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Accidental percutaneous hexachlorophane intoxication in children*

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Summary

Eighteen children with normal skin were accidentally intoxicated by a talc powder containing 6% hexachlorophane. Four died and two remained paraplegic. The clinical picture was intracranial hypertension, eight patients developing signs of spinal cord damage. The condition seemed to result from massive intramyelinic oedema. In the spinal cord vascular disturbances may occur as mechanical complications of oedema, giving rise to permanent sequelae.

Introduction

Percutaneous hexachlorophane (HCP) absorption has caused severe and even fatal intoxication in patients with burns or ichthyosis.¹⁻⁴ HCP absorption through normal skin has been indicted as a cause of myelin lesions in premature infants bathed in 3% HCP solutions.⁵⁻⁷ Fatal toxicity in full-term babies with normal skin has not been reported, nor have permanent neurological sequelae in man. Since myelin lesions due to HCP are usually reversible,⁸⁻⁹ and the possible dangers from HCP remain a matter of controversy,¹⁰ we report our experience of 18 children percutaneously intoxicated by a talc powder containing 6% HCP.

Patients and methods

The 18 children were admitted to this hospital between April and July 1972. The talc powder, which had been accidentally contaminated with 6% HCP, had been applied to the napkin area several times a day and allowed to remain between changes. HCP was sought in the serum in four cases and in the cerebrospinal fluid (CSF) in one.

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Four children died, in two of whom the brain and spinal cord were examined. Multiple sections of cortex, basal ganglia, cerebellum, brain stem, and spinal cord were embedded in paraffin and celloidin and examined by conventional techniques. Samples of white matter were taken from a frontal lobe fixed in formalin. After washing in 7% glucose phosphate buffer, small blocks were fixed in modified Karnovsky fixative, postfixed in 2% phosphate-buffered osmium tetroxide, dehydrated, embedded in Araldite, and examined with a Siemens 101 electron microscope.

Results

The children (5 girls and 13 boys) were between 3 months and 3 years of age. Twelve were under 1 year. The onset of the disorder was marked by anorexia and vomiting, rapidly followed by agitation, drowsiness, and coma. Nine patients had a temperature of 38° C or more. Since the diagnosis was made retrospectively, the exact duration of use of the talc was unknown. The time between appearance of first symptoms and admission to hospital varied from a few hours to 15 days, though in 10 cases it was under 48 hours. Seventeen children had severe erythema in the napkin area resembling second-degree burns. Erythema preceded the neurological signs by three to 15 days in six cases and followed them in four. In the remaining cases either the erythema occurred simultaneously with the neurological signs or its time of appearance was unknown.

On admission 17 of the children had disturbances of consciousness. Fourteen had bilateral pyramidal tract signs and severe tremor, and 10 exhibited abnormal movements, with bouts of extensor hypertonia and pronation of the arms. Four patients had a history of "convulsions" before admission, though none was seen or recorded in the electroencephalogram during their stay in hospital.

Eight patients showed abnormal signs in the spinal cord. In two a full-blown picture of acute transverse myelitis at T8 and T4 was evident with normal consciousness in one. These two children remained paraplegic with sphincter dysfunction. Two infants had transitory paralysis of the legs followed within a few days by regressive spasticity. In the four children who died flaccid paraplegia was noted several hours before death.

Six patients had ocular abnormalities—namely, ocular jerks (four cases), mydriasis (one), and sixth-nerve palsy (one). In the infant with sixth-nerve palsy strabismus disappeared 27 days after admission to hospital, only to return in association with erythema of the buttocks, papilloedema, and blindness shortly after returning home, where the talc was again applied. Papilloedema was present in six cases, associated in at least three with other signs of increased intracranial pressure, such as suture diastasis and tense fontanelles. In one infant head circumference increased by 2 cm in four days.

Electroencephalography was performed at least once on 16 children. The tracings were abnormal in 15 cases, with bilateral slow waves predominantly during wakefulness and on awakening. In three cases

the first record was normal, the slow waves first appearing 24–48 hours after admission. In one child pneumoencephalography one month after appearance of the first symptoms showed dilatation of the left frontal and temporal horns. CSF examination in 16 children showed raised protein concentrations (>0.3 g/l) in seven, pleiocytosis ($>5 \times 10^6$ mononuclear cells/l) in seven, and the presence of red cells ($>10 \times 10^6$ /l) in eight. The HCP concentrations in serum and CSF are given in the table.

OUTCOME

In the four fatal cases death occurred three to five days after the symptoms first appeared. All these patients had evidence of spinal cord involvement and died suddenly after cardiorespiratory arrest. Two children were left with a characteristic spastic paraplegia. One infant still had bilateral pyramidal signs one month after onset, but was not followed up. Eleven patients apparently recovered completely, though none was followed up for more than 38 months.

HCP concentrations in serum and CSF

Case No	Date of sampling (No of days after admission)	HCP concentration ($\mu\text{mol/l}$)	
		Serum	CSF
1	2 days	38.89	
2	12 days	0	
3	16 days	0	
4	15 days	0	
5	6 days	7.37	
	3 days (post mortem)		0.32

Conversion: SI to traditional units—Serum and CSF HCP: $1 \mu\text{mol/l} \approx 0.41 \mu\text{g/ml}$.

NEUROPATHOLOGY

The results of neuropathological examination of two of the children who died (cases 5 and 6) were as follows. Brain weights were considerably increased (910 g and 970 g; means for ages 590 g and 750 g). The gyri were enlarged and flattened. In case 5 the optic nerves were swollen. In both cases the spinal cord was extremely swollen and tightly encased within the dura, especially in its lowermost part. In case 6, the posterior funiculi were severely haemorrhagic from T8 down to the conus. Microscopically there was massive cystic spongiosis of the white matter of the hemispheres without visible demyelination. Oedema was most pronounced in the U fibres, internal capsule, white fasciculi coursing through the basal ganglia, and optic nerves. The cortex was also affected, especially the deep layers, though not the neurones. In case 6, the molecular layer was severely oedematous, the oedema infiltrating down into the deeper cortex along Virchow-Robin spaces. In both cases the cerebellar white matter also had a spongy appearance, though to a less extent. Spongiosis of the white matter was prominent in the brain stem around the reticular nuclei and in the pes pontis. The most severe lesions were in the spinal cord, where due to cystic oedema all white fasciculi appeared as a lacework (fig 1).

FIG 1—Case 6. Anterior horn of spinal cord. Cystic oedema giving lacework appearance to white matter. (Haematein and eosin. $\times 32$.)

FIG 2—Case 6. Degenerated axon in dashed arrows indicate intralaminar spaces. Solid arrows indicate areas of separation of myelin lamellae. Some honeycombing (HC) is present. ($\times 43\ 636$.)

The grey matter of the spinal cord was spared. In case 6 severe venous congestion and perivascular haemorrhages partially destroyed the posterior funiculi in the lumbar region.

Electron microscopical examination confirmed the intramyelinic location of the oedema with splitting and separation of the myelin lamellae. Honeycombing of the myelin sheaths was also apparent (fig 2). Oligodendrocytes and endothelial cells appeared to be well preserved in the white matter.

Discussion

Although definite chemical evidence of intoxication was obtained in only three cases, there is little doubt that all 18 children were suffering the effects of percutaneous HCP intoxication—all came from an area where a shipment of contaminated talc powder was known to have been distributed; repeated application of the same brand of talc powder was documented in many cases; clinical symptoms were closely similar; and no other cause, toxic or viral, could be found despite intensive investigation. The neuropathological findings, occurrence of more than one case in the same family, and recurrence of signs and symptoms in one patient after returning home constitute further evidence of HCP toxicity. The absence of HCP in the serum in cases 2 and 3 (see table) may be explained by the late collection of blood—namely, 16 and 15 days respectively after admission.

Severe toxicity resulting from percutaneous absorption of HCP has been reported in patients with extensive burns^{1,2,4} or neonatal ichthyosis.³ Only one case of intoxication through normal skin has been described.¹¹ In our patients the degree of absorption was exceptionally high, as shown by the severity of the clinical and pathological features and serum HCP concentrations of $38.9 \mu\text{mol/l}$ ($15.8 \mu\text{g/ml}$) two days after admission in case 1 and $7.4 \mu\text{mol/l}$ ($3.0 \mu\text{g/ml}$) six days after admission in case 4 (see table). These concentrations were similar to those found by Larson¹ in burnt patients (9.8 – $182.0 \mu\text{mol/l}$; 4.0 – $74.0 \mu\text{g/ml}$) and much higher than those found in monkeys with normal skin² or in newborn babies after application of a 3% HCP solution^{12–14} or a powder containing 0.33% HCP.¹⁵ Probably both the high concentration of HCP in the talc powder and the prolonged contact with the skin were responsible for the degree of absorption, which may have been further increased by the cutaneous erosion induced by HCP.

Our data permit a better definition of the clinical features of HCP toxicity in man, especially the intracranial hypertension and spinal lesions. Intracranial hypertension seems to be responsible for a major part of the symptoms—for example, papilloedema, suture diastasis, sixth-nerve palsy, tense fontanelles, and, probably, disturbances of consciousness. Attacks of de-

cerebration and sudden cardiorespiratory arrest may also result from increased intracranial pressure, although direct involvement of the brain stem reticular substance may play a part.⁷ The extent of the spinal cord involvement is remarkable. It is a well-known result of HCP toxicity in rats,⁸ in which paralysis of the hindquarters often occurs, but has been only rarely described in man.¹ No obvious cerebral sequelae were noted in the 14 surviving children. Follow-up was not long enough, however, to exclude the possibility of more subtle damage, which may be manifested by learning difficulty or behaviour disorder. The asymmetrical ventricular dilatation noted in one patient one month after appearance of the first symptoms suggests that damage may occur in some patients and might eventually become symptomatic.

Our neuropathological results accord with experimental data⁹ and with the findings of Martinez *et al*¹⁶ and Mullick³ in infants. The main pathological effect of HCP is intramyelinic oedema without demyelination. The oedema is located within myelin sheaths between lamellae and is unaccompanied by disturbances of the blood-brain barrier.⁹ Brain-stem lesions in our patients were consistent with the findings of Shuman *et al*⁶ and Powell *et al*⁵ in premature babies bathed in a 3% HCP solution. In our cases, however, myelinic oedema was much more widespread, as shown by the large increase in brain weight and the intense lacework oedema in the spinal cord.

The neuropathological findings satisfactorily account for the clinical picture, especially the intracranial hypertension. The lack of demyelination and preservation of neurones probably explain the apparent reversibility of the lesions. Extensive oedema occurring within a rigid structure such as the spinal canal, however, can result in infarction of nervous tissue, as observed in case 6, thus giving rise to permanent damage. In

addition, axonal degeneration has been noted after chronic intoxication in rats¹⁷ and could be another source of permanent damage in man.

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Is your dosage really necessary? Antibiotic dosage in urinary infection

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Summary

Dense cultures of bacteria were exposed to changing concentrations of beta-lactam antibiotics in an in-vitro model of the urinary bladder.

The results suggest that uncomplicated urinary infection may respond to lower doses than are usually given without compromising the success of subsequent treatment in those cases in which such minimal treatment fails.

Introduction

There are strong indications that uncomplicated urinary tract infection will respond satisfactorily to less intensive treatment than is usual.^{1 2} Nevertheless, the optimal dosage for the treat-

ment of bacterial infections of the urine remains to be defined. The laboratory has been of little help in this respect because the conditions in which bacteria and drug interact in the urine are so far removed from those of conventional in-vitro tests that it is difficult to predict the response to treatment.

As an approach to this problem, and to attempt to discriminate between the many agents now available, we have developed an in-vitro model in which bacteria grow in the conditions of dilution and periodic discharge that obtain in the urinary bladder and in which dense bacterial cultures (as are common in infected urine) can be exposed to the changing drug concentrations that are provided by therapeutic regimens.

We describe here our investigation into the effect of penicillins and cephalosporins on *Escherichia coli* and *Proteus mirabilis*, the organisms most often associated with urinary tract infection in domiciliary practice. Because of the bewildering variety of β -lactam antibiotics now being produced, we limited our study to representatives of the group that have distinct properties in terms of their antibacterial activity against urinary tract pathogens.

Method

An overnight culture of bacteria in "complete" broth³ was diluted with fresh broth at 1 ml/min (the normal diurnal rate of urine flow into the bladder). Every hour the accumulated broth was pumped

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