

Human Reaction to Bovine TSH:

Concise Communication

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The incidence of allergic reaction to bovine TSH and its relation to dose have been studied in 42 patients with thyroid cancer who had total ablation of functioning thyroidal tissue and have been followed prospectively for up to 25 yr. Of these patients, 43% showed an allergic reaction to bovine TSH. The remaining 57% have shown no reaction, even though they have received cumulative TSH doses larger than those who did show a reaction. The reaction rate is linear up to a cumulative dose of 150 units and is not dose-related thereafter.

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Thyrotropin (TSH) is a natural stimulant used clinically to test the altered or reserved function of the thyroid gland (1). More often, TSH is used to enhance radioiodine I-131 uptake by the postsurgical thyroid remnant or by metastatic foci during treatment for thyroid cancer. Commercially available thyrotropin is bovine in origin and may evoke allergic reactions requiring emergency treatment (2). The reported instances of reaction to TSH in euthyroid patients consist of such diversified signs and symptoms as nausea, vomiting, pain and induration at the injection site, fever, cardiac arrhythmia, myocardial infarction, urticaria, anaphylaxis, and death. Although some of these signs and symptoms indicate true allergic reactions to TSH, others represent merely an exaggerated body response to liberated thyroid hormone owing to the stimulation by TSH, and hence are not truly allergic in nature (3). In patients with intact thyroid gland it is often difficult to separate signs and symptoms due to allergic reactions to TSH from those due to thyroid hormones released abnormally after the stimulation of TSH. Previous reports have not clarified the nature of true allergy to TSH. Even though TSH has been used for many years, neither its true allergic incidence nor its relation to dose is known in man. In this communication we report the results of a prospective study initiated 25 yr ago for the management of thyroid cancer. The study enables us to estimate the

true allergic incidence and the dose effect of bovine TSH in humans.

MATERIALS AND METHODS

The 42 patients included in this study are part of an ongoing prospective project initiated 25 yr ago for the management of thyroid cancer. Details of the protocol are available elsewhere (4,5). All patients had total or subtotal thyroidectomies followed by I-131 ablation as part of their clinical management. Following total ablation, the patients received an I-131 diagnostic scan yearly for 5 yr, and once every 2 yr, thereafter. The patients were seen in the outpatient clinic regularly at 6-mo intervals and their clinical status was thoroughly checked. Thyroid replacement therapy was withdrawn 4 wk before I-131 diagnostic scans, and the patients were given three bovine TSH injections to enhance the uptake of I-131 by any postsurgical thyroid remnant or metastatic tumor deposit.

TSH test procedure. On the first day, 10 units of TSH* were dissolved in 2 ml of the diluent supplied with the dose. First 0.2 ml (0.1 unit) were given intramuscularly (I.M.) and the patient was observed for 30 min. In the absence of any reactions a dose

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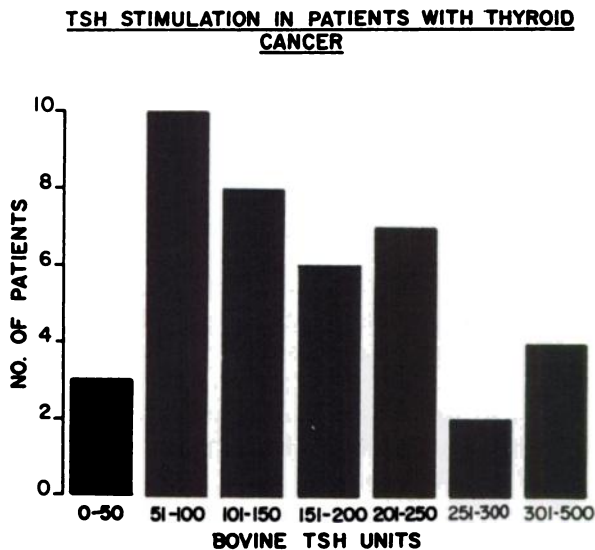


FIG. 1. Cumulative dose of bovine TSH received by thyroid cancer patients.

of 0.8 ml was then given I.M. and the patient was observed for another 30 min, at which time, in the absence of reactions, the remaining 1 ml of TSH solution was given I.M. The patient was observed for an additional 30 min before he was discharged from the clinic. On the second day the full 2 ml of TSH solution was given I.M. if there had been no reaction to the first-day injections. A similar procedure was followed on the third day. On the fourth day, the patient received a 5 mCi dose of I-131 for the diagnostic scan. Further details of the therapeutic procedure are available elsewhere (4,5). Induration at the injection site larger than 4 cm in diameter,

generalized urticaria, or anaphylactic shock were considered allergic reactions to TSH. No further TSH was given if there were allergic reactions. Slight pain with induration less than 4 cm in diameter, nausea, or vomiting were not considered an allergic reaction. Between diagnostic scans the patients were maintained on 3-5 grains of thyroid extract.

RESULTS

During the past 25 yr, 42 patients have received TSH and have been followed for a mean period of 10 yr (range 2-25 yr). The cumulative dose of TSH has varied from a minimum of 30 units to a maximum of 490 units (Fig. 1). The cumulative rate of allergic reactions is shown in Fig. 2. Eighteen of the 42 patients (43%) showed allergic reaction to TSH. Three of these patients had received less than 50 units before they showed a reaction. Three had received more than 150 units before reaction: one 180 units, the second 240 units, and the third 400 units). The remaining 12 patients had received TSH doses varying from 50 to 150 units.

Twenty-four of the 42 patients (57%) had no allergic reaction to TSH. The mean cumulative dose of TSH in these patients is 200 units (range 30-490 units); 16 of them have received more than 150 cumulative units and six of these have received more than 250 units without manifesting allergic reaction.

DISCUSSION

Reactions to TSH can be considered under two headings: immunologic and nonimmunologic type. The immunologic type is manifested either by allergy or immunity. Allergic reactions are detrimental and may be manifested by either urticaria or anaphylactic shock. The immune type of reaction is generally considered beneficial and often may not have outward clinical manifestations. It should be recognized, however, that not all immune reactions are beneficial. In the case of TSH the immune reaction results in the loss of its effectiveness owing to the formation of blocking antibodies (6,7). The nonimmunologic type of reaction is primarily due to the stimulating effect of TSH on the thyroid gland, which may respond in the usual way by liberating stored thyroid hormone rapidly into the circulation. These liberated hormones may cause tachycardia, nervousness, cardiac arrhythmias and even myocardial infarction.

In previous reports, the incidence of reactions to TSH in euthyroid patients included both allergic reactions and the effect of thyroid hormones on the body tissues (1). All patients in our study had had total thyroidectomies; accordingly, the reactions observed represent allergic reactions solely due to TSH. In euthyroid patients who received smaller doses of

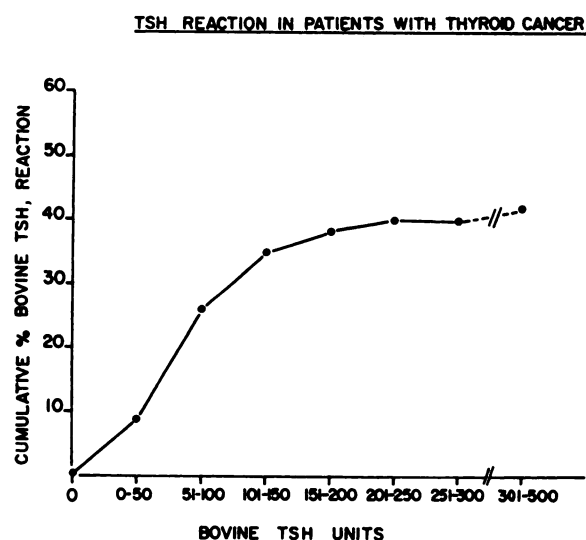


FIG. 2. Cumulative rate of allergic reaction to bovine TSH. Note linearity of rate up to 150 TSH units and plateau thereafter.

TSH, the reported reactions included such signs and symptoms as fever, nervousness, swelling of the salivary glands (8), nausea, vomiting, pain in the injection site, cardiac arrhythmia, myocardial infarction, and even death (1). In our study the most common reaction was local induration and urticaria. Only one patient developed anaphylactic shock requiring hospitalization. In patients who showed generalized urticaria, no cardiac arrhythmia, fever, or chest pain was noted. Because the test procedure was closely controlled by the protocol of multiple injections of small doses as described, TSH injections could be stopped at the earliest manifestation of an allergic reaction. Taunton et al. report that 16 of their 87 euthyroid patients (18%) showed reactions after 3–5 injections of TSH (1). Only two patients (2.2%) had urticarial rashes; the other 14 patients had symptoms that were nonspecific and could be attributed to the effects of liberated thyroid hormone.

In contrast to the series of Taunton et al. (1), the patients in our study had received large doses of TSH over a long period (up to 25 yr). The cumulative TSH dose ranged from 30 to 490 units. The reaction rate was linear up to 150 units and reached a plateau thereafter (Fig. 2). In the 18 patients who showed reactions, the mean dose of TSH was 116 units. The minimum dose of TSH received before the development of an allergic reactions was 30 units.

Commercially available TSH is often contaminated with proteins, usually albumin or globulin or both. When a highly purified TSH is injected repeatedly in humans, hemagglutinating and neutralizing antibodies directed against the pure TSH are formed, and they prevent further action of TSH on the thyroid. These antibodies do not evoke allergic reactions (6,7). On the other hand, when TSH contaminated with albumin or globulin is injected, antibodies directed against the contaminating proteins are formed. These antibodies may evoke systemic allergic reactions of the type described (2,9). In a patient reported by Sherman and Werner (2), the antibody responsible for the observed allergic reaction was found to be directed against the TSH molecule; it differed from the antibody type described by Kirkpatrick et al. (9), in which the reaginic antibody was shown to be directed against the TSH-contaminating proteins. We have also used commercial preparations of TSH, and it is likely that the antibodies responsible for the systemic allergic reactions observed were directed against contaminating proteins. The high incidence of reaction (43%) noted in our study suggests that a test dose of TSH should be administered before injecting the full dose, especially in cases where the patient has already

received one or two injections of TSH. It is not clear why the remaining 24 patients studied have not shown allergic reactions, even though they have received cumulative TSH doses larger than those received by patients who did have allergic reaction to TSH. It is possible that these patients have not yet developed reaginic antibodies. Another possibility to be considered is that a different kind of antibody may be formed—not related either to blocking or reaginic antibodies—which inactivates injected Bovine TSH and prevents its action as an effective antigen. Lately, the commercial source of TSH is claimed to be pure with less percentage of contaminating proteins. It is yet to be shown if this purer TSH would result in fewer allergic reactions.

Thyrotropin releasing hormone (TSH) is now commercially available. In the author's limited experience in four patients, varied responses to TSH stimulation were observed, and no definite conclusions could be drawn. The role of TSH stimulation in enhancing I-131 uptake by thyroid remnant in the management of thyroid cancer is an open area for more research.

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FOOTNOTE

* Thytropar, Armour, Phoenix, Arizona.

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