Vessell, E. S., Passananti, G. T., Glenwright, P. A. & Dvorchik, B. H. (1975). Studies on the disposition of antipyrine, aminopyrine and phenacetin using plasma, saliva and urine. *Clin. Pharmac. Ther.*, **18**, 259–272.

Welch, R. M., Deangelis, R. L., Wingfield, M. & Farmer, T. W. (1975). Elimination of antipyrine from saliva as a measure of metabolism in man. *Clin. Pharmac. Ther.*, **18**, 249–258.

Decreased α_1-acid glycoprotein in liver cirrhosis: consequences for drug protein binding

An increase in plasma concentration of α_1-acid glycoprotein (AAG) may be found in various pathophysiological conditions (Piafsky, 1980). This elevation results in a decrease in the free fraction of basic drugs which are mainly bound to this protein (Piafsky *et al.*, 1978). Decreased free fraction may induce alterations in drug pharmacokinetics and reduction of pharmacological effect (Piafsky, 1980). By contrast, circumstances resulting in lowered concentrations of AAG have been scarcely reported. Although considerable variations of the AAG concentrations may be observed in liver cirrhosis (Chio & Oon, 1979), probably owing to the various degrees of hepatic impairment, low levels have been reported in some patients.

Erythromycin is a drug mainly bound to AAG (60–70%) and to a minor extent to albumin (8%), (Prandota *et al.*, 1980). The aim of this study was to determine the free fraction of erythromycin in a homogenous group of 18 cirrhotic patients (eight females and 10 males; mean age 51 years; range 42–65) and to compare the results with those obtained in 14 normal healthy subjects (seven females and seven males; mean age 44 years; range 30–60). Six of them, four cirrhotic and two healthy subjects were smokers. The cirrhotic patients suffered from severe liver disease on the criterion of prothrombin time ≤35%. The prothrombin times were determined with Neoplastine® (Diagnostica Stago) and a semi-automated coagulometer KC 10 (Amlung-Lemgo, FRG). The free fraction of erythromycin was measured *in vitro* by equilibrium dialysis of serum samples (Dianorm® apparatus) against 4 μM of [^{3}H]-erythromycin dissolved in phosphate buffer at pH 7.4. AAG measurements were performed with Beckman Immunochemistry System ICS™ II based on nephelometric measurement.

In patients with severe liver disease, the mean (± s.d.) serum AAG concentrations was 4.2 ± 1.7 μM (195 ± 75 mg/l), significantly lower than that obtained in the control group, 15.3 ± 4.2 μM (673 ± 185 mg/l), ($P < 0.001$).

As shown in Figure 1, the free fractions of erythromycin measured in sera collected in cirrhotic patients were much more elevated (two to threefold) than in sera of the control

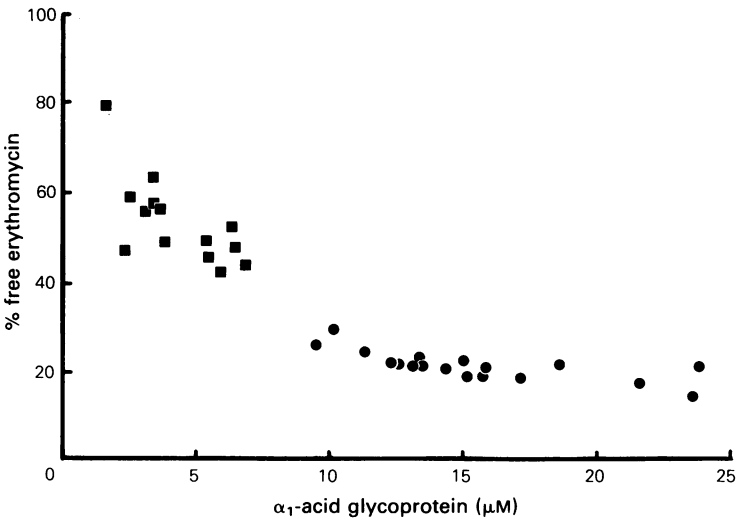

Figure 1 *In vitro* binding of [^{3}H]-erythromycin (4 μM) in sera collected in normal healthy subjects (●) and in patients suffering from alcoholic cirrhosis (■). ($r = 0.888$, $P < 0.01$).

group. Our results clearly show that AAG levels are markedly reduced in severe alcoholic liver cirrhosis. So far, such a fall has been rarely encountered (Piafsky, 1980). This reduction in serum AAG can result in a dramatic increase in the free fraction of drugs predominantly bound to this protein as it is exemplified by our *in vitro* erythromycin binding experiment. Additional factors may contribute to enhance this phenomenon. Firstly, AAG was shown to be partially desialylated in hepatocellular failure (Serbourge-Goguel *et al.*, 1983) which may result in altered binding characteristics. Secondly, conformational modifications of AAG structure or accumulation of endogenous compounds inhibiting drug binding may account for the increase in the free fraction of erythromycin in liver cirrhosis. All these points are presently under investigation.

The elevation of free fraction of drugs can lead to a considerable increase in their pharmacological effect. An indepth analysis of the pharmacokinetic consequences of such a phenomenon is not easy. Whatever the drug, one can expect an increase in the volume of distribution more or less proportional to the increase in the serum free fraction. With respect to the clearance, the prediction is much more complex. Regarding erythromycin, a drug mainly cleared by the liver with a low extraction ratio (Austin *et al.*, 1980), the systemic clearance is given by the product of the unbound fraction by the hepatic intrinsic clearance. Since the latter parameter is likely to be impaired in liver cirrhosis, the increase in the free fraction of erythromycin may be offset by a fall in intrinsic clearance. Thus, depending on the relative degree of the decrease in the intrinsic clearance and of the elevation of the unbound fraction, the systemic clearance will increase in a lesser extent than that of the volume of distribution and may even decrease. The elimination half-life should therefore be prolonged in all cases.

In conclusion, a marked elevation of free fraction of drug was found to be associated to lowered levels of AAG in cirrhosis. This phenomenon may have many important consequences for pharmacological effects and pharmacokinetics.

J. BARRE[1], G. HOUIN[2], J. ROSENBAUM[3], R. ZINI[4], D. DHUMEAUX[3] & J. P. TILLEMENT[1]

[1]*Département de Biochimie I et Pharmacologie, Hôpital Intercommunal, Créteil, France,* [2]*Laboratoire de Pharmacologie, Faculté de Pharmacie, Toulouse, France,* [3]*Service d'Hépatologie et de Gastro-Entérologie, Hôpital Henri Mondor, Créteil, France, and* [4]*Département de Pharmacologie, Faculté de Médicine de Paris XII, Créteil, France.*

Received March 2, 1984,
accepted June 2, 1984

References

Austin, K. L., Mather, L. E., Philpot, C. R. & McDonald, P. J. (1980). Intersubject and dose-related variability after intravenous administration of erythromycin. *Br. J. clin. Pharmac.*, **10**, 273–279.

Chio, L. F. & Oon, C. J. (1979). Changes in serum α_1-antitrypsin, $\alpha_1$acid glycoprotein and β_2 glycoprotein in patients with malignant hepatocellular carcinoma. *Am. Cancer. Soc.*, **43**, 596–604.

Piafsky, K. M. (1980). Disease-induced changes in the plasma binding of basic drugs. *Clin. Pharmacokin.*, **5**, 242–246.

Piafsky, K. M., Borga, O., Odar-Cederlof, I., Johanssson, C. & Sjoqvist, F. (1978). Increased plasma protein binding of propranolol and chlorpromazine mediated by disease-induced elevations of plasma α_1-acid glycoprotein. *New Engl. J. Med.*, **229**, 1435–1439.

Prandota, J., Tillement, J. P., d'Athis, Ph., Campos, H. & Barre, J. (1980). Binding of erythromycin base to human plasma proteins. *J. int. med. Res.*, **8**, Suppl. (2), 1–8.

Serbource-Goguel, N.., Corbic, M., Erlinger, S., Durand, G., Agneray, J. & Feger, J. (1983). Measurement of serum α_1-acid glycoprotein and α_1-antitrypsin desialylation in liver disease. *Hepatology*, **3**, 356–359.

Sampling from the adult population for pharmacokinetic and pharmacogenetic studies.

Clinical pharmacology does indeed perform its experiments on 'very selected' groups of subjects and it is thus difficult to extrapolate to the population at large. Efforts to overcome this are laudable but a disservice is done to science if unwarranted conclusions are then drawn.

Blain *et al.* (1984) drew an excellent sample from the electorate of Newcastle upon Tyne