ALBUMIN STRUCTURE, FUNCTION AND USES

Editors
ROSENOER
ORATZ and ROTHSCILD
Albumin Structure, Function and Uses
To Leone, Roz and Bobby
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PREFACE

Serum albumin constitutes perhaps one of the most paradoxical proteins of the body. It has one of the longest phylogenetic histories. It is, and has been, vitally necessary as species have evolved from the sea to the land. It performs numerous vital functions within the body, and clear, detailed reports of its importance in health and disease go back well over 140 years. The synthesis of serum albumin appears to be the one most susceptible to disease and to altered nutrition. On the other hand, patients who are born without the ability to synthesize this particular protein do not appear to be acutely ill, nor, in fact, to have significant chronic disease in any form. The mechanism for the regulation of albumin synthesis appears to have a fine-edged upper level, for whereas hypoalbuminemia may accompany many different syndromes, hyperalbuminemia is an extremely rare condition. The many facets of this protein, its history, its evolutionary development, its structure, its function, its metabolic behavior and its use and misuse in the treatment of disease are reviewed in this text. We feel that this information, compiled in a single volume, will permit the more effective handling of the knowledge of serum albumin today and in the future.

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INTRODUCTION

THE USE, MISUSE AND ABUSE OF ALBUMIN INFUSIONS

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It is a great honor and privilege to have been asked to introduce this text. When I was first invited to do so and the contributors and contents were outlined, I asked innocently, "Why would you want a clinician like me to write the prologue to a non-clinical text like this?" The question was answered in kind.

"Where would we be without the clinician?"

Myriad aspects of albumin structure, function, synthesis, degradation, distribution and transport will be described in the ensuing pages. I will restrict my remarks to two facets of the problem.

In the Broadway hit, "Same Time Next Year", the secret lovers, to break the ice at their annual trysts, each tell a good and a bad story about their respective spouses. I shall start by relating a good and a bad story about albumin. First, the good story, which, in characteristic fashion, I shall approach from the rear.

It is widely known that adrenocorticosteroid therapy is frequently complicated by the appearance or reactivation of peptic ulcers and that these ulcers are often associated with bleeding and perforation. (1)

The basis for this knowledge is difficult to define. Studies of steroids and of peptic ulcer have failed to establish any sound pathophysiological mechanism to account for such an association. Nevertheless, the presence of an active ulcer, the history of peptic ulcer, symptoms suggestive of an ulcer, or even the presence of occult blood in the stool, are often considered contraindications to the administration of steroid therapy, or reasons for its discontinuation.

In the planning of a controlled clinical trial of steroid therapy in alcoholic hepatitis, it became important to know the truth about this relationship. Dr. Bennett Blitzer and I, therefore, undertook an armchair investigation—a retrospective analysis of all of the prospective controlled studies of adrenocorticosteroid therapy that we could find. (2) Studies in which patients were not selected randomly, in which only very short courses of treatment were carried out, in which other potentially ulcerogenic drugs were administered or those performed in children were excluded. We recorded new peptic ulcers, recurrent peptic ulcers, hemorrhage from ulcer and perforation of ulcer from the steroid and control groups. In addition, upper gastrointestinal

1
hemorrhage of unknown origin, symptoms of peptic ulcer unconfirmed by other means and superficial gastrointestinal ulcers or erosions were also recorded.

Twenty-six prospective controlled double-blind investigations, which included 3600 patients with a variety of disorders, comprise the primary portion of the study. In addition, 16 prospective, controlled nondouble-blind investigations, which included almost 1500 additional patients, comprise the second portion of this study. The overall analysis, therefore, is based on 42 studies and 5400 patients.

I shall limit myself to the double-blind portion of the study. The mean course of therapy was 97 days, at an average daily dose of 19 mg of prednisone or its equivalent.

Peptic ulcers were reported in 1% of the 1491 control patients and in 1.3% of the 2067 steroid-treated patients, an insignificant difference (Table 1). Furthermore, among the group of 3600 patients there was no difference between the steroid and placebo groups in the frequency of hemorrhage from peptic ulcer (0.3%) in both groups or in perforation from peptic ulcer (0.1% in both groups). The prevalence of suspected but unproved peptic ulcers was not higher in the steroid-treated patients. Indeed, upper gastrointestinal hemorrhage of unknown origin occurred more frequently in the placebo-treated patients than in those who received steroids (p<0.05). Finally, the total of proved and unproved ulcers was 2% in both groups (Table 2).

Table 1. Proved Peptic Ulcer in Adrenocorticosteroid Therapy (Double Blind)

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Patients with peptic ulcer</th>
<th>Hemorrhage from peptic ulcer</th>
<th>Perforation of peptic ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>1491</td>
<td>15 1.0%</td>
<td>4 0.3%</td>
<td>1 0.1%</td>
</tr>
<tr>
<td><strong>Steroid</strong></td>
<td>2067</td>
<td>28 1.4%</td>
<td>7 0.3%</td>
<td>1 0.0%</td>
</tr>
</tbody>
</table>

In only one of the twenty-six investigations was the frequency of peptic ulcer significantly higher in the steroid group. In this investigation of alcoholic cirrhosis by Tygstrup and his associates of the Copenhagen Liver Study Group, 9% of the 334 patients had peptic ulcers at the time of the study. In half of both groups, peptic ulcers improved and in a quarter they remained unchanged, whether the patients received steroids or placebo. Only new ulcers were associated with steroid therapy. Six of 169 steroid patients and one of 165 placebo patients developed new ulcers (p<0.05).

Another study—a non double-blind investigation of the nephrotic syndrome—
showed more ulcers in the steroid group. The authors of this study suggested that they may not have looked for ulcers so vigorously in the untreated control patients as they did in those receiving steroids.

One must not conclude that steroids are in no way associated with the development of peptic ulcer. Where there is clinical smoke, one must carefully exclude clinical fire. Now let us see how this is all relevant to albumin. The apparent increased prevalence of peptic ulcer in cirrhotic and nephrotic patients, who have in common hypoalbuminemia, raises the possibility that high blood levels of unbound steroid may be ulcerogenic. Indeed, the Boston Collaborative Drug Surveillance Program has shown that the incidence of steroid side effects, including gastrointestinal bleeding, is two to three times greater in hypoalbuminemic patients than in eualbuminemic individuals. In a sense, the steroid ulcer may be dose-related and the decreased catabolism of prednisolone in cirrhotic patients may further enhance an ulcerogenic effect of steroid in cirrhosis (Table 3). Thus, albumin as a binding site for steroids may provide protection against steroid toxicity. This subject deserves careful investigation.

### Table 3. Relation of Peptic Ulcer to Dose and Duration of Steroid Therapy

<table>
<thead>
<tr>
<th></th>
<th>Short duration (&lt; 30 days)</th>
<th>Long duration (&gt; 30 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Peptic ulcer</td>
</tr>
<tr>
<td>Control</td>
<td>482</td>
<td>3</td>
</tr>
<tr>
<td>Steroid</td>
<td>502</td>
<td>2</td>
</tr>
<tr>
<td>Low daily dose</td>
<td>(&lt; 20 mg prednisone)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1015</td>
<td>11</td>
</tr>
<tr>
<td>Steroid</td>
<td>1567</td>
<td>21</td>
</tr>
<tr>
<td>Low total dose</td>
<td>(&lt; 1000 mg prednisone)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>905</td>
<td>0</td>
</tr>
<tr>
<td>Steroid</td>
<td>1452</td>
<td>1</td>
</tr>
</tbody>
</table>

(a) p < 0.05.  (b) p < 0.01

Now, the bad story, which may be subtitled "The Use, Misuse, and Abuse of Albumin Infusions".

At present there is an acute shortage of albumin. Despite attempts to monitor its use at my hospital, where I am one of the monitors, we have exhausted our quarterly supply by the tenth day of each quarter.

Where has all the albumin gone? Unfortunately, I believe, it has gone down the drain. Let me start with an almost incredible instance:

Early in my house officer training, I was involved with a patient who had bled from varices and was being considered for portacaval shunt. The surgical resident had pointed out to his Chief that the patient did not satisfy one of Blakemore's criteria—his albumin was 2.8%, less than the 3.0 g%, the arbitrarily recommended level.

"Oh, that's alright", the Chief replied, "Schedule him for morning and give him two units of albumin tonight."
This is the ultimate in metabolic misunderstanding and in the misuse of albumin. This primitive strategy may have other practical applications. If one's gas gauge points to empty, one simply need smash the glass and move the indicator up to full.

As a rule of thumb, the serum albumin level is reduced on average by 1 g% in any patient sick enough to be admitted to the medical service of a general hospital. It reflects the presence and chronicity of disease and the metabolic and nutritional state. The albumin level is further reduced in diseases in which albumin is lost or in which synthesis or degradation is adversely affected.

How is albumin being misused?

First, it is often used as a nonspecific tonic merely to raise a moderately reduced serum albumin level. In chronic hypoalbuminemic states the infusion of albumin is conceptually indefensible. The albumin largely diffuses from the vascular compartment in a matter of hours. Furthermore, the infusion of albumin tends to slow the accelerated synthetic rate and to accelerate the slowed catabolic rate. We have found that after increasing the serum albumin concentration from 2 to 5 g% in cirrhotic patients the increment is barely detectable a week later.

Second, it is sometimes used as a nutrient—a high-quality protein—almost as a form of parenteral nutrition. When given in large amounts, about the most it does is to increase the urea : creatinine ratio, and to worry the physician unnecessarily about the possibility of prerenal azotemia.

Third, it is sometimes used as a substitute for blood or plasma during exchange transfusion therapy of fulminant hepatic failure. There is no evidence that exchange transfusion or exchange anything else is effective in this serious disorder.

What are real indications for its use?

First, in profound hypoalbuminemia where albumin loss via the kidneys or burns may cause severe hypoalbuminemia, hypotension, azotemia or dilutional disturbances, albumin may be beneficially used.

Second, it may be used as an adjunct to diuretic therapy in the nephrotic syndrome.

Third, it may be used as an adjunct to exchange transfusion in the treatment of neonatal hyperbilirubinemia. Conceivably, it may help in acute drug intoxication for substances with a high binding affinity for albumin.

We have found albumin infusions useful to expand plasma volume in the hepatorenal syndrome which is characterized by decreased effective plasma volume. It can be used either alone or, preferably, in combination with small paracenteses, which paradoxically increase plasma volume and cardiac output. The same thing can be accomplished with ascites reinfusions, but this procedure somehow still seems aesthetically unacceptable to house officers.

Whenever albumin infusions are used, it should be for short periods, for correction of specific, transient problems caused by hypoalbuminemia or its hemodynamic equivalents. These indications deserve controlled clinical investigation.

I have heard the shortage of albumin attributed to very stringent Food and Drug Administration requirements, which make it economically unfeasible for commercial production. Both parties present defensive postures, but in my opinion, it is a nonissue. The available albumin is being grossly misused by our medical colleagues. I think it is fair to say about the medical profession, as one used to say about the masturbating boy, that he is amusing himself by abusing himself.
REFERENCES


CURRENT CONCEPTS CONCERNING
ALBUMIN PURIFICATION†

FRED ROTHSTEIN‡, VICTOR M. ROSENÖER§ AND WALTER L. HUGHES||

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I. INTRODUCTION

In the three decades since the classic work of Cohn and Edsall and their collabora-
tors(1) both the tools available to the chemist for the fractionation of plasma proteins
and the store of empirical data have grown, but the predictive aspects of protein
fractionation remain essentially qualitative. This reflects the diversity in the primary,
secondary, tertiary and quaternary structure of proteins. Each protein species has a
unique amino acid composition and sequence which appear to dictate the three-
dimensional structure of polypeptide chain characteristic of a given protein in a
given environment. It is this diversity and resultant complexity which impedes the
development of a quantitative predictive approach to the fractionation of protein
solutions of even simple mixtures. Furthermore, it should be recognized that our
understanding of the solution behavior of polyelectrolytes leaves much to be desired

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