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The effect of age on serum concentrations of albumin and α_1-acid glycoprotein

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1 Human serum albumin (HSA) concentrations and α_1-acid glycoprotein (AAG) concentrations were measured in 68 subjects, 35 males and 33 females, aged 20–90 years without evidence of acute or chronic inflammatory disease or malignancy. Subjects were drug free for at least 1 month. HSA and AAG concentrations were measured using rate nephelometry.

2 Age had no effect on α_1-acid glycoprotein concentration, whereas plasma albumin levels decreased as a function of age in both sexes. We observed no difference between males and females in the plasma concentrations of HSA and AAG.

3 These data show that in healthy subjects the HSA concentration decreases with increasing age, whereas age, uncomplicated by disease does not influence AAG concentration.

Keywords α_1-acid glycoprotein albumin ageing

Introduction

Human serum albumin (HSA) and α_1-acid glycoprotein (AAG) are the two major drug binding proteins in serum (Koch-Weser & Sellers, 1976a, b; Kremer *et al.*, 1988; Paxton & Briant, 1983; Piafsky & Borga, 1979; Routledge, 1986). HSA is largely responsible for the binding of acidic drugs and binds to some extent neutral and basic drugs. On the other hand AAG binds mainly basic lipophilic and neutral drugs. Alterations in the binding of drugs to plasma proteins can have important pharmacokinetic and/or pharmacodynamic implications, especially when they are highly bound and their apparent volume of distribution is small (Gibaldi & Koup, 1981).

Many pathophysiological and pharmacological factors, such as renal disease, hepatic disease, trauma, stress, surgery, pregnancy and concomitant drug therapy can alter the concentration of HSA and/or AAG (Blain *et al.*, 1985; Blaschke, 1977; De Leve & Piafsky, 1981; Edwards *et al.*, 1982; Jackson *et al.*, 1982; Piafsky, 1980). In addition, sex (Routledge *et al.*, 1981) and heavy smoking (Benedek *et al.*, 1984) may contribute to the variability in AAG concentration. Furthermore, there is evidence that environmental factors affect the variance in AAG concentrations (Blain *et al.*, 1985).

Plasma albumin concentrations have been reported to decrease with increasing age in both men and women and this would be expected to result in reduced binding of drugs, for which albumin is the major binding protein (Davis *et al.*, 1985; Verbeeck *et al.*, 1984; Wallace *et al.*, 1976). However, a recent study (Campion *et al.*, 1988) indicated that in healthy male subjects the serum albumin level did not change at all with increasing age.

The effect of age on AAG is not well established, possibly because of the large intrasubject variability in AAG levels (Paxton & Briant, 1983; Yost & De Vane, 1985). Some studies indicated a significant increase with age (Abernathy & Kerzner, 1984; Davis *et al.*, 1985; Verbeeck *et al.*, 1984). The study of Davis *et al.* (1985) showed a significant, albeit weak correlation with age ($r = 0.273$, $n = 63$, $P < 0.05$), whereas another study did not show any change at all (Chapalle *et al.*, 1981).

Generalisations cannot be drawn from the

results of the previous studies. Whether age has a measurable effect on the concentrations of HSA and AAG is obviously dependent on the manner in which the study is conducted. Clinical studies on the effect of ageing, conducted with in-patients, may be influenced by superimposed systemic illness and concomitant drug therapy. In this study we investigated the relationship between age and the serum concentrations of AAG and HSA in drug-free patients who had no diseases known to be associated with alterations in these proteins.

Methods

The study was approved by the Committee on Medical Ethics of the University Hospital. On the day of admission, informed consent was obtained from 68 patients who were scheduled for a minor surgical, orthopaedic or gynaecological procedure. Only subjects who had to undergo elective operations, such as sterilisation, elective plastic cosmetic surgery, or minor elective orthopaedic procedures such as correction of Hallux Valgus were enrolled. All patients were interviewed by the same anaesthetist about their drug usage, including over-the-counter and recreational preparations, and contraceptives. The patients enrolled in the study were drug free (not taking any drugs for at least 1 month before the study) males (35) and females (33), ranging in age from 20 to 90 years. Medical examination and standard laboratory tests showed that none of the subjects had diseases or conditions known or suspected to be associated with alteration in serum proteins to which drugs are bound (see Table 1). All subjects had a normal full blood count, plasma urea, creatinine, electrolytes, bilirubin, asparate transaminase, alkaline phosphatase and gamma glutamyl transferase. Moderate and heavy smokers, smoking more than 10 cigarettes per day (Vestal, 1975) were excluded from the study. Nineteen subjects (12 males and seven females) smoked between 3 and 10 cigarettes daily.

For comparative purposes, subjects were divided into four age groups: less than 30 years old (group A), 30 to 49 years old (group B), 50 to 69 years old (group C), and 70 years and older (group D).

Blood samples (10 ml) were collected by venepuncture using unheparinized glass tubes. Since AAG may be subject to diurnal variation (Yost & De Vane, 1985) samples were obtained at a fixed time (17.00 h) before dinner. Serum was obtained by centrifugation of clotted blood at 2800 *g* for 10 min and was separated immediately and stored at −20° C for subsequent analysis. Serum HSA and AAG concentrations were measured by rate nephelometry with the Array Protein System® (Beckman) (Sternberg, 1977).

The influence of age and the co-variables sex and smoking on the measured HSA and AAG concentrations was examined by multiple linear regression analysis and an *F*-test (Zar, 1974). The significance of the effects of sex and smoking was then evaluated using two-tailed Student's *t*-tests. Comparison of groups was performed using one-way analysis of variance and Newman-Keul's test for multiple comparisons. When $P < 0.05$, differences were considered to be statistically significant.

Table 1 Exclusion criteria: clinical conditions associated with alterations in HSA and AAG. (Reprinted with permission from the International Anesthesia Research Society from 'Plasma drug binding: implications for anesthesiologists' by Wood M. (1986). *Anesth. Analg.* **65**, 786–804)

Decreased albumin	*Increased AAG*	*Decreased AAG*
Burns	Burns	Neonates
Renal disease	Crohn's disease	Oral contraceptives
Hepatic disease	Renal transplantation	Pregnancy
Inflammatory disease	Infection	
Nephrotic syndrome	Trauma	
Cardiac failure	Chronic pain	
Postoperative period	Myocardial infarction	
Malnutrition	Postoperative period	
Malignancy	Malignancy	
Neonates	Rheumatoid arthritis	
Elderly	Ulcerative colitis	
Pregnancy		

Results

Neither sex nor light smoking had a significant influence on either the HSA or the AAG serum concentrations (Table 2). HSA concentrations decreased with increasing age ($r = -0.50$, $P < 0.0001$, Figure 1). The regression equation reflecting the influence of age on the HSA serum concentration was:

$$\text{HSA concentration: } g\,l^{-1} = (-0.107 \times \text{age in years}) + 51.4$$

AAG concentrations did not change with age (Figure 2).

The mean values and standard deviations obtained in the four age groups are shown in Table 3. HSA concentrations were significantly lower in subjects over 70 years of age compared with subjects less than 30 years of age ($P < 0.001$) and subjects between 30 and 49 years of age ($P < 0.01$). Subjects between 50 and 69 years of age had significantly lower HSA concentrations than subjects less than 30 years of age ($P < 0.005$). There were no significant differences between the AAG concentrations in the four age groups.

Discussion

Available evidence indicates that age-related alterations in distribution elimination and action occur with various drugs. These alterations with normal ageing are accompanied by changes in drug disposition resulting from multiple disease states, often present in geriatric patients (Green-

Table 2 Simple and overall coefficients of determination for HSA and AAG

Dependent variable	*Independent variable*	*Simple* r^2	*Overall* r^2
HSA	Age + sex + smoking	—	0.260
	Age + sex	—	0.254
	Age + smoking	—	0.259
	Age	0.253	—
AAG	Age + sex + smoking	—	0.036
	Age + sex	—	0.031
	Age + smoking	—	0.008
	Age	< 0.001	—

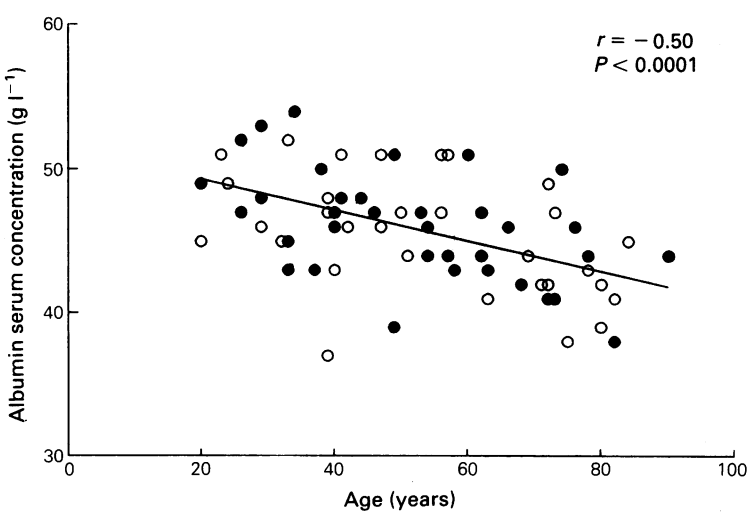

Figure 1 Effect of age on the serum concentration of albumin in 35 male (●–●) and 33 female (○–○) subjects.

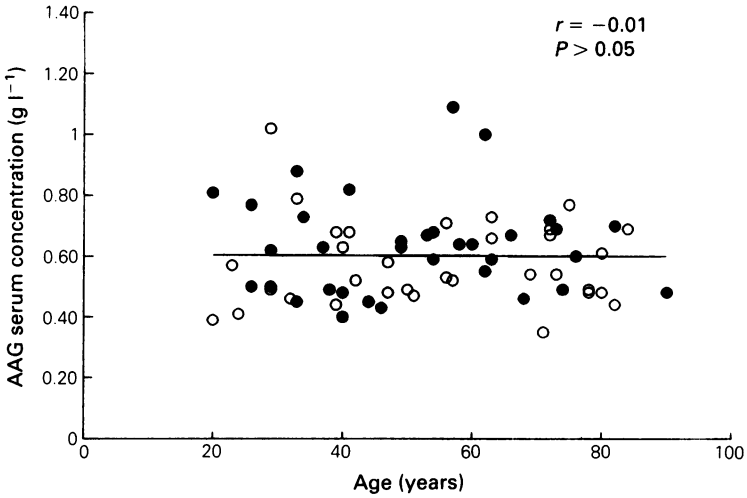

Figure 2 Effect of age on the serum concentration of AAG in 35 male (●–●) and 33 female (○–○) subjects.

Table 3 Serum AAG and HSA concentrations in the subjects grouped according to age (mean ± s.d., range in brackets)

	< 30 years (n = *10*)	*30–49 years* (n = *22*)	*50–69 years* (n = *19*)	*> 69 years* (n = *17*)
AAG ($g\ l^{-1}$)	0.61 ± 0.20 (0.39–1.02)	0.58 ± 0.14 (0.40–0.88)	0.64 ± 0.16 (0.46–1.09)	0.58 ± 0.13 (0.35–0.77)
HSA ($g\ l^{-1}$)	49.3 ± 2.8 (45.0–53.0)	46.7 ± 4.1 (40.0–51.0)	45.0 ± 2.9* (41.0–51.0)	43.0 ± 3.5†‡ (38.0–49.0)

Significantly different from subjects aged less than 30 years: $*P < 0.005$.
Significantly different from subjects aged less than 30 years: $\dagger P < 0.0001$.
Significantly different from subjects aged between 30–49 years: $\ddagger P < 0.01$.

blatt *et al.*, 1982; Schmucker, 1983; Shand, 1982; Vestal, 1978). The present study, therefore, has concentrated on the effect of age on plasma HSA and AAG in a group of subjects, who were free from diseases known to affect concentrations of these plasma proteins.

In the present study, the decrease in albumin levels from approximately 52 $g\ l^{-1}$ at 20 years to 38 $g\ l^{-1}$ at 80 years, was similar to previous reported alterations in albumin concentrations with ageing in healthy subjects (Davis *et al.*, 1985; Verbeeck *et al.*, 1984; Wallace *et al.*, 1976) and in-patients (Greenblatt, 1979), although Campion *et al.* (1988) reported that age did not affect serum albumin concentrations.

The values for AAG concentrations in our population did not change with increasing age. Although others have suggested that AAG concentrations increase with increasing age in healthy subjects, the effect of age in these studies was small (Abernathy *et al.*, 1984; Davis *et al.*, 1985; Verbeeck *et al.*, 1984) with little or no clinical consequences, as it has been shown that the plasma binding of lignocaine and pethidine is correlated significantly with AAG concentrations, but not with age (Davis *et al.*, 1985; Herman *et al.*, 1985).

Our results suggest that in healthy elderly subjects, any effect of age on AAG concentration is likely to be relatively small, and therefore age-related changes in protein binding and in the volume of distribution of drugs that bind to AAG are more likely related to other factors.

In addition we evaluated sex and cigarette smoking (3–10 cigarettes per day) as potential sources of variability, but found no relationship at all to either HSA or AAG concentrations. The lack of effect of sex on HSA confirms

results reported by others (Davis *et al.*, 1985; Verbeeck *et al.*, 1984; Wallace *et al.*, 1976). However, with respect to AAG reported results are conflicting. Davis *et al.* (1985) found no effect of sex on AAG concentrations. Routledge *et al.* (1981) also found no significant differences in AAG concentrations between males and females not using oral contraceptives. On the other hand, Verbeeck *et al.* (1984) reported that AAG concentrations increased with increasing age in males, but not in females.

The lack of effect of light smoking in 19 patients is consistent with the observations of Davis *et al.* (1985). Light smoking (3–10 cigarettes per day) did not distort the effect of age on HSA concentration or the lack of effect of age on AAG concentration. No generalisations with respect to the influence of smoking should be drawn from these studies, because heavy smoking (more than one pack per day) has been demonstrated to influence AAG concentrations (Benedek *et al.*, 1984).

The consequence of the altered albumin concentration in elderly patients will vary with the drug and its extent of binding to both albumin and tissues (Wilkinson & Shand, 1975). In addition, for drugs that are eliminated predominantly by metabolism in the liver, the consequences will depend upon the hepatic extraction ratio (Smallwood *et al.*, 1988; Woodhouse & Wynne, 1988).

We conclude that ageing, uncomplicated by disease, is accompanied by a gradual decrease in human serum albumin concentration. From this study, and other studies on the effect of ageing uncomplicated by disease, we conclude that age-related changes in AAG are absent or so small that these account only for a very small portion of the variability, such that the clinical consequences are generally negligible.

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