SUBCHRONIC NINETY DAYS DELAYED NEUROTOXICITY OF TRIO ORTHO CRESYLPHOSPHATE (TOCP) OF SPINAL CORD IN ADULT HEN BY ORAL GAVAGE

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ABSTRACT
The subchronic daily dosage for 90 days study of delayed neurotoxicity of triorthocresyl phosphate (TOCP) in adult hens by oral gavage using corn oil as vehicle at three dosage levels. The present topic showed evidence of recovery of peripheral neuropathy of the sciatic nerve, which was so prominent in case of acute single dose of neurotoxicity of TOCP and while the peripheral neuropathy of the sciatic nerve was reduced there was progressive increase in severity of the central nervous system neuropathy of the spinal cord with increase in incidence and number of degenerate vacuolated nerve fibers associated with clumps of degenerate myelin in contrast to the lesion of the acute single dose of delayed neurotoxicity in which the severity of the central neuropathy in spinal cord was quite less than the peripheral neuropathy of sciatic nerve. In conclusion the subchronic of 90 days delayed neurotoxicity of daily doses at three dosage levels showed progression of the central neuropathy of the spinal cord in contrast to the reduction of the peripheral neuropathy of the sciatic nerve.

KEYWORDS: Triorthocresyl Phosphate, Sub Chronic, Spinal Cord and Hen.

INTRODUCTION
The present research was 90 days sub chronic delayed neurotoxicity in adult hen. the review describes a group of organophosphorus compounds with delayed neurotoxic properties [1]. Delayed neurotoxicity is a delayed onset of prolonged loco motor ataxia resulting from a single or repeated exposure to an organophosphorus compound [2, 3]. For many years, this effect was wrongly termed "demyelization" or "demyelinating disease" because of the early misinterpretation of pathological lesions as reflecting demyelination instead of being primary axonal degeneration followed by demyelination [4]. Since 1978, this effect has been termed organophosphorus ester-induced delayed neurotoxicity or OPIDN [5]. OPIDN was first recognized at the end of the nineteenth century in humans poisoned with TOCP [6, 7]. Since then an estimated 40,000 cases of
delayed neurotoxicity in humans have been documented. In the 1920s about 20,000 persons in the United States developed "Ginger-Jake" paralysis after the consumption of an extract of ginger called "Jamaica Ginger" that had been adulterated with TOCP [8-16]. Later this syndrome was recognized in Europe, South Africa, and India as a result of the deliberate or accidental use of TOCP-containing preparations [17-29]. In 1951 three persons were poisoned with a then newly developed insecticide, mipafox, and developed symptoms of delayed neurotoxicity [30]. Between 1974 and 1975 the experimental insecticide leptophos was implicated in the poisoning and paralysis of some workers in the Texas factory where it was manufactured and packaged [31, 32]. Symptoms associated with TOCP[33-37] and mipafox[30, 38] poisoning in human subjects are well documented. The clinical conditions of persons in the leptophos incident were diagnosed as multiple sclerosis, encephalitis, or psychiatric disorder [30,32,39].

MATERIALS AND METHODS

Birds
Adult hens were used as the experimental animals in the present research project.

Treatment
To study the delayed sub chronic neurotoxicity effect of triorthocresylphosphate (TOCP) on adult hen a total of eighty adult hens were randomly allocated. The birds equally divided into four groups: A, B, C and D(20 birds in each group). They were treated with triorthocresylphosphate (TOCP) for 90 day. Birds of the group A, B, and C were dosed orally(by oral gavage) given daily doses of of 1.75mg/l, 2.5mgand 5mg of TOCP in corn oil, as low, intermediate and high dose, respectively, whereas group D was acted as untreated control dosed with 1ml corn oil, daily for 90 days. All the birds were supplied with food with water add Libitum. The birds were killed after 90 day by cervical dislocation and the organ spinal cord was remove and fixed in 10% neutral buffered formalin. section of spinal cord were taken on different levels such as cervical, thoracic ,lumber region and sacral regions, those were stained by haematoxylin and eosin, and were photographed at different level and at different powers.

Examination
Samples for histopathological examination were taken from spinal cord, those were cut in pieces of 2 to 3 cubic centimeters, samples were fixed in 10% phosphate buffered formalin and left in fixative for several days, the materials were embedded in paraffin, then paraffin
blocks were made and cut by microtome as 5-7 microtones passing through different concentration of alcohol for dehydration and then rehydration to remove the paraffin then sections were stained by haematoxylin and eosin. Stained sections were examined with light microscope on different powere for histopathological changes(40).

RESULTS

Light microscopy of spinal cord from treated adult hens of sub chronic 90 day delayed neurotoxicity showed mark vaculation of nerve fibers with presence of clumps of degenerate myelin as in (fig1), while in another figures there were varying degree of vaculating nerve fibers with presence of clumps of degenerate myelin, one of them is quite mark(fig2). Same changes were present at low magnification in (fig3). Furthermore some birds also showed varying degrees of vacuolation of nerve fibers, some of them with clumps of degenerate myelin (fig4). In addition in (fig5) numerous number of vacculated degenerate nerve fibers, some of them associated with clumps of degenerate myelin. In another section, fields of nerve fibers with vacuolation and degeneration, note large vacules in the center, clump of dark stained degenerate myelin(fig6). On some condition some sections of spinal cord where varying degrees of degenerate vacuolated nerve fibers, some with clumps of degenerate myelin(fig7).

Fig(1): spinal cord, longitudinal section note mark vacuolation of nerve fibers with presence of clumps of degenerate myelin.(arrows) (40X, H&E stain).
Fig(2): spinal cord, varying degree of vacuulating nerve fibers with presence of clumps of degenerate myelin, one of them is quite mark. (arrows) (40X, H&E stain).

Fig(3): spinal cord, varying degree of vacuulating nerve fibers with presence of clumps of degenerate myelin, one of them is quite mark. (arrows) (20X, H&E stain).

Fig(4): spinal cord, transverse section, ventral region notevarying degrees of vacuolation of nerve fibers, some of them with clumps of degenerate myelin. (arrows) (20X, H&E stain).
Fig(5): spinal cord, numerous number of vacuolated degenerate nerve fibers, some of them associated with clumps of degenerate myelin. (arrows) (20X, H&E stain).

Fig(6): spinal cord, high magnification of vacuolated degenerate nerve fibers, note large vacuole in the center, clump of dark stained degenerate myelin. (arrow) (40X, H&E stain).

Fig(7): spinal cord, varying degrees of degenerate, vacuolated nerve fibers, some with clumps of degenerate myelin. (arrow) (40X, H&E stain).
DISCUSSION
The present topic of 90 days delayed neurotoxicity of TOCP showed recovery of the changes in the peripheral nervous system especially the sciatic nerve characterized by reduction in number of degenerate vacuolated nerve fiber with clumps of degenerate myelin. It appeared that the neurotoxicity changes ascending to the spinal cord as the treated birds showed increase number of degenerate vacuolated nerve fibres in spinal cord (cervical, thoracic, lumber and sacral regions). The neurotoxicity of TOCP (tri-ortho-cresyl-phosphate), with sub chronic ninety days neurotoxicity, while in single oral dose of 500 mg/kg with corn oil in adult hen, the numbers of degenerate, vacuolated nerve fibres were far less. The age related and species related effects of TOCP neurotoxicity was discussed by [1] and this applied on the present study as it was found that adult hen the best model for delayed organophosphorus neurotoxicity, even with development of the lesions affecting long tract myelinated nerve fibers. In addition [41] discussed mechanisms of organophosphorus stressing the fact that TOCP and some other organophosphorus induced delayed neurotoxicity with clinical signs and light microscopic lesions in spinal cord. Delayed neurotoxicity by TOCP and some other organophosphorus compounds were in references [1-5]. The lesions reported were in agreement with the light microscopic findings in spinal cord also agreed with clinical findings too, [1] review the neurotoxicity of organophosphorus and reported OPIDN due to TOCP and that agreed with our findings in spinal cord of adult hen, including the clinical signs, but one thing that the lesions in sciatic nerve in acute delayed neurotoxicity more severe than those of spinal cord, some of which only recede in chronic neurotoxicity of peripheral nerve will be less and that of spinal cord will progress and that will be in OPIDN. [6-39], the history of organophosphorus with clinical signs and pathological neural lesions were in agreement with what we found clinically and on base of light microscopy of spinal cord. In spinal cord in ninety day neurotoxicity study, the changes of spinal cord were more prominent than the sciatic nerve, and that means the changes of the sciatic nerve were reduced in ninety day but increased in spinal cord.

Research highlights
The present topic studied the delayed neurotoxicity of TOCP in 90 days oral intubation of adult hen to be used as a guide for neurotoxicity of other neurotoxic compounds such as insecticides in long term exposure.
Finding and policy aspects
The findings and policy aspects of TOCP neurotoxicity will act as positive control to study long exposure for any other compounds with neurotoxic effects.

Justification of research
The presence of so many insecticides and other chemicals with the possibility of an effects on the nervous system in general, therefore there will be need for a positive control on neurotoxicity and TOCP in the best.

Conclusion
From the 90 days delayed neurotoxicity of TOCP in adult hen proved to be the best model for neurotoxicity of different insecticides and other chemicals in human and animals.

Recommendation
The above neurotoxicity research showed that TOCP is recommended as the best model for comparative neurotoxicity study and as positive control.

REFERENCES

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