Intra-articular yttrium 90 in rabbits

Comparison of behaviour of various radiocolloids in rabbits and in man

J. M. GUMPEL

From the Rheumatic Diseases Study Group, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ

SUMMARY Comparative studies of the retention of various yttrium 90 radiocolloids and of non-colloidal yttrium 90 chloride were performed in rabbits with arthritis induced in one knee. Two colloids, the citrate and resin forms, showed a statistically significant difference in retention between inflamed and normal knees, isotope being retained better in the normal knee. Marked differences were found in the handling of the various yttrium preparations in rabbits compared with previously reported results in man. These differences suggest that the rabbit with induced arthritis is not a suitable model in which to test retention of different radiocolloids before use in man.

Animal experiments are a vital stage in the development and assessment of drugs before use in man. The rabbit has been extensively used in studies of radiocolloids for intra-articular use (Webb *et al.*, 1969; F. W. S. Webb and J. M. Gumpel, unpublished observations, 1970; Pavelka *et al.*, 1975), particularly when a chronic arthritis of the Dumonde-Glynn type has been previously induced. This animal model was used to check the even distribution of a newly developed yttrium 90 (⁹⁰Y) radiocolloid (ferric hydroxide; Gumpel *et al.*, 1973a; Bayly *et al.*, 1973). These initial experiments were extended to see whether more could be learnt about the role of particle size and colloidal form in the handling of radiocolloids by the synovium.

Marked differences in the handling of the various colloids were found between rabbits and man. An interesting difference between normal and inflamed knees in rabbits was noted in terms of retention of two of the four radiocolloids used.

Materials and methods

Certain characteristics of the radiocolloids are shown in the Table. A part of routine batches of ⁹⁰Y citrate, ferric hydroxide, and silicate ordered for human use was used in rabbits. ⁹⁰Y resin colloid is no longer manufactured and a special consignment was supplied for this experiment. Additionally, ⁹⁰Y chloride, the raw material from which some of these colloids are made, was also used.

Accepted for publication July 21, 1977

A Dumonde-Glynn form of chronic synovitis was induced in the right knee of each rabbit by intra-articular injection of gammaglobulin after sensitisation with gammaglobulin. Rabbits were immunised in batches of 6 and then challenged so that animals of one batch could be used for more than one radiocolloid. 100 µCi ⁹⁰Y was injected into each knee of 3 rabbits at one time; one rabbit would be sacrificed at intervals of 24 hours, 48 hours, and 168 hours. Both knees, regional lymph nodes, and liver were separately removed and counted. Immediately after counting, some synovium was processed for autoradiography.

The ⁹⁰Y content (T_½ = 64 hours; maximum beta energy = 2.27 MeV) of each sample was determined by measurement of the bremsstrahlung using two NaI (Tl) crystals (10.2 cm diam. × 7.5 cm thick) in a low background shield, with the sample in a

Table Characteristics of yttrium 90 products

	Citrate	Chloride	Ferric hydroxide	Resin	Silicate
Manu- facturer	CEA France	Radiochemical Centre Amersham			
Availability	Yes	No	Limited	No	Yes
Particle size of colloid (nm)	1-10 (60%) 10-1000 (30%) >1000 (10%)	Noncol- loidal	~100	20-50	100
pH	7	2	6-7	6-7	10

sealed container placed between the faces of the crystals. The limit of detection varied from about 0.2% of dose for samples from animals sacrificed at 24 hours, to 0.1% of dose for those sacrificed at 168 hours, using counting times of 100 seconds for the energy range 0.1 to 0.65 MeV. A full account of the retention of these ^{90}Y colloids in man has already been published (Gumpel *et al.*, 1975). Student's *t* test for paired values was used.

Results

Two patterns of retention of isotope in the knee were noted (Fig.). When the ferric hydroxide and silicate colloids and the noncolloidal chloride were used the retention of isotope in the inflamed knee was comparable to that in the noninflamed knee. With ^{90}Y citrate and resin colloids, isotope was retained considerably better in the noninflamed knee, and these differences were statistically significant ($P > 0.001$ for citrate, $P > 0.01$ for resin).

Some uptake of isotope in the liver was noted in all 3 rabbits injected with resin colloid, 4.9%, 4.3%, and 4.3% of the injected dose being detected. Liver uptake of more than 1% of the dose was noted in 3 out of 15 rabbits injected with ferric hydroxide, in 1 of 3 injected with silicate, and in 1 of 3 injected with chloride. Uptake of isotope by lymph nodes greater than 0.1% of the injected dose was found in only one rabbit, 0.6% of the injected dose being detected in the rabbit killed 24 hours after citrate injection. The low frequency of this finding may in part have been influenced by the difficulty in consistently identifying inguinal and popliteal lymph nodes.

Only one form of isotope produced any obvious insult to the knees. In the animals killed 24 and 48 hours after injection with ^{90}Y chloride, the synovium was markedly oedematous and inflamed, and free

fluid was evident on opening the joint. Histologically the degree of induced synovitis in the right knees was moderate and comparable in all rabbits except in which it was moderately severe. This knee produced the highest level of retention with ^{90}Y citrate.

Discussion

The factors that influence the retention of radiocolloids in a joint are imperfectly understood. First immobilisation of a joint for 3 or so days after injection has been shown to markedly reduce extra-articular spread (Oka, *et al.*, 1971; Gumpel *et al.* 1973b; Williams *et al.*, 1976). A second important factor has been thought to be the degree of inflammation present in the joint. Goode and Howey (1973), in nonquantitative work in man, thought that premedication with intra-articular steroids reduced extra-articular spread with colloidal gold 198 by reducing the activity of inflammation, although we have been unable to confirm this finding using ^{90}Y silicate, perhaps because less isotope leaves the joint. The finding of a marked differential in these rabbits in retention between inflamed and noninflamed knees with two ^{90}Y colloids suggests that there may be differences in the handling of particular radiocolloids. If these results can be extrapolated to man, premedication with steroid 2 days before injection of ^{90}Y citrate may markedly reduce the extra-articular spread noted with that radiocolloid.

Other possible factors are particle size and the stability of the colloid *in vivo*. *In vitro* studies of the behaviour of these colloids with synovial fluid were unrevealing (S. C. Peake and J. M. Gumpel, unpublished, 1974), while in previous studies in man (Gumpel *et al.*, 1975) retention of isotope in the knee appeared to depend neither on the size of the colloidal particles nor on the known stability of the colloid. This impression was confirmed by the findings in this study that a noncolloidal preparation of ^{90}Y was retained no better and no worse than some of the colloidal preparations.

On the other hand, certain differences in retention in inflamed joints can be noted between rabbits and man. In man, retention of isotope in inflamed knees was best with silicate and resin, followed by ferric hydroxide and then citrate. Liver uptake was noted with ^{90}Y silicate, and was uncommon with resin. In inflamed rabbit knees silicate and resin were poorly retained and ferric hydroxide moderately well retained. Liver uptake was noted in all 3 rabbits treated with resin. One possible, but weak explanation is that the rabbits were not immobilised after injection but were confined to small rabbit cages.

Fig. Retention of isotope in knees. (Right knee with induced arthritis.)

These results showing differences in retention between inflamed and noninflamed knees in rabbits, and between man and rabbits, may help to elucidate the mechanisms of handling radiocolloids.

This work could not have been performed without the help of the Radioisotopes Division of the Clinical Research Centre, and of the Radiochemical Centre, Amersham.

References

- Bayly, R. J., Peacegood, J. A., and Peake, S. C. (1973). ^{90}Y ferric hydroxide colloid. *Annals of the Rheumatic Diseases*, **32**, Suppl., 10.
- Goode, J. D., and Howey, S. (1973). Effect of premedication with intra-articular hydrocortisone on the retention of ^{198}Au in the knee joint in rheumatoid arthritis. Use of $^{99\text{m}}\text{Tc}$ in assessment. *Annals of the Rheumatic Diseases*, **32**, Suppl., 43-45.
- Gumpel, J. M., Hesp, R., and Loewi, G. (1973a). Comparison of ^{90}Y ferric hydroxide colloid with the citrate and resin colloids. A preliminary animal study. *Annals of the Rheumatic Diseases*, **32**, Suppl., 11-12.
- Gumpel, J. M., Williams, E. D., and Glass, H. I. (1973b). Use of yttrium 90 in persistent synovitis of the knee. 1. Retention in the knee and spread in the body after injection. *Annals of the Rheumatic Diseases*, **32**, 223-227.
- Gumpel, J. M., Beer, T. C., Crawley, J. C. W., and Farran, H. E. A. (1975). Yttrium 90 in persistent synovitis of the knee—a single centre comparison. The retention and extra-articular spread of four ^{90}Y radiocolloids. *British Journal of Radiology*, **48**, 377-381.
- Oka, M., Rekonen, S., Ruotsi, A., and Seppala, O. (1971). Intra-articular injection of Y-90 colloid in the treatment of rheumatoid knee joint effusions. *Acta Rheumatologica Scandinavica*, **17**, 148-159.
- Pavelka, K., Meier-Ruge, W., Müller, W., and Fridrich, R. (1975). Histological study of effects of colloidal yttrium 90 on knee joint tissues of rabbits. *Annals of the Rheumatic Diseases*, **34**, 64-69.
- Webb, F. W. S., Lowe, J., and Bluestone, R. (1969). Uptake of colloidal radioactive yttrium by synovial membrane. *Annals of the Rheumatic Diseases*, **28**, 300-302.
- Williams, E. D., Caughey, D. E., Hurley, P. J., and John, M. B. (1976). Distribution of yttrium 90 ferric hydroxide colloid and gold 198 colloid after injection into knee. *Annals of the Rheumatic Diseases*, **35**, 516-520.