Acute-Phase Proteins: Alpha-1-Acid Glycoprotein

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1. Introduction

Acute-phase proteins are proteins whose plasma concentrations increase in response to inflammation. The variability in protein plasma levels, and following impact on drug binding extent, cause modifications in the mode of drug action, distribution, disposition and elimination. One of the most important acute phase proteins is α1-acid glycoprotein (AAG or AGP), principal binding protein for basic drugs. Although plasma concentration of AAG is much lower than that of albumin, AAG can become the major drug binding macromolecule in plasma with significant clinical implications. Moreover AAG is involved in drug-drug interactions, especially in the displacement of drugs and endogenous substances from their binding sites, with important pharmacokinetic and clinical consequences.

AAG is an acidic glycoprotein of about 41 kDa, a single chain of 183 amino acids, the tertiary structure of which partially resembles those of cellular beta 2-agonist receptors. The carbohydrate content (glycans) represents 45% of its molecular weight. The biological function of AGP remains unknown; however, a number of activities of possible physiological significance, such as various immunomodulating effects, have been described. The immunomodulatory as well as the binding activities of AGP have been shown to be mostly dependent on its carbohydrate composition. AAG is one of the plasma acute phase proteins synthesized by the liver and is mainly secreted by hepatocytes and its serum concentration increases in response to systemic tissue injury, inflammation, infection or cancer.

Human alpha1-acid glycoprotein displays genetic polymorphism. AGP of most individuals exists as a mixture of two or three main genetic variants (i.e. A variant and F1 and/or S variants). Concerning native human AGP composition, the relative occurrence of the three main phenotypes in the population was found to be about 50% for F1+S+A, 35% for F1+A and 15% for S+A. Different drug binding properties of the two main genetic products (F1-S and A variants) have been demonstrated.

Various drug molecules have different selectivity in binding affinities for the genetic variants, ranging from the lack of selectivity to the total preference of one of the variants. In binding competition experiments performed by dialysis, radioactive imipramine and warfarin were chosen as high-affinity selective marker ligands for the A variant and the F1-S
variant mixture, respectively. Since the majority of the published AGP drug binding results relate to the mixture of the variants, structure-binding relationships at the molecular level are not well understood.

Expression of the AGP gene is controlled by a combination of the major regulatory mediators, i.e. glucocorticoids and a cytokine network involving mainly interleukin-1 beta (IL-1 beta), tumor necrosis factor-alpha (TNF alpha), interleukin-6 and IL-6 related cytokines.

A-1-acid glycoprotein (AAG) is of particular interest as a major binding protein for several basic drugs, including lidocaine, verapamil, imipramine, propranolol and others. AGP binds numerous neutral lipophilic drugs from endogenous (steroid hormones) and exogenous origin. In contrast, findings suggest that regarding fentanyl, although a basic drug with a pKa value of 8.43, its binding to alpha 1-acid glycoprotein is of minor importance. Seven binding sites of AAG have been described. In addition AAG can also bind acidic drugs such as phenobarbital.

The pharmacokinetic-pharmacodynamic relationship of the model drug S(-)-propranolol with structural similarities to AAG’s molecule was evaluated, using mechanism-based estimations of in vivo receptor affinity under conditions of altered plasma protein binding resulting from different levels of alpha-1-acid glycoprotein.

If plasma AAG concentration increases or changes rapidly, plasma drug concentration and drug effect may be unpredictable. Under these circumstances an estimate of free drug fraction may be clinically helpful.

In myocardial infarction elevated AAG concentration may result in clinical toxicity of lidocaine. It has been shown that the rise in alpha-1-acid glycoprotein after myocardial infarction is associated with lidocaine accumulation, but increased plasma binding attenuates the rise in free drug. The co-administration of lidocaine with propranolol or clonidine has been documented to induce rise in lidocaine levels. This suggests that the toxicologic implications of lidocaine accumulation may have been exaggerated and therapeutic monitoring of total plasma levels may be misleading and must be interpreted appropriately. This provides the strongest rationale for monitoring free rather than total drug concentration as an aid in lidocaine therapy.

Studies in normal subjects and patients with myocardial infarction, renal disease, hepatic failure and receiving antiepileptic drug therapy have all shown a remarkably good relationship between AAG concentration and the binding ratio for lidocaine.

Possible elevation of serum concentrations of the acute-phase reactant a1-acid glycoprotein may be experienced, between many other physiologic derangements, by cigarette smokers. The results of the relevant studies are controversial, some reported elevated AAG concentrations in cigarette smokers, whereas others found no effect of smoking.

Basic drugs competing for the same binding site on AGP molecule may enhance the pharmacological active free fraction of the less affinity drug, with critical consequences for the therapeutic management of the patients.

The large variations observed in the binding ratios of basic drugs in plasma in several physiological and pathological states are correlated with the large variations in the plasma level of AGP with implications for the monitoring of their free fractions of basic drugs during clinical therapy.

AAG serum concentration, which is stable in physiological conditions, increases several-fold during acute-phase reactions and its plasma levels can be used as a diagnostic and prognostic parameter, during clinical therapy (e.g. free or relapse intervals in cancer...
treatment). Furthermore AGP levels estimation may interfere in the proper dosage adjustment, in order to obtain the optimum therapeutic target. The binding of drugs to plasma proteins has been recognized as one of the major determinants of drug action, distribution, and disposition. Initially albumin was considered as the main binding protein, but alpha 1-acid glycoprotein (AAG) has increasingly become important although its plasma concentration is much lower than that of albumin. Serum albumin is the principal binding protein for acidic compounds and a1-acid glycoprotein (AAG) or (AGP) or orosomucoid (ORM) is the principal binding protein for basic drugs. [1] AAG was first described in 1950 by Karl Schmid and Richard J. Winzler and colleagues [2,3]

2. AAG properties and activities

AAG is an acidic glycoprotein of about 41 kDa in molecular weight, has a normal plasma concentration between 0.6-1.2 mg/mL (1-3% of plasma proteins) and its tertiary structure partially resembles those of cellular beta2-agonist receptors. Fig 1 Human AAG is a single polypeptide chain of 183 amino acids and consists approximately of 45% carbohydrate attached in the form of five complex-type N-linked glycans. A notable characteristic of AAG is its unusually high solubility in water and in many polar organic solvents. The biological function of AAG is not only the ability to bind basic drugs and many other molecules like steroid hormones (leading to the suggestion that AAG might be a member of the lipocalin family) but it also exert various immunomodulating effects. [4]

The binding as well as the immunomodulatory activities of AGP have been shown to be mostly dependent on its carbohydrate composition. Different forms of AGP can be distinguished in serum depending on the type of glycosylation and multiple amino acid substitutions. [5,6]

AAG serum concentration which is stable in physiological conditions (about 1 g/l in humans and 0.2 g/l in rats) increases several-fold during acute-phase reactions and AGP is considered as a major member of the positive acute phase protein family and its plasma levels can be used as a diagnostic and prognostic parameter, during clinical therapy. [5,7]

Fig. 1. Alpha-1-acid glycoprotein (AAG) a simplified name for orosomucoid (ORM) consisting of 183 amino acid and 5 sugar chains.

3. AGP production

Alpha-1 acid glycoprotein is one of the plasma proteins synthesized by the liver and is mainly secreted by hepatocytes, although extra-hepatic AGP gene expression has also been
reported. Hepatic production of AAG and other acute phase proteins is increased following the response to various stressful stimuli: physical trauma, such as surgery or wounding, bacterial infection, or various other unspecific inflammatory stimuli. Extra-hepatic production of AGP and of other acute phase proteins has been described but the hepatic expression remains the most abundant. [8,9]

The first evidence of the presence of AAG as well as other serum glycoproteins in extra-hepatic tissues was probably done by investigators examining qualitative and quantitative alterations of normal serum glycoproteins in cancer.[10]

AGP gene expression is modulated quantitatively (protein levels) as well as qualitatively (microheterogeneity of the glycan chains) in various physiological and pathological disorders. Studies in transgenic mice by Dente et al. [11,12] showed that both cis-acting regulatory elements and cellular environment (diffusible factors, cell–cell interaction) are responsible for the liver specificity of AGP gene expression. Finally, AGP gene expression appears to be highly conserved since it is expressed in all the species studied including Euglena gracilis, an ancestral eucaryote unicellular alga. [13]

Among the AAG of animals the rat AGP is a protein of 187 amino acids (mature form) sharing 59% amino acid sequence homology with human AGP and its molecular weight is 40–44 kDa [14]

4. AAG genetic polymorphism and mediators

Native AGP isolated from plasma is not homogeneous; beside the high heterogeneity of glycans, the protein part shows genetic polymorphism and the different forms of AGP in serum depend on the type of glycosylation and multiple amino acid substitutions. In human population two variants of AGP (ORM1 and ORM2) were detected reflecting a gene polymorphism. A 22 amino acid difference was detected between these two variants of AAG encoded by two different genes. In addition, at position 32 and 47, other amino acids can be present. [15]

AGP of most individuals exists as a mixture of two or three main genetic variants (i.e. A variant and F1 and/or S variants). Concerning native human AGP composition the relative occurrence of the three main phenotypes in the population was found to be about 50% for F1+S+A, 35% for F1+A and 15% for S+A. [16]

12–20 glycoforms of AGP has been detected in normal human serum and this micro-heterogeneity is strongly dependent on the pathophysiological conditions. For example, substantial increases in glycoforms expressing di-antennary glycans are apparent in the early phase of an acute-phase reaction as well as an increase in the degree of 3-fucosylation, since fucose is a terminating sugar. These changes in glycosylation could of course affect the biological properties of AGP. [17]

Changes in glycosylation of AGP occur in a wide variety of various pathophysiological conditions like pregnancy, severe rheumatoid arthritis, alcoholic liver cirrhosis and hepatitis. [18,19]

Expression of the AGP gene is controlled by a combination of the major regulatory mediators, i.e. glucocorticoids and a cytokine network involving mainly interleukin-1 beta (IL-1 beta), tumour necrosis factor-alpha (TNF alpha), interleukin-6 and IL-6 related cytokines. It is now well established that the acute phase response may take place in extra-hepatic cell types, and may be regulated by inflammatory mediators as observed in hepatocytes. [4]
5. Drug binding to AGP

Due to its physical–chemical properties, AGP mainly binds basic drugs like tamoxifen [20] and propranolol [21] but also acidic drugs, such as phenobarbital [22] and endogenous steroids (cortisol). [23] AGP as a drug carrier for steroids has been demonstrated since the end of the sixties [24]. AGP was found to also bind synthetic steroids (RU486) [23]. Up to seven binding sites have been described for estradiol – depending on the isolation method used [25] – while in vitro studies provided evidence that two classes of binding sites for basic and neutral drugs are present on AGP. From the literature, it appeared that there is only one binding site on AGP for acidic drugs [26] except for phenobarbital for which two sites have been described. [22]

The presence of two binding sites on AGP for propranolol may reflect differences in the binding characteristics of the stereoisomers. [27]

The nature of drug binding to AGP has been the subject of several studies and has mainly pointed to hydrophobic bindings due to hydrophobic residues near the AGP binding site. However, the binding capacity of AGP depends upon the conformational change of the protein, the polarity of the ligand (interaction is weakest for the steroid with the highest polarity), the temperature, and several other amino acid residues lying at the periphery of the hydrophobic domains of AGP. Although the binding of drugs to AGP has been shown to be mostly hydrophobic in nature, several data also point to an electrostatic interaction and a lot of studies have reported that in plasma, drug bindings are stereoselective, especially in the case of basic drugs. Among factors influencing the characteristics of drug bindings to AGP, pH is one of the important parameters, i.e. drug binding in plasma increases with increasing pH [28]. Desialylation can also affect binding [29]; it reduced the propranolol binding, whereas the progesterone binding did not change.

Much of the inter-individual variability in the extent of plasma protein binding of basic drugs is due to variability in plasma levels of AAG. [27]

5.1 Drug binding of the two main genetic AGP variants

Different drug binding properties of the two main genetic products, F1-S and A variants, have been demonstrated. Various drug molecules have different selectivities in binding affinities for the genetic variants, ranging from the lack of selectivity to the total preference of one of the variants. Since the majority of the published AGP drug binding competition experiments results relate to the A variant and the F1-S variant mixture, structure–binding relationships at the molecular level are not well understood. [30,31]

Concerning the binding of various basic drugs to the F(1)S and A genetic variants of alpha(1)-acid glycoprotein, it was found that, the higher the affinity of basic drugs for AGP, the more they inhibit the binding of other basic drugs, and further, the inhibitory potency depends on the selectivity of binding to the AGP variants. [32]

During specific circular dichroism (CD) probes, dicumarol and acridine orange were found to specifically bind to the F1-S and A variants, respectively. Dicumarol binding to the F1-S variant produced induced Cotton effects originating from the favored chiral conformation of the bound label. Acridine orange gave induced biphasic Cotton effects due to chiral intermolecular exciton interaction between label molecules bound to the A variant. Displacement of the CD probes by specific marker ligands was demonstrated. The induced CD spectrum of dicumarol was found to change sign in the presence of imipramine, as a manifestation of high-affinity ternary complex formation on the F1-S variant. Warfarin was
found to bind selectively to the F1-S variant of AGP. The structurally related compound dicumarol could be expected to prefer this variant, and it was confirmed by the results obtained here. While the binding of dicumarol to the A variant is weak and non-specific, the binding of dicumarol to the F1-S genetic variant is highly specific. The induced characteristic polyphasic Cotton effects reported for native AGP can be attributed to this fraction, amounting to about 70% of the native AGP. This is in agreement with the binding site number of 0.6 found previously in CD binding studies performed with native AGP. This induced CD of dicumarol can be used for selective binding interaction studies, provided that the intrinsic or extrinsic Cotton effects of the other ligands are negligible. It was shown that in the presence of imipramine the induced CD of dicumarol bound to the F1-S variant is inverted and it is accompanied with mutually enhanced binding of both ligands. This phenomenon detected previously with native AGP was explained by ternary complex formation on a wide and flexible drug binding area, where the binding sites of acidic and basic drugs are partially overlapping. It was proved that this interaction takes place on the F1-S variant, which is known to be the low-affinity isoprotein in the AGP binding of imipramine. It also means that in the presence of dicumarol the preference of A variant in the binding of imipramine to native AGP is less pronounced. [33]

The pharmacokinetic-pharmacodynamic relationship of the model drug S(-)-propranolol was evaluated using mechanism-based estimations of in vivo receptor affinity, under conditions of altered plasma protein binding resulting from different levels of alpha-1-acid glycoprotein (AGP). Male Wistar Kyoto rats with isoprenaline-induced tachycardia received an intravenous infusion of S(-)-propranolol, on postsurgery day 2 (n = 7) and day 7 (n = 8) with elevated and normal plasma protein binding, respectively. Serial blood samples were taken in parallel to heart rate measurements. AGP concentration was a covariate for intercompartmental clearance for the third compartment of the pharmacokinetic model of S(-)-propranolol. It was confirmed that, plasma protein binding restricts the pharmacodynamics of S(-)-propranolol. [34]

5.2 AGP drug binding in disease states

The large variations observed in the binding ratios of basic drugs in plasma during several physiological and pathological states are correlated with the large variations in the plasma level of AGP, defining the pharmacokinetics and ultimately the pharmacodynamic effect of the drugs used. The binding of several drugs has been shown to increase following surgical interventions, inflammation and stress, and this increased binding is due to an increase in the plasma concentration of AGP. [35, 36]

Piafsky at al have already since 1978 demonstrated the importance of disease-induced increases in plasma concentrations of α1 acid glycoprotein. The propranolol binding in plasma was increased in patients with Crohn’s disease, inflammatory arthritis and with chronic renal failure, compared with healthy controls. Chlorpromazine binding yielded similar results. Percentage of free drug and α1 acid glycoprotein concentration were inversely correlated (r = -0.77 with propranolol, P<0.001, and r = -0.69 with chlorpromazine, P<0.001). Increases in plasma protein binding in patients with inflammatory disease appear mediated by increases in α1 acid glycoprotein concentration, which may influence drug kinetics. [37]

The AAG levels’ variations have implications for the monitoring of the free fractions of basic drugs during clinical therapy. The consequences of elevated serum AGP levels, often seen in
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several disease states, on the pharmacokinetic of drugs have been investigated using transgenic animals. Holladay et al. studied steady-state kinetics of imipramine in transgenic mice expressing serum AGP levels about 9-fold elevated over normal. [38,39]

It was found that of the many physiologic derangements experienced by cigarette smokers, possible elevation of serum concentrations of the acute-phase reactant a, alpha-1-acid glycoprotein (AAG) is of particular interest because AAG is a major binding protein for several basic drugs, including lidocaine, amitriptyline, verapamil, and perhaps others. [40]

It is generally assumed that in plasma, acidic drugs are mainly bound to human serum albumin. However, binding to AGP will contribute significantly to the total plasma binding of these drugs, especially in diseases in which the concentration of AGP increases and/or of human serum albumin decreases. Cited By in Scopus[6,41] It should be mentioned that warfarin binding affinity to AAG increases with decreasing Ph indicating that one of the intermolecular forces by which AAG binds its ligands (be they basic or acidic) is the donation of a hydrogen bond. [42]

5.3 AAG binding experimental studies

The binding of drugs at therapeutic concentrations to alpha-1 acid glycoprotein in vitro at physiological and non physiological concentrations, consistent with those that might be seen in a variety of clinical conditions was investigated.

In a study with the antiarrythmic verapamil there was a good correlation (r = 0.83) between the binding ratio and AAG concentration, suggesting that AAG could bind verapamil. While the data indicate that AAG is responsible for most of the variability in plasma verapamil binding, which in turn contributes somewhat to variation in effectiveness of a given total plasma concentration, neither of these causes of individual variations is likely to have a major clinical impact in patients who, apart from arrhythmia, are otherwise healthy. [43]

The same was observed in studies with the antiarrythmic quinidine. [44]

Concerning the opiate meperidine binding to AAG did not have any important impact upon fetal and maternal concentrations.[45]

The binding of prednisolone to alpha 1-acid glycoprotein (AGP) was determined in vitro by equilibrium dialysis and indicated the both low affinity and low capacity of AGP for prednisolone. Overall, contribution of AGP to the total plasma binding of prednisolone is less than 3% when considered in the competitive protein binding system with transcortin and albumin. Disease induced alterations of AGP concentrations are relatively unimportant regarding plasma protein binding of prednisolone. [46]

Acetaminophen, phenobarbital, theophylline, and valproic acid showed negligible binding to alpha-1 acid glycoprotein whereas lidocaine and phenytoin demonstrated binding to this protein, and increases in the alpha-1 acid glycoprotein concentration produced decreases in the unbound (free) or "active" concentration of these two drugs. These findings are significant when lidocaine, phenytoin, phenobarbital, theophylline, or valproic acid are used in patients with clinical conditions that may affect the concentration of the binding proteins. [47]

The relationship between binding ratio of imipramine and plasma alpha 1-acidglycoprotein (AAG) was determined in normal subjects, patients with chest pain syndrome, and patients after myocardial infarction. Binding ratio of imipramine significantly correlated with plasma AAG concentration, but not with plasma albumin. In addition, binding ratio of imipramine and pure AAG was significantly related, indicating AAG is an important determinant for
imipramine binding. If plasma AAG concentration increases or changes rapidly, plasma drug concentration and drug effect may be unpredictable. Under these circumstances an estimate of free drug fraction may be clinically helpful and can be estimated from the formula: \( y = 7.95 + 0.03 \times \text{AAG} \). [48]

The binding of taxol to plasma proteins was studied by equilibrium dialysis. Human serum albumin and alpha 1-acid glycoprotein were found to contribute about equally to the binding, with a minor contribution from lipoproteins. The binding was found to be extensive (about 95%), concentration independent, indicating nonspecific hydrophobic binding, without a significant difference between healthy volunteers and cancer patients. None of the drugs commonly co-administered with (dexamethasone, diphenhydramine, ranitidine, doxorubicin, 5-fluorouracil and cisplatin) altered the binding of taxol significantly. The protein binding of taxol was found to dramatically decrease the red blood cell uptake of taxol. Fig 2.[49]

\[ \text{Fig. 2. Taxol, a potent anticancer natural product with activity against a number of leukemias and solid tumors.} \]

Disopyramide, a drug with narrow therapeutic range, used for cardiac arrhythmias, is more than 90% bound to AAG and less than 10% to albumin. Changing the AAG level therefore has clinical significance for this drug and similars bound to AAG (danger for toxic effects). [50]

In contrast to other basic drugs, fentanyl binding to alpha 1-acid glycoprotein is of minor importance. Due to unspecific binding of fentanyl by hydrophobic interactions, a major role of albumin, which amounts to about 60% of total protein, seems to be evident. [51]

Gimatecan, a camptothecin with a lipophilic substitution in position 7, is orally absorbed and its variable plasma levels seem to be related to AAG plasma concentrations. Data obtained in mice, together with the fact that AAG levels largely exceeded gimatecan plasma concentrations, suggest that the increased gimatecan levels in patients with high AAG levels are not related to the binding of the drug to AAG with consequent reduced tissue drug distribution, but possibly to other mechanism associated with inflammation being AAG simply a marker of the inflammation process. [52]

Ropivacaine is a long-acting local anesthetic used frequently for peripheral nerve blocks (continuous peripheral nerve block catheters). In a study, the free ropivacaine drug levels
over time were evaluated in trauma patients, by measuring the serum concentration of bound and unbound local anesthetic. There was no correlation between free ropivacaine concentration and alpha-1-acid glycoprotein concentration except in patients who had already been receiving ropivacaine infusions before entering the study. Despite this lack of correlation, the total duration of local anesthetic infusion did not seem to influence the free concentration of the drug. [53]

High-performance affinity chromatography was used to study binding by the drug lidocaine to human serum albumin (HSA) and alpha(1)-acid glycoprotein (AGP). AGP had strong binding to lidocaine. Fig 3 Lidocaine had weak to moderate binding to HSA. Competitive experiments with site selective probes showed that lidocaine was interacting with Sudlow site II of HSA and the propranolol site of AGP and provided a better quantitative understanding of how lidocaine binds to these serum proteins and is transported in the circulation. Fig. 4 [54]

Fig. 3. Lidocaine a local anesthetic chemically designated as 2-(diethylamino)-N-(2,6-dimethyl-phenyl)-acetamide with the above structural formula.

Fig. 4. Propranolol a "beta-adrenergic antagonist

Studies in normal subjects and patients with myocardial infarction, renal disease, hepatic failure and receiving antiepileptic drug therapy have all shown a remarkably good relationship between AAG concentration and the degree of plasma binding of lidocaine. In situations where AAG is altered, particularly myocardial infarction, the usual therapeutic range for total plasma lidocaine concentrations may not apply and must be interpreted appropriately. This provides the strongest rationale for monitoring free rather than total drug concentration as an aid in lidocaine therapy. [55]
In patients with confirmed myocardial infarction, alpha-1-acid glycoprotein rose significantly from 117 mg/dL at admission to 140 mg/dL at 36 hours (p less than 0.01). The patients were given prolonged infusions of lidocaine (2 mg/min). In patients with myocardial infarction, the rise in plasma alpha 1-acid glycoprotein concentration was associated with increased lidocaine binding and a rise in total lidocaine concentrations between 12 and 48 hours (p less than 0.05). Because of the binding changes, however, the rise in free drug concentration (31.2%) was significantly less than the 56.3% rise in total drug level (p less than 0.05). No changes in alpha 1-acid glycoprotein or lidocaine disposition were seen between 12 and 48 hours in the control subjects. The results show that the rise in alpha 1-acid glycoprotein after myocardial infarction is associated with lidocaine accumulation, but increased plasma binding attenuates the rise in free drug. This suggests that the toxicologic implications of lidocaine accumulation may have been exaggerated and therapeutic monitoring of total plasma levels may be misleading. [56]

Three models of stressor stimuli (experimental mandible osteotomy, forced cold swimming stress and Freund's adjuvant induced arthritis) were performed in order to investigate the discrepancy of lidocaine plasma concentration in comparison to the control. Lidocaine was administered at 5 doses of 3 mg/kg intramuscularly every 2 hours. Lidocaine levels and its binding to proteins were estimated in plasma and mandible. In groups under stress, lidocaine concentrations in serum showed a marked elevation. In addition, these animals demonstrated a significant decrease in the percent of lidocaine binding in the mandible. [57]

<table>
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<tr>
<th>Drug</th>
<th>Drug Characteristics</th>
<th>elevated AAG dependent activity</th>
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<tr>
<td>lidocaine</td>
<td>antiarrythmic</td>
<td>total plasma lidocaine cumulation [55-58]</td>
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<tr>
<td>propranolol</td>
<td>beta blocker</td>
<td>reduced unbound propranolol fraction [37]</td>
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<tr>
<td>imipramine</td>
<td>antidepressant</td>
<td>reduced free drug fraction [48]</td>
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<tr>
<td>disopyramide</td>
<td>antiarrythmic</td>
<td>reduced free drug fraction [50]</td>
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<td>phenytoin</td>
<td>antiepileptic</td>
<td>reduced free drug fraction [47]</td>
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<tr>
<td>paclitaxel</td>
<td>cancer medication</td>
<td>reduced free drug fraction [49]</td>
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Table 1. Drugs’ documented AAG dependent activity

Moreover role of stress (trauma, cold swimming, and adjuvant rheumatoid arthritis) on lidocaine concentrations as well as lidocaine's protein binding in heart and liver tissues in male Wistar rats was investigated. Since lidocaine is a cationic molecule it is bound to AGP. The levels of AGP are increased mainly in inflammatory conditions and the protein binding of lidocaine was increased and consequently its free plasma concentration was reduced. [58]

In co-administration of lidocaine and clonidine, a significant increase of lidocaine free fraction is documented. Both drugs are cationic (clonidine pKa =8.25 and lidocaine pKa=7.9) and have higher binding affinity to alpha- acid glycoprotein than to albumin. Probably a displacement process takes place and lidocaine is displaced by clonidine from its binding sites in serum and tissue proteins thereby leading to rise in its free fraction. [59].

Drugs that are documented to be of AAP depended activity are presented in the following table (1)
6. AAG clinical aspect

Alpha-1-Acid glycoprotein is found in increased amounts in patients with a variety of cancers. The application of discriminated analysis to the comparison of plasma levels of AAG in patients with lung cancer and patients without known cancer, yielded a sensitivity of 89% and specificity of 84% in the detection of active lung cancer via AAG measurement. In addition it was demonstrated that normalization of alpha-1-acid glycoprotein levels during antineoplastic therapy correlates with a significantly prolonged relapse-free survival in lung cancer patients. [60]

Alpha-1-acid glycoprotein is suggested to provide prognostic information in patients with glioblastoma multiform since it was higher in patients with glioblastoma multiform who died within one year after admission than in those with a longer survival time. [61]

Unlike other cancers, patients with breast cancer were found to have normal glycoprotein levels with early disease and elevated levels when the disease was advanced (positive bone scans), suggesting that such investigations may be useful in selecting patients with truly localized disease. Most reported estimates of serum glycoprotein levels in disease have been based on biochemical estimates of protein-bound sugars in serum fractions and estimates of serum protein-bound fucose have been advocated as a means of differentiating between benign and malignant breast disease (AAG is a specific glycoprotein containing fucose in its molecule). [62]

The effect of altered concentrations of serum proteins in malignant disease was studied on drug binding with lidocaine, a basic drug and tolbutamide, an acidic drug. Patients with cancer had increased serum concentrations of AAG and lowered serum concentration of albumin. Lidocaine binding was increased at all concentrations studied and that of tolbutamide was decreased at the highest concentration. Not all of the increase in lidocaine binding was explicable on the basis of increased serum AAG concentration. Estimation of binding parameters with a model with two independent sites showed increased affinity at the high affinity site in cancer patients with no change in the calculated number of binding sites. Therefore, in cancer there is increased lidocaine binding in association with increased AAG concentrations. [63]

AGP as a pool of cationic drugs may play an important role with clinical impact in various medication regiments, since its discrepancy may represent a prognostic index of the therapy procedure and furthermore may interfere in the proper dosage adjustment in order to obtain the optimum therapeutic target.

7. References


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The two volumes of Acute Phase Proteins book consist of chapters that give a large panel of fundamental and applied knowledge on one of the major elements of the inflammatory process during the acute phase response, i.e., the acute phase proteins expression and functions that regulate homeostasis. We have organized this book in two volumes - the first volume, mainly containing chapters on structure, biology and functions of APP, the second volume discussing different uses of APP as diagnostic tools in human and veterinary medicine.

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