INFLUENCE OF DIETARY PROTEIN ON THE EFFECT OF COUMAPHOS AND TRIFLUPROMAZINE INTERACTION IN SHEEP

by

T. GOPAL

B.V.Sc., M.V.Sc.
University of Agricultural Sciences, Bangalore
India, 1967

A MASTER'S THESIS

Submitted in partial fulfillment of the

requirements for the degree

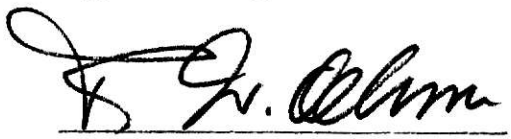
MASTER OF SCIENCE

Pathology

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1976

Approved by:



Major Professor

TABLE OF CONTENTS

ACKNOWLEDGEMENTS 1

INTRODUCTION 2

INFLUENCE OF DIETARY PROTEIN ON THE EFFECT OF COUMAPHOS AND TRIFLUPROMAZINE INTERACTION IN SHEEP

Summary. 4
Introduction 5
Materials and Methods 6
Results 9
Discussion 15
References 22
Figures 26
Tables 38

APPENDIX I

Group and Individual Data 44

APPENDIX II

Literature Review 100

A. The Organophosphorus Compound Coumaphos 102
B. Phenothiazine and Its Derivatives 116
C. Interaction of Organophosphorus Compounds and Phenothiazine Derivatives 124
D. References 127

ABSTRACT . . . . . .

ACKNOWLEDGEMENTS

I express my sincere thanks and gratitude to Dr. F. W. Oehme, for his valuable advice, guidance and unceasing encouragement during my graduate studies. I am equally indebted to Drs. V. V. St. Omer, J. E. Cook, H. W. Leipold and D. W. Upson for their advice as members of my advisory committee.

The generous support provided by the Graduate School, the Departments of Physiological Sciences and Pathology, KSU is gratefully acknowledged. My special thanks are due to Mr. Marc Rachofsky, and Mr. Steve Galitzer for their help in conducting this investigation. I am grateful to all my friends, especially to Drs. P. Lakshmipathy, T. G. Nagaraja, and M. S. A. Kumar for their untiring help during this study.

I also extend my thanks to all Oehmes, Donahys and all the graduate students and staff of Comparative Toxicology Laboratory for extending a warm welcome during my stay. I thank Miss Bev Mueller for her excellant typing.

I am highly indebted and grateful to my wife, parents and daughters, whose sacrifice and encouragement made my graduate studies more meaningful.

To them I dedicate this thesis.

INTRODUCTION

Despite the fact that organic chemicals are increasingly being synthesized and extensively studied for their use in agricultural and medicinal practices, the biological behavior of many of these chemicals is not completely understood. The biological behavior of any given compound may have such wide variation that it is often difficult to predict its effect. More than one factor may modify this biological behavior. Such modification can be further complicated by the presence of another chemical which may possess similar pharmacological activity. The interaction which takes place may result in synergistic benefits, total or partial supression of therapeutic effects, or totally unexpected potentiation with adverse reactions.[1]

Synthetic organophosphorus compounds are chiefly used as pesticides and systemic insecticides and have provided many benefits to man and animals. However, their pharmacological activity is subjected to modification by several biological or extraneous factors which may potentiate their activity. Although laboratory studies provide information for safe therapeutic application of such chemicals, field experiences indicate that toxicity occurs even when the compounds are used as recommended. There is wide species variation reflecting variability in the biotransformation of these agricultural chemicals. Stress and malnutrition may further influence animal susceptibility.[2]

Phenothiazine and its derivatives are used in veterinary practice as antihelmintics and tranquilizers. Combination therapy with organophosphorus compounds and phenothiazine derivatives has produced additive therapeutic benefits. However, reports also indicate toxic potentiation of their effects, resulting in acute poisoning and death.[3]

To obtain an understanding of this biological phenomenon, an investigation was undertaken in sheep to study the interaction of the organophosphorus compound coumaphos and the phenothiazine derivative trifluprомazine. Since malnutrition is suggested as a contributing factor to toxicity, the influence of induced protein stress in modifying the host response was included in the investigation.

References

1. Gralla, E. J.: Drug Interaction. Vet Toxicol, 17, (1975): 84-88.

2. Nelson, D. L. and Crawford.: Organophosphorus Compounds: The Past and Future. Clin Toxicol, 5, (1972): 223-230.

3. Wills, J. H: Toxicity of Anticholinesterases and Its Treatment. In Anticholinesterases. International Encyclopedia of Pharmacology and Therapeutics. Vol. I Edited by A. G. Karczmar. Pargamon Press, NY (1970): 357-437.

THE FOLLOWING PAGE WAS BOUND WITHOUT A PAGE NUMBER.

THIS IS AS RECEIVED FROM CUSTOMER.

INFLUENCE OF DIETARY PROTEIN ON THE EFFECT OF COUMAPHOS AND TRIFLUPROMAZINE INTERACTION IN SHEEP

T. Gopal, BVSc, MVSc; Frederick W. Oehme, DVM, PhD;
Vt. St. Omer, DVM, MSc, PhD

SUMMARY

Coumaphos[a] (C), 8 or 17 mg/kg body weight orally, and Triflupromazine HCl[b] (TFP), 1.1 mg/kg body weight IM, or

---

From the Comparative Toxicology Laboratory, Department of Surgery and Medicine and Department of Physiological Sciences, Kansas State University, Manhattan, Kansas 66506. Dr. St. Omer's present address is Department of Veterinary Anatomy-Physiology, College of Veterinary Medicine, University of Missouri, Columbia, MO 65201.

Supported by a grant from the Dean's Office Research Committee, College of Veterinary Medicine, Kansas State University.

The authors acknowledge the generous supply of BAYMIX provided through the courtesy of Dr. James A. Shmidl, Chemagro, the assistance of Mr. Marc Rachofsky and Mr. Steve Galitzer in the conduct of this study, and the statistical expertise of Drs. A. D. Dayton, K. E. Kemp and M. A. Quadeer, Department of Statistics, Kansas State University.

Reprint requests should be sent to Dr. Oehme.

---

[a] BAYMIX, Chemagro Division of Baychem Corporation, Kansas City, MO

[b] VETAME, Squibb, E. R. Squibb and Sons, New York, NY

physiological saline, were given to 8 groups of 5 sheep on low or normal protein ration. Onset of clinical signs mortality rate, mean survival time, necropsy lesions, plasma and erythrocyte cholinesterase (ChE) activity was monitored for each group. Observations suggested potentiation effect between the administered compounds. Inhibition of ChE activity was enhanced in groups receiving both drugs. Low dietary proteins adversely affected the development of clinical signs, the mortality rate, the mean survival of time and ChE activity. Recovery of ChE activity of TFP -treated animals was faster than in their respective controls, and animals on normal protein diet had faster ChE recovery than those fed the low protein diet. Inhibition of erythrocyte ChE found to be a better index of organophosphorus toxicity than plasma ChE.

Drug interaction from the concomitant use of different drugs has been of increasing interest during the past two decades. The result of such interaction may appear as additive response, suppression of desired therapeutic action, or unexpected potentiation that adversely affect the patient.[15] The interaction of organophosphorus compounds (OPC) with phenothiazine derivatives (PHE) has clinical and pharmacological importance.[12,14,19,21,31]

The inhibition of cholinesterase (ChE) activity with OPC has been observed in vitro and in vivo studies;[11,17,25,28] PHE are also reported to inhibit ChE activity.[7] Although PHE have been effectively used to treat OPC toxicities,[9,36] aggravation of OPC toxicity has resulted from the concomitant use of PHE in humans.[3] This effect was confirmed in rats, where concurrent administration of OPC and PHE resulted in higher mortality than when each compound given alone,[14] and also by in vitro study that demonstrated significant inhibition of ChE activity.[7,12] In contrast, potentiation was not observed when therapeutic doses of both compounds were tested in healthy calves.[31]

The clinical practice of concurrently using potentiating drugs may give rise to unforseen toxicity, and the combined use of OPC and PHE has produced potentiation and toxic effects in man and rats.[3,14] The subjection of OPC treated animals to stress may be associated with unpredictable toxic episodes.[6,8,18,24,30,32] Emaciation due to heavy parasitic infestation increases susceptibility to OPC toxicity.[6] This is not unexpected since ChE is a protein and in rats a dietary deficiency of protein causes emaciation and reduced ChE synthesis by the liver.[24] The present investigation was undertaken to evaluate the interaction of coumaphos (C), an organophosphorus insecticide and triflupromazine HCl (TFP), a phenothiazine tranquilizing agent, in sheep on low and normal protein ration.

MATERIALS AND METHODS

Animals - Forty 2-3 month-old clinically healthy female lambs of white suffolk and southdown breeding (mean body weight 28.7 ± 4.1 kg) were adjusted to a specially formulated low (7%) protein ration for 14 days. On the 15th day the lambs were individually weighed, and they were randomly divided into two groups of equal numbers. One group (low protein) was maintained on the 7% protein diet and the other groups (normal protein) was gradually switched to a 12% protein diet. Both groups were maintained on their respective diets throughout the period of experimentation. At the end of 28 additional days, each group was randomly subdivided into four groups of five lambs each and housed in individual pens. (One lamb in group V died before the treatment due to causes unrelated to the study.) Respective feeds and water were provided ad lib.

Experimental Procedure - The groups were treated as outlined in Table 1. Dosages of C and TFP were adjusted to current body weights. C was administered by balling gun as a single dose in a gelatin capsule. TFP or an equal volume of sterile physiological saline was administered IM in the gluteal muscle; a second injection of TFP or saline was repeated 24 hours later. The lambs were kept under constant observation for ten days, and they were examined daily for the remaining 15 weeks of the experiment.

Collection of Samples - Pretreatment CHE values of plasma (ChEP) and erythrocytes (ChER) were determined at weekly

intervals and on the day of treatment. Post-treatment determinations were conducted on samples collected at the same hour at 24 hour intervals for the first 10 days and at weekly intervals during the remaining 15 weeks.

Heparinized tubes[c] were used to collect 5 ml blood by jugular venipuncture. The samples were centrifuged immediately, and plasma and erythrocytes were separated. ChEP and ChER activity were determined by Michel's electrometric method[23] using different molar concentrations of acetylcholine iodide[d] substrate in separate phosphate buffer systems for the respective assays. The reaction was allowed to proceed for one hour at 24 C. Change in pH (ΔpH) was determined at the end of one hour with an expanded scale pH meter.[e] Values were recorded as percent of mean pretreatment ChEP and ChER activity.

Clinical Studies - The time of onset of clinical signs, and the nature of signs observed and the time of death was recorded for each lamb. Dead lambs were subjected to complete postmortem examination.

Statistical Evaluation - Statistical analysis utilized ChEP and ChER values for the last 15 weeks from the groups receiving the low C (8 mg/kg) treatment. Since the experimental situation was a randomized split-plot design, least square analysis was used for groups I, II, V and VI (low

---

[c] Venoject. Kimble-Terumo Inc., Teledo, OH.

[d] Acetylcholine iodide; M.W. 271.1 Calbiochem, San Diego, CA.

[e] Corning pH meter, Model 10 Corning Scientific Instruments Medfield, MS.

C + TFP or saline). A level of $P \leq 0.05$ was considered significant for the different variables analyzed.

Analysis could not be applied to the data during the first 10 days because of high death losses in groups III, IV, VII and VIII (high C + TFP or saline). On these groups the clinical effects (mean times of toxicity onset, percent mortality, and mean survival times) were subjectively evaluated.

RESULTS

Clinical Signs - The onset of clinical signs varied in relation to the treatment received by each group (Table 2). Signs of toxicity were consistent and characteristic of ChE inhibition. Affected lambs exhibited restlessness, excessive salivation and lacrimation, respiratory distress, and abdominal palpitation. Frequent micturition and straining were noticed at the later stage of toxicity. Muscular twitchings and fasciculations, involving ventral abdomen, flank and lumbar regions, were seen as the clinical signs progressed. Tremors occurred in the hind quarters with over extension of limbs. Affected lambs became progressively weak and recumbent, and remained comatosed until death.

Groups I, II, III, IV (low protein) all showed signs of toxicity (Table 2). Group III (high C + TFP), showed signs of toxicity as early as 2 hours. The longest mean onset time (6 hours) was noticed in group I (low C + saline). The lambs most affected were in group VII (high C + TFP). One

lamb in group V and three in group VI did not show signs of toxicity. Other lambs in these two groups had mild signs which disappeared by the 3rd to 5th day.

Relapse of clinical signs were noticed in groups II and VI during the 5th and 7th day. Transient salivation occurred. Complete recovery was noticed in all affected lambs that survived by the 10th day, with the exception of one lamb in group I. This lamb remained weak and debilitated throughout the period of study. All others were clinically healthy.

Mortality and Survival Times - The mortality rate was directly related to the 15 mg C/kg, all but one lamb given this dose died regardless of the level of protein and TFP administered (Table 2).

In groups receiving low protein, the percent mortality was highest in groups III and IV (high C) (Table 2). Although the first death was noticed in group IV 4.5 hours post-treatment, the mean survival time of that group was 50.9 $\pm$ 14 hours as compared with 40.4 $\pm$ 13.6 hours in group III (Table 2). Only one lamb each from groups I and II died.

Mortality rates different from those seen in low protein groups were noticed in the high protein groups (Table 2). There were no deaths in groups V and VI (low C + TFP saline). In group VII (high C + TFP), the survival time varied from 4 to 36 hours, with a mean of 19.4 $\pm$ 5.2 hours. This is the shortest survival time of any of the groups. Four of the lambs in group VIII (high C + saline) died, but the survivor

remained clinically healthy throughout the study. The survival time in the group varied from 12 to 144 hours, with a mean of 66 ± 24.9 hours.

Necropsy Findings - Necropsy examination was conducted on all lambs dying during the study. Lesions were similar and consistent and were unrelated to various treatments and different dietary protein levels. Congestion and edema of trachea and lungs, with pulmonary emphysema were found. Petechial hemorrhage in the myocardium (Fig 1) were characteristic in all lambs with acute toxicity. Areas of ecchymosis on the omasal mucosa (Fig 2) and occasional abomasal and anterior duodenal congestion were seen. These lesions were noticed in groups II, III, VII and VIII. Liver and kidneys had varying degree of congestion, and occasional congestion of bladder mucosa was also present. One lamb in group II had small ulcerations in the intestinal mucosa. Another lamb in group VII had pleuropneumonia with thoracic adhesions. All lambs died of acute respiratory and myocardial failure.

Cholinesterase Activity During First 10 Days - During the first 10 days the ChE activity was markedly depressed in all lambs regardless of treatment. Only the extent of inhibition and the pattern of recovery varied among the groups in relation to the treatments.

The mean ChEP and ChER in low and normal protein groups are given in Tables 3 and 4 for the first 10 days of study. Although there was variation in the degree of ChEP inhibition

between low and normal protein groups, ChER inhibition did not reach zero activity at any time.

Cholinesterase activity of low protein groups - The ChEP activity in groups I, II, III and IV was inhibited to zero levels in a few lambs (Table 3). Groups III and IV (high C) showed more ChEP inhibition than groups I and II (low C) (Fig 3). The degree of inhibition in groups I and II were similar except for differences in the recovery of enzyme activity. Recovery of ChEP in group I (low C + saline) was first noticed on the 2nd day, whereas in group II (low C + TFP), recovery began on the 3rd day. By the end of 10th day 60% activity was restored in group II and 52% ChEP activity was present in group I. The pattern of ChEP varied in the two high C groups. There was a sudden drop to zero ChEP activity in group III (high C + TFP) resulting in deaths. ChEP inhibition was gradual in group IV (high C + saline) and continued until the 4th day when deaths occurred, even though ChEP activity was zero on the 3rd day.

The ChER activity in groups I, II, III and IV varied. Groups III (high C + TFP) and IV (high C + saline) had gradual inhibition to levels approximately 5% of the pretreatment ChER activity; deaths occurred on the 3rd day in group III. There was initial recovery of ChER in group IV on the 4th day, but all lambs died by the next day (Fig 4). In groups I (low C + saline) and II (low C + TFP) a similar pattern was noticed in ChER inhibition, but the degree of inhibition noted in groups III and IV was absent. Recovery to 35-40%

of pretreatment levels was noticed by the 4th day (Fig 4).

Cholinesterase Activity of normal protein groups - The ChEP activity in groups V, VI, VII and VIII never decreased to zero level, but stayed between 4-15% (Fig 5). The most severe effect was in VIII, although deaths occurred in group VII (high C + TFP), where mean ChEP activity was 6% on the first day at which time deaths occurred. The degree of ChEP inhibition was more in group V (low C + saline) than in group VI (low C + TFP); however, there was no difference between the two groups at the end of 10 days.

The degree of ChER inhibition in groups V, VI, VII and VIII was relatively less than in the low protein groups. ChER activity dropped to between 30-35% in groups V and VI (low C), but recovery occurred from the 2nd day. Group VI (low C + TFP) reached a maximum recovery by the 6th day. Groups VII and VIII (high C) had ChER activity that was less than 20% of pretreatment levels; at that time all lambs in group VII (high C + TFP) died. The one survivor in group VIII (high C + saline) had a slow ChER recovery (Fig 6).

Cholinesterase Activity During the Last 15 Weeks - Mean ChE activities for the surviving lambs in groups I, II, V and VI (low C + TFP or saline) are given in Tables 5 and 6. The recovery of the ChE activity in these groups is presented in Fig 7. There was a significant variation in all the four groups when ChER values were compared (Fig 7). Groups II and VI (low C + TFP) had a faster ($0.01>P>0.009$) ChER recovery than group I and V (low C + saline). The shortest time was

in group VI (normal protein, C + TFP); ChER returned to pretreatment levels in 22 days compared to 27 days in group II (low protein, C + TFP). A similar response was noticed in group V (normal protein, C + saline); 36 days were required compared to 64 days for group I (low protein, C + saline) (Fig 7).

No significant statistical difference in ChEP activity between groups was found in relation to protein levels and TFP or saline treatment.

Low protein groups - ChE response varied in relation to the administration of TFP or saline, and a wide variation was also noticed in ChE in individual subjects from week to week (Table 5). Although recovery occurred earlier in group II (C + TFP) than in group I (C + saline), there was no consistency in the response of ChEP as compared to ChER (Table 5).

The recovery of ChEP and ChER was more rapid in group II (C + TFP) than in group I (C + saline). Levels above pretreatment were reached by the 3rd week in group II, but required 4 weeks in group I. A marked difference between the ChER of groups I and II was seen at the end of 15 weeks. ChER levels at the end of study were as high as 140% of pretreatment in group II, but approximately 100% of pretreatment levels in group I (Table 5). In some instances, particularly in group II (C + TFP), lambs had ChEP levels as high as 340% above pretreatment values (Table 5). Such an elevation was also seen in lambs of normal protein group. Elevations of ChER activities much above pretreatment levels were noticed in both protein groups (Table 6).

Normal protein groups - ChEP in group V (C + saline) had levels lower than pretreatment, although it reached that level during the 7th and 9th week (Table 6). Groups VI (C + TFP) had a ChEP response that remained at levels above pretreatment from 4th to 15th week. ChER activity remained same in both groups except that group VI (C + TFP) returned to pretreatment levels on the 1st week, while group V (C + saline) required 3-4 weeks. The activity of ChER remained above pretreatment levels in both groups. The highest individual ChEP level reached was 261% in group VI (C + TFP) (Table 6).

DISCUSSION

Organophosphorus compounds (OPC) form phosphorylated complexes with ChE, which are not easily hydrolyzed.[11] Toxicity depends on the degree of ChE inhibition and death occurs as a result of acute respiratory failure.[17,28] Lambs dosed with C regardless of dosage, showed clinical muscarinic and nicotinic signs characteristic of OPC toxicity and 55% of them died due to ChE inhibition.

OPC usage has resulted in unpredictable adverse effects[6] indicating potentiation, when administered at recommended doses.[25] The chemical nature of OPC,[24] its bioavailability and biotransformation, lethal synthesis or detoxification[10,21,24] are important in the determination of potentiation. The extent of detoxification in the animal exposed to OPC[13,32] can be adversely modified by physiological stressors; such

as emaciation,[18,30] and malnutrition, (e.g., inadequate dietary proteins).[8]

The inhibition of ChE by PHE is reversible.[7,12] The combined use of C and TFP is beneficial due to its synergetic effect on internal parasites.[19,21] In the present study, OPC toxicity was produced with recommended doses of C. The degree of ChEP and ChER inhibition seen in low (7%) and normal (12%) protein level groups had significant variation.

Low protein level appear a contributing factor in causing the toxic effects produced in this study. The shortest time of onset of signs (3.2 hours) in low protein groups was in group III (high C + TFP), suggesting that potentiation between C and TFP occurred. The mean onset of clinical signs in group IV (high C + saline) was 5.2 hours, indicating the absence of TFP caused delay in onset of signs. A 1.2 hour difference in onset of signs between groups I and II (low C + TFP or saline) may be explained in the same way.

Although 100% mortality occurred in both groups III and IV (high C + TFP or saline), the difference in mean survival times is clinically evident (Table 2). Only one animal in each groups I and II died. There is no definite explanation as to why the group II (low C + TFP) lamb survived 84 hours while the group I (low C + saline) animal lived only 36 hours. TFP may stabilize the liver lysosomes[16] and thereby reduce the availability of esterases that normally detoxify the metabolite of C.[7]

The longer mean times required for development of clinical signs in the normal protein groups (Table 2) suggests that this dietary protein level reduced the severity of C toxicity.[8] Whereas animals receiving low protein diets and low C showed clinical signs. One lamb in group V (low C + saline) and three in group VI (low C + TFP), all on normal protein, did not develop any signs of toxicity. Those that did develop signs of toxicity had them after 6 hours following treatment (groups I and VI). None of the lambs from these two groups died during the study (Table 2).

In the animals receiving normal protein diets, those receiving high dosages of C developed clinical signs first and those also receiving TFP (group VII) had the shortest survival time of all (19.4 hours). Healthy animals maintained on adequate protein diet should have well developed detoxification enzyme systems.[8] However, biotransformation of C results in the formation of an oxidative metabolite, coroxon, by replacing P=S with P=0.[20,27] Coroxon is a more potent inhibitor of ChE than its parent compound. The presence of adequate enzymatic proteins to catalyse this reaction contributes to the severity of toxicity. Further, the presence of TFP, another ChE inhibitor, likely produced a potentiation[3,34] which resulted in the high mortality rate, short survival time in group VII.

The toxicity exhibited by C and C + TFP interaction suggests a distinct hazard if one of the other more toxic OPC were used in place of C. In those instances, judgement as to

dosage, the sensitive state of nutrition, and the potential effect of OPC-PHE synergism becomes of clinical importance.

The longer survival time of group VII (66 hours) and the presence of one surviver in this group suggests that normal protein levels result in decreased toxicity when potentiating substances are not present.

The inhibition of ChE appears a primary factor of C toxicity. Significant ChE inhibition was characteristic of all experimental groups, regardless of dietary protein levels and use of TFP or saline (Tables 3, 4; Fig 3, 4, 5, 6). The degree of inhibition was a noticable difference between various treatments. A similar group difference in ChEP and ChER inhibition was also apparent. There was lack of correlation between ChEP and ChER depression and mortality rates. Individual lambs in groups I, II, VI and VIII had 0% ChEP activity. These lambs completely recovered at the end of 10 days, and pretreatment levels of ChEP and ChER were reached by the 3rd and 4th week. ChER inhibition among survivors in groups V and VI never dropped below 30-35% of pretreatment levels. The more prominent drop in ChEP activity, often to 9% of pretreatment levels and then recovery, is in contrast to the less severe depression of ChER. This was a consistent trend and supports the observations of others[2,3,4,35] that ChER more closely reflects the physiological level of ChE than does ChEP.

Deaths occurred in low protein groups when ChEP activity was near 0% and ChER was 5%. In normal protein groups this inhibition resulted in 5% of ChEP and 20% ChER activity. This

discrepancy indicates lack of correlation between percent of ChE inhibition and mortality. Although complete inhibition of ChEP occurred in individual animals of groups I, II, V and VI (low C + TFP or saline), recovery took place without any fatalities. On the other hand, ChER activity below 5% of pretreatment levels appeared invariably fatal; this is in agreement with other workers.[11,28]

Since ChE, particularly ChER, has a definite physiologic role in OPC toxicities, its recovery becomes important from the clinical and therapeutic point of view. ChER recovery to pretreatment levels probably occurred by reactivation of the phosphorylated enzyme, new enzyme synthesis or both.[5,11,35] Recently phosphorylated ChE may undergo spontaneous hydrolysis,[11] which can be further inhibited by additional OPC or its metabolites. Aging causes stabilization of the phosphorylated enzyme making it more resistant to enzymatic degradation.[24,36] Spontaneous hydrolysis occurs most frequently soon after ChE phosphorylation, but as aging progresses, spontaneous recovery becomes slower and enzymatic degradation takes preference.[5,35] This is a constant feature with dialkyl OPC toxicity.[2]

Evaluation of ChE response during the first 10 days of the present study did not reveal specific differences in recovery between the low and normal protein groups. The ChEP response had only a slight variation at the end of the 10th day.

The additional ChEP inhibition on day 2 in the groups receiving C + TFP probably resulted from the second TFP