TREATMENT OF ACUTE POST-OPERATIVE INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION WITH DIPHENYLHYDANTOIN

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ABSTRACT

Post-operative inappropriate antidiuretic hormone (ADH) secretion was observed 6 times in a group of 26 patients without diabetes insipidus before surgery for craniopharyngioma. Fourteen patients with existing diabetes insipidus did not show this disturbance. Intravenous administration of diphenylhydantoin (250 mg q. 8 h) controlled the hyponatraemia during the interphase of abnormal urine concentration and established an increased transitory water excretion in an 8 year old child operated upon for craniopharyngioma.

The triphasic course of diabetes insipidus after surgery of craniopharyngiomas (Randall et al. 1957) and after pituitary stalk section (Timmons & Dugger 1969) is a well known entity. This condition is characterized by an initial phase of polyuria with a loss of urine concentration for 2 to 5 days followed by an interphase of oliguria, abnormal urine concentration and hyponatraemia which lasts for 3 to 6 days. A second phase of diabetes insipidus then follows.
The phase of oliguria is probably caused by an uncontrolled release of antidiuretic hormone (ADH) from damaged hypothalamic neurons. A reduction in serum sodium below 130 mEq./l can lead to symptoms of water intoxication (somnolence, coma, seizures) in the early post-operative period (Wise 1965, 1972). Triphasic diabetes insipidus is not uncommon. It was observed six times in our series of 40 craniopharyngiomas operated between 1966 and 1972. The condition never occurred in patients with pre-existing diabetes insipidus (14 cases out of 40) and therefore seems to be related to an intact pre-operative ADH production.

The hyponatraemia in triphasic diabetes insipidus can usually be prevented by appropriate water restriction. Sometimes intravenous administration of 3% sodium chloride solution is necessary (Wise 1965). Hence the excretion of the retained water, using a substance which suppresses the production, release or action of ADH would seem to be a logical method of therapy. The use of alcohol might be suggested because it inhibits ADH release very effectively (Kleeman et al. 1955). But alcohol should be avoided in comatous and stuporous patients. Fichman et al. (1970) reported their results on the short time effect of diphenylhydantoin in cases of chronic and subacute cerebral and extracerebral ADH overproduction. The substance was used as a diagnostic aid during an acute water load. Stimulated by this report we used this medication with good results in a patient with inappropriate ADH secretion following surgical excision of a craniopharyngioma.

CASE REPORT

This is an 8 year old girl operated on for a craniopharyngioma which had led to increased intracranial pressure, disturbance of vision and growth retardation. A diabetes insipidus with urine volumes up to 1800 ml/h was observed immediately after surgery (Fig. 1). The specific gravity of the urine fell to 1000–1006. The patient received a dose of 250 and two doses of 125 mg diphenylhydantoin for the prevention of possible seizures. Due to an over-correction of fluid loss a short period of hyponatraemia occurred. The inter-phase of abnormal urine concentration started about 36 hours after surgery. The urine production fell to 5–10 ml/h. The specific gravity rose to 1030. In spite of an immediate reduction of fluid administration the serum sodium fell to 127 mEq./l, and the patient became less responsive.

Diphenylhydantoin was given intravenously at regular intervals after an initial trial dose of 125 mg. The patient received 250 mg every 8 h. The specific gravity of urine fell after the second dose, and the urine volume increased at the same time. A new phase of diabetes insipidus was then established by the
Diuresis (solid vertical bars) and specific gravity of urine (broken line) of case presentation. The abscissa indicates the time in 6 hour intervals. 24 = midnight. Right side ordinate shows hourly amount of urine extrapolated to 24 hours. The specific gravity of urine during the period of glucosuria is marked by white dots. The serum sodium values are indicated by numbers on top and are placed on the line if normal (134–142 mEq./l). The treatment (diphenylhydantoin, pitressin) is shown in lowest line.

medication. The serum sodium values returned to normal, and the child became more alert. Glucosuria was noted during this time because of the administration of large volumes of 5% glucose solution. A second phase of abnormal urine concentration started about 12 hours after the last dose of diphenylhydantoin. The urine production fell again to 0–30 ml/h and the specific gravity rose to 1026. Diphenylhydantoin was again administered intravenously. This caused a new interruption of the abnormal urine concentration. The effectiveness of the drug decreased after the second administration during this period. The urine production became normal until another period of diabetes insipidus started on the seventh day after surgery. This condition could be easily controlled by intramuscular pitressin injections. The girl showed an excellent restitution of vision but continues to use a substitution of vasopressin.
COMMENT

Diphenylhydantoin showed a definite effect on the water metabolism in this patient during the period of inappropriate ADH secretion. The antidiuresis was stopped and a phase of increased diuresis was initiated. This effect of the drug can only be noted in this abnormal condition and not in patients with normal water metabolism. No similar increase of diuresis is noted in patients treated with diphenylhydantoin because of seizure disorders (Sparberg 1963). Hence the action of this drug is not on the kidney. It only affects the abnormally increased ADH release. This result is further substantiated by the fact that diphenylhydantoin fails to work in patients with extra-cerebral inappropriate ADH secretion such as is seen with bronchial carcinomas (Fichman et al. 1970).

It has recently been shown that diphenylhydantoin inhibits the release of vasopressin from isolated hemilobes of rat neurohypophyses, both during resting conditions and after electrical stimulation (Guzek et al. 1974). The origin of the vasopressin cannot be determined in our case. It may be released from the injured posterior lobe of the pituitary or from the affected neurosecretory cells of the supraoptic and paraventricular nuclei. The post-operative delay of the clinically observed inappropriate ADH secretion remains unexplained.

It is interesting to note that diphenylhydantoin was less effective during the second phase of administration. A similar loss of activity has been observed by Fichman et al. (1970). The necessity of intravenous or intramuscular injections of the drug has been postulated by the same investigators. Appropriate fluid administration is necessary to maintain the favourable effect of the drug after successful normalization of the hyponatraemia especially since this drug activity is limited in duration.

REFERENCES


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