Albumin Pharmacology – Molecular Structure to Physiological Properties to Therapeutic Function

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Disclosures

I provide services to the pharmaceutical and biotechnology industry, including the manufacturers of therapies described in this presentation, who are also major sponsors of this Symposium.
Physiologic Functions of Albumin

- Accounts for 50-60% of plasma proteins
- Creates 75% of colloid osmotic pressure
  - Colloid osmotic pressure (COP) ≈ 20 mm Hg for 4-5% albumin (5× = 100 mm Hg for 25% albumin)
- 60% of total albumin mass is extravascular
- Reversibly binds cations and anions
- Transport and inactivation of drugs, metals, dyes, fatty acids, hormones, enzymes, bilirubin

Congenital Analbuminemia

- Web based register of cases, 50 cases as of June 2012
- Various mutations, autosomal recessive trait
- “Benign” BUT
  - Family histories indicate high sibling neonatal mortality
  - Lack of albumin in 2nd or 3rd trimester of fetal life may fail to protect against hyperbilirubinemia
  - Homozygotes may die in utero, survival to birth is rare
  - Survivors compensate through different protein composition
Role of the Endothelial Glycocalyx Layer in the Use of Resuscitation Fluids.

Classic Starling principle: \( F = (P_c - P_i) - \sigma (\pi_p - \pi_i) \)

Revised Starling principle: \( F = (P_c - P_g) - \sigma (\pi_p - \pi_g) \)
Study role of endothelial glycocalyx with respect to extravasation of fluid and development of tissue edema.

Supplementing perfusate with albumin caused a significant decrease in transudate, also vs. HES (<0.05).

Albumin also lowered edema formation vs. the other perfusion modes (<0.05).
Body fluid distribution

40% Plasma
40% Intracellular
60% Extracellular

0.9% NaCl
0.9% EC

5% Albumin

25% Albumin
Non-oncotic properties of human albumin: binding, transport and detoxification capacities.
❖ Albumin is the principal extracellular antioxidant found in human plasma †

❖ Cysteine-rich protein with a single exposed thiol

❖ Albumin increases intracellular GSH levels in vitro to levels sufficient to prevent H₂O₂–induced cytotoxicity and inhibit NF-κB activation *

❖ Dysfunctional oxidant-antioxidant “balance” in states of acute illness ‡

Plasma antioxidant capacity in patients given albumin

Plasma albumin levels (green) and total thiol levels (red) in patients with sepsis syndrome up to 18hr after albumin administration

Albumin’s use in shock is based on correction of hypovolemia through its ONCOTIC properties

Albumin’s range of physiological properties and roles lends itself to HYPOTHESES BUILDING for other, pharmacological effects

- Sepsis
- Hepatology
- Pulmonology
- CABG
- Burns
Microcirculatory perfusion in sepsis
Potential impairing factors

Possible targets for albumin benefit

Spronk et al Critical Care 2004, 8:462-468
- Neutrophils from healthy human subjects
- Dilution with various intravenous fluids
- Crystalloids and synthetic colloids increased neutrophil activation (intracellular oxidative burst activity) and adhesion (CD18 expression)

Albumin effect on endothelium
Inhibition of TNFα-induced VCAM-1 expression

Fluid Therapy in Septic Patients

*Albumin retains its plasma expansion capacity*

- **Infusion volume**
- **Plasma volume expansion**

**Volume (ml/kg)**

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<th>Saline</th>
<th>5% Albumin</th>
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<td><strong>Infusion</strong></td>
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<td><strong>Plasma</strong></td>
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ALBUMIN vs OTHER COLLOIDS
POST-PARACENTESIS CIRCULATORY DYSFUNCTION

Sort et al NEJM 1999

Bar chart showing the percentage of patients (%):
- Less than 5 liters: Albumin (9) vs Dextran-70 or polygeline (3), p<0.02
- 5-9 liters: Albumin (20) vs Dextran-70 or polygeline (30), p<0.04
- Greater than 9 liters: Albumin (10) vs Dextran-70 or polygeline (50)

The x-axis represents the amount of Ascites removed (L), ranging from <5 to >9 liters.

Legend:
- Gray: Albumin
- Orange: Dextran-70 or polygeline
Heterogeneity in albumin products
Binding site II for diazepam

Klammt et al. Zeitschrift für Gastroenterologie 2001;39 Suppl 2():24-7
Hypertensive reaction to one batch
Different bottles from same batch had effect
No bacterial or other contaminants
Other batches from same manufacturer had no effect

The company stated that such a “slight adverse drug reaction might be ascribed to the variability in reactions to biological products”
Summary

- Albumin is an essential multifaceted natural protein

- A historical focus on its oncotic effects is being overtaken by an interest in other pharmacologic properties

- These allow hypotheses building in relation to certain disease states

- Clinical data in sepsis and cirrhosis indicates that these pharmacologic effects can lead to clinical benefit

- Albumin preparations show heterogeneity, with uncertain effects in the clinic

- More investigations exploring albumin’s role in illness are merited