

Changes in the blood platelets of alcoholics during alcohol withdrawal

RICHARD FINK,* RONALD A HUTTON

*From the Departments of Haematology and *Chemical Pathology, Royal Free Hospital, Pond Street, London NW3 2QG*

SUMMARY The effects of alcohol withdrawal on platelet count and platelet function was studied sequentially in a group of alcoholics. Baseline values for platelet count, platelet adenine nucleotides and plasma beta-thromboglobulin (β TG) level were within the normal range but platelet aggregability (especially with ADP and adrenaline) and circulating platelet aggregates were decreased for the group as a whole.

After alcohol withdrawal there was a pronounced increase in all parameters measured which reached statistical significance in many cases and persisted for two to four weeks.

The potential implications and possible mechanisms for these changes are discussed.

Excess alcohol consumption is associated with an increased risk of cerebrovascular stroke^{1,2} and thromboembolic disease.³ Alcohol induced hypertension^{4,5} is one possible cause of these disorders, although abnormal platelet function might also be a factor in their pathogenesis.

While thrombocytopenia and decreased platelet function during alcohol ingestion is documented,⁶ little information is available concerning platelet function in alcoholics during and after alcohol withdrawal. As intermittent heavy drinking is a common pattern of alcohol abuse, we have investigated platelet function in a group of alcoholics on the day of admission to a treatment unit, and sequentially during four weeks of supervised abstinence.

Patients and methods

The subjects studied were selected from those whose drinking problem led to admission to hospital for "drying out" and psychotherapy. All had been drinking excessively up to the day of admission and had measurable blood alcohol concentrations (20-160 mg/100 ml) at that time. Those who could not positively deny having ingested drugs known to affect platelet function for at least 10 days prior to admission were excluded. Twenty-four subjects entered the study and 18 completed the four-week trial period. Of the patients who failed to complete

the study, three discharged themselves within the first week and three inadvertently received drugs affecting platelet function. Therapy for suppression of the withdrawal syndrome consisted of complete bed rest for two days and the administration of two sedative drugs Epanutin and chlormethiazole for up to five days. Thereafter, only an occasional mild sedative (nitrazepam or diazepam) at night and vitamin preparations were given. All subjects had been eating, albeit somewhat irregularly up to the time of admission and none was grossly malnourished. During the study all subjects were fed a normal hospital diet.

Controls were normal hospital personnel with the same sex ratio and covering a similar age range to the alcoholics. None smoked more than 20 cigarettes/day or admitted taking more than an occasional alcoholic beverage. Prior to study, none had ingested alcohol for at least 72 h or antiplatelet drugs for at least two weeks.

Blood was collected with minimal stasis through a 19-gauge butterfly infusion set using a two-syringe technique and discarding the first 5 ml. Samples were collected on the day of admission (day 1) on days 3 or 4 and 7 or 8 and then at weekly intervals for at least three weeks thereafter. Liver function tests, blood alcohol estimation, platelet count, platelet aggregation studies and platelet adenine nucleotide assays were performed as previously described.⁷ Blood for plasma β TG level was collected into an anticoagulant mixture containing EDTA, theophylline and adenosine (final concentrations 0.013 mol/l, 0.001

mol/l and 0.002 mol/l respectively) and measured by a double antibody radioimmunoassay,⁸ the second antibody being immobilised on Sepharose 4B.⁹ Circulating platelet aggregates were measured by the method of Wu and Hoak¹⁰ but enumerating the unclumped platelets in a haemocytometer.¹¹

Results

CLINICAL OBSERVATIONS

One subject had infected cuts on the wrist on admission, which responded to antibiotic therapy over five days. None showed clinical evidence of cirrhosis or hepatitis and although mild to moderate disturbances of liver function were present in most subjects, none was frankly jaundiced. Symptoms of alcohol withdrawal were minimal and were restricted to the first week of the programme. No clinically overt thrombotic lesions developed during the study or were elicited in the previous histories.

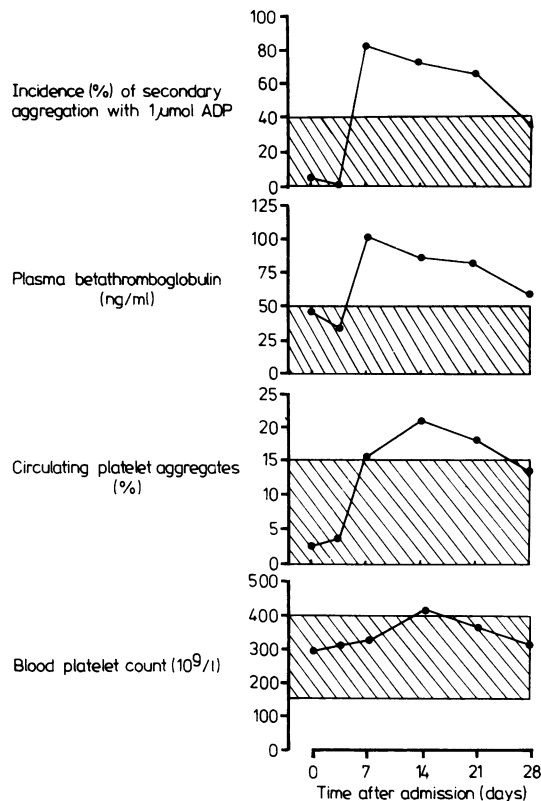
PLATELET STUDIES

Results are shown in the Figure. None of the subjects was thrombocytopenic on admission, but all except two (whose initial counts were high) showed a rise in platelet count which peaked at two weeks and which was significantly raised for the group as a whole at weeks 2 ($p = 0.001$) and 3 ($p = 0.025$).

Platelet aggregability was invariably depressed on admission. The most striking change was the absence of secondary aggregation, although in some cases the primary wave was also reduced. The defect was maximal with adenosine diphosphate (ADP) and adrenaline as agonists but in many cases was also observed with collagen and ristocetin. During the first week after alcohol withdrawal, platelet aggregability was variable. In those whose defect was most marked on admission, improved responses were usually seen. In milder cases, platelet function often decreased initially. However, by seven to 14 days after withdrawal, compared to controls, all subjects had hyperaggregable platelets and again, this was most obvious with ADP and adrenaline where it reached statistical significance ($p = 0.01$). Over the ensuing two to three weeks, platelet aggregability gradually returned towards control values, more or less in line with the platelet count.

Although a few subjects had slightly raised β TG concentrations on admission, results were within the normal range for the group as a whole. After withdrawal, concentrations rose in most cases, often dramatically and mean values remained significantly ($p = 0.005$) above normal until week 4, peak concentrations being found at seven to 14 days in different individuals.

On admission, circulating platelet aggregates were



Changes in platelet parameters during alcohol withdrawal.

close to zero and significantly ($p = 0.002$) lower than in controls. During alcohol withdrawal, a significant increase occurred and the mean level exceeded the normal range (15%) ($p = 0.001$) at weeks 2 and 3. Slightly low concentrations of ATP and ADP were observed in a few patients initially. Values rose steadily over three weeks at which point the total content was significantly ($p = 0.01$) above baseline. Mean results for total nucleotides and ATP:ADP ratio were within the normal range throughout.

Discussion

We have demonstrated significant increases in number of accepted laboratory markers of *in vivo* platelet activation in a group of heavy drinkers during alcohol withdrawal. On admission all subjects were alcoholaemic and showed decreased platelet aggregability, but within a few days of commencing withdrawal, increases in platelet count, platelet aggregability, circulating platelet aggregates and β TG concentrations occurred in all subjects. These values peaked significantly above the normal range

but had returned to the reference range by four weeks.

Platelet hyperaggregability, increase of circulating platelet aggregates or β TG concentrations are found in myocardial infarction,¹³ transient ischaemic attacks¹³ and in conditions such as diabetes mellitus¹⁴ in which an increased risk of thrombosis occurs. The reason why the alcoholics in the present study did not show clinical evidence of thromboembolism could relate to the absence of additional risk factors such as dehydration, congestive cardiac failure or cardiac arrhythmia. Alternatively, subclinical thrombosis may have occurred. The cerebral microcirculation is a possible site for this increased thrombotic activity, as previous studies have shown that cerebral blood flow is reduced by 30% during alcohol withdrawal.¹⁵

In contrast to the present study, previous workers have reported deep vein thrombosis and pulmonary embolus in 4/7 alcoholics after admission to hospital, and suggested that these complications were associated with "rebound thrombocytosis" observed seven days after cessation of drinking.³ Non-alcoholics recovering from an alcoholic binge also appear to be at risk from thrombosis, with a recent study of cerebrovascular accidents in patients under the age of 40 yr, showing that in 15% of cases, illness was preceded by excess alcohol consumption.¹⁶ A high incidence of pulmonary embolus occurs in association with alcoholic cardiomyopathy¹⁷ and a significant proportion of normotensive men under the age of 50 yr presenting with cerebral thrombosis have been shown to be heavy drinkers.² However, neither of these latter two studies specify whether the thromboembolic episode coincided with drinking or abstinence.

The aetiology of the platelet changes is uncertain. Increased platelet aggregability may be partly attributable to influx into the circulation of newly formed platelets with increased functional potential since it occurred concurrently with rises in platelet count and platelet adenine nucleotides. Since platelet age and size are inversely correlated, this suggestion is in accord with previous work showing increased platelet size during alcohol withdrawal.¹⁸ Catecholamine release can cause platelet activation but the sympathetic response to alcohol withdrawal subsides within two days of abstinence and would not therefore account for changes observed 14 days after cessation of drinking. Similarly, although hypertriglyceridaemia is a common finding in alcoholics, this abnormality generally corrects within four to five days after complete alcohol withdrawal. More speculatively, it has been reported that the intraplatelet level of the aggregation inhibiting prostaglandin PGE₁ falls to below normal during alcohol withdrawal¹⁹ and this might promote platelet

aggregation. No data on the time course of this phenomenon or of its significance are available and further studies are required.

With regard to our finding of platelet hypoaggregability during alcohololaemia, this is previously described⁶ and may be relevant to the observation that moderate levels of alcohol consumption is associated with protection from acute myocardial infarction.²⁰ Unfortunately with larger dosage, cardiovascular mortality increases but it is unknown whether death occurs during alcohol consumption or during withdrawal. If the latter is shown to be the case, then the findings of the present study will prove to be of considerable clinical importance.

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Requests for reprints to: Dr RA Hutton, Department of Haematology, Royal Free Hospital, Pond Street, London NW3 2QG, England.