[13:30～14:10]

Pharmacokinetic-Pharmacodynamic Relationships Under Non-controlled Conditions. Disease-Drug Interactions

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An increase in drug concentration is generally assumed to result in increased effect and toxicity. Indeed, pharmacokinetic data are usually considered as a surrogate of pharmacodynamic outcomes. Several investigators have reported substantial increases in the plasma concentration of many drugs due to diminished hepatic clearance caused by inflammation (1-6). For example, the effect of various inflammatory conditions (e.g., human arthritis, Crohn's desaese, rat adjuvant arthritis) on the pharmacokinetics of propranolol, a β-adrenergic antagonist, has been studied by many investigators who have all observed reduced clearance (1-4). This reduction in clearance (Figure 1) is often attributed to a diminished hepatic metabolism brought about by increased expression of pro-inflammatory mediators such as nitric oxide (NO) and/or cytokines (6). In addition, inflammation causes increased plasma concentration of α_1-acid glycoprotein (7). This may increase the extent of protein binding and reduce the unbound fraction which, in turn, may result in reduced clearance of the total drug. Both latter changes have been suggested as the underlying causes of reduced clearance of many drugs [1-7].

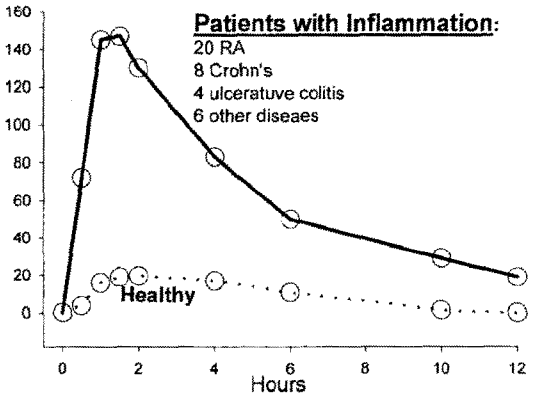

Figure 1. Effect of various inflammatory doseases the pharmacokinetics of prpranolol following a single 40 mg oral dore (Schneither RE *et al* Int J Clin Pharmacol Ther Toxicol 19:158-162,1981).

Nevertheless, the effect of inflammation on the metabolism of drugs seems to be limited to the oral clearance of drugs with intermediate to high hepatic extraction ratios (8).

The therapeutic consequences of the observed increases in plasma concentrations, however, have not been thoroughly examined.

In a recent report (6), several fold increase in plasma concentration of the calcium channel blocker verapamil has been seen in patients with rheumatoid arthritis (RA) (Figure 2). This increase, secondary, perhaps, to a inflammation induced reduced hepatic clearance, has been shown to be accompanied by increases in serum IL-6 and NO_2^-, the break-down product of NO (Figures 3), supporting the notion that the reduced drug clearance may be linked to increases in expression of pro-inflammatory mediators.

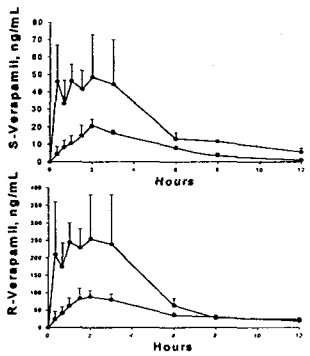

Figure 2. Effect of rheumatoid arthritis (higher concentrations in both curves) as compared with healthy subjects (lower concentrations in both curves) on the pharmacokinetics of verapamil enantiomers following administration of single oral doses of 80 mg racemic drug. (Mayo et al, 2000, Reference 6).

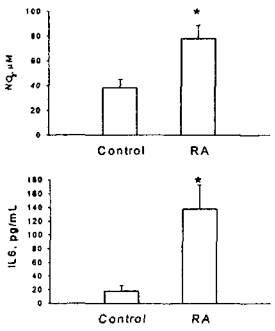

Figure. 3. Effect of rheumatoid arthritis (RA) on the serum nitrite and interleukin-6 concentration (Mayo et al, 2000, Reference 6).

Such an increase in verapamil concentration was expected to increased potency or toxicity of the drug in RA. Quite contrary, however, the effect of verapamil was even lower in RA as compared with healthy subjects. Indeed, less dromotropic effect as measured by PR-interval prolongation was observed in RA (Figure 4) Furthermore, AV blocks were noticed only in controls and not in RA patients. Similarly, other cardiac indices (i.e., blood pressure and heart rate), that were expected to be affected by higher verapamil concentrations observed in RA, remained at the level of control subjects.

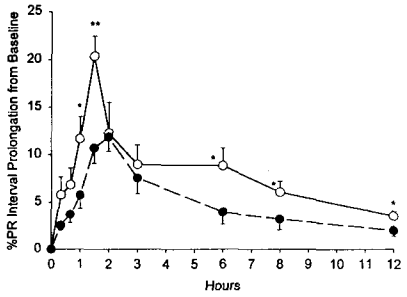

Figure 4. Effect of rheumatoid arthritis (lower values, •) as compared with healthy subjects (higher values, o) on the potency of verapamil to prolong cardiac PR interval following administration of single oral doses of 80 mg racemic drug. (Mayo et al, 2000, Reference 6).

Two explanations may be plausible for the reduced potency despite increased concentration: 1) reduced response due to a reduced plasma unbound verapamil concentrations secondary to elevation of plasma α_1-acid glycoprotein levels in RA, and/or 2) reduced sensitivity of calcium channel receptors. Subsequent data (9) ruled out the former explanation in favor of a down-regulation of the calcium channel receptors secondary, perhaps, to the elevation of pro-inflammatory mediators in RA. We have also observed a reduced binding of calcium channel antagonists to the rat heart cells attributed to reduced protein density.

In addition to the calcium channels, the down-regulation of the receptors has also been observed with β -adrenergic and K-channel receptors (9).

Implications of this observation may reach beyond rheumatoid arthritis since other inflammatory conditions (e.g., infection, asthma) may also create similar conditions (10). For example, aging is associated with increased expression of pro-inflammatory cytokines (11) and reduced effectiveness of verapamil has been also observed in the elderly population (12). Recently, the rate of therapy failure [13] (Figure 5) and mortality [14] following myocardial infarction have been shown to be associated with the elevation of serum C-reactive protein, an indicator of inflammation. With ever aging general population, multiple disease states are more likely to occur. Treatment of cardiovascular diseases in a patient with rheumatoid arthritis may, therefore, require closer attention to prevent therapeutic failure.

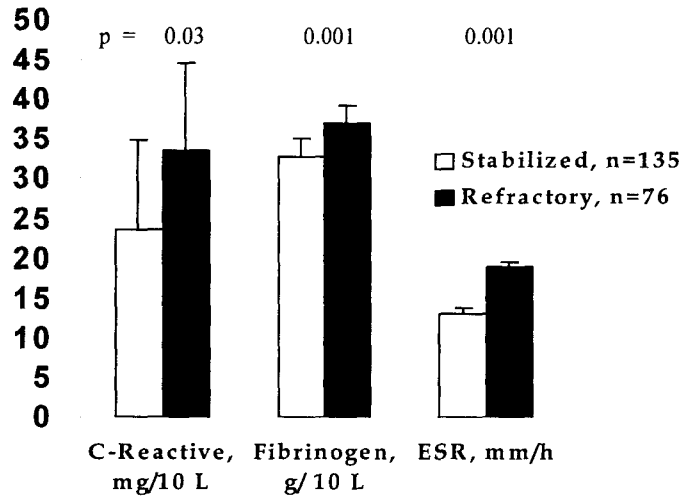

Figure 5. Higher pro-inflammatory markers (C-reactive proteins, fibrinogen and erythrocyte sedimentation rate) in post- myocardial infarction patients who did not respond to treatment (Refractory) (Verheggen et al, *Eur Heart J* 1999; **20**, 567-574).

In conclusion, factors such as increased expression of pro-inflammatory mediators, which are responsible for reduced hepatic enzymes activity, appear to also be involved in down regulation of receptors and reduced responsiveness. In evaluating therapeutic consequences of increased drug concentrations, other changes must also be considered since an elevated drug concentration does not always reflect increased potency or toxicity.

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