Letter from Dr. D.S. Sitar

Sir:
The study of drug disposition and effect as a function of the aging process is an increasingly important area of investigation. Cuny et al. (1) have recently reported results of their study concerning the effect of aging on salicylate disposition in this journal. Upon review of their publication, important deficiencies were noted which require comment.

First, and most important, the model which they used to describe salicylate disposition is incorrect. In the dose administered to their volunteers, salicylate is eliminated by dose-dependent (Michaelis-Menten) kinetics (2-4). This fundamental error has resulted in inappropriate values for the elimination half-time by a factor of about 2. It has also resulted in a drastic underestimation of the apparent volume of distribution. If one plots the data from their publication on rectilinear graph paper, the plot is a classic example of a dose-dependent process. A detailed approach to optimal data analysis in this situation is available (5).

Second, their calculation of ‘metabolic clearance’ is overestimated. This is due to a mathematical error, as they used $t'/2$ instead of $k_{EL}$ for this determination. Thus plasma clearance is overestimated by about one third. Use of the model independent formula ‘dose/ area under the plasma concentration versus time curve’ would have yielded values more in agreement with other publications (6).

Third, the method of statistical analysis is inappropriate. A nonparametric test (Mann-Whitney U test) should have been used to eliminate the problem of differences in data variance due to effects of age.

The use of the values of apparent volume of distribution and elimination rates as published in the report by Cuny et al. (1) for dosage regimen determinations would result in inappropriate use of salicylate. The above criticisms bring into question the significance of their findings with respect to effects of aging on salicylate disposition in man.

References


First, the model we used in this study was designed to look for the influence of aging on salicylates disposition, and it does not pretend to represent in detail all the metabolic processes of salicylates. Papers quoted by D. Sitar refer to experimental conditions very far from the conditions in our study: in one of them (2), 3 g acetylsalicylic acid were administered orally and metabolites were measured in urine; in the other (3), multiple doses were administered. In our study, all the patients received orally the same dosage (1 g) of acetylsalicylic: it allows comparison of total salicylate elimination half-lives between the two groups, even if elimination kinetics are dose-dependent. Half-lives (young patients, 2.38 h; old patients, 3.71 h) have the same magnitude as half-lives previously reported: 2.9 h (4). The interest of our study is very practical and it shows functional retention of salicylates in old people; however, it is not possible to interprete the origin of these differences: change in first-order elimination processes; in the saturation level of salicylurates and salicylphenollicglycuronides synthesis, or in protein binding.

In order to eliminate the influence of saturation processes and according to the statement that elimination kinetics are first-order rate after the 8th h for an oral dose of 1 g of acetylsalicylic acid, we estimated elimination half-lives, taking only into account plas-matic concentrations after this time. They are not different from those initially determined: young patients 2.34 h (SEM 0.12 h, n = 7), and old patients 3.57 h (SEM 1.11 h, n = 14). The difference between the two groups is significant (Cochran test, Mann-Whitney U test, p < 0.05).

Second, metabolic clearance calculation determined in our paper by Vd/t'1/2 is actually slightly different from the usual definition of this pharmaco-kinetic parameter:

\[ V_d \times k_{EL} = V_d \times 0.693/t'_{1/2} \]

It does not influence the comparison between the two groups which does not reveal any significant difference.

Third, the Mann-Whitney U test gives the same significant results: elimination half lives, U = 16 (p < 0.05); lag period before maximum, U = 16 (p < 0.05); apparent volume of distribution, U = 9 (p < 0.01); maximum concentration, U = 8 (p < 0.01).

References

Prof. G. Cuny et al., Service de Médecine B,
Hôpital de Brabois,
F-54500 Vandœuvre-lès-Nancy (France)