J. UOEH, 10 (4): 433–442 (1988)

[Review]

Triorthocresyl Phosphate Poisoning
— A Review of Human Cases —

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Abstract: Since the end of the nineteenth century, numerous cases of triorthocresyl phosphate (TOCP) poisoning due to accidental contamination of drink, food or drugs have been reported. Following the ingestion of preparations contaminated by TOCP, gastrointestinal symptoms may occur and after an interval of ten to twenty days, a well-known delayed neurotoxicity gradually develops. In general, the initial symptoms are pain and paresthesia in the lower extremities. In most cases, muscle weakness progresses rapidly developing into a striking paralysis of the lower extremities with or without an involvement of the upper extremities. Severe cases show pyramidal signs. The histopathological findings show axonal degeneration in the peripheral nerves and degenerative changes in the anterior horn cells. Degenerative change also occurs in the lateral and dorsal tracts of the spinal cord. The cardinal therapy is physical rehabilitation.

Key words: triorthocresyl phoshate, TOCP, polyneuropathy, delayed neurotoxicity.

(Received 5 August 1988)

Introduction

It is well-known that certain organophosphorus compounds give rise to the outstanding delayed neurotoxicity in man. Triorthocresyl phosphate (TOCP) was the first compound which was noticed to possess the potent delayed neurotoxicity at the end of the nineteenth century and has received great attention for some time. The occurrence of widespread epidemics of TOCP poisoning has encouraged numerous studies on the clinical effects and histological changes induced in the nervous system in man by this chemical (Prineas, 1969). The biochemical actions of TOCP have been studied extensively in animal experiments (Cashida *et al.*, 1963; Eto *et al.*, 1962; Johnson, 1972; Bischoff, 1977). Nevertheless, the clinical profiles in human poisoning are not widely appreciated and are not fully documented. In this paper, we will survey extensively human cases, concentrating on the incidence and clinical features of TOCP poisoning.

Historical Background

TOCP poisoning has occurred throughout the world. Table 1 lists the major outbreaks.

Table. 1. Major outbreaks of TOCP poisoning

Years	Place	No. of cases	Vehicles of TOCP	Reference
1898	France	6	Phospho-creosote	Lorot (1899)
1900−1928	Europe	43	Phospho-creosote	Roger & Recordier (1934)
1930−1931	U. S. A.	50,000	Ginger extract	Morgan (1982)
1931	Europe	Several hundred	Apiol pill	Susser & Stein (1957)
1938	South Africa	68	Cooking oil	Sampson (1942)
1940	Switzerland	80	Cooking oil	Walthard (1945)
1941−1945	Germany	More than 200	Cooking oil	Mertens (1948)
1945	England	17	Cooking oil	Hotston (1946)
1955	South Africa	11	Water or solvent	Susser & Stein (1957)
1956	Japan	6	Cooking oil	Kaneko *et al.*, (1958)
1957	Morocco	About 10,000	Cooking oil	Smith & Spalding (1959)
1960	India	58	Solid food	Vore *et al.*, (1962)
1962	India	More than 400	Flour	Chaudhuri (1965)
1967	Fiji	56	Flour	Sorokin (1969)
1980	Romania	12	Liquor	Vasilescu & Florescu (1980)
1981	Sri Lanka	More than 20	Cooking oil	Senanayake & Jeyaratnam (1981)

In 1899, Lorot initially reported six cases of polyneuropathy out of 41 cases of pulmonary tuberculosis treated with phospho-creosote. Later it was proved to contain 15 per cent TOCP. In the next 30 years, 43 additional cases caused by the drug were reported in various parts of continental Europe (Roger & Recordier, 1934).

In the spring of 1930, there appeared suddenly, in the midwestern and south-western states of the United States of America, the most dramatic outbreak of paralysis characterized by bilateral foot- and wrist-drop (Burley, 1930; Merritt & Moor, 1930). Ultimately 50,000 people developed the paralysis by a popular substitute for alcohol called "ginger jake" (Morgan, 1982). By July, 1930, Smith *et al.* proved that the adulterated beverage contained about two per cent of TOCP and that this was a causative substance of the paralysis.

In 1931, several hundred women in Europe (especially, Germany, Netherlands, Yugoslavia and France) were poisoned by TOCP contained in the Apiol pill and taken as an abortifacient (Roger & Recordier, 1934; Susser & Stein, 1957). The TOCP was presumably included as an additional stimulus to abortion (ter Braak & Carrillo, 1932). The next report came from Durban in South Africa in 1938. Sixty-eight people were affected by salad oil contaminated with TOCP (Sampson, 1942). Walthard (1945) described an outbreak in 1940 when 80 men of the Swiss army were poisoned. There food was erroneously prepared in cooking oil contaminated with TOCP in machine gun oil. A small incident of TOCP intoxication was reported in 1945 in Liverpool. Seventeen people were affected by using TOCP-contaminated cotton seed oil for cooking (Hotston, 1946). In Germany during the Second World War, more than two hundred people were intoxi-

cated by consuming TOCP-contaminated cooking oil (Mertens, 1948).

During ten years after the war, numerous epidemics of the acute polyneuropathy due to cooking oil occurred in Japan (Kaneko, 1956). In these cases, TOCP poisoning has been suspected. The first epidemic in which TOCP could be identified, was reported by Kaneko *et al.* (1958). Six members of a family were affected by contaminated cooking oil. The second outbreak in Durban in 1955 was described by Susser and Stein (1957), in which 11 people were involved. From a epidemiological survey it was suggested that water as well as solvents might be a vehicle for TOCP.

In 1959, a great outbreak of the poisoning occurred in Morocco. About 10,000 Moroccans were intoxicated by TOCP, due to jet engine oil being illegally mixed into their cooking oil (Smith & Spalding, 1959; Svennilson, 1960). In 1960, incidental poisoning by TOCP-contamination in solid food also occurred in Bombay, India, where 58 victims were recorded (Vora *et al.*, 1962). During the period from April to June, 1962, more than 400 cases of paralysis occurred in the Malda district in India. The cause of this disease was proved to be due to consumption of flour contaminated with tricresyl phosphate (Chaudhuri, 1965). In 1967, a similar poisoning was recorded in Fiji, where 56 people showed neuropathy (Sorokin, 1969). The cause was stated to be contamination of dry sharps flour by TOCP in the sacking material. In 1980, Vasilescu and Florescu in Romania reported 12 patients with toxic neuropathy following accidental ingestion of liquor polluted by TOCP. In 1981, Senanayake and Jeyaratnam reported that an outbreak of acute polyneuropathy affected over 20 young females in Sri Lanka during 1977－78. The cause of the neuropathy was traced to tri-cresyl phosphate which was found to be a contaminant in a special cooking oil (gingili oil). Contamination probably occurred during the transportation of the oil in containers previously used for storing mineral oils.

On the other hand, occupational poisoning due to exposure to TOCP has been considered to be quite rare, because of the low volatility of TOCP and the low vapor pressure at ordinary temperature. However, TOCP may be a hazard when it is heated to boiling point. Skin penetration and inhalation are thought to be the main causes of occupational poisoning. In 1943, Gärtner and Elsaesser reported a case who developed pyramidal signs after exposure to TOCP for two years in a German chemical plant. In 1944, Hunter *et al.* reported three cases with toxic polyneuropathy due to working for six to eight months in the manufacture of tricresyl phosphate in England. Thereafter, Parnitzke (1946) reported a typical case of TOCP poisoning after 3－years exposure in a German plant.

Clinical Features

TOCP may enter the body by ingestion, vapour inhalation or absorption through the skin and mucous membranes.

Most of the cases of TOCP poisoning have occurred by ingestion and in outbreaks,

large or small, due to contamination of drink, food or drugs (Roger & Recordier, 1934; Cavanagh, 1964).

The severity of signs and symptoms varies depending on the quantity absorbed, but they do not always appear to be proportional to the dosage. It has also been suggested that individual susceptibility varies greatly. According to Staehelin (1941), the toxic symptoms can be produced by only 0.15 g of TOCP. A severe neurological disturbance developed due to doses of 0.5 to 0.7 g in a Swiss outbreak.

In general, the signs and symptoms of TOCP poisoning are distinctive, while the symptomatology varies somewhat according to whether a single relatively large dose or small cumulative doses are taken. In the case of the former, the initial symptoms were gastrointestinal of varying degrees, ranging from slight to severe nausea and vomiting, sometimes, accompanied by abdominal pain and diarrhea. Among these symptoms, vomiting is most frequently observed (Staehelin, 1941). These symptoms are usually transient, lasting from a few hours to a few days (Walthard, 1945; Susser & Stein, 1957). The gastrointestinal symptoms are by no means invariable.

In the case of chronic low level exposures, these symptoms may not be present and the major symptoms are neurological (Parnitzke, 1946).

In acute poisoning, there follows a latent period from ten to twenty days, the duration of which is probably dependent on the dose and the period of time over which TOCP was absorbed. In chronic poisoning, the latent period is sometimes very prolonged (Levèque, 1983).

Thereafter, a well-known "delayed neurotoxicity" gradually appears. The initial neurological symptoms are sharp, cramp-like pains in the calves, and some numbness and tingling in the feet and sometimes the hands. Within a few hours or a day or two at most these pains are followed by increasing weakness of the lower limbs, and soon the patient becomes unsteady and then unable to keep his balance. The cramp-like pains may cease with the onset of weakness or persist for some days. One or two weeks after the onset in the lower limbs and while paralysis may still be progressing, weakness spreads in the hands. While some patients show complete wrist drop and total loss of power in the hands, sometimes with weakness up to the elbows, the predominant neurological abnormalities are observed in the lower limbs. Bilateral foot drop with complete loss of power from the ankle down is a common finding. Depending on the severity of the affection, the patient may have weakness at the knees, less at the hips, and, only in the most severe cases, weakness of the trunk. About three weeks or more after the onset of paralysis, a most striking and rapid wasting may be observed. While the small muscles of the feet, calves, the anterior tibials, and the thighs do not escape, the change is most obvious in the small muscles.

In the initial stage, the ankle jerks are absent and knee reflexes may be normal or occasionally depressed. Plantar reflexes are unobtainable. The mild cases do not show any upper motor neuron signs at all. On the other hand, in the severer cases, even at the ear-

ly stage, knee jerks may be exaggerated, presaging the development of upper motor neuron involvement. In general, upper motor neuron signs, e. g. pyramidal signs gradually become evident about the third week or a little later. The knee reflexes now become exaggerated and so also may the biceps, triceps and supinator jerks. A finger flexor reflex may appear for the first time (Susser & Stein, 1957). As the pyramidal tract lesion becomes evident, involuntary flexor withdrawal of all the limbs follows gentle plantar stimulation. Babinski responses are observed much later. Muscle tonus of the limbs gradually increase and spasticity appears in the lower limbs. In severe cases, the signs of upper motor neuron involvement are delayed, probably masked by the gross flaccid muscle weakness.

Several authors state emphatically that the sensory disturbances do not occur. Sampson (1942) reported sensory disturbances although these were admittedly unobtrusive in contrast with motor dysfunction. Reports of muscle tenderness and peripheral nerve tenderness are fairly frequent. If the sensory disturbances are observed, there will be hypesthesia with loss of pin-prick and temperature sense; vibration sense was sometimes affected distally. The sensory disturbances vary in extent from merely the sole of the feet to the whole limb.

Usually cranial nerve involvements do not occur. In general, mental signs are rare. But, transient euphoria and confusion have been observed in the early stage of the poisoning (Schwab, 1948).

Prognosis

The muscle weakness progresses over several weeks, sometimes even months, before it becomes stationary. Sensory changes often begin to regress in the early weeks and then muscle strength gradually returns in patients who are only mildly affected. The milder the case, the sooner sensory disturbances regress. Improvement begins with sensation, then muscle strength in the hands, then an increase of strength in the lower limbs.

In the cases with pyramidal signs, recovery is generally poor. The degree of the pyramidal involvement may determine the ultimate prognosis for functional recovery (Senanayake, 1981). Zeligs (1938), reporting eight years after the United States outbreak, surveyed the records of 316 patients. He was able to follow up 60 patients, all of whom were disabled and still in institutions. Aring (1942) examined more than 100 patients in the 10 years after the same outbreak and these appear to have been still affected. Morgan and Penovich (1978) followed up 11 survivors in the forty-seven years after the same outbreak. The principal findings were the spasticity and abnormal reflexes of an upper motor neuron syndrome.

Of the 80 patients in the Swiss army accident, 14 were quite well after five years, 15 were totally incapacitated, and 38 showed spasticity (Walthard, 1945).

Regarding the Durban outbreak, after 18 years, all patients still showed some effects of

the disease (Susser & Stein, 1957). The mildest case suffered from a slight weakness at the ankles, while the most severely affected had foot drop, muscle atrophy and pyramidal signs (spasticity, ankle clonus and positive Babinski sign).

The residual signs and symptoms are mainly confined to the lower limbs. There are weakness and muscle atrophy of varying degrees in the feet and the small muscles of the hands. Disability is principally related to the pyramidal signs with resultant spasticity of the lower extremities.

Laboratory Examinations

Little information has been obtained on the laboratory examinations. There is no significant change in the urine and blood (Sampson, 1942; Senanayake & Jeyaratnam, 1981), but the cerebrospinal fluid may shows an increase of protein with or without pleocytosis (Sampson, 1942; Susser & Stein, 1957). Mertens (1948) also reported frequent increases of the cerebrospinal fluid protein.

Neurophysiological Examinations

There are very few electrophysiological studies on human TOCP poisoning. Svennilson (1960) reported an electromyographic study on 65 patients in the Moroccan outbreak. These cases showed varying degrees of denervation and polyphasic abnormal potentials in the paralytic muscles. The clinically healthy proximal groups of muscles also showed marked polyphasic action potentials, but not denervation.

Vasilescu and Florescu (1980) made more detailed studies on 12 patients in Romania. In their studies, they showed a more than 50% decrease in the muscle evoked potential amplitude. The fibrillation potentials and the decreased motor nerve conduction velocity were observed.

In the other neurophysiological studies by Senanayake (1981) in Sli Lanka, the cardinal findings were widespread neurogenic patterns and prolongation of terminal latencies with a relatively mild slowing of motor nerve conduction velocities. These studies confirmed the evidence of axonal degeneration.

Electrophysilogic evaluation revealed partial denervation of affected muscles, with increased insertional activity, abnormal spontaneous activity (fibrillation potentials and positive sharp waves), and a reduced interference pattern; large polyphasic motor unit potentials may also be found (Lotti *et al.*, 1984). The compound muscle action potentials to supramaximal stimulation of motor nerves are reduced in amplitude, and terminal motor latencies are delayed; maximal motor conduction velocity is usually normal or only slightly reduced.

These findings are in accordance with the results of pathological investigations that show that in TOCP poisoning, peripheral nerves are affected and that the main pathologi-

cal feature is axonal degeneration.

Pathological Investigations

Numerous pathological studies in autopsy or biopsy have been made since the Jamaica ginger accidents in 1930. In 1930, Goldfain described that some changes were observed in the peripheral nerves and spinal cord, quoting Jeter's autopsy report. Histopathological investigations by Goodale and Humphreys (1931) indicated degeneration of myelin sheath and axis cylinders in the radial, sciatic and tibial nerves in all cases examined. Vonderahe (1931) found marked degenerative changes in the anterior horn cells, characterized by swelling, central chromatolysis (disappearance of the Nissl substance), excentric nuclei, and shrinking of the cells. The pathological studies also revealed degenerative changes in the radial and tibial nerves, and in the anterior roots. There were no pathologic signs of inflammation.

According to Smith and Lillie (1931), the paralysis due to Jamaica ginger is essentially a degeneration of the myelin sheaths of the peripheral nerves, with a variable amount of relatively moderate central degenerative changes affecting the anterior horn cells throughout the spinal cord, but more often in the lumber and cervical regions. In the Durban epidemic, Sampson (1942) also reported that the degeneration of the anterior horn cells did appear in some instances and that peripheral nerves showed axonal degeneration. Aring (1942) described posterior column degeneration in later investigations of survivors of the outbreak, and degeneration in the lateral columns, confirming the origin of some of the spinal symptoms. It was noteworthy that the latter changes were evident in the lumbar region, while the dorsal column changes, in which only the fasciculus gracilis was involved, were features of the cervical cord.

Yuasa *et al.* (1970) reported the detailed histopathological findings of a severe case. They found that the main lesions were in the spinal cord, peripheral nerves and muscles. The myelin loss with degeneration in axons was present in the lateral corticospinal tract throughout the cord. This was greater in the middle and lower segments of the cord. The fasciculus gracilis had also degenerated moderately, but not the fasciculus cuneatus. Some nerve cells in the anterior and lateral horn of the cord had degenerated. Anterior root fibers in the lumbar and upper sacral segments had degenerated markedly, but posterior root fibers showed no pathologic change. The tibial nerve revealed a degenerative change and the posterior tibial muscle showed neurogenic atrophy. There was no pathologic change in vessels.

Muscle biopsy studies in Moroccan outbreak showed a moderate degree of muscle atrophy and a slight increase of the muscle fibre nuclei (Svennilson, 1960). Spherical axonal swelling and terminal knobs were noted as a sign of peripheral nerve degeneration in muscles. Similar changes were also obtained by the biopsy studies from the Malda district in India (Chaudhuri *et al.*, 1962).

Treatment

In view of the delayed onset, the neurological symptoms appear long after absorption. Preventive effort is unhelpful. But, vitamin B_1 and B_{12} and corticosteroids may protect nervous tissue against further involvement (Geoffroy *et al.*, 1960). The cardinal therapy is physical rehabilitation, and administration of anti-spastic drugs may be required in spastic patients.

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リン酸トリオルソクレシル中毒
—ヒトにおける中毒例の文献的考察—

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要　旨: リン酸トリオルソクレシル（TOCP）中毒は，19世紀末以来数多く発生してきた．その中毒のほとんどが，TOCPに汚染された飲食物や薬物を気付かずに摂取して集団発生をきたしたものである．TOCP摂取後，まず胃腸症状が出現する．そして10日から20日の潜伏期を経て，遅発性神経毒性として神経症状がみられる．初発症状は下肢の疼痛と異常感覚である．運動障害が主体となり，両下肢や四肢に麻痺が起こる．重症例では錐体路徴候が加わる．病理学的には，末梢神経の軸索変性，脊髄前角細胞，側索や後索に変性がみられる．主な治療法は運動機能回復訓練である．

J. UOEH（産業医大誌），10（4）: 433－442 (1988)