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Suppression of Thyrotropin by Morphine in a Severely Stressed Patient

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Abstract. Opiates suppress TSH in experimental animals but are reported to increase TSH in human subjects. We describe a patient in severe pain treated with morphine, whose previously normal TSH fell to a level usually associated with hyperthyroidism. After returning to a normal concentration, TSH again decreased with morphine administration. This suggests that, in contrast to the stimulation of TSH secretion that has been reported in unstressed experimental subjects, morphine can inhibit TSH secretion during stress in man as it does in experimental animals. This observation is consistent with the known sensitization of opiate receptors by stress. Consideration should be given to the possibility that severe suppression of TSH by opiates in stressed patients may induce clinically significant central hypothyroidism.

Key words: Opiate, Morphine, Stress, Thyroxine, Thyroid stimulating hormone

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TSH, the efferent limb of the homeostatic control of free thyroxine (FT4), normally serves to stabilize the free T4 concentration; however stress inhibits TSH secretion independently of free hormone homeostasis [1, 2]. This effect is mediated by endogenous opiates [3, 4] and in the rat similar suppression of TSH occurs with morphine [5–10]. For reasons that have remained unclear, experimental administration of opiates to normal human subjects has the opposite effect, increasing TSH [11–14]. However, in the case described here, morphine, given to control severe pain, appears to have suppressed TSH on two occasions. We propose that the opposite effects of morphine on TSH secretion in this patient as compared to previously reported experimental subjects, reflects a stress induced sensitization of opiate receptor mediated inhibition of TSH release.

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Case Report

A 59-year-old woman on hemodialysis for end stage renal disease was scheduled to have an epidural steroid injection for a herniated disc and severe lower back pain. She collapsed while waiting on line for pre-admission financial counseling. Her pain had been treated with morphine (MS Contin 60 mg po tid) for 2 years but she had been unable to refill the prescription for 1 month. On the day of admission she had restarted MS Contin 60 mg. In the emergency room she was lethargic but responded to simple instructions. Neurological examination did not reveal a focal lesion. Because of hypoventilation and the history of morphine ingestion she was given naloxone. She became agitated, crying and screaming because of the severity of her lower back and hip pain. Intravenous morphine 4 mg and Benadryl 25 mg improved her pain. She was placed on positive air-pressure (BIPAP) and then intubated and transferred to intensive care. Head CT was negative. Thyroid function tests were obtained because of a suspicion that hypoventilation might be due to hypothyroidism. TSH determined by Abbott AxSYM hTSh II at 0.06 μIU/ml was not significantly above the detection limit of 0.05 μIU/ml for this assay.

Table 1. Time course of thyroid function tests

Medications received	Day	TSH (0.4–4.6 μIU/ml)	T-T4 (4.7–11.4 μg/dl)	F-T4 (0.71–1.85 ng/dl)	T-T3 (45–137 ng/dl)	T3U (24–40%)
MS Contin 60 mg po,	1					
Morphine iv 4 mg (day 1)	3	0.06	4.59	1.00	30	36
	7	0.14	—	0.91	28	37
Tramadol 50 mg po	8					
q12h (day 8–26)	13	0.25	5.41	0.95	54	34
	15	0.38	5.49	0.92	72	33
	23	0.33	5.12	0.72	43	32
MS Contin 30 mg qd,	27					
Percocet 1 tab bid	37	0.24	4.14	0.77	68	30
(day 27–99)	48	0.18	3.72	0.75	50	33
Increased MS Contin to	100					
30 mg bid, continue	125	0.32	4.26	0.63	28	32
Percocet 1 tab bid	174	0.53	4.33	0.75	61	31

The free T4 was normal at 1 ng/dl (0.71–1.85), total T4 4.6 μg/dl (4.7–11.4), T3 resin uptake (T3RU) 36% (26–37), triiodothyronine (T3) 30 ng/dl (45–137). On the fourth hospital day she was successfully extubated and returned to the general medical service in stable condition, although still lethargic. Vital signs remained stable except for a variably slowed respiratory rate of 9–14/min. The endocrine service was consulted regarding the low TSH and borderline low T4.

The patient appeared older than her stated age. She did not recall having been treated for thyroid disease. A TSH obtained 4 years previously had been normal at 0.7 μIU/ml. Her respiratory rate was about 10/min, BP-150/80, HR-68, T = 97.8F. The thyroid was not enlarged and the remainder of the physical examination was normal except for the diminished responsiveness. TSH concentrations gradually rose to low normal (0.38 μIU/ml). By day 7 her symptoms had improved sufficiently so that she could be discharged on Tramadol 50 mg q 12 hrs. However, nineteen days after discharge she was started on MS Contin 30 mg qd and Percocet one tablet bid for severe lower back pain and TSH, T4 and T3 concentrations again fell below normal. Three months later MS Contin was increased to 30 mg po bid with improvement in her back pain. TSH concentrations rose into the low normal range (Table 1).

Discussion

Non-thyroid illness decreases TSH, but rarely to the degree seen here [15, 16]. As is shown in Fig. 1, the serum TSH concentration after morphine was not significantly above the level of detection. It partially recovered, only to fall again after MS Contin was restarted, supporting the view that morphine had suppressed TSH. During this time the patient did not receive medications, such as steroids or vasopressors that might be expected to suppress TSH. Caloric deprivation cannot account for the virtual disappearance of serum TSH since the patient was on enteral feeding and even complete fasting causes only a moderate decrease of serum TSH [17]. Although TSH was first measured 2 days after morphine administration, it is likely that, not withstanding the intervening dialysis, morphine and morphine metabolites persisted at this time [18–20] accounting for the patient's respiratory depression. Recovery of TSH and T4 concentrations were closely related. The relatively delayed response of the T3 and free T4 concentrations (Table 1) may be related to the effects of dialysis [21, 22] and the increase in binding protein as the patient improved.

Morphine suppresses TSH in experimental animals [5–10]. Surprisingly however, previous studies have reported that the administration of morphine to normal human subjects increases their serum TSH concentration [3, 11–14]. We suspect that in our patient morphine caused a complete suppression of TSH because of the associated severe stress [1, 3]. That morphine was responsible for the suppression of TSH in this patient seems consistent with the second fall in TSH concentration after MS Contin was restarted on day 26.

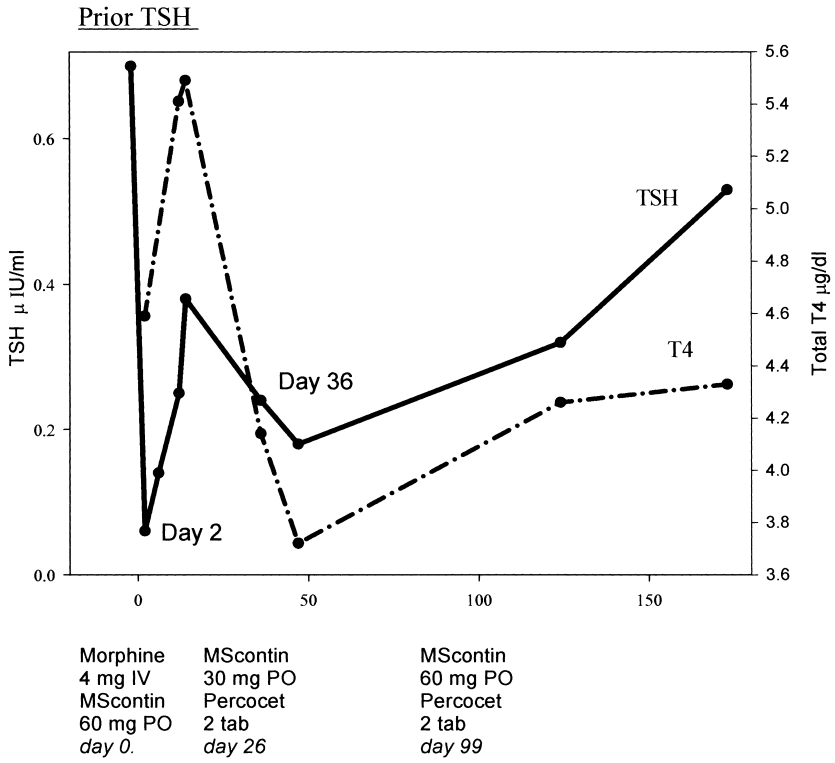

Fig. 1. Thyroid Function After Morphine. The initial TSH after morphine administration was 0.06 μIU/ml. After recovery into the low normal range, TSH fell again with the initiation of MS Contin. Recovery of TSH and T4 concentrations are closely related.

Stress sensitizes the inhibitory response to morphine through two closely related mechanisms. It increases hypothalamic mu opiate receptor (morphine sensitive) mRNA [23]. The consequent increase in mu receptors would be expected to potentiate endorphin and morphine mediated inhibition of TRH synthesis in the hypothalamus and, secondarily decreases TSH release from the pituitary [6, 24–27]. In addition, an activation of preformed opiate receptors induced by stress, may also sensitize TRH synthesis to inhibition by opiates. Thus, Commons [28] found that swim stress shifts cytoplasmic opiate receptors to the cell membrane where they become available to circulating opiates. The combined effects of the stress induced increase in endorphins and an increased synthesis and activation of opiate receptors probably accounts for the early, sustained inhibition of TSH secretion that occurs in response to stress. This is the probable cause of the central hypothyroidism seen in the euthyroid sick syndrome [29–31]. The apparent discrepancy between an inhibitory effect of morphine on TSH in the rat [5–10] and its stimulatory effect in normal human subjects [11–14] is likely to depend on the unavoidable presence of stress in experimental animals and its absence in human subjects who volunteer to receive morphine. In our patient, the TSH concentration after morphine was suppressed to a degree similar to that seen in hyperthyroidism. The euthyroid sick syndrome that is consistent with the weak thyroid hormone binding and low total T4 and T3 in this patient is usually associated with partial, rather than complete suppression of TSH [16, 31–33]. Our patient was on chronic dialysis, but this increases rather than decreases TSH [22, 34, 35]. We propose that the severe pain our patient experienced, induced an increase in available hypothalamic opiate receptors [23, 28] that sensitized the hypothalamus to endogenous (β-endorphins) and exogenous (morphine) dependent inhibition of TRH [25], secondarily decreasing TSH synthesis and secretion [27]. If this hypothesis is correct, TSH suppression and central hypothyroidism can be expected to occur frequently in severely stressed patients receiving morphine.

Although it is clear that severe nonthyroid illness causes temporary functional central hypothyroidism [29, 30], opinions differ as to whether this should be remedied with thyroid hormone replacement, since it

may have evolved as an adaptation to illness [36]. However, the latter argument does not seem relevant to the pharmacologically induced central hypothyroidism that seems to have occurred in our patient. Since thyroid hormone is involved in wound healing [37, 38] and probably in other reparative processes, an induced hypothyroidism should be corrected. We propose that pending a systematic study of morphine effect in stressed patients, thyroid function tests should be obtained after morphine treatment and a markedly suppressed TSH should be temporarily treated with replacement thyroxine.

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