Aspirin and platelet function

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Reading the historical sketch by H. Weiss [1] and the memories of J. B. Smith [2], and J. F. Mustard [3] I remember our efforts to measure platelet function in the early 1960s and our first studies with aspirin.

In 1963 we had developed a method to measure enhanced platelet aggregation (PAT I) [4]. We rotated (20 U min⁻¹) platelet rich plasma (PRP) in a 20-mL siliconized glass flask at 37 °C for 10 min. Plastic slides were covered with this plasma and left standing for 30 min. The preparations were then rinsed, fixed and dyed and evaluated microscopically. Normally no aggregates had formed. Partial or complete aggregation was considered to be abnormal.

Spontaneously enhanced platelet aggregation, as we named it then, was rarely found in young healthy volunteers but with increasing frequency in older individuals. In patients with coronary heart disease (CHD), peripheral arterial occlusive disease (PAOD), acute thrombosis, but also in patients with acute infections enhanced aggregation was found in the majority of patients studied [5,6]. We later modified our method to obtain in principle the same results as with the PAT I [7]. Both methods were frequently used in different laboratories in Europe, but to my knowledge they remain unknown in the USA.

The mechanism which leads to enhanced platelet aggregation was never fully elucidated. It seemed to be partially due to platelet activation and was also partially influenced by plasmatic factors, of which increased von Willebrand factor may be one.

From the beginning our main hypothesis was that spontaneous platelet aggregation is an indicator of existing vascular disease or, as in the case of infections, a process which includes vascular inflammation.

We later found that abnormal spontaneous aggregation is correlated with a high risk of new vascular occlusions in diabetic patients (PARD study) [9]. In a large prospective study it was shown to be a risk factor for coronary events in healthy individuals [10].

During our studies with the PAT test we became interested in drugs which might inhibit spontaneous platelet aggregation. In 1966 we found that aspirin inhibited platelet retention. At that time we were studying the effects of dipyridamole and prostaglandins on the PAT. Morris’ results which were later published in 1967 [11] brought us to investigate the effects of aspirin. We soon found that in microscopic test into a photometric method where PRP is rotated in a disk-shaped cuvette (PAT III) [7]. With this new method we obtained in principle the same results as with the older PAT I [8]. Both methods were frequently used in different laboratories in Europe, but to my knowledge they remain unknown in the USA.

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patients with an abnormal PAT single doses of 500 mg aspirin normalized enhanced platelet aggregation for several days. We first reported this in 1967 [12]. Figure 1 was published in 1969 [13] and shows the duration of the effect of 500 mg aspirin in patients with an abnormal PAT. Also in our later studies we used spontaneous aggregation (PAT I or III) as the parameter to study the effects of aspirin. Our hypothesis at that time was that the normalization of platelet activation, as measured with the PAT methods, may be of benefit to patients taking aspirin. I still think that it may well be that patients with an abnormal PAT test benefit from aspirin. At that time the effects of aspirin on platelet thromboxane A2 formation was not known. For our first clinical studies we usually used 3 × 500 mg aspirin per day in different indications. The same or similar doses were applied by different investigators in Europe in the following years. We started to use aspirin for the prevention of postoperative thromboembolism [13–15] but soon concentrated on the use of aspirin in patients with CHD. When we had started our GAMIS trial in 1969 [16] we frequently met with Elwood who was performing a similar trial using 300 mg aspirin day−1 [17]. Patient recruitment in our myocardial infarction (MI) study was low because physicians at that time were convinced that vitamin K antagonists would be much more effective than aspirin in preventing MI recurrences. Another study in post-MI patients at that time which we frequently discussed with C. Klimt was the PARIS trial in which aspirin, aspirin + dipyridamole and placebo were compared [18]. All three trials showed benefits of aspirin which were not significant. In our GAMIS trial aspirin was more effective than phenprocoumon but this was also not significant. It took much larger studies such as ISIS-2 [19] to prove that aspirin prevents MI recurrence. At that time my good friend Bill Fields reported on the effects of aspirin in patients with transient ischemic attacks [20].

We later studied the effect of the aspirin preparations used in the AMIS [21], PARIS and GAMIS trials and found no principal difference in their effects on platelet parameters [22].

References

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