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DISODIUM PAMIDRONATE VERSUS MITHRAMYCIN IN THE MANAGEMENT OF TUMOUR-ASSOCIATED HYPERCALCEMIA

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Twenty-eight consecutive hypercalcemic patients with cancer referred to our department were included in a randomized study, comparing the second generation bisphosphonate pamidronate (APD) with our standard treatment consisting of rehydration, mithramycin (repeatedly) and supportive care. Three patients were excluded, due to rapid deterioration and death, leaving 25 evaluable patients. APD was administered as a single i.v. infusion of 30, 60 or 90 mg depending on the serum calcium, while mithramycin was given in doses of 1.25 mg and repeated if necessary within the first three days. The primary endpoint of the study was the serum calcium day 6. APD normalized serum calcium in all patients, and 12 out of 14 were still normocalcemic day 12. In contrast, mithramycin was effective only in 3 out of 11 patients, and in these patients hypercalcemia recurred rapidly. The success of APD was underscored by the fact that the patients in this group achieved a significantly better performance status after treatment. No serious side-effects were recorded in either group.

Hypercalcemia is a relatively frequent complication of cancer and 10–20% of all cancer patients will eventually experience this condition (1). Mortality is high in untreated patients (2). The patients are most often in an advanced stage of the disease, and may appear terminal at presentation. This is, however, often hard to judge and rapid diagnosis and treatment of the hypercalcemia can provide useful palliation for patients even during the last few weeks of their lives (3). Although the hypercalcemia often signals progression of the cancer, it may as well indicate an easily treated intercurrent disease. In any case, time is required to diagnose and, if possible, to treat the underlying condition. The pathophysiology of tumour-related hypercalemia is complex, but the increase in serum calcium is mainly due to a marked stimulation of bone resorption (4, 5). Increased renal tubular reabsorption of calcium is also well documented, and present in half the patients (6). The increased bone resorption may be due to skeletal metastasis, but an underlying humoral mechanism can be revealed in 80–90% of unselected patients, irrespective of whether they have bone metastasis or not (7). A number of mechanisms have been proposed as the mediator of the hypercalcemia (reviewed in 4, 5 and 8), but today many authorities will consider the PTH-related peptide as the single most important factor.

The treatment of hypercalcemia includes initial saline infusion to rehydrate the usually water- and sodium-depleted patient. This will relieve some of the symptoms, but is rarely sufficient to restore normocalcemia (9). Further treatment involves inhibitors of bone resorption. Until recently, the most important drugs have been calcitonin and mithramycin. The former is effective and fast-acting, and still the drug of choice in emergency situations. However, the effect is very short (1–2 days), and repeated administration usually less effective (1, 10). Mithramycin is a cytostatic drug, with toxic side-effects (especially bone marrow depression), but it is given in low, usually sub-toxic doses for hypercalcemia. However, the patients may have marginal reserves, and the common need for repeated administration can give a cumulative toxicity. The success rate is between 40–80%, and recurrence is common within the first week

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(11, 12). The bisphosphonates is a relatively new group of drugs which act as potent inhibitors of bone resportion. They are characterized by tropism to mineralized bone due to their common P-C-P group, and they bind strongly to the hydroxyappatite crystals (13). The drugs appear to have an inhibitory effect on osteoclast differentiation, recruitment and activity (13–15). The bisphosphonates have been successful in the treatment of tumour-associated hypercalcemia in 90–100% of the patients, with little or no side-effects (9–12, 16), and are now considered to be the treatment of choice in many countries.

Encouraged by these resports, we conducted a clinical, randomized trial comparing one of these new drugs with our previous standard treatment, namely a combination of rehydration, mithramycin and supportive care. We decided to test pamidronate (APD), which is a second generation bisphosphonate, and perhaps the most potent of the bisphophonates currently available (17). The primary endpoint of the study was the serum calcium day 6. The symptoms and performance status of the patients were recorded and so were the possible side-effects in each treatment arm.

Material and Methods

All patients referred to our department with symptomatic tumour-associated hypercalcemia, were initially treated with saline infusion and furosemide in a standardized manner. (Patients with severe primary renal or heat failure were excluded.) Administration of calcitonin was optional, and given when indicated by severe or life-threatening symptoms due to hypercalcemia. Only one patient in the control group was considered to need this. Hypercalcemia was in the study defined as albumin-corrected serum calcium (see below) > 2.8 mmol/l. Normocalcemia was correspondingly defined as corrected serum calium = 2.8 mmol/l or below. In the following, serum calcium always refers to the albumin corrected value. Corrected serum calcium = s-calcium + (40 − s-albumin) × 0.02. Those patients who did not achieve normocalcemia after 48 h were invited to participate in the study. Twenty-eight patients were included after informed consent had been given, and randomized to one of the two treatment arms in the trial (Fig. 1).

Day 0 the patients received either mithramycin 1.25 mg in 500 ml saline infusion over 4 h or pamidronate (APD) 30–90 mg in 1 000 ml saline over 12 h. The dose of APD was varied according to the s-calcium level (30 mg when s-calcium < 3.2 mmol/l, 60 mg when 3.2 mmol/l < s-calcium < 3.6 mmol/l and 90 mg when s-calcium > 3.6 mmol/l). In the control group, a second (optional) dose of mithramycin was allowed with three days of inclusion. Five out of 11 patients received this. All patients were examined thoroughly both physically and biochemically, and s-calcium was monitored daily. Performance status of the WHO was noted. The complete status was recorded days 0, 6 and 12. The primary endpoint of the study was the serum calcium day 6 after inclusion. Those who had not achieved normocalcemia, were registered as primary failures, and cross-over was performed.

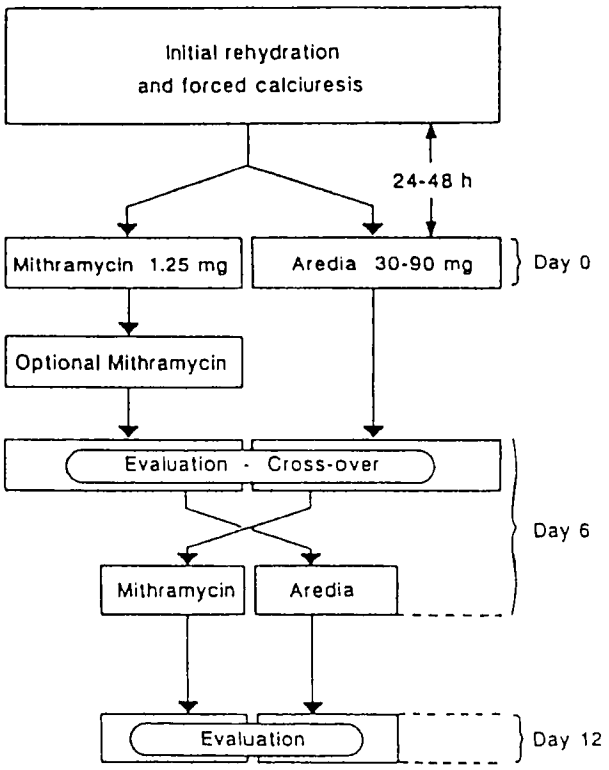

Fig. 1. Schematic design of the trial. Mithramycin versus pamidronate (Aredia).

Another objective of the study was to compare the duration of the normo-calcemia achieved with the different drugs. Recurrence after transient normocalcaemia is very common and in the following termed secondary failures. Early secondary failures (between days 6–12) were offered the alternative treatment like the ordinary cross-overs. Statistical differences between the groups were calculated by means of the Wilcoxon's rank sum test.

Results

The 28 patients included were representative of the patients referred to our department in general with lung cancer (28%) and breast cancer (18%) as the most frequent primary diagnoses. The two treatment groups were balanced as to age and sex. Three of the patients were not evaluable due to rapid deterioration and early death. Of the remaining 25 patients, 14 were randomized to the APD treatment arm, and 11 patients to the control group. The mean serum calcium was slightly higher in the control group (3.4 mmol/l) (range 2.82–3.84 mmol/l) than in the APD group (3.2 mmol/l, range 2.81–3.93 mmol/l) but this difference was not significant. In the control group only 3

out of 11 achieved normocalcemia on day 6. The mean value in the group was 3.0 mmol/l (2.43–3.48). In the APD group, all of the 14 patients had achieved normocalcemia on day 6 with a mean serum calcium = 2.5 mmol/l (2.14–2.76). This difference is highly significant ($p = 0.0001$) and the difference between the groups reached significance day 4 ($p = 0.01$) (Fig. 2). The 3 responders in the mithramycin group recurred quickly and were given APD days 7 and 8 (secondary failures). Thus, all 11 patients in this group were crossed over within 8 days, and all but one achieved normocalcemia day 12 (mean value = 2.51 mmol/l). In the APD group, 2 patients recurred day 12 and were at that time refractory to any therapy.

The effect of APD seemed more durable, with a mean serum calcium = 2.71 mmol/l on day 12, achieved with a single dose of the drug given day 0. (Statistical comparison of secondary failures is not performed because of the crossing-over, and the imbalance of the groups). The result in the APD group, however, seemed to be dependant on the intial dose given. Those who got 30 mg ended up on day 12 with a mean s-calcium of 2.94 mmol/l (2.43–3.75), while those who got 60 mg or 90 mg ended up day 12 with a mean s-calcium of 2.50 mmol (2.40–3.02), although the latter group had more severe hypercalcemia at the start of treatment.

The WHO performance status was closely related to the calcium levels. While nearly all patients in both groups were bedridden most of the day at admission, the patients in the APD group improved their performance status from an average score of 3.7 at admission to 1.7 on day 6 ($p = 0{,}003$). No improvement was noted in the mithramycin group.

No serious side-effects were noted in any of the groups. The haematological parameters were closely monitored, but no significant bone marrow depression was recorded.

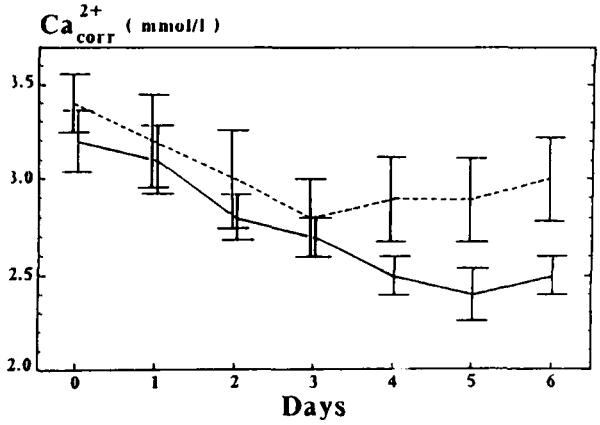

Fig. 2. Albumin-corrected serum-calcium in the two treatment arms. The difference between the two groups reached significance on day 4 ($p = 0.01$), and was highly significant on day 6 ($p = 0.0001$). —— pamidronate (Aredia); - - - mithramycin.

Table

Treatment effects on the kidney and the liver. Mean values for s-creatinine, ASAT and ALAT

	Mithramycin	Pamidronate (APD)
S-creatinine day 0 (μmol/l)	130	130
S-creatinine day 6 (μmol/l)	112	105*
ASAT day 0 (u/l)	23	43
ASAT day 6 (u/l)	37	32
ALAT day 0 (u/l)	26	42
ALAT day 6 (u/l)	75	33

* Renal function is significantly improved in the pamidronate group ($p = 0.05$).

A slight elevation of serum ALAT was noted in the mithramycin group, but this was transient and not significant (Table). As expected most of the patients had modest renal failure at admission, probably due to the dehydration. Both groups experienced improvement of renal function along with the treatment, but the improvement was slightly superior in the APD group ($p = 0.05$) (Table). None of the patients developed chronic renal failure.

Discussion

In this randomized trial pamidronate (APD) was obviously more effective than mithramycin in the treatment of tumour-associated hypercalcemia. The difference in serum calcium on day 6 after treatment was highly significant and the difference between the groups reached significance day 4. This is in accordance with other reports (11, 12). Our results, however, differ from the previous studies regarding the extremely poor results in the mithramycin group. This may partly be due to the late endpoint (day 6) in our study. In addition to the 3 recorded patients, another 2 patients in the mithramycin group became transiently normocalcemic, which means that 5 out of 11 patients in the control group achieved normocalcemia during the first 6 days. This is comparable to the earlier studies. A higher response rate at day 6 might also have been achieved by increasing the dose, but this is not recommended, because of the well-documented cumulative toxicity of the drug. The maximal effect of mithramycin was seen on day 3, while that of APD was more sustained. Twelve out of 14 patients were normocalcemic day 12 after treatment with APD, compared to none day 8 in the control group. However, in the APD group there was a tendency to increasing serum calcium at day 12, especially in the patients who had received the lowest dose (30 mg). Some reports state that the mean duration of the effect of APD is 3 weeks (18) but those patients all received at least 60 mg APD. Our results underscore the reported dose–response relationship of ADP (19, 20), with special emphasis on duration time. Taken into account the reported low toxicity of APD, confirmed in the present study, we will

recommend 60 mg as a suitable first dose, even in patients who are slightly hypercalcemic.

Our study also demonstrates the close relationship between the serum calcium level and the well-being of the patient, recorded as the WHO performance status. The patients in the APD group achieved a significantly improved performance status after treatment, in sharp contrast to the control group. This feature is very important, bearing in mind the palliative objective in these patients with a usually poor prognosis. The virtual absence of side-effects is of course also important from this point of view.

Our protocol may be too strict with regard to initial rehydration and exclusion of patients with renal impairment. Newer data demonstrate that administration of the drug from the beginning, along with rehydration, is well tolerated and pre-existent renal impairment does not seem to be deteriorated after administration of the drug (21).

In conclusion, we found that pamidronate is a highly effective and safe drug in the treatment of tumour-associated hypercalcemia. It is, in our opinion, a first-line drug in the management of this condition, and we recommend an initial dose of at least 60 mg i.v. besides the necessary rehydration.

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