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^{32}P-PYROPHOSPHATE IN THE TREATMENT OF PERSISTENT METASTATIC BONE PAIN

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Among the beta-emitting radiopharmaceuticals used in the alleviation of pain caused by bone metastases, probably the one in most common use is ^{32}P-orthophosphate, given either intravenously or orally (FRIEDELL & STORAASLI 1950, MAXFIELD JR et coll. 1958, MILLER 1974). However, the dose required for adequate palliation frequently causes such severe bone-marrow depression as to prevent its adoption for routine use.

As the beta energy and physical half-life of ^{32}P are suitable, other compounds of this nuclide were sought with a less marked tendency to cause bone-marrow depression than the orthophosphate, while being at least as effective as a palliative. The pyrophosphate was considered to merit examination for this purpose. Furthermore, it was hoped that in the metabolism of the ^{32}P-pyrophosphate the nuclide metabolites would prove to be incorporated in the neighbouring tumour cells with potential tumoricidal effect.

Of intravenously administered ^{32}P-pyrophosphate 40 per cent is known to be excreted by the kidneys. In addition, in preliminary in vivo experiments, ^{32}P-pyrophosphate uptake was at least 5 times greater in metastatic deposits in bone than in normal bone (SÖDERBORG & WERNER, unpublished results). The radiation dose from 37 MBq (1 mCi) of ^{32}P-pyrophosphate administered intravenously to adults was calculated to be of the order of 4.0 Gy in metastatic regions, against 0.8 Gy in normal bone in which case the dose received by the bone marrow would be much lower.

It was accordingly considered of interest to examine the haematologic and palliative effects of therapeutic amounts of ^{32}P-pyrophosphate in patients with persistent metastatic bone pain. (Permission was obtained from the Ethic Committee of Karolinska Sjukhuset, and the informed consent of each patient was obtained.)

Materials and Methods

^{32}P-$Na_4P_2O_7$ was prepared by mixing solutions of H_3 $^{32}PO_4$ (0.1 ml, 37 GBq (1 Ci)/ml) and Na_2HPO_4 (120 mg, 30 mg/ml). The mixture was evaporated to dryness and heated at 400°C for 2 hours. The residue was dissolved in sterile water and then sterile filtered. The solution was divided into single doses (370–555 MBq), which were freeze dried, the product then being stable for up to 3 weeks, as determined by paper chromatography. For reconstitution sterile saline was used (0.9 mg/ml).

Eight patients (7 females, 1 male) with persistent pain due to bone metastases from mammary carcinoma were given ^{32}P-pyrophospate. For at least 6 months before the administration none of the patients had advanced depression of the haematologic system or had received radiation therapy or

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Table

Lowest peripheral blood counts before and after administration of ^{32}P-pyrophosphate. Effect on pain and duration of relief

Case No.	Hb ($g \times l^{-1}$)		Leukocytes ($10^9 \times l^{-1}$)		Thrombocytes ($10^9 \times l^{-1}$)		Effect	Duration (weeks)
	Before	After	Before	After	Before	After		
1	126	91	7.0	0.2	200	60	++	10
2	118	81	3.7	0.3	245	3.6	0	–
3	114	80	8.2	1.6	340	36	+	4
	126	92	7.1	4.4	149	70	+	6
4	133	130	6.1	7.0	255	250	+	5
5	106	80	4.7	1.8	196	16	++	10
	76	59	8.2	0.8	37	8	++	16
6	79	104	5.1	2.4	94	28	+	4
7	100	98	4.6	1.1	136	18	++	10
8	127	103	9.3	4.7	289	189	++	9

chemotherapy. 444 MBq of ^{32}P-pyrophosphate was given intravenously to the first 3 patients and 370 MBq to the other 5, once to 6 of the patients and on two occasions to the other 2.

Peripheral platelet and leukocyte counts, determination of the haemoglobin concentration and liver and renal function tests were performed before administration of the nuclide and afterwards at intervals of one week for the first 6 weeks, and then in alternate weeks. Bone radiography and bone scintigraphy using ^{99}Tc^{m}-pyrophosphate were performed immediately before administration and again after 3 months.

The effect of the therapy on pain was evaluated subjectively according to a three-grade scale: increased pain or no reduction (0), some alleviation (+), and complete alleviation with no further reliance on analgesic drugs (++).

Results

After the ^{32}P-pyrophosphate therapy all but one of the patients reported some relief of pain (Table). It occurred first in the second week after the injection and lasted for 1 to 4 months. The alleviation was greatest for patients with small metastases, and less marked for those with collapsed vertebrae or extensive bone destruction.

In all but one of the patients were the peripheral blood cell elements depressed. For white cells and platelets this decrease began in the third week after the therapy: the nadir occurred at 4 to 5 weeks and normalization was usually recorded at 6 weeks. The erythrocyte counts were still slightly depressed after 2 to 3 months.

After the therapy the serum levels of alkaline phosphatase usually tended to be slightly reduced; other biochemical tests of the hepatic, renal and coagulation systems were unaffected. In one case an elevated serum calcium level was normalized following treatment.

In 6 patients no changes were found at bone scintigraphy or radiography up to 3 months after treatment; in the other 2 patients lytic areas were calcified.

In 2 patients deep venous thrombosis appeared in a leg 3 weeks after administration of the nuclide. In both of them anticoagulant therapy was successful.

Discussion

The various organic and inorganic ^{32}P compounds that have been tested in therapeutic amounts in man have proved to be roughly equally effective in alleviating pain. They have also produced similar side effects arising mainly from depression of haematopoietic tissues (KAPLAN et coll. 1960, POTSAID et coll. 1978).

In the present series all but one of the 8 patients experienced less pain, a proportion that is similar to those reported after use of other ^{32}P compounds with or without pretreatment with testosterone or other hormones (MAXFIELD JR et coll., MILLER). It is notable that the only patient not experiencing any pain reduction had essentially normal values of serum alkaline phosphatases despite generalized

dissemination of the disease and an elevated uptake of $^{99}Tc^{m}$-pyrophosphate in metastatic bone as demonstrated at scintigraphy.

In all but one of the patients haematologic depression occurred, serious in one case but not lethal. The platelet count seemed to be most susceptible with a nadir at 3 to 4 weeks after the administration of ^{32}P. At the same time also a profound but less marked depression of the leukocyte count occurred.

In the comparison of various methods for relieving pain the selection of the patients is obviously important. Patients receiving nuclides early in the course of the disease will probably experience a greater relief than those with extensive bone destruction. Irrespective of any such selective factor in the present series the side effects were clearly too marked for ^{32}P-pyrophosphate to be recommended for routine palliative treatment of persistent pain due to bone metastases. From the observed side effects it would appear that the pyrophosphate molecule is broken down and that ^{32}P is then probably taken up by the bone marrow cells.

SUMMARY

Eight patients with persistent pain due to disseminated bone metastases from mammary carcinoma were given about 370 MBq (10 mCi) of ^{32}P-pyrophosphate on 10 occasions. All but one of the patients experienced alleviation of pain lasting 1 to 4 months. The side effects, which derived mainly from haematopoetic tissue, prevent the routine use of this compound.

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