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Gold Therapy in Rheumatoid Arthritis

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Introduction

Steroid therapy has been regarded as a decisive measure among the treatments of rheumatoid arthritis since the report of HENCH et al [7] in 1949. With extensive clinical application, side-effects appeared and consideration had to be given to utilizing nonsteroidal agents for treatment of the disease. Gold therapy is regarded as being the most effective.

The history of gold preparations being prescribed for rheumatoid arthritis outdates that of steroids, going back to 1927 when a report to that effect made for the first time by LANDE[9]. Many reports of therapeutic results of gold therapy have since been published. The effectiveness of gold therapy was established following reports using the double blind test by the Empire Rheumatism Council in 1960 [4) 5)] and American Rheumatism Association in 1973 [3)], and using joint scintigraphy [16)]. Although this therapy used, nevertheless, problems unsolved regarding mechanism of action, administration methods and means of minimizing side-effects.

In recent years, the atomic absorption spectrophotometer has enabled determination of the relationship between the gold concentration and therapeutic effects or side-effects, the results of which has been documented [6) 8) 14)]. The authors gave their attention mainly to the determination of administration methods which resulted in optimum therapeutic effects and minimal side-effects.

Materials and Methods

Materials

Two male and 19 female out-patients at an age ranging from 20 to 66 years (average 45) had been diagnosed as classical or definite rheumatoid arthritis according to the ARA standard[2]. All had been subjected to treatments other than gold therapy at other medical institutions. Liver and renal functions were confirmed as being normal before initiation of gold therapy.

Methods

Gold sodium thiomalate was employed. The drug was administered i.m. once weekly at 10mg the first week, 25mg the second and 50mg for the third week downward. After a total dose of 1000mg the administration was switched to a maintenance

therapy where as a rule, a single dose of 25mg was administered every week. Changes in this pattern of administration are made when there is an abnormal rise in the serum gold level or appearance of side-effects. Actually, administration patterns often vary with a lapse of time even when the total dose is the same.

Atomic absorption spectrophotometer is utilized for determining serum gold concentration in blood samples taken before administration of the preparations. Accordingly, the time which elapses from the previous administration of a gold preparation varies with the interval of hospital visit.

To determine therapeutic effects, the Lansbury index[10) 11)] was computed after examining morning stiffness, fatigue, grip strength, joint score and blood sedimentation rate. Aspirin demand was neglected. At the same time, CRP and RAT were also examined.

Results

Relationship between Therapeutic Effects and Total Dose of Gold

Seventeen out of the 21 patients showed a definite improvement as determined by the Lansbury index while treatment was ineffective in four. However, when the relationship between the total dose and Lansbury index was examined in all cases combined, the effectiveness was demonstrated at the total dose of 500mg of gold and a significant improvement was observed from 700mg onward as is shown in Fig. 1.

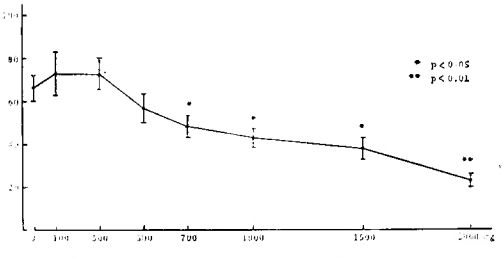

Fig. 1 Lansbury index was significantly improved with 500 mg of total dose or more.

When parameters constituting Lansbury index were examined respectively, the morning stiffness showed a tendency to aggravation up to the total dose of 300mg of gold, however, such improved from 500mg with a marked improvement particularly in 1000mg or more (Fig. 2). Fatigue-free time showed a tendency to increase from the initiation of gold therapy (Fig. 3). Grip strength also increased at the onset of the treatment and there was a significant difference with 700mg or over (Fig. 4). The joint score decreased in the total dose of 500mg onward, and a significant effect was observed particularly with 700mg (Fig. 5). The number of inflammed joints also showed a great tendency to decrease with 700mg or more (Fig. 6). If the joint score regarding hands only is examined, there is a tendency to decrease as a total dose increases, however, no great change observed the number of inflammed joints of the hands, thus indicating that the affected finger joints are difficult to cure. The blood sedimentation rate decreased remarkably from the total dose of 500mg onward, showing a significant difference with 1000mg or more (Fig. 7). When viewed as a whole, the values of CRP and RAT also showed a tendency to

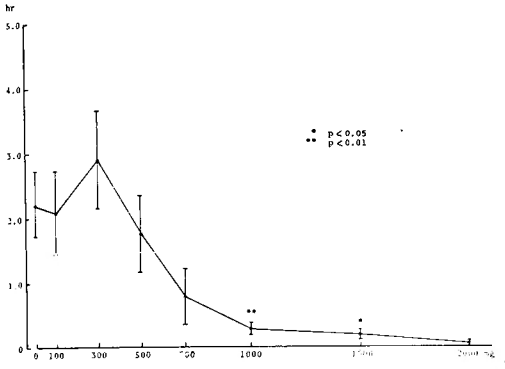

Fig. 2 Morning stiffness was improved with 500 mg of total dose or more.

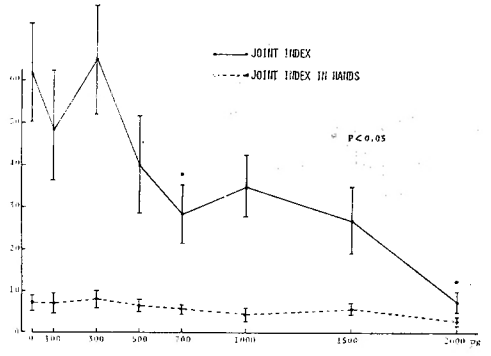

Fig. 5 Joint index was significantly improved with 700 mg of total dose or more, but not so joint index in hands.

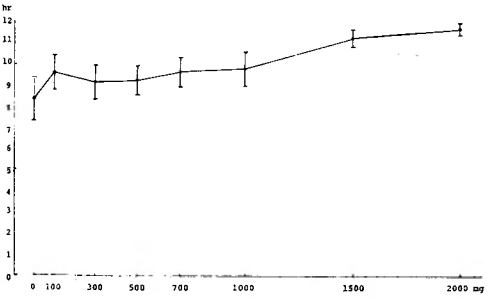

Fig. 3 Fatigue-free time was prolonged initially in gold therapy.

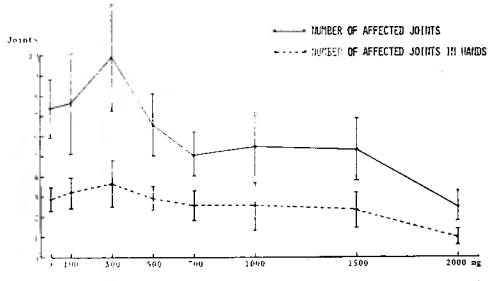

Fig. 6 Number of affected joints was decreased with 700 mg of total dose or more, but not those in the hands.

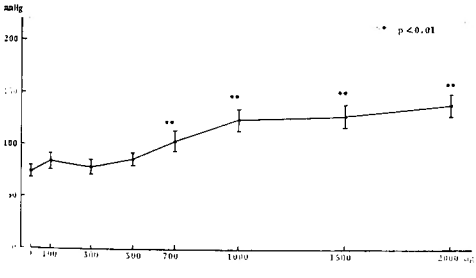

Fig. 4 Grip strength was markedly increased with 700 mg of total dose or more.

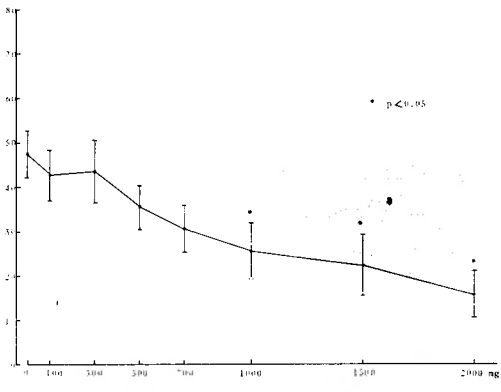

Fig. 7 ESR was significantly improved with 1000 mg of total dose or more.

improvement. As above, the relationship between the total dose and therapeutic results was given attention, however, this is merely the average taken of the whole. A joint scintigram taken after gold therapy clearly showed decrease in uptake of isotope in relieved patients. A few patients on a total dose of 2000mg or more showed a rebound tendency in the scintigram despite the fact that gold therapy appeared to be effective

as the symptoms were relieved clinically.

Relationship between the Doses and the Serum Gold Level

Serum gold level averaged 130μg/dl with the adminstration of 100mg, at 359μg/dl on 300mg, at 352μg/dl on 500mg, at 292μg/dl on 1000mg, at 149μg/dl on 1500mg and at 144μg/dl on 2000mg.

A change in the serum gold level according to the doses and the interval of administration was as follows: the concentration averaged 392μg/dl on the 50mg weekly administration, 212μg/dl on 50mg every two weeks, 213μg/dl on 25mg every week and 134μg/dl on 25mg every two weeks in cases where the same dose was administered for a fixed period of time regardless of the total accumulated amount.

Relationship between Therapeutic Effects and Serum Gold Level

In our studies, 300-400μg/dl of serum gold level was required to obtain therapeutic effects before shifting to maintenance therapy. In two out of 4 ineffective cases, the level of 300μg/dl had not been exceeded even once. In the effective cases, meanwhile, there was only one case that did not exceed the 300μg/dl level and remaining 16 all showed 300-400μg/dl during the initial stage of administration. However, the total dose has to reach a certain serum level before effectiveness is apparent, that is, when the level reaches 500mg, a significant improvement in Lansbury index is observed.

The serum gold level during the maintenance therapy showed 100-200μg/dl on fortnightly 25 mg administration, and a marked reversion was not observed clinically when this level was maintained. When the serum gold level is only 100μg/dl or less, there is a tendency to reversion, hence, the necessity to occasionally adminiter an additional 50mg.

Side-Effects

Cases, where the standard administration of 50mg per week was continued up to the total dose of 1000mg, numbered only 7 out of 21. In 4 cases the dose was reduced because of side-effects and in 9 cases was reduced when the serum gold level reached 400μg/dl or more. Despite the reduction in dose, itchiness later occurred in 8 out of 9 cases. However, after the reduction in dose, side-effects consisted merely of a slight itchiness of the skin in all but two cases of dermatitis the same of which required several weeks to cure. Such reduction of dose in the initial stage of gold therapy is considered to be effective in minimizing side-effects.

The occurrence of side-effects throughout the course of gold therapy was demonstrated in the initial stage of therapy and during maintenance therapy. In the mean gold dose was 498mg and the mean gold level at 468μg/dl. In the latter, the mean gold dose was 1323mg and the mean serum gold level 180μg/dl. Side-effects in the initial stage always occurred when the serum gold level exceeded 400μg/dl; and there was only one patient which did not develop itchiness even when the concentration exceeded that figure. This implies a close relationship between the high serum gold level and the occurrence of side-effects in the initial stage of gold therapy. By con-

trast, side-effects not related to the high serum gold level occur during the maintenance therapy even at 100-200μg/dl concentration. Side-effects during maintenance therapy are attributed accumulation of gold salts.

Itchiness of the skin is the most common side-effects followed by exanthema, stomatitis and other related minor disorders. Side-effects during the initial or maintenance therapy were more or less observed to be about the same degree for exanthema, which during maintenance therapy was always mild.

Discussin

All clinicians agree to the fact that the administration of gold salt is effective for rheumatoid arthritis; however, as to the serum gold level and therapeutic effects, KRUSIUS et al [8] recognize the relationship between the two, while GERBER et al [6] deny it. Generally speaking, however, now that gold salt is utilized as a drug, it would appear reasonable that gold salt has to be present at a certain period of time regradless of the mechanism of action. In accordance with the theory of LORBER et al [12) 13)], efforts were made to maintain the serum gold level during the initial stage of therapy at 300-400μg/dl. As a result, a definite improvement was observed in 17 out of 21 cases. The effectve rate of 81% is in good parallel with the results of ADAMS et al[1)] and other investigators. Gold therapy brought about not only a significant improvement in Lansbury index and its consistituting parameters, but also a good influence on CRP and RAT.

The effectiveness of gold therapy was in general remarkable, however, the agent did fail to decrease the number of affected joints in many patients. Rheumatic hands have swelling on the dorsal side of the wrist joints due to tenosynovitis in the extensor tendon sheath. This swelling leads to tendon rupture. Further, rheumatic hands also have limitation of motion of fingers or snapping finger due to tenosynovitis in the flexor tendon sheath in the palm, or proximal or middle phalanx of the fingers. There was no occurrence of tendon rupture in our study; however, tenosynovitis on the back of the hands and palms was observed even during the gold therapy and there were complaints such as limitation of motion of fingers or snapping fingers due to tenosynovitis. A steroid was injected into the tendon sheath in 9 out of 21 patients and the symptoms were relieved. There were also patients in whom pain and swelling of the wrist and finger joints were not easily improved even during gold therapy and an intra-articular injection of steroid was given; however five were refractory, and the pain and swelling did subside with intra-articular injection of radioisotope gold [17)].

GERBER et al [6)] and MASCARENHAS et al [14)] do not acknowledge a relationship between side-effects and serum gold level. KRUSIUS et al [8)] observed that the incidence of side-effects was high in the case of high serum gold level. SMITH [15)] considers that side-effects are the result of accumulation of gold which has exceeded a certain

threshold. In our patients, side-effects could be classified into two according to the time required for onset, that is the side-effects observed during the initial therapy and those evident during maintenance therapy. The former is liable to develop at 400μg/dl or more of the serum gold concentration; therefore if the serum gold concentration could be maintained at 400μg/dl or less, then it could be expected that the side-effects would be minimal.

Side-effects occur even at 200μg/dl or less of the concentration, and it is presumed that the side-effects are due to the serum gold accumulation. With our patients, this concentration was maintained at a level of 100-200μg/dl when the therapy was shifted to the maintenance one. If 25mg of gold is administered fortnightly over a long period of time during the maintenance therapy or if the total dose reaches 2000mg or more, then the serum gold level will decrease to less than 150μg/dl and a tendency to revert to the inflammatory stage is observed under joint scintigraphy [16]. For this reason a non-steroidal anti-inflammatory agent such as ibuprofen, or 50mg of gold preparation was injected every three weeks.

Conclusion

Therapeutic effects of gold sodium thiomalate on 21 patients with classical and definite rheumatoid arthritis were studied.

Seventeen out of 21 patients showed a definite improvement in Lansbury index and its constituents. The effectiveness was demonstrated at the total dose of 500 mg of gold and a significant effect was observed in 1000 mg or more.

Side-effects are observed during the initial therapy (up to 1000 mg of the total dose) and the maintenance therapy (total dose of gold 1000 mg onward). In the former, side-effects developed at 400μg/dl or more of the serum gold concentration, and were minimized when the gold concentration is controlled less than 400μg/dl. Side-effects during the maintenance therapy occurred even at 100-200μg/dl of the serum gold level, however, were comparatively mild.

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和文抄録

慢性関節リウマチの金療法

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慢性関節リウマチの患者21症例（全例 classical or definite RA）に対し金療法（gold sodium thiomalate）を行なった．治療効果と副作用を，金の総投与量と血清金濃度の面から検討した．

治療効果は，21症例中17例（81%）に有効でランズバリー指数及びこれを構成する朝のこわばり，疲労発現時間，握力，関節点数，血沈値に改善を認めた．効果発現は金投与総量500mgでみられ，とくに1000mg以後で有意にみられた．

副作用としては，掻痒感，皮疹，口内炎等があり，初期療法中（金投与総量1000mgまで）に発現する副作用は血清金濃度400μg/dl以上ものに発現し易く，金濃度を400μg/dl以下にコントロールすることにより，副作用を最小限に抑えられた．維持療法中（金投与総量1000mg以後）の副作用は血清金濃度100～200μg/dl でも現われるが，皮疹は初期療法中のものに比し軽症であった．