TREATMENT OF RENAL AMYLOIDOSIS WITH DIMETHYLSULPHOXIDE (DMSO)

M H van Rijswijk, A J M Donker, L Ruinen, J Marrink

University Hospital, Groningen, The Netherlands

Summary
Amyloid fibrils can be dissolved by dimethylsulphoxide (DMSO) in vitro and in vivo. This prompted us to investigate the therapeutic value of DMSO in renal failure caused by amyloidosis.

Two patients with renal failure caused by secondary amyloidosis due to rheumatoid arthritis, showed a remarkable improvement of renal function. The effect of DMSO in amyloidosis secondary to rheumatoid arthritis seems to depend on its anti-inflammatory action, resulting in a decrease in amyloid formation.

No evidence was found for an increase in amyloid degradation.

The effect of DMSO in primary amyloidosis was inconclusive.

Introduction

Amyloidosis is a disease caused by extracellular deposition of protein fibrils. The fibrils are composed of polypeptide chains arranged in the beta-pleated sheet configuration, which results in:

1. insolubility under physiological conditions.
2. resistance to proteolytic digestion.
3. green birefringence after staining with congo red.

In this respect all types of amyloid are identical.

Further differentiation has become possible by amino acid sequence analysis of the major protein components of amyloid [1–3].

Most important for clinical practice are AL-amyloid, derived from the variable part of the immunoglobulin light chains, and AA-amyloid, derived from the immunochemically related serum protein SAA, which behaves like an acute phase reactant [4,5].

Wright et al [6] described a simple histochemical method to distinguish between these two major types of amyloid. AA-amyloid loses its affinity for congo red (disappearance of the green birefringence) after incubation of tissue
sections with potassium permanganate, while the affinity for congo red remains unchanged in case of AL-amyloid. There exists a close correlation between the potassium permanganate sensitivity and the classification based on the presenting clinical picture (see Table I and references [6–10]).

TABLE I. Classification of Generalised Amyloidosis with Regard to Biochemical, Histochemical, Histological and Clinical Characteristics

<table>
<thead>
<tr>
<th>Acquired Idiopathic</th>
<th>Secondary Amyloidosis</th>
<th>Myeloma Associated Amyloidosis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Amyloidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amino acid analysis</td>
<td>AA-amyloid</td>
<td>AL-amyloid</td>
<td>1,2,3</td>
</tr>
<tr>
<td>Precursor</td>
<td>SAA</td>
<td>variable part Ig-light chain</td>
<td>4,5</td>
</tr>
<tr>
<td>Histochemical picture</td>
<td>KMnO₄-sensitive</td>
<td>KMnO₄-resistant</td>
<td>6,7</td>
</tr>
<tr>
<td>Histological picture</td>
<td>perirecticular</td>
<td>pericollagenous</td>
<td>8</td>
</tr>
<tr>
<td>Clinical picture</td>
<td>Typical distribution (nephropathy)</td>
<td>Atypical distribution (cardiopathy, nephropathy, glossopathy)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Pattern II</td>
<td>Pattern I</td>
<td>10</td>
</tr>
</tbody>
</table>

Further support for this classification is provided by the values of SAA levels obtained in patients with generalised amyloidosis, classified according to Table I. It appears that patients suffering from progressive AA-amyloidosis always have elevated SAA levels, whilst patients with progressive AL-amyloidosis show normal SAA levels (except during intercurrent infections).

In 1976 Isobe et al [11] showed that dimethylsulphoxide (DMSO) can cause a reversible blockade of the Bence-Jones thermoprecipitation reaction, and that amyloid fibrils can be dissolved in DMSO. In 1977 Kedar et al [12] observed in the murine AA-amyloid model, a disappearance of amyloid under the influence of DMSO, with a coincidental appearance of amyloid-like material in the urine. Ravid et al [13] described a similar appearance of amyloid-like material in the urine of patients with renal amyloidosis after a single dose of DMSO.

These observations, suggesting the possibility of making amyloid soluble by DMSO, prompted us to investigate the value of DMSO in the treatment of human amyloidosis.

Patients and Methods

All patients had biopsy proven renal amyloidosis. They were classified according to the clinical picture of organ dysfunction and the presence or absence of an underlying disease known to be associated with generalised amyloidosis (Table I). This classification was fully supported by the results of potassium permanganate incubation of the biopsy specimens, and of the SAA levels determined by radio-immunoassay, as described by Sipe et al [14].
Glomerular Filtration Rate (GFR) and Effective Renal Plasma Flow (ERPF) were determined simultaneously by the use of radiopharmaceuticals according to the method described by Donker et al [15].

DMSO was administered by mouth as a 20g/L solution in distilled water or, if necessary, intravenously as a 10g/L solution in physiological saline. The dosage used was 200 to 300mg/Kg body weight/day in 2 or 3 doses. Urine samples taken before and during DMSO treatment were searched for amyloid-like material according to the method described by Kedar et al [12].

Results

Two patients with renal failure caused by generalised amyloidosis secondary to rheumatoid arthritis showed a remarkable improvement of renal function and general condition. Data on the first and second patient are shown in Figures 1 and 2 respectively. In a third patient with amyloidosis secondary to rheumatoid arthritis, DMSO treatment was started in an earlier phase and resulted in stabilisation of the creatinine clearance at 45ml/min (Figure 2, patient 3).

Figure 1. Improvement of renal function and decrease of the concentrations of SAA and CRP in serum during treatment with dimethylsulphoxide in a patient with secondary amyloidosis

502
Figure 2. Concise data of renal function and SAA-levels in patients with primary and secondary AA-amyloidosis during treatment with dimethylsulphoxide

Three patients with primary AA-amyloidosis (patients 4, 5 and 6, Figure 2) did not show any improvement in renal function, despite an identical decrease of SAA level. Two patients with primary AL-amyloidosis presenting with a life threatening cardiomyopathy and a minor disturbance of renal function, remained in a steady state for six months so far during DMSO treatment. One patient with myeloma-associated amyloidosis showed a gradual decrease of renal function during DMSO treatment.

The finding of amyloid-like material in the urine was very inconsistent and could not be related to the results of DMSO treatment.

Discussion

In secondary amyloidosis, DMSO treatment seems to be of value. The original idea that DMSO could make amyloid fibrils soluble or accessible to proteolytic
digestion could not be substantiated by the appearance of amyloid-like material in the urine during DMSO treatment.

The fall of SAA levels during DMSO treatment, rather, indicates the possibility of a decrease in amyloid formation. This implies that the effect of DMSO depends on its anti-inflammatory action, which is probably mediated by stabilising lysosomal membranes [16]. This is supported by the subjective improvement of the rheumatoid patients (decrease of pain and increase of joint mobility).

Except for a transient rise of serum transaminase levels no major side effects were observed. The bad-smelling breath produced by dimethylsulphide sometimes evoked social problems which could be managed by careful coaching of the patients.

Conclusions

1 In our experience DMSO is a non toxic drug.
2 DMSO can be useful in the treatment of renal failure caused by amyloidosis secondary to rheumatoid arthritis.
3 The mechanism of action of DMSO in the rheumatoid patients (patient 1, 2 and 3) is probably due to its anti-inflammatory effect.
4 There seems to be a difference in pathophysiological mechanism between secondary and primary AA-amyloidosis, as indicated by an identical fall in SAA levels without improvement of renal function in the latter group.

Acknowledgments

Amyloid Research in Groningen, The Netherlands is supported by The Netherlands League against Rheumatism.
Renal function studies were made possible by a grant (no. C9 V) of the Dutch Kidney Foundation.

References

6 Wright, JR, Calkins, E and Humphrey, RL (1977) Lab. Invest., 36, 274
9 King, LS (1948) Amer. J. Path., 24, 1095
Open Discussion

ZONDER (Israel) We had a patient 2 years ago suffering from Familial Mediterranean Fever and primary amyloidosis. We also tried DMSO and failed, since the kidney function deteriorated and the patient had to be dialysed afterwards. You mentioned a social problem and I want to stress that it is very disturbing to the patient. The bad smell of the DMSO just put him out of any social activity completely, significantly decreasing his quality of life.

VAN RIJSWIJK That is not our experience and that is not the experience of other nephrologists either, because in the first place there is no problem for the patient directly, as the patient does not smell the garlic-like odour. It is only a problem for the people around and I can assure you, when you are more than 15 minutes in the same room you don’t smell it anymore. So, it is just a matter of careful coaching of the patient. We had rheumatoid patients who stopped it because of the smell but they asked to restart because of the beneficial effect on the joint complaints.

MERY (Paris) What was the form of DMSO and the route of administration you used in your patients?

VAN RIJSWIJK We gave it orally because we prefer to see our patients in the outpatient department. We give them a 20 gram/100ml solution. You have to use the analytic quality from Merck (Germany) because of the purity. You get a heat reaction when you put it into the water and after that it is no problem to swallow it. In emergency cases, when the patient is vomiting or something like that, we gave it intravenously as a 10% solution in physiological saline, also without any problem.

FOLMER LYNGGAARD (Copenhagen) Other anti-rheumatic drugs have both an anti-inflammatory and stabilising effect on lysosomes, but without any effect on amyloidosis. Why do you think that DMSO acts in this way?

VAN RIJSWIJK Because we did not find a consistent pattern of amyloid-like material in the urine, as we expected to find, and we did find a sharp decrease in serum SAA level and a subjective improvement of the inflammatory signs in the patient. Patients were better than they had been for years. The anti-inflammatory effects of DMSO are well known. Weissman described a substantial stabilising effect on the lysosomal membranes. DMSO further potentiates the similar stabilising effect of cortisol and chloroquine. So I think that must be the reason the renal function is improving so slowly, because when you stop the amyloid-inducing disease there is a decrease of the already deposited amyloid.