Intra-articular urokinase in rheumatoid arthritis

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It has been suggested that urokinase may have some value in the management of patients with rheumatoid arthritis (Morotomi and Tatezawa, 1970; Ito and Naito, 1970). This fibrinolytic agent activates plasminogen, converting it to plasmin competitively and reversibly. Thus there is some basis, however speculative, for its use in rheumatoid arthritis—a disease which on several clinical and laboratory grounds may bear some relationship to fibrinogen and fibrinolysis (Bach Andersen, and Gormsen, 1970; Barnhart, Riddle, Bluhm, and Quintana, 1967; Caughey and Highton, 1967).

We have completed a small study of local urokinase treatment in comparison with water controls in the knee joints of ten patients with classical rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) and have monitored these patients intensively over a short period of time. The clinical assessment methods included range of knee movement as measured by a goniometer, the number of full flexions possible in 30 sec., local knee pain score, and 99mTc uptake.

Material and methods

The ten patients studied all had persistent disease of the knee joints and in all there was demonstrable synovial thickening. The average duration of the disease was 9.6 years (S.D. $\pm$ 5.6), none had Sjögren's syndrome, and the mean age of the group was 57.8 years (S.D. $\pm$ 7.9). There were five males and five females. All of these patients were receiving non-steroidal anti-inflammatory agents and none had at any time received corticosteroids, gold, or cytotoxic agents. Each patient voluntarily agreed to participate in the study after full explanation of its content and implications. The assessment order and procedure for each patient was standardized and identical. The indices described above were all performed by one of us (CW) who is fully trained in these particular assessment methods and whose intra- and inter-observer variation has been quantitated. In addition, a rheumatologist (RS) made a separate subjective assessment of change in joint activity. The order of the assessments comprised firstly a general question followed by particular questioning for expected knee joint symptomatology. After this the

standard assessment indices were performed. 5000 Plough units of urokinase in 2 ml sterile water were injected into one knee and sterile water alone into the other. As will be seen from the clinical assessments (Table I) the initial assessment values for each patient group were similar. The patients were re-assessed in exactly the same way at 24 hours and at 7 days.

Results

The Table shows that there was no significant difference between the treatment groups in any of the clinical assessments taken at 24 hours and 7 days.

Comment

It must be emphasized that the results detailed may not be extrapolated beyond the time limits of the study. The patients studied will be monitored for a considerable length of time and any changes which may emerge will be reported immediately. The numbers involved are small but, from previous experience of active compounds (Chalmers, Cathcart, Kumar, Dick and Buchanan, 1972), we should have expected to observe improvement in some of the patients whereas, even in the patients whose individual results showed slight though insignificant alteration, change was in the direction of deterioration rather than amelioration. It is also noteworthy that the dose employed was far in excess of tissue levels likely to be obtained in systemic urokinase treatment with standardly employed dose levels.

We would tentatively conclude from these results that the use of intra-articular urokinase alone in the treatment of rheumatoid arthritis is unlikely to produce any short-term benefit. However, there is evidence to suggest that the use of urokinase in combination with intra-articular steroid may be more effective (Morotomi and Tatezawa, 1970) and investigations are proceeding to confirm this observation.

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Table Mean findings in treated and control knees

Parameter	Pre-urokinase	Post-urokinase		Difference	Pre-H ₂ O	Post-H ₂ O		Difference
		24 hrs	7 days			24 hrs	7 days	
Pain score	$\bar{X}=2.7$ ($\pm$ S.E. 0.8)	$\bar{X}=2.5$ ($\pm$ S.E. 0.8)	$\bar{X}=2.25$ ($\pm$ S.E. 0.8)	N.S.	$\bar{X}=2.5$ ($\pm$ S.E. 0.8)	$\bar{X}=1.7$ ($\pm$ S.E. 0.9)	$\bar{X}=1.6$ ($\pm$ S.E. 0.9)	N.S.
Range of movement	$\bar{X}=103.4$ ($\pm$ S.E. 10.0)	$\bar{X}=102.6$ ($\pm$ S.E. 10.7)	$\bar{X}=113.4$ ($\pm$ S.E. 10.0)	N.S.	$\bar{X}=104.5$ ($\pm$ S.E. 11.3)	$\bar{X}=105.0$ ($\pm$ S.E. 11.1)	$\bar{X}=109.5$ ($\pm$ S.E. 10.2)	N.S.
No of full flexions in 30 sec.	$\bar{X}=13.7$ ($\pm$ S.E. 2.6)	$\bar{X}=15.3$ ($\pm$ S.E. 2.8)	$\bar{X}=16.7$ ($\pm$ S.E. 2.3)	N.S.	$\bar{X}=14.8$ ($\pm$ S.E. 2.2)	$\bar{X}=15.6$ ($\pm$ S.E. 2.5)	$\bar{X}=18.2$ ($\pm$ S.E. 2.5)	N.S.
99mTC uptake	$\bar{X}=51.5$ ($\pm$ S.E. 7.6)	—	$\bar{X}=43.3$ ($\pm$ S.E. 6.5)	N.S.	$\bar{X}=42.65$ ($\pm$ S.E. 7.3)	—	$\bar{X}=37.1$ ($\pm$ S.E. 5.6)	N.S.

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