Secondary adrenal insufficiency after intrathecal steroid administration

Case report

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A 38-year-old man developed secondary adrenal insufficiency as a consequence of intrathecal methylprednisolone administration. Evidence in support of this diagnosis included an absent plasma cortisol response to insulin-induced hypoglycemia, an inadequate adrenal response to exogenous corticotropin stimulation, a typical delayed response to prolonged corticotropin infusion over 3 days, and the finding of an elevated level of prednisolone in the cerebrospinal fluid a full 2 months after its administration. It is therefore recommended that patients receiving intrathecal steroids be carefully observed for the possible development of secondary adrenal insufficiency.

KEY WORDS · adrenal insufficiency · methylprednisolone · intrathecal infusion · corticosteroid administration

Secondary adrenal insufficiency is frequently the result of suppression of the hypothalamic-pituitary-adrenal axis by the prolonged exogenous administration of glucocorticoids in supraphysiologic amounts. This suppression may be seen after oral, rectal, topical, or respiratory delivery of the drug. We wish to describe an unusual variant of this problem resulting from the intrathecal administration of a corticosteroid preparation.

Case Report

This 38-year-old man was well until 1975, when at the age of 32 years, he began to experience low-back pain. In 1977, he underwent lumbar laminectomy for removal of a herniated nucleus pulposus. Because of persistent back pain postoperatively, which was unresponsive to routine analgesia, he was finally treated with the intrathecal administration of 10 mg of depotmethylprednisolone in June, 1978. Since this therapy proved successful in ameliorating the patient’s pain, intrathecal steroids were again administered in March and April, 1979. Between January and June, 1979, the patient gained 22 kg of body weight. Past medical history was noncontributory. Specifically, he had not received other steroid therapy or anticoagulant drugs, and there was no prior history of tuberculosis, or autoimmune or other endocrine disorders. The family history was unremarkable for endocrine pathology.

On physical examination, the patient was noted to be an obese white man with a uniform fat distribution. He weighed 98 kg. Blood pressure was 120/70 mm Hg sitting, and 118/68 mm Hg standing; his heart rate was 70/min, and the funduscopic examination was normal. The remainder of the physical examination was normal, including the absence of findings connected with hyper- or hypocortisolism.

To investigate the patient’s weight gain, an extensive laboratory and roentgenographic data base was obtained, including complete blood count, biochemical profile, thyroid function tests, skull radiographic series, and a collagen vascular screen, all of which were normal or negative. An 8 a.m. plasma cortisol determination by radioimmunoassay was 1 μg/dl. As a result of this latter finding, the patient was referred to the National Naval Medical Center for endocrine evaluation. History and physical examination at that time failed to uncover additional data other than a complaint of weakness. The diagnosis of adrenal in-
sufficiency secondary to pituitary suppression was made, based on the evaluation described below. This evaluation was performed 60 days after the patient received his last dose of intrathecal methylprednisolone.

The basal (morning) plasma cortisol concentration, determined by a sensitive and specific radioimmunoassay was less than 1 µg/dl. Following the administration of 250 µg of alpha 1,24 corticotropin, plasma cortisol was 7.2 µg/dl at 30 minutes, 10.0 µg/dl at 60 minutes, and 11.0 µg/dl at 90 minutes (Fig. 1). Basal 24-hour urinary 17-hydroxycorticosteroids and 17-ke-tosteroids were less than 1 mg and 2.5 mg, respectively. Following the daily 8-hour (8 a.m. to 4 p.m.) intravenous infusion of 250 µg alpha 1,24 corticotropin for 3 days, urinary 17-hydroxycorticosteroids rose from 0.3 mg/24 hrs on Day 1 to 24.0 mg/24 hrs on Day 4 (Fig. 2). The intravenous administration of 0.1 units of regular insulin per kilogram of body weight resulted in a blood glucose decline to 32 mg%. Plasma cortisol concentration was unchanged (< 1.0 µg% at 20 minutes, < 1 µg% at 40 minutes, 1.5 µg% at 60 minutes, and 1.5 µg% at 90 minutes) while the plasma growth hormone level rose to 15 ng/ml (Fig. 3). Cerebrospinal fluid (CSF) methylprednisolone concentration was 189 ng/ml (measured as prednisolone) in a specific radioimmunoassay, where concomitantly run control CSF specimens contained values of less than 1 ng/ml. Basal serum thyroxine, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, and testosterone concentrations, all measured by specific radioimmunoassay, were normal.

In November, 1981 (1 year after our initial endocrine evaluation), testing was repeated. Basal plasma cortisol concentration was 10 µg/dl, and rose to 15.2, 19.6, and 21.4 µg/dl at 30, 60, and 90 minutes after intravenous administration of 250 µg of corticotropin. A similarly normal adrenal response was observed with insulin tolerance testing. With the induction of insulin-induced hypoglycemia, plasma cortisol levels rose from 9.6 µg/dl to 12.7, 20.4, 22.6, and 19.7 µg/dl at 20, 40, 60, and 90 minutes after insulin injection. These data clearly indicated return of normal hypothalamic-pituitary-adrenal axis function.

Discussion

Evaluation of the pituitary-adrenal axis in our patient indicated that he had secondary adrenal insufficiency. This was substantiated by follow-up testing which showed complete recovery of the pituitary-adrenal axis with time. Although it cannot be absolutely determined that he did not have an unrelated pituitary disorder, the results of provocative and static endocrine studies, the normal skull films, and the high level of CSF prednisolone suggest that adrenocorticotropic hormone (ACTH) suppression was induced by the exogenous steroid administration. Although the administration of steroids into the intrathecal space is common in the treatment of lumbar disc disease, adrenal insufficiency resulting from this technique has not previously been reported. This may reflect the insidious clinical nature of secondary adrenal insufficiency. Generally absent are the findings of hyperpigmentation, hypotension, and weight loss.

* Antibody kindly provided by Dr. R. H. Buller, Upjohn Co., Kalamazoo, Michigan.

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**Fig. 1.** Plasma cortisol concentration over time (minutes) following intravenous administration of 250 µg of alpha 1,24 corticotropin at time zero.

**Fig. 2.** Urinary 17-hydroxycorticosteroid excretion in mg/24 hrs during daily 8-hour infusions of 250 µg of alpha 1,24 corticotropin for 3 days beginning on Day 1. Baseline 24-hour excretion (not shown in figure) was less than 0.2 mg/24 hrs.
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![Graph showing response of serum glucose, plasma cortisol, and plasma growth hormone to insulin injection](image)

FIG. 3. Response of serum glucose (upper), plasma cortisol (center), and plasma growth hormone (GH) (lower) to insulin (0.1 units/kg) given intravenously at time zero.

seen with primary adrenal insufficiency. Indeed, in our patient the discovery of hypocortisolism was made serendipitously as part of an evaluation for weight gain. While the patient with hypothalamic-pituitary-adrenal axis suppression may experience few clinical sequelae in the basal state, such an individual has a compromised response to stresses such as trauma, infection, and major surgical procedures.

Abnormal pharmacokinetics of methylprednisolone may be an alternative reason for the appearance of secondary adrenal insufficiency in our patient and not in other similarly treated patients. There are no data in humans about CSF levels of glucocorticoids after exogenous administration by any route. However, pharmacokinetic studies in rhesus monkeys with implanted Ommaya reservoirs indicate that an intravenous dose of 1.6 mg/kg of prednisolone achieves CSF levels in 40 to 60 minutes of the same magnitude as our patient. Thus, the patient's CSF levels were similar to those achieved by supraphysiological amounts of prednisolone which would be expected to cause ACTH suppression. What is not clear is the reason for such high CSF levels 60 days after the last intrathecal injection. In monkeys, intrathecal prednisolone enters the blood slowly, with peak levels achieved 3 to 5 hours after administration, while clearance of prednisolone from the CSF after injection is a complex function with a 4- to 5-hour plateau phase followed by a decrease with a half-life of 100 minutes. Although not specifically tested, the data for methylprednisolone might be expected to be similar to those for prednisolone, since these agents have similar blood half-lives. It is, therefore, surprising that such high CSF levels were found 60 days after the last injection. This suggests that either methylprednisolone and prednisolone are handled in markedly different ways in the CSF or that our patient had an abnormal clearance mechanism for methylprednisolone.

The mechanism by which intrathecal corticosteroid administration may result in ACTH suppression is unknown. Since there is no evidence for a brain interstitial space-CSF barrier for steroids, direct transfer from the CSF to the hypothalamus (and to the pituitary via the portal circulation) may cause feedback inhibition in the same manner as systemically administered steroids. Alternatively, the blood levels achieved after intrathecal injection may be sufficient to directly suppress pituitary corticotrophs (which lie outside the blood-brain barrier).

Conclusions

It is well known that exogenous glucocorticoid therapy may cause suppression of the pituitary-adrenal axis. In this case, repeated intrathecal steroid administration was associated with secondary adrenal insufficiency. This unusual variant of adrenal insufficiency is reported in order to alert the clinician to the possible life-threatening consequences of clinical stress in such a circumstance.

References

5. Landon J, Greenwood FC, Stamp TCB, et al: The plasma sugar, free fatty acid, cortisol, and growth hormone response to insulin, and the comparison of this procedure with other tests of pituitary and adrenal function. II. In patients with hypothalamic or pituitary dysfunction or anorexia nervosa. J Clin Invest 45: 437–449, 1966

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