


Correlation of iron exchange between the oral iron chelator 1,2-dimethyl-3-hydroxyprid-4-one (L1) and transferrin and possible antiaemic effects of L1 in rheumatoid arthritis

S: Iron and ferritin are probably able to stimulate local free radical damage in joints of patients with rheumatoid arthritis (RA) by forming hydroxyl radicals and in this way contribute to the persistence of synovitis. In the anaemia of chronic disease in RA iron stores are increased, but they are probably less available for erythropoiesis. Owing to the possible deleterious effects of iron stores on RA activity the treatment of RA with desferrioxamine, a general iron chelating agent, has been studied. The results were controversial. In addition to the possible beneficial effects of iron chelators on RA activity, it is claimed that iron chelation might improve bone marrow iron availability and hence erythropoiesis. Giordano et al found a haemoglobin increase after treatment with desferrioxamine. We confirmed their findings using a new oral iron chelator-1,2-dimethyl-3-hydroxyprid-4-one (L1). L1 has been shown to be an effective iron chelator with promising potential in the treatment of haemosiderosis and, possibly, RA. If increased bone marrow iron availability is the mechanism through which a haemoglobin increase occurs after iron chelation it can be assumed that this takes place through a higher iron saturation of transferrin, which indeed was the case in our study.

Hewitt et al found that L1 released 90% of iron-59 (59Fe) bound to transferrin. This implies that after L1-iron chelation a high proportion of iron may be bound to L1, instead of transferrin, suggesting a delayed first rather than an increased amount of iron bound to transferrin available for bone marrow. We therefore examined both the ability of L1 to remove iron from human transferrin and of human transferrin to remove iron from L1.

The following method was used: 388 μl of L1 (0:1 mg/ml) was added to 100 μl of 59Fe-transferrin (9:7 mg/ml). After incubation with the iron chelator-1,2-dimethyl-3-hydroxyprid-4-one (L1) was added. It was found that after L1-iron chelation a high proportion of iron may be bound to L1, instead of transferrin, suggesting a delayed first rather than an increased amount of iron bound to transferrin available for bone marrow.

The table shows the obtained Activity was measured with a Packard-autogamma 500 C.

The results obtained indicate that L1 is able to remove a substantial amount of iron from transferrin, confirming findings of Hewitt et al., depending on the time of incubation and the amounts of L1 and transferrin added. It was also found, however, that transferrin can release iron from L1, depending on the same factors. Thus, possibly, in a patient treated with L1, the iron saturation of transferrin and L1, determines the direction of iron exchange between them. In the anaemia of chronic disease in RA iron saturation of transferrin generally is low so it is possible that iron exchange between ferritin and transferrin mediated by L1 takes place, explaining the haemoglobin increase after iron chelation in these patients. It has also been found that L1, diffuses easily through the erythroblast membrane and thus it may incorporate iron into erythroblasts and hence...
Response criteria for slow acting antirheumatic drugs.

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