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Correlation of Serum Aspirin Esterase Activity and Half-Life of Salicylic Acid

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Abstract

An inverse correlation was found between the serum aspirin esterase activity in human subjects and the biological half-life of salicylic acid in serum and a direct relationship between the values of the elimination rate constant and the activity of this enzyme. The rate of acetylsalicylic acid breakdown may be one of the factors which influences the biological half-life of salicylates in the organism and may participate also in determining the individual response to the administered drug.

Aspirin and its derivatives are among the most widespread drugs used in the treatment of diseases. As an analgesic aspirin is the most effective salicylate [1] and also the most potent inhibitor of platelet aggregation. Damage of the gastric mucosa by aspirin is caused by the intact aspirin molecule and to a lesser extent by its metabolites. Aspirin is very rapidly hydrolyzed in vivo to salicylic and acetic acids by a presumed enzyme system – acetylsalicylic acid-acylhydrolase (trivial term: aspirin esterase). This enzyme is present in the mucosa of the digestive tract, in the liver and in serum [2–4]. After administration of aspirin it has been found that a total of only 68% reaches the peripheral circulation intact. Aspirin begins to disappear from the circulation after 20 minutes whereas the level of the main metabolic product, salicylic acid, continues to rise [4].

Some investigations indicate that the activity of aspirin esterase is influenced by some factors such as age and sex [3, 5]. In our study we focused attention on an analysis of the relationship between the activity of aspirin esterase in serum and the serum level of salicylic acid. We wanted to find out whether there exists in

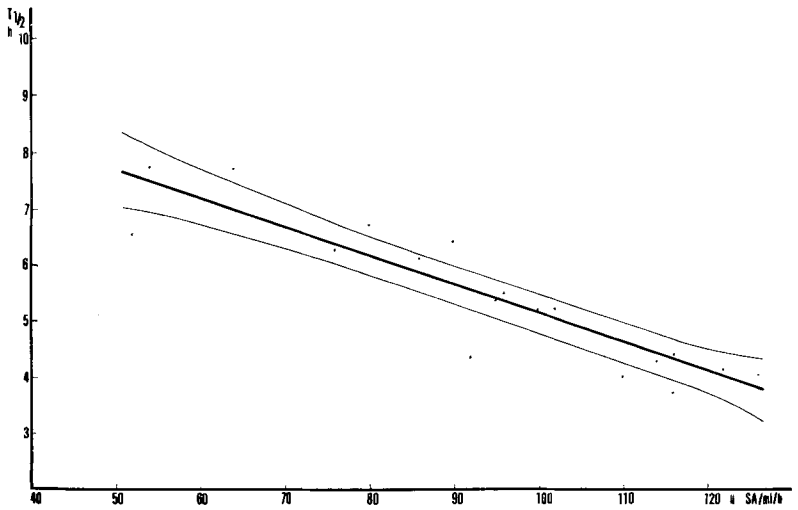

Figure 1
Correlation between the biological half-life and the activity of aspirin esterase after the administration of 1 g of acetylsalicylic acid. Regression curve with confidence limits 95%, $r = -0.90122$, $a = 10.30442$, $b = -0.05191$.

man an individual relationship between the activity of this enzyme and the biological half-life of the main aspirin metabolite. The simple procedure of estimating the aspirin esterase activity could be of value for assessing the individual capacity to metabolize aspirin to salicylate.

Materials and methods

The study was made in healthy volunteers, men and women, aged 20–50 years, weighing 60–80 kg. None of them had taken salicylates before the experiment. The first group comprised a total of 18 experimental subjects (7 women and 11 men). The subjects fasted overnight and no food was permitted during first 2 hours after drug administration. This group took at 7 a.m. two tablets of Acylpyrin (manufactured by Spofa, Czechoslovakia, containing 0.5 g of acetylsalicylic acid in one tablet). Before the administration of aspirin, a blood specimen was taken for the estimation of aspirin esterase. Blood was subsequently withdrawn by venopuncture at time intervals of 2, 3, 5, 7 and 10 hours after the ingestion of the drug. The second group comprised 13 volunteers (11 women and 2 men). To this group 3.5 tablets Superpyrin (manufactured by Spofa, Czechoslovakia, containing 400 mg aloxiprin per tablet – a condensation product of acetylsalicylic acid with aluminium hydroxide, containing in the administered amout a total of 1.06 g acetylsalicylic acid). Collection of blood was performed as in the first group.

Aspirin esterase was estimated by the method of MENGUY and coworkers [3]. In this method an aliquot of 0.5 ml serum is incubated with 0.4 ml 15 m*M* aspirin solution in 2.1 ml 0.06 *M*. Tris HCl buffer at pH 7 under constant shaking at a temperature of 25 °C for 60 minutes. The enzyme activity is expressed in μg of released salicylic acid/ml serum/60 min. For the estimation of salicylic acid we used the method described by BRODIE and coworkers [6]. This method is measuring both the salicylate and the salicylurate which is quite acceptable because the plasma level of the conjugates is negligible for practical purposes. The biological half-life of salicylic acid in serum ($t_{0.5}$) was assessed by the semilogarithmic method. Next we assessed the elimination rate constant K_E which, when expressed in reciprocal hours, gives the fraction of body drug content eliminated per hour. It is related to the half-life according to the equation $K_E = 0.693/t_{0.5}$. For statistical evaluation of results, a regression and correlation analysis was used.

Results

Figures 1 and 2 show the relationship between aspirin esterase activity and the biological half-life and elimination rate constant K_E of salicylic acid after administration of 1 g acetylsalicylic acid. The biological half-life of salicylic acid in this group varied between 3.7 and 7.7 hours with an average of 5.8 hours. The value of the elimination rate constant K_E varied between 0.090 and 0.187 with an average of 0.134. The finding of (1) an indirect relationship between serum aspirin esterase activity and the biological half-life of salicylic acid in serum and (2) the direct relationship between values of constant K_E and the enzyme activity is of interest. Figures 3 and 4 illustrate similar relations after the administration of Superpyrin (aloxiprin). Here the biological half-life of salicylic acid varied between 4.7 and 9.2 hours with an average of 7.7 hours. The relationship between the en-

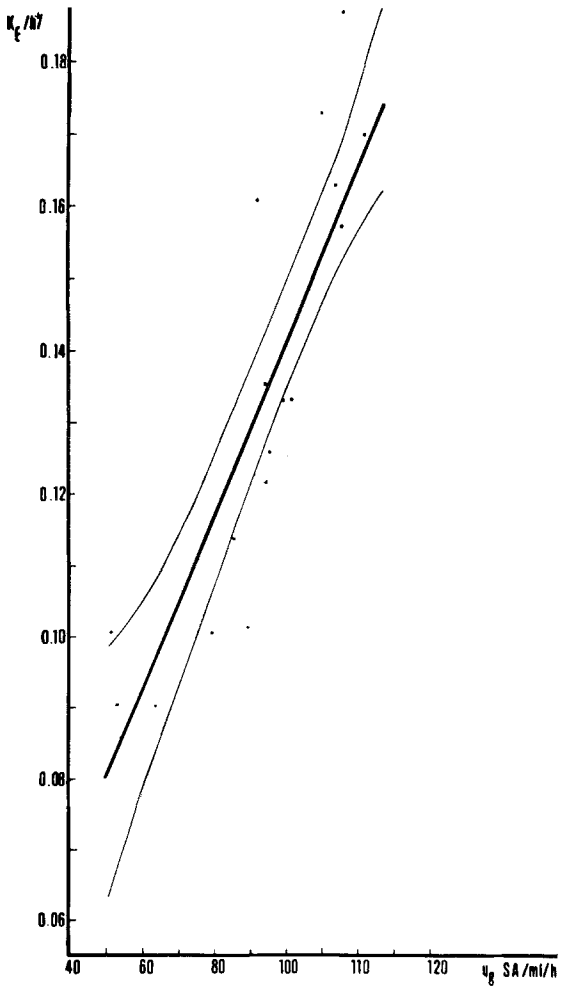

Figure 2
Correlation between the elimination rate constant and the activity of aspirin esterase after the administration of 1 g of acetylsalicylic acid. Regression curve with confidence limits 95%, $r = 0.88026$, $a = 0.01893$, $b = 0.000123$.

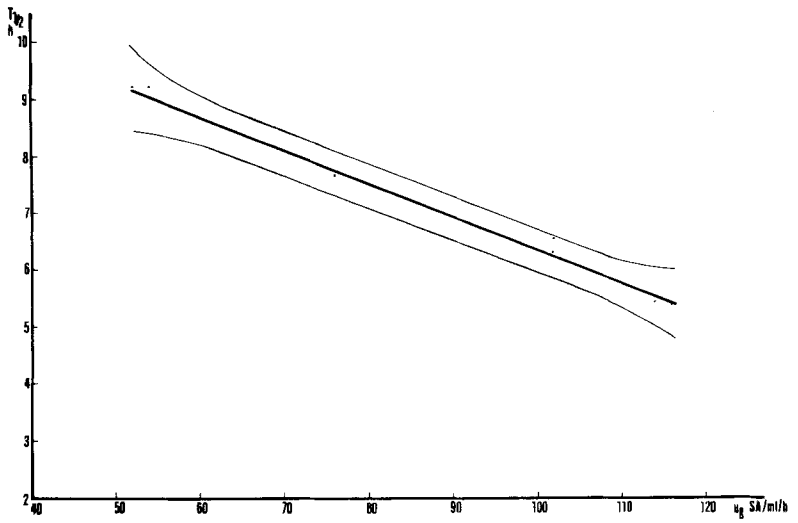

Figure 3
Correlation between the biological half-life and the activity of aspirin esterase after the administration of 1.4 g of aloxiprin. Regression curve with confidence limits 95%, $r = -0.91401$, $a = 12.16108$, $b = -0.05817$.

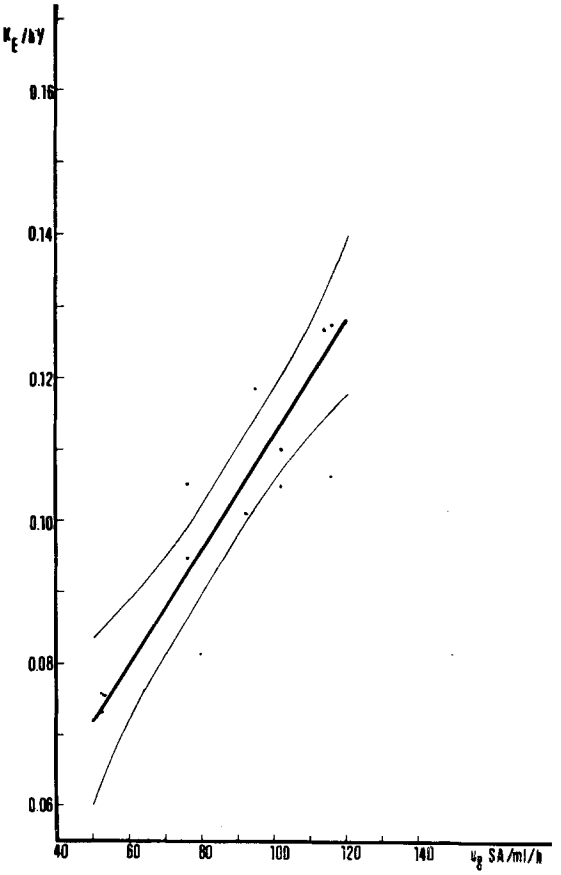

Figure 4
Correlation between the elimination rate constant and the activity of aspirin esterase after the administration of 1.4 g of aloxiprin. Regression curve with confidence limits 95%, $r = 0.87842$, $a = 0.03143$, $b = 0.00081$.

zyme activity and the biological half-life and constant K_E are the same as in the first trial. Regression coefficient b (expressing the slope of the regression line) did not show any statistical difference between the slopes in Figures 1 and 3, 2 and 4 respectively ($p > 0.1$).

Discussion

Aspirin absorbed into the blood stream is rapidly hydrolyzed by enzymes mainly in the liver, about 20% by serum aspirin esterase [3]. The findings of Leonards indicate that hydrolysis by esterase from the wall of the digestive tract is relatively small [7]. The aspirin esterase activity may probably account for differing reactivity of the individual to therapeutic and toxic effects of salicylates. Studies of the biological half-life and elimination rate constant of salicylic acid indicate considerable difference between individuals [8]. This may be due to the size of the administered dose, the type of the administered salicylate preparation, pH of urine possibly also due to certain pathological conditions and physiological status. Individual differences in the assessed parameters were found also in our investigation. In the present study this variability was associated also with variations in the activity of serum aspirin esterase. The finding of a reciprocal correlation of aspirin esterase value and the biological half-life of salicylic acid indicates that variation of the half-life of salicylates after administration of aspirin is due in part to variations in the activity of aspirin esterase. The values of the elimination rate constant are directly proportional to the

values of enzyme activity. This finding suggests that the rate at which the released salicylic acid enters the blood stream is important. The half-life of salicylic acid is conditioned by the half-life of aspirin and depends to a considerable extent on the activity of aspirin esterase. The assessment of aspirin esterase activity may elucidate some of the biochemical mechanisms responsible for interindividual variations in the kinetics of salicylates.

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