Since the realization that vitamin D could cause increased calcium absorption and hypercalcemia, the vitamin has been used in the treatment of Hypoparathyroidism, whatever its origin. Relatively little is written about this treatment, and it remains more of an art than a science. For this reason, it is best practiced by those who see the condition frequently rather than by those who are unfamiliar with the problem. Inevitably in this situation much will depend on personal preference rather than universally accepted practice. The contents of this chapter reflect this situation; it illustrates the views and practices of the author.

Interestingly, there are wide variations in treatment regimes used in different parts of the world. To some extent this depends on the preparations of vitamin D, its analogs, and its metabolites that are available. In the United States and in the United Kingdom, vitamin D2 (calciferol, ergocalciferol) and to a lesser extent vitamin D3 (cholecalciferol) have been used rather commonly. Dihydrotachysterol (Tachyrol, AT10) has been used extensively in the United States and in mainland Europe and to some extent in the United Kingdom. 25-Hydroxy cholecalciferol has been available in the United States, while 1 alpha Hydroxy cholecalciferol (Alfacalcidol, 1 alpha-alfacalcidol) has been available in Europe but not in the United States. 1,25-Dihydroxycholecalciferol (Calcitriol, Rocaltrol) has been available both in Europe and in the United States.

At this point, let me define several terms. When a particular form is being considered, it will be given its own name, but, when a general comment is being made, the term "vitamin D" is used and this will apply to any of the forms of the vitamin that were introduced above.

The advantage of using 1-hydroxylated forms of vitamin D is that they act more quickly. The serum calcium can rise with their use, from 1.5 millimol/liter (6 milligram/dl) up to 2.2 millimol/liter (8.8 milligram/dl) in only a few rather than the few weeks it would take if vitamin D or vitamin D3 had been administered. The 1-hydroxylated forms of vitamin D are also much more potent. While the maintenance dose of Calcitriol might be 0.5 micrograms/day and that for 1 alpha might be 1 microgram/day, it might be necessary, to give as much as 1-2 mg of vitamin D2 or vitamin D3 (40,000-80,000 units a day). Just as the action of 1-hydroxylated compounds develops more rapidly, so the effect of their excess disappears more quickly. Thus hypercalcemia can be reversed within a few days if Calcitriol treatment is stopped but may take a few weeks or even months if vitamin D, or vitamin D3 have been given. The longer duration of vitamin D2 or vitamin D3 is due to storage in body fat and slow release. In addition, 25-hydroxy ergocalciferol and 25-hydroxy cholecalciferol, the initial hydroxylated products of vitamin D2 and vitamin D3, respectively, circulate bound to a plasma carrier protein and so are less labile.

PREPARATIONS

Only the main preparations are considered here. It is a major undertaking to switch from one preparation to another, and this should not be done lightly. For example, a change from a long-acting preparation to a more quickly acting one should be phased in over a period of 1-2 months. Because the equivalence of the different preparations is not well defined, there is considerable room for confusion among physicians, pharmacists, and patients. Uncertainty about dosage equivalence is caused further by the availability of different strengths of preparations. For some preparations, the dose can be given in terms of weight (micrograms or milligrams) or in international unitage, and in such cases it is wise to cite both. For example, when 1.25 mg calciferol is given daily, it is wise to specify the dose as 50,000 units daily as well. Rather confusingly, in Britain, the descriptions "high-
"strength" and "strong" were also used for different preparations of vitamin D (the former referred to 10,000 units and the latter to 50,000 units). Such terms are undesirable. Whatever preparation is being used, it is best in discussions with the patient to be very precise, referring to the content and the color of the capsules. Patients should be encouraged to bring their capsules to show the physician and to be equally precise in describing their treatment. They should be warned to query any change in the appearance of their medication. In some centers, special preparations are available for particular purposes. These must be used with caution be-cause of the problems of quality control and stability. In solutions, preservatives are needed. In a capsule containing high-quality Arachis oil with antioxidants, they may be stable for 1 year, but re assay will be necessary to confirm this. Even commercial preparations made on a large scale can cause problems for reasons that are not always clear. Recently, in the United Kingdom, the supply of dihydrotachysterol has been discontinued and the supply of calciferol (ergocalciferol) has been interrupted temporarily. Some manufacturers allow "overage" to ensure that with pro-longed storage there will still be a specified content in the preparation. This may mean that to allow greater "shelf-life" and still have, say, 1.25 mg calciferol, there may initially be 10-20% excess in a fresh batch. Since this is not generally known, and the presence of excess is not clear, errors may be caused unwittingly. Attention should be paid whenever an expiration date is given, of course. If a particular preparation is not available temporarily, it is better to change to another preparation containing the same form of vitamin D rather than restabilize the patient on a different compound. For example, if a pharmacy runs out of stock, it would be better to substitute 0.25 microgram capsules of alfacalcidol in place of 1 micro gram capsules, and not to change to Calcitriol, even though they are both 1-hydroxylated compounds.

MANAGEMENT

**Long-Standing Hypoparathyroidism**

Patients with long-standing Hypoparathyroidism (be it due to Idiopathic Hypoparathyroidism, Pseudo Hypoparathyroidism, or surgical Hypoparathyroidism) can be considered together. It is likely that these patients on long-term therapy have been treated with vitamin D$_2$ or vitamin D$_3$ in doses of 1-3 milligram or with dihydrotachysterol (0.2-1 milligram/day). Long-term follow-up is necessary, with measurement of serum calcium every 3-4 months. The response to change in dosage will be slow, so any alteration to gain better control must be gradual. The adjustments will depend on the variety of sizes of tablet or capsule available. Since this variety is likely to be limited, it may be necessary to prescribe different doses on different days of the week or month. For example, a patient taking 1.25 milligram calciferol/day might be given an extra tablet once per week; patients might take one tablet on odd days and two on even days to facilitate compliance. If hypercalcemia develops in a patient taking a long-acting preparation, treatment should be stopped until normocalcemia is restored. Assuming that the patient is not symptomatic and that renal function has not deteriorated because of vitamin D intoxication, nothing else will be needed. If the hypercalcemia is minimal (say, 2.6 millimol/liter, 10.4 milligram/dl), it is reasonable merely to reduce the dose and to review the situation in several months if the disorder has previously been well controlled. If a serious episode of hypercalcemia has occurred and treatment has had to be stopped until normocalcemia is restored, a decision has to be made about whether to restart the patient on a smaller dose of the same preparation or to change to a newer, more rapidly acting form. In general, it would be much simpler to restart the patient on a lower dosage of the same preparation.

**Newly Diagnosed Cases**

It is reasonable to start these patients on a newer preparation such as Calcitriol. If the patient has idiopathic Hypoparathyroidism or Pseudo Hypoparathyroidism, the hypocalcemia will probably have been long-standing, and it is better tolerated than it would be, for example, in a patient who has had thyroid surgery and inadvertently has been rendered hypoparathyroid. In the latter situation, hypocalcemia and Tetany will develop within a few days, and, under such circumstances, intravenous calcium may be needed while other therapy is taking effect. In an adult it would be reasonable to start with 0.5 micrograms Calcitriol twice daily or 1 micrograms alfacalcidol twice daily, monitoring serum calcium frequently, and changing the dose upward or downward as necessary.
Changes in dosage can be made in general every 2-3 days. The maintenance dose of Calcitriol is approximately 0.5 micrograms/day and that of alfacalcidol is approximately 1 microgram/day, but at the start of treatment larger doses may be needed (up to 3 micrograms Calcitriol/day, for example). It should be possible to stabilize the treatment regimen within 1 month.

A special situation is presented by the patient whose Hypoparathyroidism was heralded by seizures. If the patient is to be treated with alfacalcidol, it should be remembered that this compound has to be 25-hydroxylated in the liver to be active. Antiseizure medications will inhibit this hydroxylation step. In these patients, therefore, a higher dose of alfacalcidol will be needed while the antiseizure medication is used. When the antiseizure medication is reduced, the dose of alfacalcidol also will have to be reduced. If the patient has a long-term seizure disorder and Hypoparathyroidism has occurred separately, treatment for the seizures will have to be continued. Caution, however, is needed if any form of vitamin D apart from Calcitriol is used, since metabolism to the active form is needed, and the dose required will change with any alteration in treatment of the seizure disorder.

Once treatment has been stabilized, serum calcium should be monitored every few months. Measurements of urine calcium are not essential. If they are taken, hypercalcuria will often be found. In the absence of renal stone formation, hypercalcemia per se is not worrisome. It is wise, however, to obtain a plain x-ray or ultrasound of the abdomen every few years to ensure that nephrocalcinosis or stone formation is not developing. It is sensible to check for occult kidney stones or nephrocalcinosis at the beginning of treatment to establish the baseline.

In a small proportion of patients (perhaps a few percent) control will not be satisfactory, and serum calcium will fluctuate wildly, being sometimes too high and sometimes too low, apparently with the same dose. The reason for this is generally not clear. Poor and variable compliance could be suspected. In part, the fluctuations may be attributed to variation in calcium intake, sometimes being high and at other times low. Strict dieting to reduce weight may also contribute to this. If a patient is on a rapidly acting form of vitamin D (e.g., Calcitriol), it may be reasonable, in desperation because of rapid swings, to change to a longer acting preparation (e.g., vitamin D2). It may also be sensible to try giving calcium supplements to provide high intake that will not be greatly affected by dietary variations. In this way, the speed of swings may be slowed, but it is unlikely that they will be eliminated. Motivation of the patient is important, and this has to be encouraged to obtain the best results of therapy.

Use of Calcium Supplements

It is possible to maintain patients very well on vitamin D, with calcium supplements. If hypercalcemia develops, it can be rapidly reversed by reducing the calcium intake, without changing the vitamin D intake (Bijvoet, personal communication). In general, however, it seems preferable to control the problem with a single substance, i.e., vitamin D or one of its derivatives. In acute hypocalcemia (after an inadvertent para thyroidectomy during thyroid surgery, for example), intravenous calcium may be needed intermittently to avoid Tetany while long-term therapy is established and stabilized. A special example of this occurs in patients undergoing radical surgery for pharyngeal or laryngeal neoplasms, since they are often very ill for long periods postoperatively, are not eating, and may become hypoalbuminemic. In this case, intravenous calcium will be needed until the patient can swallow satisfactorily, since vitamin D, even Calcitriol, will have little benefit in the absence of a normal calcium intake.

Treatment of Patients After Surgery for Hyper Parathyroidism

It is expected, after para thyroidectomy for Hyper Parathyroidism, that serum calcium will fall to normal within a few days, though this can sometimes take 7-10 days. Symptoms of hypocalcemia may develop postoperatively, even when the serum calcium is still elevated. Those symptoms do not require treatment. Transient hypocalcemia after neck exploration is quite common, and normocalcemia should be achieved, again within 1 week. Generally, it is reasonable to do no more in this situation, apart from giving oral calcium supplements if there are symptoms. It seems reasonable to delay more specific treatment if possible for 2-3 weeks, since, once vitamin D treatment is started, it is likely to be lifelong. It has been argued that a previously suppressed normal gland can be stimulated
back to activity by permitting serum calcium to fall. The evidence for this, however, is not great.

If, preoperatively, there is hyper parathyroid bone disease (as witnessed on x-ray changes or raised alkaline phosphatase), then hypocalcemia is to be expected postoperatively. This is more likely to occur in patients with large tumors. In such patients, it is wise to start treatment as soon as serum calcium falls below normal (indicating the success of surgery). It has been suggested that preoperative treatment with alfalcacidol or Calcitriol helps in postoperative control. This is difficult to prove. The so-called hungry bone disease that occurs after removal of Parathyroids in patients with hyper parathyroid bone disease can cause severe, serious hypocalcemia and is resistant to treatment. High doses of Calcitriol can be given, with large calcium supplements. The initial dose of Calcitriol in this situation may reasonably be 1 micro gram twice per day, doubling this dose every 3to 4 days as necessary, and increasing calcium supplements until control is achieved. This may require as much as 20 micrograms Calcitriol/day, with 120 mM calcium per day, for example, as calcium lactate gluconate daily (this can be given as Sandocal 400 effervescent tablets each of which contains Ca+ + 10 mM, 400 milligrams). Potentially, of course, this is a dangerous regime, and daily monitoring of serum calcium is necessary for a few weeks. As soon as normocalcemia is achieved, quite rapid reduction in dosage is necessary. In the longer term, high doses of Calcitriol (4 micrograms/ day) may be needed for several months. Suddenly, when the bone disease is healed, the requirement for vitamin D and calcium will fall dramatically. The best way to anticipate this and to avoid hypercalcemia is to follow the alkaline phosphatase activity. The alkaline phosphatase level may take 6 to 9 months to fall to normal, but once it is normal there is a risk of hypercalcemia. Such patients can usually then be maintained on relatively small doses of Calcitriol (say, 0.5-1 micrograms/day).

In patients in whom multiple operations have been performed to cure Hyper Parathyroidism and in whom several normal glands have previously been removed before the adenoma is found, it is likely that long-lasting Hypoparathyroidism will ultimately result. This may, of course, be the result of initial surgery, as with patients with familial multiple endocrine neoplasia type I because of the risk of recurrence if limited surgery is performed. In such cases, postoperatively treatment may start sooner than might otherwise be the case.

Management of Hypoparathyroidism in Pregnancy

Obviously it is desirable to maintain normocalcemia insofar as possible before, during, and after pregnancy, to avoid any adverse effects on the outcome. Patients can be reassured that this does not pose major problems, though particular care is needed in the third trimester and in the puerperium. The obstetrician and pediatrician should be made aware of the situation in an appropriate supervision arranged. During the last 3 months of pregnancy, the dose of vitamin D (whatever form is used) may have to be reduced; this may be the result of the placenta having a la-hydroxylase enzyme capable of synthesizing 1,25-dihydroxyvitamin D. Serum calcium should therefore he measured monthly at that stage. After delivery, even in patients treated with Calcitriol, there is again risk of hypercalcemia probably the consequence of the effect of prolactin in stimulating l alpha-hydroxylation. The dose of vitamin D therefore may have to be reduced. Breast feeding, with consequent temporary loss of calcium, is perfectly reasonable. For the first month after delivery, it is probably wise to measure serum calcium once per week.

CONCLUSIONS

It should be realized that vitamin D in all its forms can be a difficult drug to use and that treatment for Hypoparathyroidism is necessary on a life-long basis. It is therefore necessary to inform the patient accordingly. Unpredictable changes in therapeutic requirements are the rule rather than the exception. Even after a period of several years with a stable dose, hypercalcemia and vitamin D intoxication may develop, so continued vigilance is required.

Continuity of care is important, though, inevitably in the lifetime of the patient, more than one physician is likely to be involved. With care, the problems of both low and high calcium can be avoided.