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Observations on Hexachlorophene-Induced Paralysis in the Cat and Its Antagonism by Hypertonic Urea (39352)

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The toxic effects of hexachlorophene (HCP) on the central nervous system include paralysis of limbs with tonic extensor rigidity and edema and spongy degeneration of white matter in the brain and spinal cord (1-4). These effects are reversible upon cessation of HCP administration (2), making it unlikely that permanent damage to cerebrospinal neurons is sustained in surviving animals. Instead, the signs suggest a "pressure lesion" (5) with the possibility of fatal outcome in cases that are severe, sustained, and unrelieved. This led us to investigate whether toxic amounts of HCP produce elevations of cerebrospinal fluid pressure (CSFP) and if so, whether this effect could be antagonized or reversed. The wide range of neurological observations accessible to simple "clinical" test in the cat was the basis for choice of this species over the rat for studies reported here.

Materials and methods. Eighteen male mongrel cats, 1 to 2 years old, were immunized for distemper and pneumonitis and allowed to become accustomed to our laboratory for 4 to 5 weeks before use. They were removed from their cages twice each week and allowed free movement in the animal room while under observation to accustom them to the handling necessary for dosing and examination. They were systematically observed before and after treatment according to a checklist that included the criteria from Norton and DeBeer (6), including recognition of personnel, grooming, feeding, drinking, and exploratory behavior, and many of the neurological tests outlined by McGrath (7), such as muscle tone, stretch, righting, placing, and extensor and pinnal reflexes.

HCP, at a dose of 20 mg/kg, was weighed into a capsule for each animal and administered daily by the oral route. Blood samples were taken at regular intervals and HCP concentrations in whole blood were measured by the gas-liquid chromatography method of Ulsamer (8).

Cats in complete paralysis were placed under pentobarbital anesthesia and cisternal CSFP was measured by a modification of the method of Hayes and Corey (9), using a Statam P-23 pressure transducer and a Grass Model 7 polygraph. A 3-way valve attached to the pressure transducer was used to calibrate the polygraph to a full scale deflection with a 100-mm column of 0.9% saline. Pressures were taken via a 22-gauge needle inserted into the cisterna magna. Paralyzed cats were given urea in invert sugar solution, acetazolamide, or prednisolone by slow iv infusion to investigate the possibility that toxic effects of HCP could be reversed. Upon termination of the experiments brain and spinal cord were collected for neuropathology.

Results. The number of daily doses required before the cats showed the first signs of toxicity (stiffness of the hind limbs and swinging movements of the pelvic girdle) varied from 2 to 12, and the number of additional doses required for the subsequent progression to severe toxicity varied from 1 to 4 (Table I). This wide variation seemed to be related to both differing individual animal sensitivities to HCP and to the wide variation in degree of absorption of HCP after oral administration. Blood concentrations determined at various times after each dose showed that HCP was both rapidly absorbed and rapidly cleared from the blood; values reached peaks ranging from approximately 3-17 μg/ml at or before 12 hr after each dose and then decreased to relatively low levels ranging from 0.1-0.9 μg/ml 24 hr after each dose (Table II). There was great variability in HCP concen-

TABLE I. A COMPARISON OF PATHOLOGY FINDINGS WITH THE NUMBER OF DOSES OF HEXACHLOROPHENE CAUSING ONSET OF TOXICITY AND CEREBROSPINAL FLUID PRESSURE IN THE CAT.[a,b]

Cat number	Number of doses			Pathology findings				Cerebrospinal fluid pressure (mm saline)	
	First toxicity	Severe toxicity	Total	Spinal cord	Brainstem	Cerebellum	Cerebral hemisphere	Before HCP	After HCP
27715	4	8	8	2	4	4	4	–	240.0
3285	4	7	7	4	4	4	4	–	135.0
CP-5[c]	–	–	–	n	n	n	n	–	50.0
CP-6[c]	–	–	–	n	n	n	n	–	82.5
28826	12	15	15	4	4	4	4	–	167.5
3249	–	–	8	1	2	2	2	–	132.5
3289	2	3	3	2	2	2	2	–	182.5
26400	9	13	13	2	4	4	4	–	185.0
3281	6	9	9	2	4	4	4	22.5	262.0
3291	6	7	8	1	4	4	4	27.5	115.0
5167	6	7	8	1	4	4	4	14.0	85.0
3292	5	6	7	n	4	4	4	22.5	120.0
3280	4	5	6	4	4	4	4	27.5	275.0
28606	4	5	6	4	4	4	4	17.5	185.0

[a] Pathology scores: 1 = slight focal vacuolization of white matter; 2 = slight focal or diffuse; 3 = moderate vacuolization with some displacement of architecture; 4 = moderate to severe; n = normal.
[b] The daily hexachlorophene dose was 20 mg/kg.
[c] CSFP was taken 1 month after the last HCP dose.

TABLE II. HEXACHLOROPHENE CONCENTRATIONS[a] IN WHOLE BLOOD OF CAT AT SEVERAL INTERVALS AFTER A SINGLE ORAL DOSE OF 20 mg/kg.

Experiment number	Interval after dosing (hr)				Number of cats
	2.5	6.0	12.0	24.0	
C-3	7.98 ± 1.29	7.63 ± 1.69	6.47 ± 1.76	0.89 ± 0.20	6
C-4	–	3.08 ± 0.59	3.93 ± 0.95	0.54 ± 0.15	5

[a] Expressed in μg/ml ± SEM.

trations in blood between cats and from day to day in the same animal. One major cause of the variation may be the fact that cats often vomited; when this occurred within 3 to 6 hr after HCP dosing much of the substance was lost and concentrations in blood were low. Since vomiting did not appear within a few minutes, it probably resulted from an action on the vomiting center and therefore may have been the earliest sign of toxicity within the neuraxis.

The toxic effects of HCP in the cat were seen as a gradually progressing degeneration of first motor and then autonomic functions that began in the hindquarters and proceeded craniad. The first signs were stiffness of the hind limbs that resulted in rigid gait and an elevated and widely swinging movement of the pelvic girdle. These signs later extended to include incoordination of all limbs, ataxia and weakness of the limbs, and occasionally patellar hyperreflexia and impairment of righting reflex. Sustained urinary retention also occurred and was often accompanied by hematuria, resulting in a greatly distended bladder that could be relieved by manual expression of urine. Signs suggesting pain, discomfort, and possibly disorientation appeared at this stage of toxicity and were accompanied by what might be called distressed crying; food consumption dropped to low levels with progressive and severe weight loss and signs of dehydration. As intoxication worsened it progressed to complete prostration; signs during this stage included loss of righting reflex, spastic and/or flaccid paralysis of hindlimbs, inability to stand or walk, and depressed or absent forelimb placement reactions followed by spastic paralysis of the forelimbs. The forelimb paralysis was often accompanied by an exaggerated extensor reflex elicited by lifting the head and stretching the neck dorsally. Cranial nerve functions remained unaffected; i.e., ocular accommodation, pupillary and eyelid reflexes, pinnal and vibrissal responses to persons and touch, reactions to

sound, "recognition" of environmental (personnel, etc.) changes, and abdominal respiration were normal, and the animals would drink water when a container was brought into contact with the mouth. In only one case was there suggestion of unilateral (ocular) papilledema. Finally, the animals exhibited complete flaccid paralysis, loss of all reflexes, dilated pupils, and hypothermia followed by death within 24 hr.

Animals which were completely paralyzed but which had not reached the final stage of CNS depression generally survived if HCP administration was discontinued. These cats recovered slowly with the signs of toxicity disappearing in a sequence opposite to that in which they developed. Neuropathology performed at various stages of intoxication showed spongy degeneration or "status spongiosis" of white matter in brain and spinal cord without neuronal involvement; there was no dilation of cerebral ventricles or damage to ependymal linings. In several instances the white matter of the brain was more severely affected than that of the spinal cord. Complete recovery after the final dose of HCP required 4 to 6 weeks (Table I).

Cats in complete paralysis were placed under pentobarbital anesthesia and cisternal CSFP was measured. CSFP in these animals was significantly elevated to a mean of 174 mm saline, whereas untreated controls had a mean pressure of 19 mm saline (Tables I and III). The elevated pressure in HCP-treated animals began to fall several minutes after a slow iv infusion of 30% urea (in 10% invert sugar solution) at a dose of 2 g/kg and was rapidly reduced, within 1 hr, by a mean of 256 mm saline to a mean negative pressure of −100.1 mm saline relative to atmospheric pressure, which is 0 mm in our system (Table III). This effect lasted 3 to 4 hr during which time the elevation of CSFP gradually returned. Acetazolamide (200 mg/kg) given concomitantly with or after urea administration did not affect CSFP. In addition, neither acetazolamide nor prednisolone (2.5 mg/kg, iv) administered alone had any effect on the elevated CSFP in HCP-intoxicated animals.

TABLE III. EFFECT OF HEXACHLOROPHENE AND UREA ON CEREBROSPINAL FLUID PRESSURE (CSFP) OF CATS.[a]

Treatment group	Mean CSFP ± SEM	Number of cats	P
Control	19.4 ± 2.3	8	
HCP-treated	173.8 ± 17.5	12	<0.001[b]
HCP-treated, after urea infusion	−100.1 ± 27.7	6	<0.001[c]
Decrease after urea infusion	256.4 ± 10.9	6	

[a] Expressed as mm saline.
[b] Compared to control cats.
[c] Compared to HCP-treated cats.

In a series of separate experiments in which unanesthetized animals were visually observed, five cats paralyzed by HCP were able to stand and walk within 50 min after having been given urea (same dose as above) by slow iv infusion. This very striking effect lasted 3 to 4 hr before paralysis returned.

Discussion. The toxicity of HCP has been shown to be associated with spongy degeneration of the white matter of the brain and spinal cord in rats (2, 3). This degeneration is very similar to the "status spongiosis" seen in other disorders and thought to be due to diffuse brain edema (5, 10, 11). The data of the present report show that considerable elevations in cerebrospinal fluid (and therefore intracranial) pressure occurs with progressive paralysis in the HCP-poisoned cat, and that relief of the elevated pressure results in reversal of paralysis. We have shown that urea, an osmotic diuretic, lowers this elevated CSFP (12, 13), probably by removing fluid from the brain mass (14). Examination of brain sections from HCP-poisoned cats in the present study did not show dilation of the cerebral ventricles, ruling out the possibility of intracranial hypertension of obstructive origin. Thus it would appear that increased pressure does not arise from increased fluid in the ventricles, but rather in the surrounding tissue. In fact, the whole-brain sections in our study showed extensive and severe damage to white matter and myelin sheaths only, in agreement with the findings of others (2, 10, 15) who have observed demyelination and splitting, with no injury to the ependymal lining of the ventricles or the arachnoid villi. The marked elevation in CSFP produced by HCP and its relief by an osmotic

agent is consistent with the reported recovery of rats from paralysis, upon cessation of HCP administration, so long as HCP had not damaged critical life-sustaining centers of the CNS. It is also consistent with the opinion that irreversible damage to CNS neurons need not occur to account for fatal paralysis; no neuropathology sections of brain and cord of cats dying from HCP in our studies showed any neuronal damage.

Finally, the inability of acetazolamide to alter significantly the elevated CSFP in HCP-poisoned cats appears to rule out a lesion resulting in overproduction of cerebrospinal fluid. Likewise prednisolone, commonly used to reduce intracranial pressure following trauma, did not affect (up to 6 hr) the elevated CSFP in HCP-poisoned cats. This was not entirely unexpected since the latency or onset of effect of this compound has been reported to be much longer than that of urea (16) and may be a significant limitation in its usefulness in treating HCP poisoning. Also, the failure of prednisolone to have an effect suggests that the HCP lesion may not be inflammatory in origin.

The limits of usefulness and the safety of urea and other osmotically acting drugs in treatment of HCP intoxication of life-threatening severity need to be established by additional study, since the results of the present study suggest that elimination of the administered urea under conditions of our tests results in reestablishment of the intracranial hypertension. It is possible that a constant iv infusion of urea might significantly prolong its actions. Edema of other organs may also be affected by urea; however, barring the occurrence of serious cardiac arrhythmia of sudden onset, this treatment may be capable of counteracting many supralethal doses of HCP. This might have important clinical implications for the management of cases of poisoning with this substance.

Summary. Cats given HCP (20 mg/kg) orally each day developed hindlimb paralysis and greatly elevated CSFP (174 mm saline; 19 mm in controls) in 3 to 5 days. "Status spongiosis" was seen in white matter only in sections of brain and cord. There was no dilation of cerebral ventricles, or damage to their ependymal linings or to the arachnoid villi. The neurological picture excluded any but a terminal effect upon cranial nerve function. There appeared to be no damage to neurons, and recovery of survivors was complete within 6 weeks after cessation of HCP administration. Elevated CSFP in paralyzed anesthetized cats was quickly lowered by an average of 256 mm by slow iv administration of 30% urea (2 g/kg in 10% invert sugar). Unanesthetized cats similarly paralyzed were able to stand and walk for up to 4 hr after this treatment. Neither acetazolamide nor prednisolone alone had any effect, nor did coadministration with urea enhance the effect of urea. The HCP lesion does not appear to be inflammatory in origin, nor does it seem to involve ventricular obstruction or overproduction of cerebrospinal fluid. The reappearance of paralysis about 4 hr after osmotic diuresis, which corresponds with the elimination of urea, suggests that prolonged iv infusion with urea or a similar osmotically active substance may have significant clinical value in the management of HCP poisoning.

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