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THE TREATMENT OF EXPERIMENTAL HYPOPARATHYROIDISM IN DOGS

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In subtotal thyroidectomy in human subjects, a significant amount of the parathyroid tissue is frequently removed, so that some of these patients show the characteristic symptoms of hypoparathyroidism. Although preparations of parathyroid hormone are available for the treatment of this condition, administration of dihydrotachysterol (Hytakerol) has become largely the method of choice, and clinical experience with it has been almost entirely favorable (1 to 3). A review of the chemical and biological properties of this preparation has been published by another investigator (4). Vitamins D₂ and D₃ are calcemic and therefore might also be satisfactory for the treatment of these patients on theoretical grounds. In fact, there are clinical reports which indicate that the substitution may be made (5 to 8). It has been pointed out (9) that the chief bar to such substitution is psychological, *i.e.*, there is a fear of overdosage (since adequate therapy may require millions of units) or of toxicity (since the early preparations of vitamin D₂ did actually contain toxic irradiation by-products). A comparative study of the effects of adequate doses of the 3 preparations on the calcium and phosphorus metabolism of the normal dog has been reported from this laboratory (10).

Since data on human subjects are accumulated very slowly, it seemed worth while to carry out a study of the treatment of parathyroid insufficiency in dogs, comparing the methods of treatment now commonly used; namely, the administration of calcium salts, parathyroid extract, vitamin D₂, vitamin D₃, and dihydrotachysterol. The purpose of this work has been (a) to determine the doses of these preparations required to bring dogs from the borderline of tetany to normal or slightly-elevated serum calcium values, (b) to determine the duration of action of therapeutic doses, and (c) to compare the calcium and phosphorus metabolism of normal and thyroid-parathyroidectomized dogs. It was hoped that the principles

which might be developed would facilitate and stimulate further comparative trials of the 3 principles in the treatment of human parathyroid insufficiency.

EXPERIMENTAL METHODS

Ten adult mongrel dogs in good health were selected as experimental subjects. They were taken in 2 groups of 5 in order that the principles discovered experimentally in the first group could be checked in the second group. For a period of several weeks the first group of animals was accustomed to a standard diet consisting of Old Trusty Supreme Meal,¹ 1 per cent of bone meal (to prevent diarrhea) and 1 pint of milk daily (Diet I). The diet was given in adequate amounts for the size of the dogs involved. However, later it was found necessary to change this diet to one having a lower calcium and phosphorus content, but with the same caloric value.

During the preliminary control period a number of determinations of serum calcium and phosphorus were made. The values found fell within the normal range of calcium, 9.5 to 11.2 mgm. per cent, and phosphorus, 3.5 to 5.5 mgm. per cent, except that 1 dog usually had a phosphorus of 7 to 8 mgm. per cent. Calcium was determined (usually 3 times weekly throughout the experiment unless stated otherwise) by the method of Clark and Collip (11), and phosphorus (less frequently) by the method of Fiske and Subbarow (12).

Total thyroid- and parathyroidectomy was performed under aseptic conditions. Calcium determinations were then made daily until such time as the dog went into tetany, or until the serum calcium fell to very low levels (*i.e.*, 7.5 mgm. per cent or less). This usually occurred within 2 or 3 days but in a few cases was delayed as long as 6 or 7 days. When the serum calcium fell to these low levels the animals were considered ready for study.

RESULTS

The experimental protocols are too extensive to give in detail. The pertinent data for 1 typical

¹ Manufactured by Old Trusty Dog Food Company, Needham Heights, Mass. Their analysis:

Protein	28 per cent	Fiber	3.5 per cent
Fat	4 per cent	Ash	10 per cent
Carbohydrate	47 per cent	Calcium Phosphorus ratio	1.5/1

Our analysis:

Calcium 1.47 per cent; Phosphorus 0.75 per cent

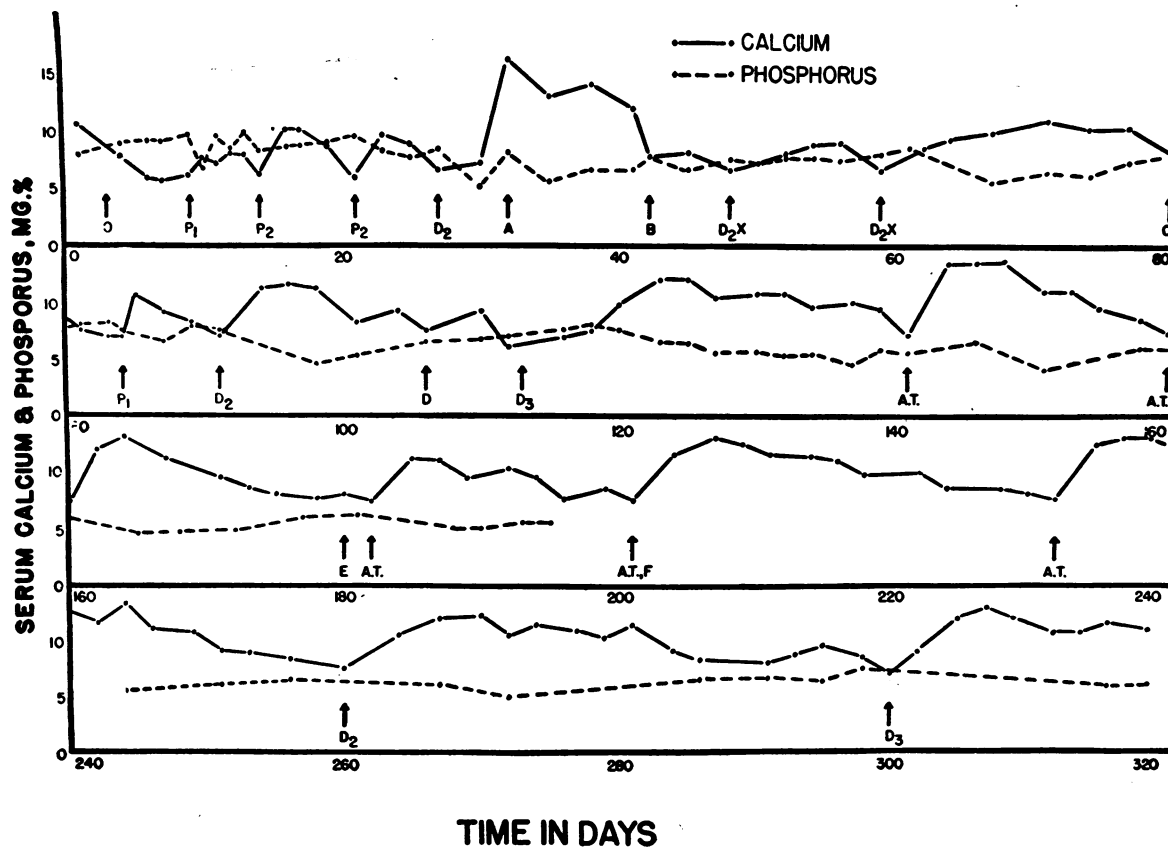


FIG. 1. BLOOD SERUM CALCIUM AND INORGANIC PHOSPHORUS OF 1 DOG FOR THE ENTIRE EXPERIMENTAL PERIOD

- O = Operated
- P₁ = Parathyroid extract, 50 units per kgm.
- P₂ = Parathyroid extract, 100 units per kgm.
- D₂ = Vitamin D₃, 2 mgm. per kgm.
- A = Changed to liver diet
- B = Returned to diet I
- D₂X = Vitamin D₃, 0.5 mgm. per kgm.
- C = Changed to liver diet
- D = Changed to diet II
- D₃ = Vitamin D₃, 2 mgm. per kgm.
- A.T. = Dihydratachysterol, 1 mgm. per kgm.
- E = Added calcium carbonate to give calcium/phosphorus: 2/1 in diet
- F = Returned to diet I

animal, for the entire experimental period, are given graphically in Figure 1, and a summary of the data on all of the animals is given in Table I. The following is a general characterization of the results and the principles derived from them.

1. *Treatment with calcium gluconate.* A suspension of calcium gluconate in water was given orally in quantities sufficient to represent 1 or 2 grams per kgm. body weight per day (1 dose per day). In addition, the animals were given 1 or

2 grams of ammonium chloride in the form of enteric-coated tablets for the purpose of relieving their alkalosis (13). In this way, it was possible to keep them alive and clinically in good condition, although the serum calcium was never found to rise over 7 mgm. per cent. In the few cases where the animals actually went into tetany, calcium gluconate was injected intravenously as a 5 per cent solution, and afterward oral calcium gluconate administration sufficed.

TABLE I

Effect of various medications and diets on the response of the parathyroidectomized dog

Medication	Units	Average serum calcium			Duration of response	Diet**
		Initial	Peak	Increase		
	<i>mgm. per kgm.</i>				<i>days*</i>	
Parathyroid extract	50	7.0	8.8	1.8	11	I
	50	6.0	9.1	3.1	7	Liver
	50	7.4	11.0	3.6	9	III
	100	6.5	9.6	3.1	10	I
	100	7.3	11.4	4.1	7	III
Vitamin D ₂	5	7.2	17.4	10.2	60	I, II
	2	6.7	16.4	9.7	31	I
	2	7.2	12.3	5.1	24	II
Vitamin D ₃	2	7.8	12.4	4.6	28	III
	2	7.2	12.2	5.0	26	II
	2	7.5	12.9	5.4	27	III
Dihydro-tachysterol	1	7.5	12.8	5.3	41	II
	1	6.8	14.0	7.2	33	III

* Defined as the elapsed time until the serum calcium again fell below 8 mgm. per cent.

** The composition of the diets is stated in the text. The analysis follows: Diet I, 2.40 per cent calcium, 1.15 per cent phosphorus; Diet II, 0.35 per cent calcium, 0.48 per cent phosphorus; Diet III, 0.96 per cent calcium, 0.55 per cent phosphorus. Liver contains about 0.02 per cent calcium, 0.53 per cent phosphorus (variable).

2. *Treatment with parathyroid extract.* The extract was injected as single doses intramuscularly at 2 different levels: 50 and 100 units per kgm. body weight. The response to this treatment was somewhat variable both as to magnitude and duration of rise in serum calcium. In general a dose of 100 units per kgm. caused a maximal rise of 3 to 4 mgm. per cent in serum calcium and a fall of 1 to 3 mgm. per cent in serum phosphorus. The rise in calcium was usually noted within 24 hours, and the maximal rise was ordinarily noted then, although in some cases higher values were obtained on the third or fourth day post-medication. The elevated calcium values persisted for about 7 days as a rule. This is in marked contrast to the response of normal dogs in which an elevated serum calcium persists for only 18 to 36 hours post-medication (14, 15). The response was not noticeably affected by diet, and the difference between the responses to dosages of 50 and 100 units per kgm. was rather small.

The animal considered to be the most typical responded as follows: After a dose of 50 units per kgm. body weight, the serum calcium rose on the third day to a level of 1.8 mgm. per cent above its base line (6.3 mgm.

per cent). The serum phosphorus fell 2.8 mgm. per cent on the first day after medication, but rose again to its base line (9.7 mgm. per cent) on the second day. On the fifth day, both calcium and phosphorus values were at their original levels, and a dose of 100 units per kgm. was given. On the second day after this dose, the serum calcium had increased by 3.9 mgm. per cent. No change in serum phosphorus was noted. The base level for calcium was reached on the seventh day, when another dose of 100 units per kgm. was given. The maximal rise was again 3.9 mgm. per cent on the second day with the base level reached on the seventh day. There was a slight temporary fall in serum phosphorus.

3. *Treatment with vitamin D₂.* The general principles we followed in studying the activated sterols were: (1) to determine the amount of the single dose required to elevate the serum calcium from a value of 6 to 8 mgm. per cent to 11 to 12 mgm. per cent, and (2) to study the duration of the effects of single doses so chosen.

It was found earlier (10) that doses of 5 mgm. per kgm. of vitamin D₂ (that is, 200,000 I.U. per kgm.) would cause a rise of 4 to 6 mgm. per cent in the serum calcium of a normal dog. Accordingly, this dosage was given orally in oil to the parathyroidectomized dogs. It proved to be far too much; the serum calcium of the dogs so treated rose rapidly to 16 to 18 mgm. per cent and remained at that level for several days. A more physiological level was obtained by changing the diet. The milk was removed from the diet, and then the bone meal. Finally, it was necessary to remove the Old Trusty Meal and substitute liver, a substance containing phosphorus, but practically devoid of calcium. This brought the calcium down to 8 to 9 mgm. per cent, but any substitution of the original ingredients of the diet produced an immediate rise. A physiological serum calcium value could only be maintained on the very low calcium diet. Subsequently on other animals it was found that a dose of 2 mgm. per kgm., with the original diet, still gave too great a response. However, a dose of 0.75 to 1 mgm. per kgm. gave a rise of 4 to 5 mgm. per cent, which was of the desired magnitude.

In later experiments, a diet (Diet II) consisting of (for a 10-kgm. dog), raw beef liver, 417 grams, Old Trusty Meal, 82 grams, and bone meal, 1.7 grams, was given. This diet contained 0.35 per cent calcium and 0.48 per cent phosphorus. For one period of about a month, it was necessary to substitute pork kidney for beef liver; this did not alter the calcium and phosphorus content of the whole diet appreciably. The diet yielded, for a 10-kgm. dog, 1.75 grams of calcium, 2.40 grams of phosphorus per day. In general, it was completely consumed.

On this diet the dogs at least maintained their body weights and some gained rapidly. A parathyroidectomized dog receiving this diet, and a single dose of 2 mgm. per kgm. of vitamin D₂ (when its serum calcium

was 7 to 8 mgm. per cent), responded with a maximal rise to 11.5 to 13.5 mgm. per cent, usually on the third or fourth day after medication, but occasionally later, and did not need another treatment for 3 to 6 weeks. The average protection was about 35 days.

4. *Treatment with vitamin D₃*. When the work with vitamin D₃ was begun, most of experimental difficulties had been corrected, and it was possible to proceed more directly to the final conclusion. The animals were continued on Diet II and a single dose of 2 mgm. per kgm. was invariably given. The responses very closely paralleled those observed for vitamin D₂. The maximal rise noted was to a level of 11.7 to 13.7 mgm. per cent at from 3 to 7 days post-medication. A rise of this magnitude would require a dosage of 5 mgm. per kgm. in the normal dog. The duration of the response was usually 23 to 30 days, or not particularly different from what was observed (10) in the normal dog. (It was considered that the response was at an end when the serum calcium again fell below 8 mgm. per cent.) The general picture with vitamin D₃ does not differ significantly from that observed with vitamin D₂.

5. *Treatment with dihydrotachysterol*. The bioassay of this material on the basis of its hypercalcemic effect was described in an earlier paper (16). Of the commercial material, 1 ml. contains about 1.25 mgm. of the active principle, and this principle has about twice the calcemic effect of vitamins D₂ or D₃ in the rat (9, 17) but more than twice the calcemic effect of vitamins D₂ and D₃ in the normal dog (10). In human hypoparathyroid subjects, the ratio seems to be about 6:1 since between 4 and 8 mgm. of vitamin D₂ are equivalent to each mgm. of dihydrotachysterol (8, 9). As a first approximation, it was decided to give the dogs 1 mgm. per kgm. of dihydrotachysterol in conjunction with the same diet (II) as used for the vitamin D₃ experiments. The serum calcium rose to the desired levels; the maxima were 11.4 to 14.6 mgm. per cent (usually about 13.0 mgm. per cent) on the third to fifth day post-medication, and the duration of the response was usually 16 to 40 days. Therefore, other dose levels were not investigated.

One animal received 5 successive treatments with this preparation (see Figure 1). The initial serum calcium values were always 7.4 to 7.8 mgm. per cent, and the peak values were 11.4 to 13.9

mgm. per cent. The duration of the response was 19 to 30 days. A radical increase in the calcium content of the diet (from 0.38 per cent calcium, 0.46 per cent phosphorus, to 0.92 per cent calcium, 0.46 per cent phosphorus) did not alter the character of the response either as to magnitude or duration.

REPETITION OF EXPERIMENTS

In order that the conclusions could be verified under better controlled conditions, and profiting by the principles already developed, a second group of dogs was prepared for experiment. They were kept from the outset on a diet (Diet III) containing (for a 10-kgm. dog) Old Trusty Meal, 98 grams, dried bread crumbs, 125 grams, bone meal, 2 grams. This was mixed with water to form a mixture of suitable consistency, and in general it was completely consumed. The dogs all maintained body weight on this diet and some showed considerable gain. The diet analyzed 0.96 per cent calcium, 0.55 per cent phosphorus, and yielded, for a 10-kgm. dog, 2.15 grams calcium and 1.23 grams phosphorus per day.

After the normal serum calcium and phosphorus values had been determined, the reaction of the dogs (before operation) to the dosages of the preparations to be given later was determined. Three dogs received 2 mgm. of vitamin D₂ per kgm. body weight, and their maximal rise in serum calcium averaged 2.2 mgm. per cent (range, 0.8 to 4.5 mgm. per cent). Five dogs received 2 mgm. per kgm. body weight of vitamin D₃, and their average maximal rise in serum calcium was 1.3 mgm. per cent (range, 0 to 3.4 mgm. per cent). Five dogs received 1 mgm. per kgm. body weight of dihydrotachysterol, and their average maximal rise in serum calcium was 4.5 mgm. per cent (range, 2.2 to 6.3 mgm. per cent). Serum phosphorus changes were not striking with any of the 3 products.

After the thyroid-parathyroidectomy, the animals were followed as before at daily intervals until the serum calcium fell below 8 mgm. per cent. Each dog then received a dosage of 50 units parathyroid extract per kgm. body weight, followed by a second dosage of 100 units per kgm. as soon as a calcium level below 8 mgm. per cent had been reached after the first. The maximal rise obtained (3.5 mgm. per cent) and the duration of the response (about 7 days) were practically the same for both dosages.

The dogs were then treated successively with vitamin D₂, vitamin D₃, and dihydrotachysterol in the dosages previously used. The serum calcium in each case rose from about 7.5 mgm. per cent to a level of 12.5 to 14.5 mgm. per cent on the third to seventh day post-medica-

tion, and did not fall below 8 mgm. per cent again for 25 to 35 days. In general the dihydrotachysterol caused greater rises in serum calcium than did the other 2 preparations, suggesting that, if anything, it is somewhat more than twice as active hypercalcemically in the dog.

DISCUSSION

The manner in which parathyroid extract and the activated sterols bring about a rise in serum calcium has been the subject of considerable investigation. The generally accepted hypothesis (18 to 20) which has been supported by other workers (21) is based on the reciprocal relationship of serum calcium and phosphorus and supposes that the various principles act either by increasing the renal excretion of phosphate or intestinal absorption of calcium. A preparation such as parathyroid extract, which was believed to act ultimately by increasing renal excretion of phosphate, was supposed to increase serum calcium chiefly by mobilization of bone salt. Vitamin D was believed to act ultimately by increasing intestinal absorption of calcium, and dihydrotachysterol appeared to occupy an intermediate position.

Recent work (22 to 24) has tended to show that this hypothesis, insofar as parathyroid hormone is concerned, is not entirely adequate. The hormone is capable of causing a solution of bone salt even in nephrectomized animals. No evidence has been brought forward to show that the hypothesis outlined is incorrect as to the mode of action of the activated sterols.

It is felt that the present work has some bearing on this problem. Thus, it has been shown that vitamin D has a considerably greater calcemic action in the thyroid-parathyroidectomized dog than in the normal animal. (This is in agreement with the findings of a group of workers on human subjects (25).) It must be kept in mind, however, that in these animals the thyroid glands were completely removed so that the dogs suffered from a thyroid deficiency, not usually observed in the human patients. This action depends on the calcium content of the diet. On a diet of average calcium content (for a normal dog), a dose of 5 mgm. per kgm. of vitamin D₂ produces an alarming rise (about 10 mgm. per cent) in the serum calcium of the parathyroidectomized dog. By the simple expedient of removing practically all of the calcium of the diet, the serum calcium may be

brought down to physiological levels (or even lower), and may be caused to rise rapidly again by restoring the calcium to the diet. These observations suggest that in the parathyroidectomized dog the elevation of serum calcium is accomplished, following vitamin D, by increased absorption from the gut. However, the animal lacks the ability to stop, or otherwise compensate for (by increased excretion or bone formation), the absorption process once the normal calcium level is reached. A normal dog, receiving the same diet and vitamin dosage, shows a more moderate rise in serum calcium (4 to 5 mgm. per cent), indicating that it has a greater ability to regulate serum calcium at physiological levels in spite of the increased absorption which is known to occur.

The present theories of the action of vitamin D and of the parathyroid gland do not appear to explain satisfactorily why vitamin D should produce a greater calcemic effect in the parathyroidectomized dog than in the normal dog. Furthermore, the administration of parathyroid extract to the parathyroidectomized dog does not cause it to react to vitamin D like a normal animal. We have found that parathyroidectomized dogs which have a serum calcium of 8 mgm. per cent, and which receive a dose of vitamin D₂ (2 mgm. per kgm.) usually sufficient to raise the serum calcium to 11 to 12 mgm. per cent, but which also receive simultaneously 100 units per kgm. of parathyroid extract, respond with a peak serum calcium value of 15 to 18 mgm. per cent. The parathyroid extract, instead of diminishing the effect of vitamin D, has an additive effect. This suggests that the intact parathyroid gland is in some manner able to react positively against elevated serum calcium (perhaps by decreasing the renal threshold for calcium), and that this antagonistic principle is not contained in the parathyroid extracts prepared according to Collip and Clark.

As is well known, parathyroid extract has been found to raise serum calcium while decreasing serum phosphorus. On the other hand, a massive dose of vitamin D in the parathyroidectomized dog causes a rise in *both* calcium and phosphorus. We observed in 1 animal a serum calcium of 16 and a phosphorus of 10 following an overdose of vitamin D₂.

Dihydroxycholesterol produces much the same responses in the parathyroidectomized dog as it does in the normal dog. Thus, in the normal dogs a dosage of 1 mgm. per kgm. causes an average rise of 4.5 mgm. per cent. Postoperatively in the same dogs this dosage caused an average rise of 7.7 mgm. per cent. Similarly, a dosage of vitamin D₂ which caused an average rise of 2.2 mgm. per cent normally caused an average rise of 5 mgm. per cent postoperatively, and for vitamin D₃ the corresponding figures were 1.3 and 5.7 mgm. per cent. The differences among the 3 preparations are not great but are consistent with the view that dihydroxycholesterol does not act in exactly the same manner. The experiment in which the calcium content of the diet was radically increased without affecting the response to dihydroxycholesterol supports the same view. Two investigators (26) have concluded that the administration of dihydroxycholesterol causes: (1) an increase in urinary phosphate excretion with the serum phosphorus becoming normal, (2) an increase in the absorption of calcium with higher serum calcium, and (3) no increased output of phosphate in advanced renal damage.

The 3 activated sterols were equally suitable for the management of parathyroid insufficiency in the dog so far as the criteria used in these experiments could distinguish. Where it is possible to judge from other symptoms, as in human subjects, the same would not necessarily apply (8).

SUMMARY

A series of thyroid-parathyroidectomized dogs has been treated with calcium salts, parathyroid extract, vitamins D₂ and D₃, and dihydroxycholesterol. With calcium salts, tetany could be avoided, but the serum calcium levels remained very low. Parathyroid extract in dosages of 50 or 100 units per kgm. elevated the serum calcium for periods averaging about 5 days. Normal serum calcium levels (above 9 mgm. per cent) prevailed for about 2 to 3 days of this time.

On a diet of medium calcium and phosphorus content, a single dose of 2 mgm. per kgm. of either vitamin D₂ or D₃ produced a rise in serum calcium of about the desired magnitude (from a base level of 7 to 8 mgm. per cent to a peak value of 11 to 12 mgm. per cent), and the effect lasted

(*i.e.*, the serum calcium did not fall below 8 mgm. per cent) for 25 to 35 days. There was no significant difference in the duration of the effects of the 2 vitamins. It was possible to produce an effect of about the same duration and of slightly greater magnitude by giving 1 mgm. per kgm. of dihydroxycholesterol. The quantities mentioned appear to be equivalent for the parathyroidectomized dog.

The possible bearing of the observations on the mechanism of the action of the activated sterols is discussed.

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