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EDITORIAL

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A LIFETIME OF BISPHOSPHONATE

One of the best teachers of medicine I ever knew, used to cut short speculations on drugs by dryly remarking: 'It is better to know one drug well, than to switch to the latest one'. The reason is of course that knowing a drug well allows you to manipulate route, rhythm and dose in order to guide results towards your aim.

A related maxim follows indeed: 'Treatment should be guided by individual results, not by general prescriptions'. One gives a drug to obtain a result; therefore, measure the particular effect in your patient and adapt your treatment accordingly. For this, one should know the pharmacology of the drug and the physiology of the disease and, most important of all, the particular form these take in your individual today.

I have been asked to tell the story of how APD [now pamidronate] and Dimethyl-APD [now olpadronate] were developed in their early stages. As it happens, there are two stories, a story in Argentina and a story in Holland, because both drugs were developed independently and without knowledge of each other at these two locations. I will stick to the Dutch story, because that is the one with which I lived.

This is my first choice. My second choice follows from the maxims quoted at the start. The story will begin with a patient and with the desired effect. From there on you may follow why we did what we did. My hope is that at the end you will understand these particular drugs, APD and Dimethyl-APD, better and that your patients may profit from it.

The story as it unfolds looks at the development of PCP's [the bisphosphonates] from a perhaps unusual direction. I have not referenced it. For those who desire an overview of the bisphosphonate history I refer to a book in whom others and I have reviewed this : 'Bisphosphonate on Bones (1995) OLM Bijvoet, HA Fleisch, RE Canfield and RGG Russell, eds. Elsevier, Amsterdam.'

The desired effect

I vividly remember a cartoon in a little book on physical diagnosis I read as a student. I think the authors were Baily and Love. The cartoon showed a man with an extraordinary large head and with strangely curved legs, and out of his mouth came a little cloud saying: 'pain!'. The caption read: "Paget's disease'. The disease was untreatable. When I was assistant in internal medicine a young farmer with exactly these symptoms was referred to me. He had jumped from his tractor and for no reason at all broke his left femur. He had a too large skull and he had continuous, excruciating bone pains. There was no treatment. It was in this period that we had just learned to assess the remodelling rate of bone by measuring its rate of breakdown as urine hydroxyproline [OHP], and the rate of formation from serum alkaline phosphatase [AP]. His bone remodelling rate, as you expect, was elevated to such a rate we had never seen. We tried with hardly any effect to reduce the bone remodelling rate with antithyroid drugs. It then just so happened that the director of a pharmaceutical firm was admitted suffering multiple bone fractures from an accident with a fast car. He told that they had just started to manufacture calcitonin in the hope to develop a treatment of osteoporosis and asked what we thought. Animal studies had already shown that calcitonin will suppress bone formation along with resorption and we wondered if reduction of the rate of bone remodelling is of use in osteoporosis. His next question: 'but then, to what use can this be put?'. For the young farmer in mind in whom we had not succeeded to reduce the rate of bone remodelling, we requested some of the drug for a trial.

Intravenous administration of calcitonin to a patient with Paget's disease is followed by an impressive and immediate decrease in urine hydroxyproline; the more the rate is elevated above normal the more impressive is the result. In many patients this is accompanied by immediate relief of the bone pain

that is so typical of Paget's disease, suggesting that the pain is associated with osteoclast activity. Such effects were unheard of hitherto and showed a way to go in such patients. The effect of a single intravenous injection on bone resorption is transient however although the effect on pain is more lasting, now the results were a clear indication that the way to go is to find a resorption-suppressing drug whose effect can be maintained, through repeated administration, for example by giving it orally and such a drug was available around the corner.

The bisphosphonates

The bisphosphonate story too, starts with a farmer, who while fertilizing oranges through an irrigation system, observed that accidental addition of a very little phosphate protected against undesirable crystal formation blocking his irrigation tubes. From one followed the other, and a highlight was the development of many bisphosphonic acid derivatives that became widely applied in various fields of technology as inhibitors of crystal-growth. Bisphosphonates are artificial substances, but Neuman suggested that pyrophosphate, having a structure that reminds one of a PCP, could play a role in bone-crystal formation under the regulatory influence of a pyrophosphatase like the enzyme alkaline phosphatase. From there on Francis and Fleisch performed experiments in animals with the PCP etidronate, the first in order to find a drug against osteopetrosis, since PCP's were expected to inhibit crystal growth and therefore ossification in bones. The complete surprise is that on histologic investigation the drug appeared to do the opposite, that is, apart from a small effect on mineralization, it exerted an impressive retarding effect on osteoclastic bone resorption -the mechanism of which is, even at present, not completely clear.

Desiring to find a better treatment for our farmer and under the impression of the effect of calcitonin, we wanted to know if perhaps oral bisphosphonate could be the answer to what we wanted to achieve and started a series of animal experiments with two aims: [1] Is inhibition of mineralization a necessary sacrifice in order to achieve suppression of osteoclastic bone resorption with a PCP? [2] We performed prolonged and complete metabolic balance studies in rats with the aim of understanding the integrated effects of prolonged continuous administration of PCP to intact animals. We were enormously helped by the firm Henkel in Düsseldorf where most of the PCP's have originally been synthesized, and in particular by professor Arnold Heins from that firm, who has continuously donated the desired material and who included the aminobisphosphonates amongst that. The answer to [1] is: Different bisphosphonates have different potencies and different ratios between direct effects on bone resorption and on the quality of new bone. The amino-PCP pamidronate is a potent inhibitor of osteoclastic bone resorption that seemed non-toxic an devoid of ill effects on the quality of newly-formed bone. (Results of some initial experiments with Dimethyl-APD [olpadronate] gave results that at that time appeared to us too dramatic to warrant further investigation!) [2] The research gave a picture, according to later human results remarkably accurate, of the interdependence of resorption and formation of bone, and how prolonged suppression of osteoclastic resorption of bone is secondarily followed by a reduction in the rate of its formation by osteoblasts, the degree of reduction being in proportion to that of the reduction of the resorption. In addition to that, the general well-being of our animals was unaffected. Bone is an eco-system of co-operating cells. The effects of APD in those animals as well in patients that would later be followed and treated offered an unprecedented opportunity to study the kinetics of the physiological effects of this form of cell-cell interactions in bone. In conclusion: There is a striking similarity between calcitonin and the bisphosphonates as to their ability to inhibit osteoclastic bone resorption. As we know at present, their effect on osteoclast function may be comparable, the mechanism of the effect on these cells is probably very dissimilar. Calcitonin may act by curtailing the activity of osteoclasts that are actually functioning, and in pathology, can reduce excess resorption by maximally 50% at most, while PCP's may act by interfering with the maintenance of and formation of new osteoclasts from precursors. Since osteoclast material has a very rapid turnover, the effect of PCP has a delay of one day on the average in humans, that of calcitonins is immediate. This is why calcitonin and PCP's may sometimes be combined when an immediate as well as a potent effect are desired as in severe hypercalcemia.

The quality of the result

Calcitonin had taught what kind of effect to aim at in Paget's disease, and animal studies with PCP had taught that results similar in nature but of more pronounced efficacy and of sustained duration could be expected from PCP administration. These expectations were amply confirmed. The main observations related to the quality of the result were:

- APD rapidly reduces the rate of bone resorption. The rate of reduction varies between individuals and depends mainly on two factors: [1] The initial excess of bone resorption, measured as the rate of excretion of hydroxyproline [OHP] in the urine, and [2] the dose of PCP. Ad [1]: At a given dose the rate of suppression is always similar if the rate is expressed as the time needed to decrease the activity by half. This means that if in patient A the excess of OHP is twice that of patient B, the reduction of OHP in A is twice as fast in A as in B, when taken in absolute numbers. This comes not at a surprise, since this is the same with calcitonin. Ad [2]: This property allows one to compare the potency of different forms or routes of administration (e.g. oral versus intravenous) of a given PCP preparation, or of different PCP's given in a similar way.

Like calcitonin, suppression of bone resorption is associated with relief of pain, with an important difference: The initial 12 to 24 hour delay in effect with PCP can be associated with an increase of pain, that is always transient. Like with calcitonin, treatment can result in improvement in structure from affected bones.

Prolongation of treatment until normalization of OHP, leading to extended treatment periods with oral APD in severe cases, will almost always allow to obtain normalization of OHP. There is an associated normalization of the rate of bone formation that is delayed by three months on the average, relative to OHP. This means that treatment-results are better assessed from OHP or related resorption-measurements, than from AP.

- A point that people have insufficiently understood and that is extremely important from the point of view of your patient: the duration of the ensuing treatment-free remission depends on the degree to which you have been able or willing to normalize his bone resorption. This means that if you diligently measure OHP and achieve normalization, than the likelihood of prolonged and even permanent remissions in great. It is as if the pathology of the disease resides in osteoclasts and complete suppression of renewal of sick osteoclasts throughout the lifetime of an osteoclast family allows one to get rid of the pathogenic material.

The road forks

Close observation of results in individual patients, combined with the first maxim of sticking to one drug if that does what you want, can always be recommended. It promotes your personal understanding of the physiology of disease; it improves the quality of treatment in the individual because now you can adapt your treatment to his individual needs, and finally, you start to understand what you can achieve with this drug better than any article of book can teach you, because you know the results as they come to you in terms of measurements and language you personally are accustomed to.

Not only that: This understanding allows one to extend ones means to obtain certain pharmacological effects towards other diseases. So, treating Paget's disease has taught us how to treat hypercalcemia of malignancy, how to use PCP's in other conditions, like myeloma, primary or secondary malignancies with affection of bone, perhaps even osteoporosis; and also to understand the limits of its use and when not to expect results. I will not enumerate here all the different by-roads; they have been sufficiently described. What I do stress again, is: do not simply follow treatment-recommendations as given together with the drug, neither you, nor the patient will profit in the end.

- The results with oral APD taught us another thing: knowing what can be achieved we became aware of what one can ask of a good bisphosphonate treatment and became aware that APD in certain patients had its limitation. First the oral form of the drug when given in a good Galenic form -this is a great art and is the propriety of good pharmaceutical companies- was well tolerated in most patients, but not in all and not at relatively high doses that we requested in some patients. Secondly, the efficacy of a given oral dose depends also on the co-operation of the patient in that combination of the drug with food will decrease its accessibility. It should be given some time before meals at least meals that

contain cations to which the drug can absorb. The answer was to develop an intravenous form. We found that with intravenous APD, one can achieve almost everything one wants. The disadvantage, however, is that that patient becomes dependent on someone to administer the drug and secondly that one has to work out time-schedules of dose versus frequency, and is so reduced in ones capacity to adapt treatment to the requirements of the individual. There is clearly a need for a PCP that allows to achieve the same effects of intravenous APD with a simple oral formulation. And this aim had been achieved with the elaboration of Dimethyl-APD.[olpadronate].

The fact that most impressed us writh the necessity of developing, and an intravenous form of APD, and a more potent oral bisphosphonate, was the very farmer with whom I started this story, and to whom I may dedicate the work we did. He lived many stages of the development, was the first patient to receive calcitonin and experiencing pain relieve. His pain however recurred slowly and he was then treated with etidronate with only limited success. This was only improved by combining etidronate with calcitonin, a now forgotten but quite effective combination, and, at a later recurrence he required oral APD. The activity of his disease was however so extreme that we never reached complete and lasting remissions, and fifteen years after his first admission the activity recurred together with the development of widely metastased osteosarcoma and he died.

The three Bisphosphonate Generations

Occasionally one meets the expression 'First-Generation", "Second-Generation"-, and 'Third-Generation-Bisphosphonate". Sometimes these are used to suggest that one PCP is better than another one or came on the market a little later and therefore is better. I do feel that in view of the history given above, the use of such terms is acceptable, but only if they express an essential and distinct property of the group under which a PCP is classified. I would call First-Generation those PCP's of those forms of a PCP that do have significant effects, but are insufficiently potent to achieve the clinically desirable effect in all circumstances where one wants to use it. So is Etidronate [EHDP] clearly a First-Generation PCP. In most patients with Paget's disease for instance, the drug is simply insufficiently potent to achieve complete remission, while at the same time there is a very real possibility of osteomalacia. The problem can therefore not be remedied by giving the drug in another fashion, say intravenously.

- APD is certainly an example of a Second-Generation Bisphosphonate. I think many of the present PCP's may belong to that class. The oral form is completely efficacious in most circumstances and one can adapt treatment to requirements. There are however limiting factors as to dosage: with oral APD the gastric side effects at high doses, although such problems can be overcome by a slightly more clumsy intravenous administration-route at the sacrifice of treatment-precision.

The Third-Generation bisphosphonates are those that allow every variation and adaptation to individual requirements with a simple oral form. A perfect example of those is Dimethyl-APD. I told you that we had investigated Dimethyl-APD quite early, but had been put off by the dramatic effects. With hindsight we now know that even the lowest dose in the dose ranging studies we performed, exceeded by far what we should have used. So we only looked back when we came to the limits of APD, and only after having, through APD, understood to formulate exact requirements. Our experience with Dimethyl-APD has largely confirmed what one has learnt with APD, but with it larger potency oral Dimethyl-APD has allowed access were APD did not allow it: difficult patients requiring high oral doses, but also new inroads, such as small infants with osteogenesis imperfecta, where no risk should be taken from the point of view of possible gastric side effects and continued intravenous PCP is impracticable.

Conclusion

It is at that moment, now almost 10 years ago, that my personal involvement with medicine and PCP's in medicine ends. Looking back I find it interesting to see how the development of this drug has allowed, within one medical generation, to reclassify one disease from untreatable, to very accessible and how that experience has allowed access to many other conditions at least one of those also shifting from the very difficult to the accessible ones -I mean of course hypercalcemia of malignancy. I enjoy seeing how much this development depends on the context of what is happening.

I have not left out the sombre outcome of the disease in the one patient who stands at the beginning of our story. The totality of our experience is one lived together with many individual patients, of better persons, who have remained interested and who in general appreciated rather than disliked the close personal attention that is associated not, I should say with experimentation, but with the individual attention that is necessary for good treatment. But as a by-product of that dedication it kept our knowledge sharp enough, to be ready when the medical context opens possibilities of improving treatment, and so the knife remains sharp on both sides.

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