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Muscular Atrophy due to Glue Sniffing*

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Summary. A glue sniffer manifested marked muscular atrophy in the four extremities while sensory functions remained more or less intact. Glue analysis revealed *n*-hexane, toluene, and ethyl acetate as leading solvents. Rat experiments revealed that metabolism of *n*-hexane was not modified by co-administered toluene and *vice versa*, indicating that the atypical symptom in the present case was not due to metabolic modification between *n*-hexane and toluene.

Key words: Glue sniffing — *n*-Hexane — Motor conduction velocity — Muscular atrophy — Toluene.

Introduction

Since the multiple outbreak of *n*-hexane intoxication in 1967 in Japan, attention has been focused on the involvement of the nervous system due to inhalation of an organic solvent. Following studies on the clinical picture of *n*-hexane toxicity, three classification have been made (Yamamura, 1969), *i.e.*, sensory polyneuropathy, sensorimotor polyneuropathy and sensorimotor polyneuropathy with muscular atrophy, indicating that sensory function is predominantly disturbed. From the view point of industrial health and toxicology, we report a case of a patient who sniffed *n*-hexane containing glue and manifested marked muscular atrophy while sensory function remained almost intact. Possible modifica-

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tion of *n*-hexane toxicity by other constituents of the glue was also investigated.

Materials and Methods

Clinical and laboratory examinations were conventional except for those for animal experiments as described below.

Animals. Female Wistar rats (80—130 g) were maintained on commercial laboratory chow and water *ad libitum*.

Blood Analysis. Blood samples, obtained by decapitation of rats, were heparinized, and shaken vigorously with 2 volumes of ethyl acetate in 25 ml glass-stoppered tubes for 10 min. The organic layer, 5 μl, was analyzed gas-liquid chromatographically for *n*-hexane and toluene. The extraction rates of the two solvents into ethyl acetate were over 90%.

Urinalysis. Hippuric acid was measured by a modification (Ikeda *et al.*, 1974) of the method of Ogata *et al.* (1969) with benzenesulfonyl chloride as a colour developing reagent, except that the mixture was allowed to stand at room temperature for 15 min after the addition of benzenesulfonyl chloride.

Gas-liquid Chromatography. The apparatus used was a Shimadzu gas-liquid chromatograph Model GC-IC, equipped with hydrogen flame ionisation detectors and 3 m long stainless steel columns (inner diameter 3 mm) packed with 20% polyethyleneglycol on chromosorb W support (60—80 mesh). The following conditions were selected: N_2 carrier gas flow-rate, 30 ml/min; H_2 gas flow-rate, 70 ml/min; detector temperature, 150°; injection temperature, 150°; column temperature, 90°.

Case Report

The patient was a single 23-year-old Japanese male truckman, with family history negative for psychiatric disorders. Past history was also non-contributory. He began the habit of sniffing glue in October, 1971. This habit, with a daily consumption of one tube containing about 150 g of the glue, continued until the autumn of 1972, when the patient found that the new glue product was not "tasty" while the brand he used to sniff was banned by the governmental regulations and was no longer available. Barbiturates were also occasionally ingested during this period. Early in November, 1972, the patient experienced a sudden onset of numbness in the lower extremities when climbing stairs. He could hardly go down the stairs without hanging on to the bannister. On day 5, he had difficulties in the dorsal flexion at the ankle joints, and could not stand up without the aid of his hands nor could he walk by himself on day 7. A chilly sensation went from the tips of his toes up to middle of his legs and often disturbed his sleep at night. There was no apparent abnormality in the sense of touch or pain. Gait disturbance progressed and he could not walk when wearing sandals. Physical examination at Otsu Red Cross Hospital 1 month after the onset recorded reduced grasping power. Fine finger movements were also disturbed so that he could not write. Administration of Vitamin mixtures and physio-therapy

were both ineffective. At the end of January, 1973, the grasping power dropped to 3 kg with the right hand and 2 kg with the left (normal range, 30—50 kg), and he could not walk at all. On admission to Kyoto University Hospital 4½ months after the episode, the patient, with normal countenance and clear consciousness, could walk only with assistance. Pulse rate, 72 per min; blood pressure, 102/50 mm Hg; respiration, normal. Physical findings of the chest and the abdomen were negative. On neurological examinations, cranial nerves were intact and ophthalmological examination was normal with R. V. and L. V. of 1.5 and 1.5, respectively. There was no deficit in visual fields. Muscular atrophy was remarkable especially in the four extremities, followed by the shoulder and hip regions. In the upper extremities, thenar, hypothenar and interosseous muscles were most atrophic with grasping power of 5 kg in both hands, while sensation was well preserved. In the lower extremities, muscular atrophy was more prominent in distal portions and the patient could hardly move ankle joints, even though there was no contracture of the joint. The sensations of hot and cold were reduced in the distal portions of the four extremities yet those to touch and pain were intact. The sense of vibration was disturbed. Knee and ankle jerks were absent while the abnormal reflexes were negative. Laboratory examinations including urinalysis, peripheral haemogram, liver function tests, serum electrolytes, cerebrospinal fluid tests were essentially normal except for the increased levels of s-GOT (57 U; normal range 10 to 50 U) and CPK (135 mU/ml; normal range, 10—45 mU/ml). Levels of serum creatinine, urinary creatinine and urinary creatine were 0.74 mg/dl, 157.0 mg/dl (0.98 g/day) and 6.4 mg/dl (68 mg/day), respectively. Chest X-ray and ECG were negative. EEG was borderline due to slightly slow background scattered with *theta* activities. On manual muscle testing (Daniels *et al.*, 1956), marked weakness was observed in distal portions of both upper and lower extremities, with an estimate of about 50—75% reduction from normal muscular power. Routine electromyography in *M. quadriceps femoris*, *M. gastrocunemius* (medial head) and *M. tibialis anterior* of the left lower limb and thenar and hypothenar muscle groups of the left hand revealed reduction of interference and many complex motor units, suggesting neurological disturbances. As shown in Table 1, marked reduction of motor conduction velocity and prolonged terminal conduction time were observed in *N. tibialis posterior* and *N. medianus*. Sensory conduction study in these two nerves as well as *N. suralis* failled to induce measurable responses.

Biopsies of the left *M. quadriceps femoris (vastus lateralis)* and the left *N. suralis* were carried out. Photo-microscopic examination of the former specimen revealed that the bundles of healthy muscle fibers were clearly separated from the area where fatty degeneration and fibrosis took

Table 1. Motor and sensory potentials of the peripheral nerves

Nerves examined	MCV[a] (m/sec)	Terminal conduction time (ms)	M-wave amplitude (mV)	SVC[b]
N. tibialis posterior dextra	29.6 (48.7 ± 3.4)	8.89 (5.36 ± 0.58)	0.4 (13.2 ± 4.1)	not measurable
N. medianus dextra	29.3 (57.9 ± 3.4)	9.26 (3.48 ± 0.58)	0.14 (11.8 ± 3.6)	not measurable
N. suralis dextra	—	—	—	not measurable

[a] MCV = motor conduction velocity.
[b] SCV = sensory conduction velocity.
Numbers in parentheses show normal ranges in terms of M ± SD (15 determinations).

place. The nerve tissue was essentially intact except that slight swelling of myelin sheaths was rarely observed.

During the 1 month hospitalization at Kyoto University Hospital, he was given physio-therapy. Thermal paraesthesia disappeared and grasping power gradually improved (right hand, 6.0 kg; left hand, 7.5 kg). The patient regained the ability to walk alone. He was discharged with clinical improvement at which time 6 months had passed since onset of the disease.

Laboratory Investigations

Glue Analysis. The glue, used by the patient for sniffing, was distilled under normal pressure up to 97°. Above this temperature, the material decomposed, yielding yellow irritating gas. The distillate, about 60% (W/W) of the glue, was subject to gas-liquid chromatography. The peaks in the chromatogram (Fig. 1A) corresponded to ethyl acetate (13%, V/V), toluene (34%) and *n*-hexane together with one unknown compound, presumably a hexane isomer (the sum of the latter two, 53% as *n*-hexane). To estimate the vapour concentration inhaled during glue sniffing, 15 g of the glue was taken into a plastic bag and allowed to equilibrate with about 0.3 litre of air. An aliquot of the air, 3 ml, was subject to analysis. The air contained about 3% (V/V) of *n*-hexane, 2% of ethyl acetate and 1% of toluene (Fig. 1B), the values well above the narcotic levels (Browning, 1965; Gerade, 1962; Fassett, 1962). These concentrations did not vary significantly even when a larger amount of the glue was put into the bag. It was not possible to estimate the daily amount of the solvents inhaled by the patient as no information was available regarding the duration of sniffing, however, the consumption rate of the glue (about 150 g daily) may suggest that, at maximum, about 45 g of

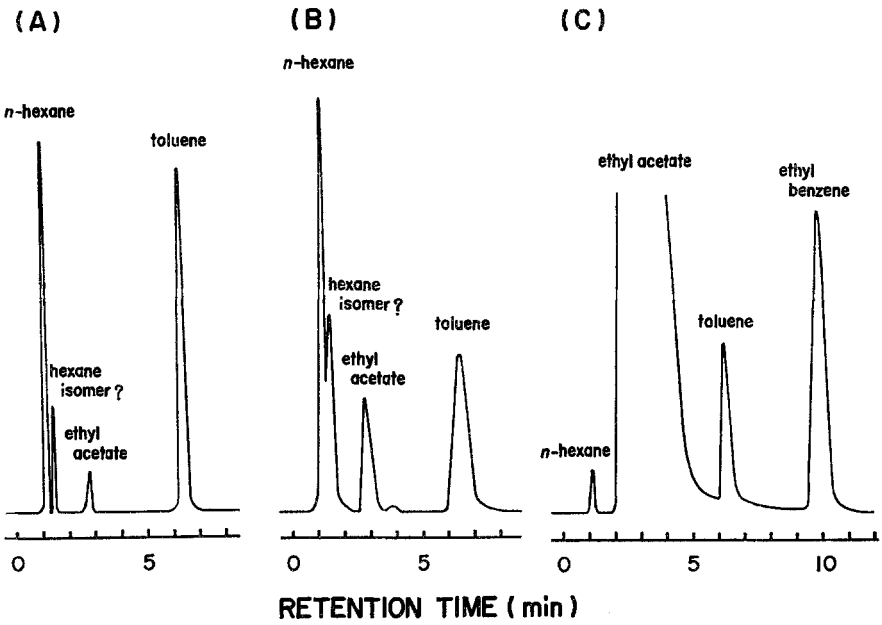

Fig. 1A—C. Gas-liquid chromatographical analyses of the glue and blood from rats given solvents. Details of procedures are described in "Materials and Methods". (A) Chromatogram of the distillate (up to 97°) from the glue. (B) Chromatogram of the air equilibrated with the glue in a plastic bag. (C) Typical chromatogram of the ethyl acetate extract from the blood of the rat given *n*-hexane plus toluene. Ethyl benzene was added as an internal standard

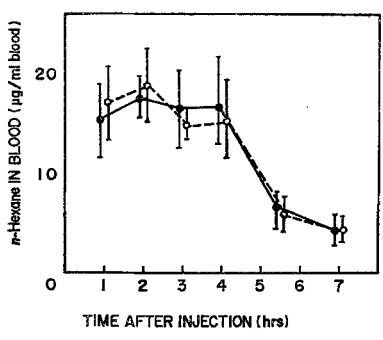

Fig. 2. *n*-Hexane concentration in the blood of rats given *n*-hexane or *n*-hexane plus toluene. Female Wistar rats (80—130 g) were injected i.p. with 0.91 g/kg of *n*-hexane (shown by solid circles) or 0.91 g/kg of *n*-hexane plus 1.18 g/kg of toluene (open circles). Rats were sacrificed at the time period indicated, and blood was gas-liquid chromatographically analyzed for *n*-hexane. The circles and arrows in the figure indicate means and SD (7—12 determinations). No significant difference ($P > 0.05$) was observed between any pair in the figure

Table 2. Hippuric acid excreted in urine after administration of toluene, *n*-hexane, or both to rats

Compounds (dose, mg/kg)	Hippuric acid (mg/kg) excreted during the time period (hrs) after injection			
	0—4	4—8	8—12	total
Toluene (434)	7.45 ± 0.63 (26.1 ± 5.5)	12.43 ± 3.69 (47.1 ± 6.2)	8.56 ± 1.77 (26.8 ± 3.3)	28.43 ± 3.13 (100)
Toluene (434) + *n*-hexane (335)	7.04 ± 0.68 (27.5 ± 5.1)	9.96 ± 2.66 (41.5 ± 8.1)	8.54 ± 1.87 (31.1 ± 6.9)	25.54 ± 3.06 (100)
n-Hexane (335)	2.38 ± 0.40	2.36 ± 0.21	2.32 ± 0.55	7.05 ± 1.11

Female Wistar rats (80—130 g) were injected i.p. with toluene, *n*-hexane or both, and urine excreted during the time period indicated was collected and analyzed for hippuric acid. Numbers in the table are means and SD of 8 determinations each. Numbers in parentheses indicate "excess" hippuric acid in percent excreted in each time period, and were calculated as

$$\frac{\text{H.A.}_{(i;\ \text{Tol., or Tol. + Hex.})} - \text{H.A.}_{(i;\ \text{Hex.})}}{\text{H.A.}_{(\text{total};\ \text{Tol., or Tol. + Hex.})} - \text{H.A.}_{(\text{total};\ \text{Hex.})}} \times 100$$

where, H.A. (*i*) is the amount of hippuric acid excreted during the time period indicated by the animals given toluene (Tol.), *n*-hexane (Hex.) or both (Tol. + Hex.). The amount of hippuric acid in the *n*-hexane group indicates the physiological level as *n*-hexane is not the precursor of hippuric acid.

Table 3. Types of polyneuropathy in relation to intensity of exposure to *n*-hexane[a]

Types	Numbers of cases	*n*-Hexane concentration[b] (ppm)	
		Means	Ranges
Sensory	17	250	50— 900
Sensorimotor	7	700	50—2000
Sensorimotor amyotrophic	4	1500	700—2000

[a] Re-arranged from the data given in Fig. 9 of the report of Inoue *et al.* (1970).
[b] Atmospheric concentration in the room in which the patient worked. Means are arithmetical. Ranges show minimum and maximum concentrations reported.

n-hexane, 30 g of ethyl acetate and 15 g of toluene was daily inhaled, even if not absorbed.

Possible Mutcal Modification of Metabolism. To investigate whether or not co-administration of toluene and *n*-hexane would result in modification of metabolism of these agents, rats were given i.p. either *n*-hexane alone or *n*-hexane plus toluene and changes in the solvent concentration in the blood were observed. As shown in Fig. 2, the co-administration

of toluene did not modify the *n*-hexane level in the blood and the level went down 5½ hrs after the injection, independent of the co-administration of toluene. Reversely, urinary excretion rate of hippuric acid, a major metabolite of toluene (Williams, 1959), was not reduced by the co-administration of *n*-hexane (Table 2).

Discussion

Extensive studies on polyneuropathy evidenced among workers using *n*-hexane containing glue (Yamada, 1967; Yamamura, 1969; Iida *et al.*, 1969; Inoue *et al.*, 1970) together with further observation in furniture polishers (Herskowitz *et al.*, 1971) as well as reproduction of the symptoms in experimental animals (Kurita, 1967) clearly demonstrated that *n*-hexane, previously considered as rather a harmless solvent, is hazardous and causes polyneuropathy. In humans these cases generally indicate that hypesthesia is the primary symptoms at the onset of the disease and sensation is predominantly disturbed. Results from the analysis of the multiple outbreak cases for dose-response relationship (Inoue *et al.*, 1970; the summary is shown in Table 3) are also in agreement with this observation. In the cases of glue sniffers who intentionally inhale the vapour of the glue (the solvent of which includes *n*-hexane), however, the clinical picture is apparently different. In typical cases, most predominant symptoms are motor disturbance coupled with muscular atrophy, while sensory disturbance, especially that of superficial sensation, is little, if any. As is the present case, the primary symptoms of a sniffer of glue (the solvent composition; *n*-hexane, toluene and ethyl acetate) reported by Takenaka *et al.* (1972) was muscular atrophy in four extremities, while superficial and deep sensations remained intact. In the case of identical twin sisters (Matsumura *et al.*, 1972) both who had sniffed glue (composition; chloroplene rubber 30%, *n*-hexane 25%, toluene 24%, and methyl ethyl ketone 20%), extensive muscular atrophy in the four extremities was followed only by slight disturbance of superficial sensation. A chemical factor common to these three reports on 4 patients is the presense of toluene in the glue solvent at the concentration comparable to that of *n*-hexane. We speculated that toluene, the solvent which by itself is rarely responsible for polyneuropathy (Satran and Dodson, 1963; Knox and Nelson, 1966; Heuser, 1968; Louria, 1969), may inhibit *n*-hexane metabolism and thereby modify the clinical picture, as is the case of mutual inhibition of biotransformation between toluene and benzene, and toluene and styrene (Ikeda *et al.*, 1972). The results from present investigation, however, do not support this hypothesis. This may be reasonable because aliphatic hydrocarbons (including *n*-hexane) are considered biochemically rather inert (Williams,

1959). In addition, the activity in microsomal preparation from mouse liver to catalyze *w*-oxidation of decane and other aliphatic hydrocarbons including *n*-hexane (Ichihara *et al.*, 1969) behaves differently from the activity to hydroxylate toluene when the animals are pretreated with various inducers of hepatic drug-metabolizing enzymes (Ichihara *et al.*, 1968), suggesting that the two reactions are catalyzed by different systems.

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