproportionately represented in patients suffering SUDEP (Timmings, 1998).

Thus**,** the aim of this study is investigation of possible postmortem concentrations changes of carbamazepine and phenytoin in blood and tissue samples of rats with comparison between ante-mortem and postmortem of blood concentrations of these drugs.

Materials and methods

Sixty adult albino healthy rats of both sexes weighing (200–250 g) were subjected for the study. They were housed in air- conditioned, humidity-controlled cages. Rats had free access to water and food during the experimental period.

The rats were divided into three equal groups (each n=20). The first group received 250 mg/kg of carbamazepine and second group received 36 mg/kg of phenytoin. The third group received 250 mg/kg of carbamazepine and 36 mg/kg of phenytoin together - (Bauer et al., 2002) . Drugs were administered by gastric gavage**.**

Carbamazepine drug was in the tablet form and obtained from Novartis Farma S.P.A., Torre Annunziata, Italy for Novartis Pharma AG Basle, Switzerland. One tablet contains 400 mg of active ingredient, dissolved in 10 ml distilled water. Phenytoin drug was in capsule form and obtained from the Nile Co. for Pharmaceuticals and chemicals industries, Cairo, A.R.E under license of Parke-Davis. One capsule contains 100 mg of active ingredient, dissolved in 10 ml of distilled water.

Heart blood samples were collected from rats of all groups after two hours of drugs administration and immediately before sacrifice for determination of ante-mortem concentrations of carbamazepine and phenytoin**.** Blood samples were placed in a fluoride/oxalate tube containing 1% (w/v) sodium fluoride as a preservative. It centrifuged 5000 round per minute for 5 minutes to obtain the serum.

Animals of all groups were sacrificed two hours after drugs administration. Tissue samples such as liver (right lobe), kidney, brain (cerebral cortex) and blood were collected at 2, 24, 48 hrs after the death. All tissue samples were placed in separate sample containers to remove any chance of cross-contamination (Forrest, 1993).

Detection of phenytoin and carbamazepine with its two major metabolites carbamazepine-10, 11-epoxide and carbamazepine-10, 11-(trans)-dihydrodiol in serum and tissues by Enzyme multiplied immunoassay technique (EMIT) using CIDIA kits of Thermo Fisher Scientific Inc.
The CEDIA Carbamazepine and Phenytoin II Assay is an in-vitro diagnostic medical device intended for quantitation of phenytoin and carbamazepine in human serum or plasma. CEDIA Core TDM Multi-Cal (Catalog No. 100007), Microgenics Corporation, 46360 Fremont Blvd. Fremont, CA 94538 USA, a registered trademark of Roche Diagnostics.

Reagents for Enzyme multiplied immunoassay technique (EMIT) —The CEDIA reagents were a part of the CEDIA kits (Carbamazepine II and Phenytoin II kits) purchased from Microgenics Corporation (Fremont, CA).

Reagents of carbamazepine were EA reconstitution buffer which contains 3-(N-morpholino) propane sulfonic acid, 49 mg/L monoclonal anti-carbamazepine antibody, stabilizer and preservative. EA reagent contains 0.171 g/L Enzyme acceptor, stabilizer, buffer salts and preservative. ED reconstitution buffer contains 2-(N-morpholino) ethane sulfonic acid and preservative. ED reagents contains 22.1 µg/L Enzyme donor conjugated to carbamazepine, 1.64 g/L chlorophenol red-ß-D-galactopyranoside, buffer salts, stabilizer and preservative. Reagents of phenytoin were EA reconstitution buffer which contains MOPS 3-(N-morpholino) propane sulfonic acid, 35 mg/L monoclonal anti-phenytoin antibody, buffer salts, stabilizer and preservative. EA reagent contains 0.171 g/L Enzyme acceptor, releasing agent, detergent, buffer salts, and preservative. ED reconstitution buffer contains MOPS 3-(N-morpholino) propane sulfonic acid, buffer salts, and preservative. ED reagent contains 19 µg/L Enzyme donor conjugated to phenytoin, 1.64 g/L chlorophenol red-ß-D-galactopyranoside, buffer salts, stabilizer and preservative.

Eluents were methanol:ammonia (100:1.5) for carbamazepine. Chloroform : Acetone (4:1) for phenytoin. Methanol (ADWIC); Ammonia (CHEMICA); Chloroform and Acetone (AR, Cambrain chemicals)**.**

Spraying agents were acidified iodoplatinate solution, 0.25g of platinic chloride (MERK) and 5g of potassium iodide (SIGMA) were dissolved in 100 ml distilled water, then 5ml diluted hydrochloric acid was added. This solution was used for detection of carbamazepine. Zwikker's reagent, 40ml of 10% solution of copper sulphate (ADWIC) was dissolved in 100 ml distilled water. This solution was used for detection of phenytoin.

Apparatus was a Syva EMIT system. It consists of a stasser III Spectrophotometer (Gilford Instrument Lab.); a Syva Pipetter Dilutor (Cavro Scientific Instrument); an EMIT clinical processor model LP 6500, Cliford 3021 Vacuum Receiver and De Vilbiss Pump. The spectrophotometer was operated in the absorption mode at 340 nm, the microflow cell was set at 30 ºC. The LP 6500 was timed to measure absorbance at 15, 95 seconds and calculate the absorbance difference (Δ A). The delay time is 15 second and the measuring time is 80 second. All reagents and standard were refrigerated 5 ºC for storage and allowed to equilibrate, for at least two hours, at room temperature before use.

Extraction of carbamazepine or phenytoin from tissues samples was done by adding 2ml of pure water to 3 gm of tissues. It was cut into fine peaces with small scalpel in a glass universal bottle. 1 ml concentrated hydrochloric acid was added and placed in a domestic pressure cooker. It was heated on number three for twenty minutes. The pressure was released and glass universal bottle was removed and allowed them to cool. The content of each universal was poured into clean 120 ml plastic pots. A rounded spatula of sodium bicarbonate was added to each and allowed the effervescence to subside. A little more was added until no further effervescence was occurred. It was allowed to settle and poured liquid supernatant into a 12 ml polypropylene tube. 1 ml of "Narcs" buffer and 5 ml of chloroform: isopropanol (9:1) were added (1ml of Narcs hydrochloric acid and 5 mL chloroform for phenytoin). It was shaken mechanically for 10 minutes and centrifuged at 3500 round per minute for 5 minutes. The upper aqueous layer was aspirated and discarded. The organic phase was filtered through a Whatman No. 4 filter paper into a 10 ml conical glass tube. It was evaporated to dryness and reconstituted with 100 ul methanol. 2.9 ml of drug free rat serum was added. It was reconstructed using vortex 30 second. Then, estimation of carbamazepine or phenytoin level in the sample was done (Yanga et al., 2007).

Analysis by EMIT was done. For quantitative calibration, two drugs were added to drug-free blood in the range corresponding to their therapeutic concentrations. Standard curves were constructed from duplicate samples at each concentration. Each sample was assayed at 340 absorbance. The minimum detection limits of the EMIT for the two drugs were determined. 50µl of methanolic supernatant of the extract was added to 250 µl of buffer solution and mixed in a 2 ml disposable cup by using the pipette diluter. 50µl of reagent A and 25µl of the buffer were added to the cup. After 30 second equilibration, 50µl of reagent B and 250 µl of the buffer were added to the cup. The contents of the cup were immediately aspirated into the flow cell of the spectrophotometer. Absorbance readings were taken automatically at 15 and 95 seconds to calculate the absorbance difference (Δ A) (Ghanem et al., 2005)**.**

Statistical analysis

Statistical analysis was performed by using SPSS version 15 (SPSS Inc., Chicago, IL, USA). Variability of results was expressed as mean ± SD. One way ANOVA test with post hoc analysis (Bonferroni) was used to study significance of differences. Probability value (p-value) < 0.05 was considered statistically significant.

Ethical considerations

The most appropriate animal species was chosen for this research. Promotion of a high standard of care and animal well-being at all times was done. Appropriate sample size was calculated by using the fewest number of animals to obtain statistically valid results. Painful procedures were performed under anesthesia to avoid distress and pain. Our standards of animal care and administration met those required by applicable international laws and regulations.

Results

Table (1) showed that postmortem blood concentration of carbamazepine was decreased significantly after 24 and 48 hours in comparison to antemortem blood concentration of carbamazepine. Postmortem blood concentration of carbamazepine was significantly lower at 24 and 48 hours than 2 hours postmortem. Postmortem blood concentration at 48 hours was significantly lower than postmortem 24 hours concentration. There was no significant difference between antemortem and 2 hours postmortem blood concentration of carbamazepine.

Table1. Relationship between antemortem blood concentration and postmortem blood concentration of carbamazepine according to time (2 hours, one day, two days) in the first group.

	Antemortem blood concentration	**Postmortem blood concentration (2 hours)**	**Postmortem blood concentration (24 hours)**	**Postmortem blood concentration (48 hours)**	**p-value**
Mean ± SD	12.76 ± 1.97 [a]	11.72 ± 2.1 [a]	6.96 ± 0.97 [b]	4.83 ± 0.37 [c]	0.001*
Range	9.4 – 15.3	8.9 – 13.8	6 – 8.3	4 – 5.2	
Median (IQR)	13.35 (11.55 – 14.15)	13 (9.65 – 13.67)	6.4 (6.2 – 8.25)	4.7 (4.7 – 5.2)	

The first group received 250 mg/kg of carbamazepine.
IQR: interquartile range (25^{th} – 75^{th} percentiles).
***** Statistically significant test (p-value for one way ANOVA test).
[a], [b], [c] indicates statistically significant difference between different time points (Bonferroni test).

Table (2) showed that postmortem blood concentration of phenytoin was decreased significantly after 24 and 48 hours in comparison to antemortem concentration. Postmortem blood concentration of phenytoin was significantly lower at 24 and 48 hours than 2 hours postmortem. Postmortem blood concentration at 48 hours was significantly lower than postmortem 24 hours concentration. There was no significant difference between antemortem and 2 hours postmortem blood concentration of phenytoin.

Table2. Relationship between antemortem blood concentration and postmortem blood concentration of phenytoin according to time (2 hours, one day, two days) in the second group .

	Antemortem blood concentration	**Postmortem blood concentration (2 hours)**	**Postmortem blood concentration (24 hours)**	**Postmortem blood concentration (48 hours)**	**P-value**
Mean ± SD	12.4 ± 2.2 [a]	12.59 ± 0.92 [a]	5.33 ± 1.2 [b]	4.1 ± 0.4 [c]	0.001*****
Range	9.3 – 15.3	11.6 – 13.4	4 – 6.9	3.6 – 4.5	
Median (IQR)	12.4 (10.35 - 14.55)	13.4 (11.6 –13.4)	5.1 (4.1 – 6.7)	3.9 (3.8 – 4.5)	

The second group received 36 mg/kg of phenytoin.
IQR: interquartile range (25^{th} – 75^{th} percentiles).

*****Statistically significant test (p-value for one way ANOVA test).
[a], [b], [c] indicates statistically significant difference between different time points (Bonferroni test).

Table (3) showed concurrent administration of carbamazepine and phenytoin in the third group. Postmortem blood concentration of carbamazepine in the third group was decreased significantly after 24 and 48 hours in comparison to antemortem blood concentration of carbamazepine. Postmortem blood concentration of carbamazepine was significantly lower at 24 and 48 hours than 2 hours postmortem, but there was no significant difference between postmortem blood concentration at 24 and 48 hours. There was no significant difference between antemortem and 2 hours postmortem blood concentration of carbamazepine. As regard phenytoin in the third group, its blood concentration after 2 hours postmortem caused a significant increase in comparison to its antemortem blood concentration followed by significant decrease at 24 and 48 hours postmortem in comparison to antemortem and 2 hours postmortem blood concentrations. There was statistically significant difference between 24 hours and 48 hours postmortem blood concentrations.

Table3. Relationship between antemortem blood concentration and postmortem blood concentration of carbamazepine and phenytoin according to time (2 hours, one day, two days) in the third group.

		Antemortem blood concentration	**Postmortem blood concentration (2 hours)**	**Postmortem blood concentration (24 hours)**	**Postmortem blood concentration (48 hours)**	**p-value**
Carbamazepine	**Mean ± SD**	12.8 ± 2.1 [a]	12.1 ± 1.9 [a]	5.66 ± 0.34 [b]	4.66 ± 0.76 [b]	0.001*
	Range	9.8 – 15.25	10 – 14.3	5.3 – 6	3.5 – 5.3	
	Median (IQR)	13.62 (10.8 – 14.3)	12.15 (10.2 – 14)	5.9 (5.3 – 6)	5.1 (3.7 – 5.3)	
Phenytoin	**Mean ± SD**	11.3 ± 1.5 [a]	12.33 ± 1.2 [b]	5.81 ± 1.04 [c]	4.39 ± 0.76 [d]	0.001*
	Range	9.25 – 13.5	11 – 13.6	5 – 7.2	3.4 – 5.1	
	Median (IQR)	11.45 (10.05 – 13.1)	12.15 (11.25 – 13.5)	5.1 (5 – 7.2)	4.9 (3.5 – 5.1)	

The third group received 250 mg/kg of carbamazepine and 36 mg/kg of phenytoin together.
IQR: interquartile range (25^{th} – 75^{th} percentiles).
*****Statistically significant test (p-value for one way ANOVA test).
[a], [b], [c], [d] indicates statistically significant difference between different time points (Bonferroni test).

Figure (1) showed that postmortem brain concentration of carbamazepine had increased significantly after 48 hours in comparison to 2 hours postmortem. There was no significant difference between 2 hours and 24 hours postmortem values or 24 hours and 48 hours values. Hepatic postmortem concentration of carbamazepine was statistically significant increase at 24 and 48 hours compared to 2 hours postmortem concentration. There was no statistically significant difference between 24 hours and 48 hours postmortem hepatic carbamazepine concentrations. Renal postmortem concentration of carbamazepine was statistically significant increase at 24 and 48 hours compared to 2 hours postmortem concentration. There was no statistically significant difference between 24 hours and 48 hours postmortem renal carbamazepine concentrations.

Figure1. Relationship between postmortem brain, hepatic and renal concentrations of carbamazepine according to postmortem time (2 hours, one day, two days) in the first group.

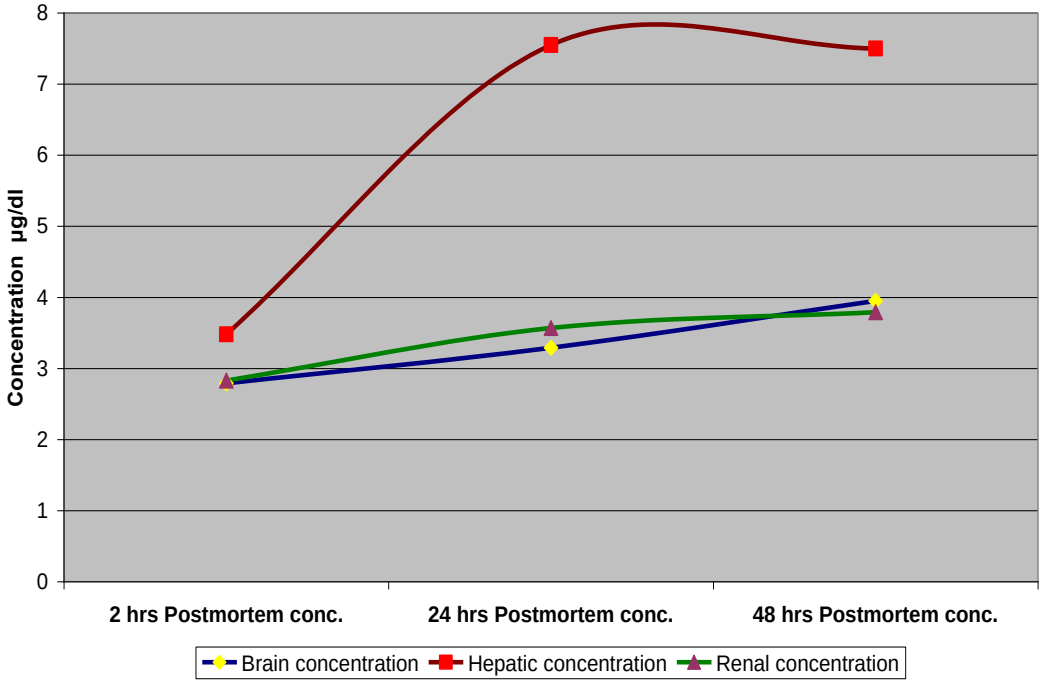


Figure (2) showed that postmortem brain concentration of phenytoin had increased significantly after 48 hours in comparison to 2 hours and 24 hours postmortem values. There was no significant difference between 2 hours and 24 hours postmortem values. Hepatic postmortem concentration of phenytoin was statistically significant increase at 24 and 48 hours compared to 2 hours postmortem concentration. There was no statistically significant difference between 24 hours and 48 hours postmortem hepatic phenytoin concentrations. Renal postmortem concentration of phenytoin was statistically significant increase at 24 and 48 hours compared to 2 hours postmortem concentration. There was no statistically significant difference between 24 hours and 48 hours postmortem renal phenytoin concentrations.

Figure2. Relationship between postmortem brain, hepatic and renal concentrations of phenytoin according to postmortem time (2 hours, one day, two days) in the second group.

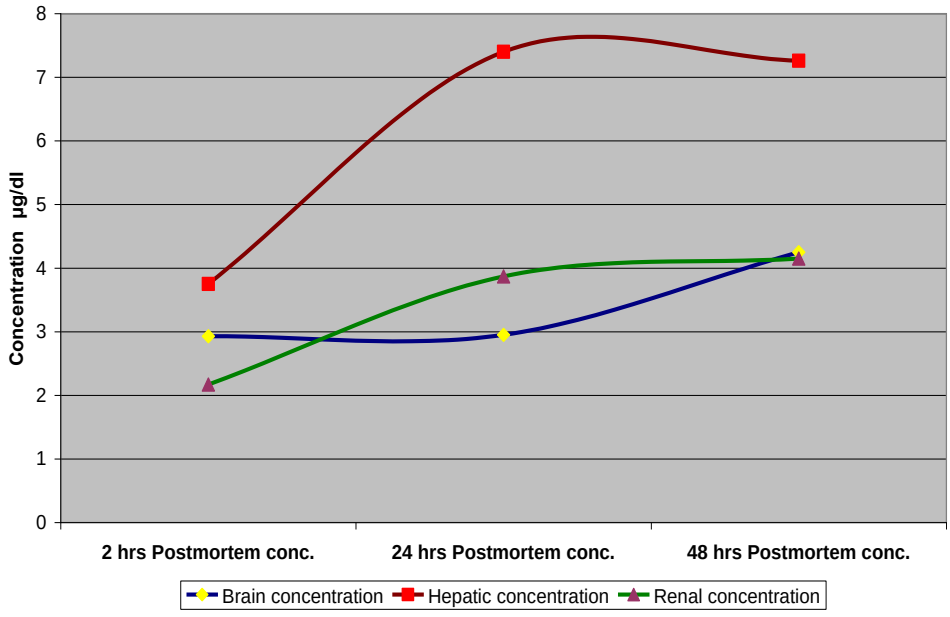


Figure (3) showed concurrent administration of carbamazepine and phenytoin in the third group. Postmortem brain and hepatic concentration of carbamazepine had increased significantly after 48 hours in comparison to 2 and 24 hours postmortem values. There was no significant difference between 2 hours and 24 hours postmortem values.

Figure3. Relationship between postmortem brain, hepatic and renal concentrations of carbamazepine according to postmortem time (2 hours, one day, two days) in the third group.

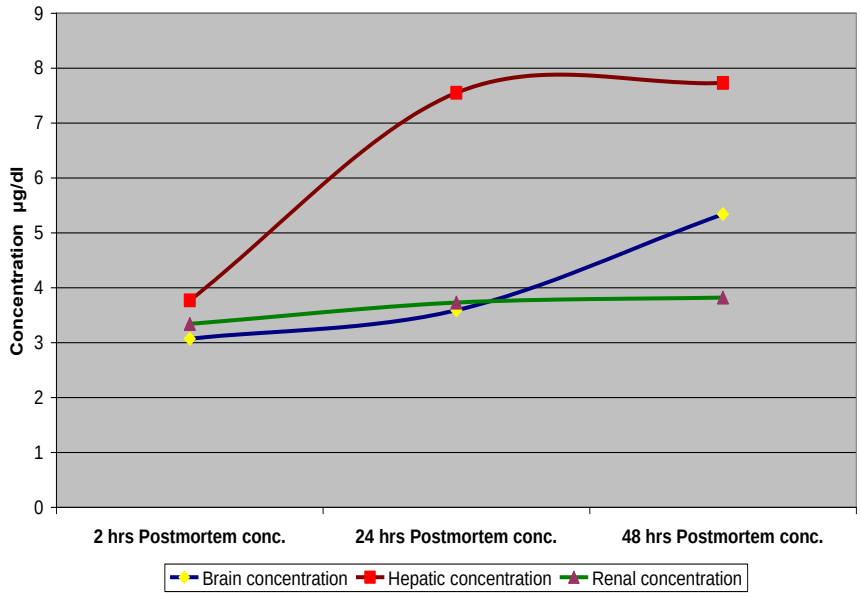
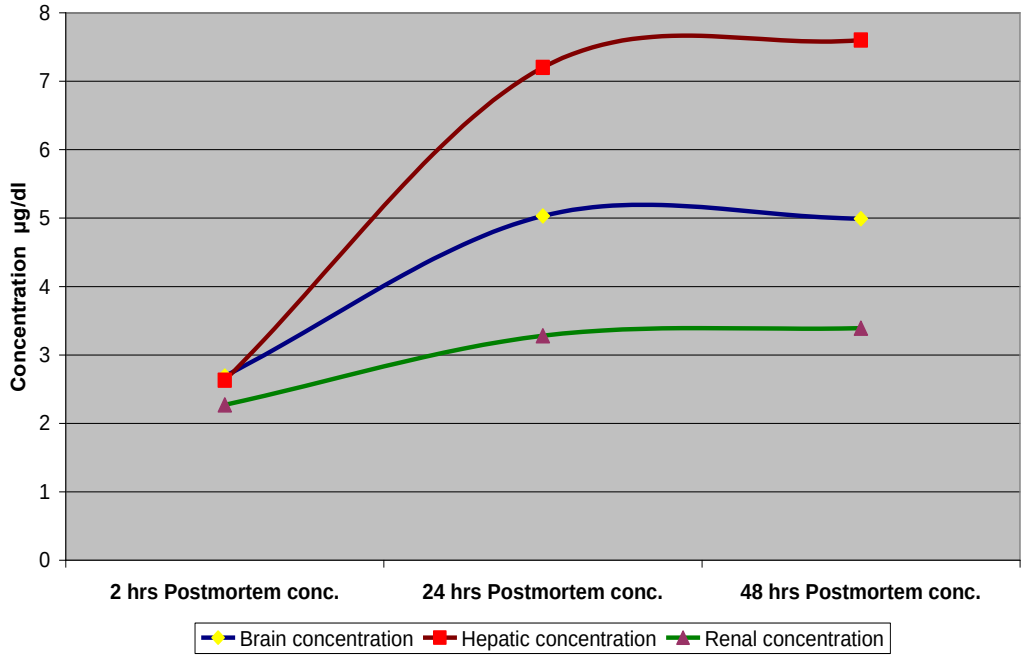


Figure (4) showed a significant increase in all of brain, hepatic and renal postmortem concentrations of phenytoin at 24 and 48 hours in comparison to postmortem 2 hours concentration in the third group with no difference reported between 24 and 48 hours postmortem measurements.

Figure4. Relationship between postmortem brain, hepatic and renal concentrations of phenytoin according to postmortem time (2 hours, one day, two days) in the third group.



Discussion

One of the most difficult responsibilities of forensic toxicologists is an estimation of drug concentration at the time of death, or number of tablets consumed. This assumes that the drug concentration found at postmortem examination is a reliable estimate of that present at the time of death (Drummer, 2007). In this study, the relation of postmortem concentration to antemortem concentration of common antiepileptic drugs (carbamazepine and phenytoin) was investigated to extrapolate postmortem distribution of these drugs.

The current study showed no significant difference between antemortem and two hours postmortem blood concentration of carbamazepine when it was administrated alone or concurrent administration with phenytoin, this consistent with (Spiller and Carlisle, 2001) and in contrast with (May et al., 1999) who confirmed that antemortem blood concentration of carbamazepine was higher than its postmortem blood concentration.

The present study reported that postmortem blood concentration of carbamazepine was decreased significantly with time while it was increased significantly in organs (brain, liver, kidney) when it was administered alone or with phenytoin except for kidney where carbamazepine had shown no significant difference in co-administration with phenytoin. This is contrast with (Torbjörn et al.,1998) who referred to postmortem blood concentration of carbamazepine was not affected with time until three days after the death in comparison with its antemortem blood concentration.

According to **(**Hilberg et al., 1999)**,** postmortem carbamazepine concentration displayed no change from antemortem concentration and mentioned that carbamazepine has not postmortem redistribution because its volume distribution is less than 3 L/kg.

Results of the current study were agreement with (Takayasu et al., 2010) who indicated that postmortem carbamazepine concentration was higher in tissues of organs than in the blood. It was explained that drug is incorporated into organ tissues and retained in unchanged form at the peak blood carbamazepine concentration. These results are reversing the usual postmortem redistribution process.

Regarding to phenytoin, results of the present study referred to its postmortem distribution was decreased significantly with time in blood while it was increased significantly in organs (brain, liver and kidney) when it is administered alone or with carbamazepine. These results were in contrast with results of Torbjörn et al., 1998 and May et al., 1999 who reported that antemortem concentration of phenytoin was higher significantly than its postmortem concentration and postmortem time had not any significant effect on postmortem concentration of phenytoin.

According to (McIntyre and Meyer, 2012), postmortem drug concentration in blood may not always reflect antemortem blood drug concentration or its concentration at the time of death due to the movement of the drugs after death such as postmortem redistribution phenomenon. It depends on time interval after the death and site of the sample. This is consistent with our results and with (Cook et al., 2000) who confirmed that chosen site and technique for postmortem sampling can greatly influence the concentration of drug measured.

The current study showed that postmortem drug concentration difference between administration of carbamzepine alone or with phenytoin was the rate of reduction because carbmazepine had a slower rate of reduction while phenytoin showed a higher rate of reduction.

Ferner, (2008) indicated that many factors can affect postmortem drug concentration such as changes of drug distribution because of integrity loss of transferring cell membrane after the death and postmortem physicochemical changes of drug.

Conclusion

Postmortem blood concentration of carbamazepine and phenytoin were decreased significantly with time in comparison with its antemortem blood concentration while it was increased significantly in all organs (brain, liver and kidney) when it was administered alone or concurrent except for kidney where carbamazepine had shown no significant difference when it was administered with phenytoin.

Recommendations

This study recommends that we should not be depending on postmortem blood and tissue concentrations of carbamazepine and phenytoin to reflect antemortem concentration and investigation the cause of death because it is a different depending on time and type of sample.

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