Changes of Plasma Fibronectin Concentration and Phagocytic Activity in Immunosuppressed Patients during Selective Decontamination

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Plasma fibronectin and phagocytic activity play important roles in combating infections. The question is discussed, whether both defense systems are also of importance in immunosuppressed patients. Further, the behaviour of plasma fibronectin determined by laser nephelometry, and phagocytic activity determined by chemiluminescence is demonstrated in patients with leukaemia under the conditions of selective decontamination of the intestinal tract. The following results are shown:

Plasma fibronectin concentration decreases 10 to 14 days before onset of the first clinical signs of an infection.

Plasma fibronectin level changes appear earlier than that of C-reactive protein (Cp). Therefore, it is suitable as a parameter for assessment of the course of an infection. Decreased plasma fibronectin levels occurring over longer periods have to be regarded as unfavourable prognostic criterion.

The phagocytic activity of immunosuppressed patients selectively decontaminated is significantly below that of healthy adults.

A clear assignment of phagocytic activity to the clinical picture, the number of granulocytes and plasma fibronectin level is not possible at present.

Additional studies are necessary. Both plasma fibronectin level and phagocytic activity do not appear to be influenced by selective decontamination of the intestinal tract.

INTRODUCTION

Selective decontamination has proven to be a very helpful and effective method for the prophylaxis of infection in patients with disturbed immune defence. Despite the unquestioned success reported on at this symposium, attacks of fever and infections do occur during selective decontamination in a number of patients. According to the present level of knowledge, these infections can develop only after overcoming the colonization resistance and the mucosal barrier. When this step has been taken, the RES (reticuloendothelial system) as an important non-specific defensive organ is the first to oppose the expanding infection.

It has been reported that opsonins, especially fibronectin, are of special importance in this connection (6). Therefore, our studies aim first at finding out, whether selective decontamination leads to changes in plasma fibronectin levels in immunosuppressed patients. Further, the studies should explain, whether sufficient fibronectin production is actually possible with the number of functioning granulocytes, being partly extremely low, and to what extent major and minor infections lead to decreases in plasma fibronectin levels.

Recently, besides fibronectin, interest has also centered on the mononuclear phagocytic system (MPS). The most important feature of this system is the phagocytic ability. Therefore the functional condition of this system is of great importance in the defence against microbial infections, since the spread of infection can be inhibited by phagocytosis and the induction of immune reactions.

As is generally known, the functional ability of MPS can be influenced by many substances. Therefore, the influence of selective decontamination on phagocytic activity in immunosuppressed patients should be investigated.
analogously to fibronectin. Furthermore, interactions between plasma fibronectin levels and phagocytic activity need to be evaluated. The point of departure is the fact described above, that a decrease in fibronectin leads to an impairment of phagocytosis.

Fibronectin is able to bind bacteria on the basis of the enzymatic mediation of clotting factor XIII a to allow their phagocytosis by macrophages (3). Therefore, fibronectin can be regarded as a direct mediator of phagocytosis. The question of to what extent this is also true under the conditions of selective decontamination in immunosuppressed patients is of great importance, at least for the analysis of the so-called non-responders to selective decontamination.

MATERIALS AND METHODS

Sixteen patients with acute myeloid leukaemia were included in the studies.

The first blood samples were taken immediately before starting the selective decontamination.

Drugs used for selective decontamination of the intestinal tract are shown in Table 1. Changes of selective decontamination because of developing resistance or occurrence of side effects were not necessary during the period of observation.

Further blood samples were taken at weekly intervals. The results were related to temperature chart and the number of functioning granulocytes.

Fibronectin was measured by laser nephelometry on the PDQ™ laser nephelometer (HYLAND) using a self-made antifibronectin antiserum and standard human serum of the firm Behring Werke (Marburg/Lahn).

Phagocytic studies were made by luminol-enhanced and zymosan-induced chemiluminescence on LKB 1251 luminometer. The chemiluminescence signal of the highest peak in MV relating to 6 × 10⁶ leucocytes/ml of blood was determined as the criterion of phagocytic activity.

RESULTS

The plasma fibronectin concentration during selective decontamination is shown in Fig. 1. In connection with the temperature chart, it is seen in all patients with successful selective decontamination that a decrease in plasma fibronectin starts approximately 10 to 14 days before the onset of infection. At the peak of fever the fibronectin concentration decreased to values of about 100 µg/l. A renewed delayed increase was seen in some patients, but was always related to improvement of the clinical picture. Moreover, from the figure it can be seen that changes in plasma fibronectin levels are at first independent of the number of functioning granulocytes.

Furthermore, there is an evident difference in comparison with the behaviour of C-reactive protein (Crp) running almost parallel to the temperature chart.

Similar results were obtained in principle in patients, in whom selective decontamination had been successful.

Examination results in a so-called non-responder to selective decontamination are shown in Fig. 2. It can be seen that the fibronectin level does not exceed 200 µg/l at any time. Nor could any definite relation with the temperature chart be established. Assessment of other non-responders could not be made as there was only one patient not responding to selective decontamination during the examination period.

The results of the studies on phagocytic activity have to be considered individually for each patient. No significant changes in phagocytic activity occurred in a number of patients selectively decontaminated during the entire period of observation, as shown by the example in Fig. 3. There were no changes connected with an increase in granulocytes exceeding 2.0 Gpt/l either. The demonstrated course of phagocytic activity was characteristic in all patients with a relatively good general state of health and rare or no attacks of fever.

Patients with bad general states of health, high fevers and the so-called non-responders showed phagocytic activity, as demonstrated in Fig. 4. Several peaks can be detected, which occur independently of the number of granulocytes and plasma fibronectin levels and unlike the afore-mentioned group seem to be relative to the temperature chart.

In a third group (Fig. 5), a significant increase of phagocytic activity corresponding with an increase in fibronectin was demonstrated in connection with improvement of the clinical
### Table 1 Drugs and dosage in selective decontamination

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
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<tr>
<td>Polymyxin B</td>
<td>$4 \times 0.05$ g</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamerazine</td>
<td>$3 \times 0.16$ g/$0.24$ g</td>
</tr>
<tr>
<td>Nystatin</td>
<td>$4 \times 1$ Mio./E.</td>
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</tbody>
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![Graph](image1)

**Fig. 1** Fibronectin and CrP plasma concentrations during longtime selective decontamination.

![Graph](image2)

**Fig. 2** Fibronectin and CrP plasma concentrations during selective decontamination [unsuccessful].
Fig. 3 Phagocytic activity during selective decontamination [successful, longtime]

Fig. 4 Phagocytic activity during selective decontamination [unsuccessful]
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Fig. 5 Phagocytic activity during successful selective decontamination

Fig. 6 Phagocytic activity in healthy adults (39) and patients under selective decontamination (36) [MV/6 Mill. leucocytes per ml blood]
state and an increase in granulocytes. This was a patient in a bad general state of health initially, which drastically improved during selective decontamination.

However, it applies to all examined patients that phagocytic activity is significantly (p<0.001) below that of healthy donors (Fig. 6). This is also true, when the results in all patients are extrapolated to a standardized level of $6 \times 10^6$ leucocytes/ml of blood.

**DISCUSSION**

Demonstrated results show that selective decontamination has no negative influence on plasma fibronectin levels. Results ascertained correspond to those of Kawahira et al. (2) and Alexander et al. (1), who found a decrease in plasma fibronectin levels in dependence of the development and severity of pneumonias and severe infections, respectively. Thus, there is a correspondence with standing theoretical fundamentals of selective decontamination, starting out from the fact, that exclusively, colonization resistance is influenced by selective decontamination and no systematic effects develop.

We also agree on the point, that the fibronectin concentration can be considered as an indicator of the severity of an infection. In our opinion this especially applies to the so-called non-responders to selective decontamination, in whom the fibronectin values were assessed at very low levels. From our experience, a missing increase in fibronectin levels in the course of treatment has to be regarded as an unfavourable prognostic sign concerning infection lethality. The number of examined persons is too small, however, to determine for instance, critical or threshold values.

As reported by Kawahira et al. (2), we also found lower plasma fibronectin levels in patients during continuous and successful selective decontamination than in persons not immunosuppressed. This result also holds up to expectations, since fibronectin is synthesized in neutrophil granulocytes and bound to their surfaces (5).

However, a spreading infection can be prognosted from an early decrease in fibronectin occurring 10 to 14 days before an increase in temperature. Hence, the fibronectin level seems to be a feasible criterion for the assessment of the course and early recognition of the spread of infections.

At present a similar statement can not be made concerning phagocytic activity during selective decontamination. Although the activity is significantly below that of healthy subjects, it does not generally correlate with the number of granulocytes or fibronectin level. Clear relations with the clinical state can only be noted in the so-called non-responders to selective decontamination and in long-lasting major infections. Further studies will have to determine, whether the established increase in phagocytic activity given a constant number of granulocytes are attributable to precursors of granulocytes or to parablasts.

Moreover, it is necessary to continue the present investigations to include a larger number of patients in the study in order to come to definite statements concerning the correlations to the clinical course.

**CONCLUSIONS**

The determination of plasma fibronectin levels have proven to be helpful in the evaluation of the risk of infection in immunosuppressed patients, since statements both about an oncoming infection and concerning long-term prognosis are possible. Selective decontamination was found to have no influence on the fibronectin level.

Phagocytic activity in immunosuppressed patients continuously given selective decontamination is significantly decreased compared with healthy subjects. At present a definite assignment of the results to clinical and paraclinical parameters is not possible, and larger patient populations need to be included into the studies. Finally, it can be noted that relatively simple identification of fibronectin as a measurable parameter for the condition of infection defence, particularly since it can be considered as a direct mediator of phagocytosis.

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ANNEX

Continuing the investigations described, we wondered whether the drugs used for selective decontamination have an influence on phagocytic activity. Studies were made according to the methods described with the additional factor of the specific drug in different concentrations. The influence of pharmaca was examined both in immunosuppressed patients and in healthy subjects.

Although the investigations have not yet been completed and given full evaluation at present, the following preliminary results can be presented:
1. Mycerine and nystatin have no influence on phagocytic activity.
2. Polymyxin leads to a slight decrease in phagocytic activity, which unfortunately is not significant.
3. The combination of trimethoprim and sulfamerazine has not been described as yet, but can give rise to undesirable selective decontamination, if the results are to be confirmed, we have initiated a larger series of investigations.

REFERENCES