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EFFECT OF THE COMBINATION OF DEXAMETHASONE AND SODIUM IPODATE ON SERUM THYROID HORMONES IN GRAVES' DISEASE

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SUMMARY

To investigate the effect of the combination of dexamethasone (Dex) and sodium ipodate (SI) on hyperthyroidism, we studied 24 patients with typical Graves' disease, divided into four groups of six persons each. Three groups (Study I) were studied acutely (24 h) to determine the effects of Dex (5 mg every 12 h intramuscularly), SI (one oral dose of 3 g) and both drugs at the same doses, upon T4, T3, and rT3 at 0900 h before therapy was started and 24 h later. The group on Dex and that on SI had a similar T3 decrement of $25{\cdot}9 \pm 4{\cdot}0\%$ and $35{\cdot}8 \pm 5{\cdot}0\%$, respectively, ($P < 0{\cdot}05$), whereas the effect of both drugs combined was greater ($64{\cdot}2 \pm 3{\cdot}6\%$; $P < 0{\cdot}01$, Dex, and $P < 0{\cdot}01$, SI, respectively). The increment of rT3 was markedly greater in those patients on SI than in those on Dex ($561{\cdot}3 \pm 149{\cdot}2\%$ and $58{\cdot}9 \pm 11\%$, respectively, $P < 0{\cdot}025$). A fourth group (Study II) was studied for seven days while receiving both Dex (1 mg orally three times per day) and SI (500 mg orally three times per day). Both T4 (from $18{\cdot}8 \pm 1{\cdot}1$ to $13{\cdot}1 \pm 1{\cdot}1$ μg/dl, $P < 0{\cdot}02$) and T3 (from 593 ± 41 to $136{\cdot}3 \pm 12{\cdot}7$ ng/dl, $P < 0{\cdot}001$) decreased at day 8. The initial brisk increment of rT3 at 24 h ($808 \pm 149\%$, $P < 0{\cdot}005$) then diminished concomitantly with the fall of its precursor, T4. The pulse rate correlated with plasma T3 concentration ($r = 0{\cdot}67$, $P < 0{\cdot}001$) and varied from $104{\cdot}7 \pm 3{\cdot}9$ on day 1 to $77{\cdot}3 \pm 3{\cdot}0$ beats/min ($P < 0{\cdot}001$) on day 4 and then remained stable. These results show that Dex and SI have potent inhibitory effects at the level of peripheral conversion of T4 and on the thyroid gland itself and that the combined use of these drugs significantly increases these effects. Considering the rapid clinical improvement of thyrotoxicosis achieved with both drugs, this regimen may be valuable in the initial treatment of some patients.

About 85% of a daily production of T4 is metabolized by monodeiodination to T3, or to rT3 which is metabolically inactive (Chopra, 1976). In normal subjects about 75% of

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circulating T3 originates from peripheral conversion of T4, and 25% from direct thyroidal secretion. In hyperthyroid patients, on the other hand, the thyroidal contribution to circulating T3 rises to 50% (Abuid & Larsen, 1974).

Peripheral conversion of T4 to T3 can decrease in several clinical conditions (Bermudez *et al.*, 1975; Carter *et al.*, 1976; Burr *et al.*, 1975; Chopra *et al.*, 1975a; Chopra & Smith, 1975; Nomura *et al.*, 1975; Vagenakis *et al.*, 1975) and also with the use of glucocorticoids (Duick *et al.*, 1974), propranolol (Verhoeven *et al.*, 1977), propylthiouracil (Abuid & Larsen, 1974), and amiodarone (Burger *et al.*, 1976). In these cases decreased generation of T3 decreases circulating T3, and decreased degradation of rT3 increases circulating rT3 concentration.

Dexamethasone (Dex) (Chopra *et al.*, 1975b) and sodium ipodate (SI) (Wu *et al.*, 1978a), an iodinated radiocontrast agent, have been reported to inhibit the enzymatic peripheral conversion of T4 to T3 noncompetitively and competitively respectively (Wu *et al.*, 1978b). In addition, in cases of thyrotoxicosis a direct effect of these drugs on thyroidal hormone secretion has been described (Williams *et al.*, 1975; Chopra *et al.*, 1975b; Wu *et al.*, 1978a, 1978b).

We were therefore interested in determining whether or not the combination of Dex and SI results in the summation of their individual effects upon thyroid hormones and whether or not this effect continues when this drug combination is administered to humans for seven days.

PATIENTS AND METHODS

Patients

Twenty-four patients (2 men and 22 women, 17 to 52 years of age) with untreated Graves' disease were studied. The diagnosis was based on typical clinical findings: diffuse goitre, ^{131}I uptake $>40\%$ at 24 h, and increased circulating concentrations of T4 and T3. Six patients had infiltrative ophthalmopathy and ten had pretibial myxoedema.

Patients were divided into four groups of six. Each group was studied according to the following protocol after informed consent had been obtained from each patient. The study was approved by the Catholic University of Chile Ethics Committee.

Study I (Acute protocol)

Blood was obtained from the antecubital vein at 0900 h on two consecutive (pre- and post-therapy) days for determination of T4, T3, and rT3 in the following patients.

Group A (patients 1–6): Each patient received 5 mg of Dex intramuscularly at 0900 h and at 2100 h.

Group B (Patients 7–12): Each patient received 3 g of SI orally at 0900 h (Biloptinin, Schering A.G., West Berlin).

Group C (patients 13–18): Each patient received 5 mg of Dex intramuscularly and 3 g of SI orally at 0900 h and 5 mg of Dex intramuscularly at 2100 h.

Study II (Prolonged protocol)

Patients 19–24 received 1 mg of Dex and 500 mg of SI orally every 8 h (0700 [except for the first dose], 1500, and 2300 h) for a total of 22 doses per patient. The first dose of the study was administered at 0900 h after control blood samples had been obtained.

After resting for 20 min, the pulse rate was recorded and blood was obtained for T4, T3,

and rT3 determinations at 0900 h on days 1 (control), 2, 4, 6, and 8. Upon completion of these studies, all patients started conventional therapy with propylthiouracil (PTU).

Methods

All serum samples were stored at −20°C until they were assayed in one batch. The serum T3, T4, and rT3 concentrations were determined by radioimmunoassay, the T3 and T4 assay being by methods previously described (Chopra *et al.*, 1971; Chopra, 1972). The anti-rT3 antibody was obtained from the Endocrine Laboratory, Hospital del Salvador, Santiago, Chile, and had less than 1:8000 cross-reactivity with T4 (Silva & Silva, 1981).

Statistical analysis was performed by paired Student's *t*-test. To compare the responses of the three groups in Study I, one-way analysis of variance test was used, followed by the Student-Newman-Keuls test. Correlation analysis (*r*) was performed between T3 and pulse rate in Study II. A *P* value $<0{\cdot}05$ was considered significant. All values are expressed as mean ± standard error (SE).

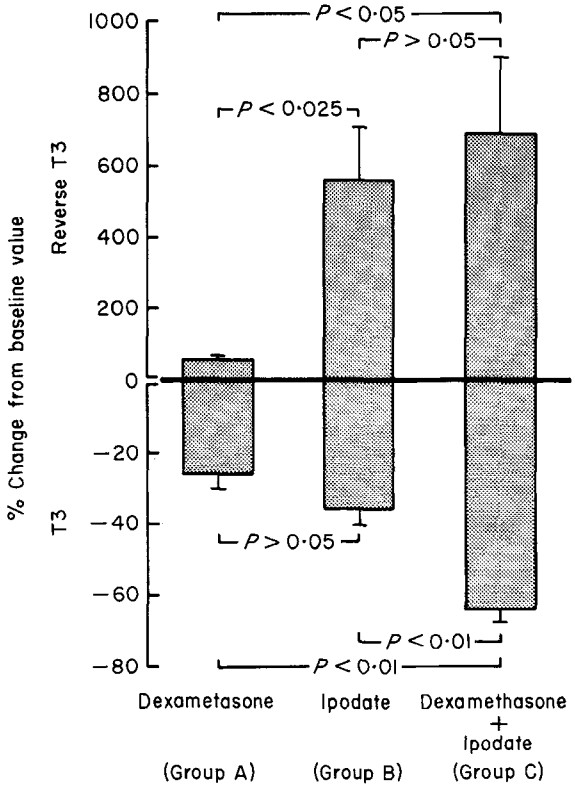

Fig. 1. Percent change from baseline of serum concentations of rT3 and T3 in three groups of six patients with Graves' disease. Group A received dexamethasone (5 mg intramuscularly at 0900 and 2100 h), Group B received sodium ipodate (3 g orally at 0900 h), and Group C received dexamethasone and sodium ipodate (Dex 5 mg intramuscularly at 0900 and 2100 h and SI 3 g orally at 0900 h). Values are presented as mean ± SE. Statistical analysis was performed by one-way variance analysis followed by Student-Newman-Keuls test.

RESULTS

Study I: Control concentrations of T4, T3, and rT3 were not significantly different between Groups A, B, and C. (See Table 1 and Fig. 1).

Group A: Dex administration resulted in a mean decrease of 25·9 ± 4·0% ($P < 0·05$) in T3 and an increase of 58·9 ± 11% ($P < 0·005$) in rT3. Thyroxine did not change.

Group B: Sodium ipodate administration resulted in a mean decrease of 35·8 ± 5·0% ($P < 0·01$) in T3, a value that did not differ significantly from that obtained in Group A. However, rT3 increased 561·3 ± 149·2% ($P < 0·01$), which was more than the increase observed in Group A ($P < 0·025$). Thyroxine did not change significantly.

Group C: The combination of Dex and SI decreased T3 by 64·2 ± 3·6% ($P < 0·02$), a greater decrease than that observed either in Group A ($P < 0·01$) or Group B ($P < 0·01$).

Table 1. Acute effect (24h) of dexamethasone (Dex), sodium ipodate (SI), and combined Dex and SI on thyroid hormones in 18 female patients with Graves' disease

Group A (Dex)*					Group B (SI)*					Group C (Dex+SI)*				
Case no.	Age (years)		Basal	Post Dex	Case no.	Age (years)		Basal	Post SI	Case no.	Age (years)		Basal	Post Dex+SI
1	34	T4	17·4	17·3	7	30	T4	13·4	14·2	13	22	T4	19·1	19·9
		T3	530	370			T3	247	180			T3	384	125
		rT3	174	353			rT3	88	166			rT3	235	821
2	27	T4	22·2	21·2	8	45	T4	21·4	22·2	14	47	T4	21·6	18·6
		T3	690	640			T3	533	257			T3	610	188
		rT3	204	305			rT3	188	1650			rT3	170	2876
3	43	T4	20·3	27·4	9	24	T4	15·2	13·6	15	52	T4	18·5	19·1
		T3	540	370			T3	362	209			T3	529	196
		rT3	246	365			rT3	226	1805			rT3	370	1541
4	25	T4	17·5	15·9	10	35	T4	16·8	17·3	16	47	T4	15·6	18·5
		T3	271	197			T3	398	268			T3	372	158
		rT3	137	180			rT3	370	1581			rT3	122	894
5	43	T4	19·2	21·9	11	43	T4	17·5	21·5	17	24	T4	16·6	17·3
		T3	1190	780			T3	574	345			T3	1220	289
		rT3	273	387			rT3	192	2303			rT3	334	3658
6	35	T4	21·3	19·9	12	28	T4	20·3	21·3	18	37	T4	17·4	18·1
		T3	450	339			T3	492	398			T3	449	217
		rT3	117	210			rT3	330	1571			rT3	180	731
Mean ±SE		T4	19·7 ±0·8	20·6 ±1·7	Mean ±SE		T4	17·4 ±1·2	18·4 ±1·6	Mean ±SE		T4	18·1 ±0·9	18·6 ±0·4
		T3	612 ±128	449† ±88			T3	438 ±51	276‡ ±34			T3	594 ±130	196§ ±23
		rT3	192 ±25	300¶ ±35			rT3	232 ±42	1513‡ ±292			rT3	235 ±40	1754† ±503

* Values are expressed in μg/dl for T4 and in ng/dl for T3 and rT3. Statistical analysis in relation to basal values was performed by paired Student's *t*-test.

† $P < 0·05$.

‡ $P < 0·01$.

§ $P < 0·02$.

¶ $P < 0·005$.

Table 2. Prolonged effect (7 days) of simultaneous administration of dexamethasone (Dex) and sodium ipodate (SI) in 6 patients with Graves' disease

Case no.	Age (years)	Sex		Days of study 1 (baseline)	2	4	6	8
19	30	F	T4	23·8	19·1	16·3	14·5	13·9
			T3	700	233	128	127	142
			rT3	234	2513	1812	1843	1280
			PR	98	93	78	68	70
20	21	M	T4	17·9	16·7	14·7	11·3	9·2
			T3	732	135	159	154	157
			rT3	314	2706	2751	1924	1103
			PR	116	114	88	84	80
21	17	M	T4	18·3	19·5	14·9	14·4	11·2
			T3	560	182	110	86	118
			rT3	165	2569	2058	1323	1050
			PR	107	104	84	88	80
22	38	F	T4	15·4	14·9	14·2	16·2	15·3
			T3	473	246	148	184	162
			rT3	171	1288	757	720	790
			PR	102	71	70	70	82
23	30	F	T4	19·7	19·7	17·7	14·6	12·5
			T3	538	172	142	79	82
			rT3	251	1633	1913	1271	1115
			Pr	114	76	74	72	70
24	36	F	T4	17·9	17·2	17·3	17·1	16·7
			T3	553	216	162	169	157
			rT3	217	1199	1327	1035	836
			PR	91	76	70	70	70
Mean			T4	18·8	17·9	15·9†	14·7†	13·1‡
±SE				±1·1	±0·8	±0·6	±0·8	±1·1
			T3	593	197§	142§	133§	136§
				±41	±17	±8	±18	±13
			rT3	225	1985¶	1770¶	1353¶	1029§
				±23	±281	±276	±189	±75
			PR	105	89	77§	75§	75§
				±4	±7	±3	±4	±2

Oral administration of SI (500 mg each 8 h) plus Dex (1 mg each 8 h) was started at 0900 h on day 1, after basal blood samples were obtained, and stopped at 0700 h on day 8 (22 doses in total). Statistical analysis, comparing each day with the baseline, was performed by paired Student's *t*-test. Values are expressed as μg/dl for T4 and ng/dl for T3 and rT3. PR = pulse rate (beats/min).

† $P < 0.05$.

‡ $P < 0.02$.

§ $P < 0.001$.

¶ $P < 0.005$.

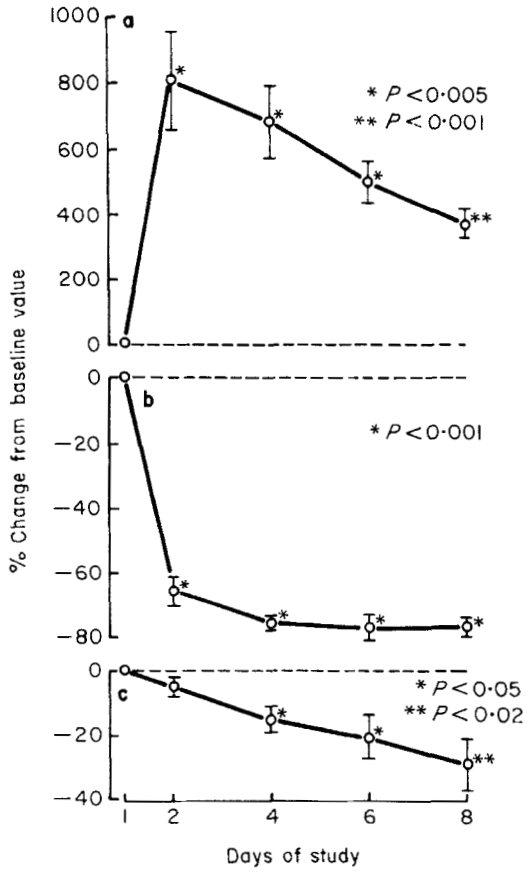

Fig. 2. Percent change from baseline (day 1) of serum concentration of **a**, rT3; **b**, T3; and **c**, T4 during administration of 22 oral doses of dexamethasone (1 mg every 8 h) and sodium ipodate (500 mg every 8 h), started at 0900 h on day 1 after baseline samples were obtained in six patients with Graves' disease. Data are presented as mean ± SEM and P values were determined by using paired Student's t-test for comparison of values at each point of study with the baseline value.

The rT3 increased by 689·5 ± 212·4% ($P < 0·05$), a value greater than that in Group A ($P < 0·05$) but similar to that in Group B. Thyroxine did not change significantly.

Study II: As shown in Table 2 and Fig. 2, 24 h after starting Dex and SI co-administration, T3 decreased by 65·5 ± 4·5% ($P < 0·001$) in a fashion similar to that observed in Group C of Study I, reaching a maximal decrease of 75·6 ± 2·2% on day 4 ($P < 0·001$) and then remained at that level until day 8. Thyroxine decreased significantly on day 4 by 14·9 ± 4·1% ($P < 0·05$), reaching a maximal fall of 28·8 ± 8·2% ($P < 0·02$) on day 8. The rT3 sharply increased 808 ± 149% at 24 h ($P < 0·005$) but declined subsequently. On day 8, rT3 still was 371 ± 43% higher than control values ($P < 0·001$). Control pulse rate was 104·7 ± 3·9 beats/min, decreased to 77·3 ± 3·0 beats/min on day 4 ($P < 0·001$), and remained stable until the end of the study. There was a positive correlation ($r = 0·67$, $P < 0·001$) between pulse rate and circulating concentrations of T3.

DISCUSSION

Our study shows that in patients with Graves' disease both Dex and SI inhibit the peripheral conversion of T4 to T3. This is demonstrated by the fall of circulating plasma T3 and the rise in rT3 (Fig. 1). The depressant effect upon T3 did not differ between the two drugs (Study I), but the rise in rT3 was significantly greater with administration of SI. This apparent discrepancy may be due to a greater direct action on the thyroid gland in the case of Dex and a principal action on the peripheral conversion in the case of SI (Williams *et al.*, 1975; Wu *et al.*, 1978a). This can explain the similar fall in T3 with both drugs and the different rise in rT3. It can also explain the greater fall in T3 when both drugs were administered together than when they were used separately. This effect in T3 was obtained with supramaximal doses of both drugs, as in Study II we obtained the same fall in T3 in 24 h using a smaller dose of each drug.

The use of both Dex and SI for 7 d (StudyII) produced a progressive fall in plasma T3 concentration, reaching a nadir at day 4 (Fig. 2) and remaining there until the end of the study period. It is interesting to note that all six patients reached normal levels of T3 after 72 h of treatment (Table 2).

The huge and brisk rise in rT3 during the first day of the combined drug treatment (Studies I and II) confirms their potent combined effect on the peripheral conversion of T4 to T3. On the other hand the progressive fall in T4, which was significant after 72 h of treatment (Study II), implies a direct action on the thyroid gland itself. This action can be the result of the inhibition by Dex of some thyroid-stimulating immunoglobulins (Williams *et al.*, 1975) plus the liberation by SI of a great amount of iodine, thereby inhibiting liberation of thyroid hormone from the thyroid gland (Wu *et al.*, 1978a). In the longer study, the initial increase in rT3 was followed by a fall as its precursor T4 fell.

Clinically, the fall in T3 was associated with improvement of signs and symptoms of hyperthyroidism and a significant fall in pulse rate (Table 2). Combined Dex and SI therapy could be effective in specific situations that require an acute response when a delayed response to propylthiouracil is dangerous. Propylthiouracil has been used successfully with SI (Sharp *et al.*, 1981), and the combination of Dex-SI plus propylthiouracil may be considered as an additional antihyperthyroid regimen with Dex-SI providing a rapid clinical response and propylthiouracil effecting long-term control of the disease.

No complications or adverse effects of Dex-SI usage for one week were observed except that the great amount of iodine administered with SI prevented the use of therapeutic ^{131}I for several months. It must be noted that after the use of SI, exaggerated hyperthyroidism could occur because of the high concentration of iodine in the thyroid gland. This was not observed in our study or that of Wu *et al.* (1978b). Long-term management (6–12 months) with PTU, after concomitant treatment with Dex-SI had been discontinued, showed the usual response seen in other patients with Graves' disease. In only one of the patients in the prolonged study with Dex-SI was a high dosage of PTU (600 mg/d) necessary to achieve euthyroidism. One can speculate that the need for this unusual dosage could be related to the amount of iodine given during SI therapy. No side effect related to Dex administration was detected. However, one can expect that prolonged usage of corticosteroids in the doses used in this study would produce secondary effects.

In summary, the combined use of Dex and SI acting directly on the thyroid gland and

on peripheral conversion of T4 can effect acute clinical improvement of hyperthyroidism, which may be useful in some situations that require such an acute response.

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