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B R I E F C O M M U N I C A T I O N

THE EFFECT OF ORALLY ADMINISTERED BENCYCLANE ON SPONTANEOUS PLATELET AGGREGATION (PA) AS A FUNCTION OF BENCYCLANE CONCENTRATION IN CODED SAMPLES

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INTRODUCTION

It is well established that the platelets are the morphological basis whereas their aggregation is the functional basis of a white thrombus formation. Therefore it seems warrented in thrombotic disorders to attempt to inhibit both platelet adhesion and aggregation for therapeutical purposes. A considerable number of chemical different drugs has been claimed to be effective in inhibiting platelet aggregation (1,2).
In addition to the known inhibitors of PA a newly developed substance, bencyclane (N- 3-(1-benzyl-cycloheptyloxy)-propyl-N,N-dimethyl-ammonium-hydrogen-fumarate) was recently added. This substance which primarily has been introduced as a vasodilator agent (3) has been demonstrated to inhibit platelet adhesion both in vitro and in vivo (4) as well as markedly reducing spontaneous PA in vitro after parenteral administration (5). The oral administration of bencyclane to normal individuals in order to test its effectivity in preventing spontaneous PA (extra vivum) and to compare with the level of the bencyclane in the plasma samples has not been undertaken so far and represents the object of the present report.

METHODS

Twelve clinically healthy subjects of either sex (aged 23-53) were given coated tablets each containing 100 mg bencyclane over a period of 6 days without any other medication. The dose was raised progressively from 300 mg to 600 mg bencyclane daily.

By venous puncture sodium citrated blood (1:10) was taken before medication and 2 hours after the last medication. Platelet rich plasma (PRP) was obtained by differential centrifugation at 200 x g for 10 minutes. PA double tests were carried out under standardized conditions strictly 2 hours after blood withdrawal as described in detail elsewhere (6,7). The PA was induced only by flow (pure mechanical factors) without addition of any classical substance such as ADP etc. Preparation and storage of the PRP and the measurement of PA were performed at room temperature. Independent of the effect on the PA, the bencyclane concentrations in coded plasma samples were determined by gas-chromatography (8).

Statistical methods. To establish any significant difference[1] between treated and untreated samples the single sided paired Student-t-test was used. A correlation between the inhibitory effect on aggregation and the corresponding plasma bencyclane levels was established according to the rules of correlation and regression analysis.

RESULTS AND DISCUSSION

Two females had to be excluded because of unsystematic dizziness and nausea. In eight of the remaining ten subjects a considerable diminishing of PA was established after the period of drug administration (see Fig. 1).

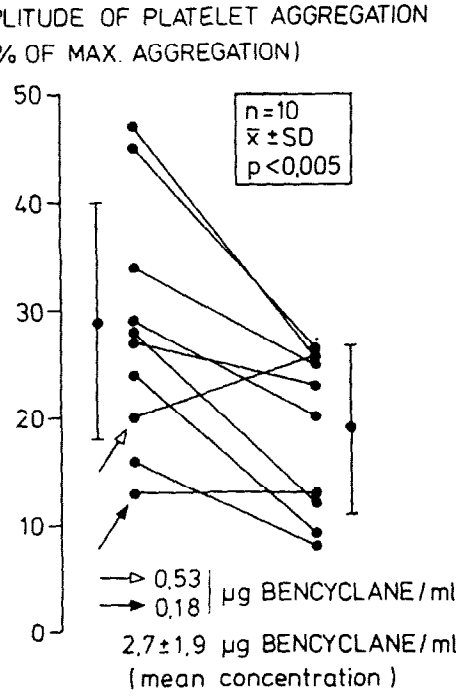

FIG. 1

The difference between the maximal aggregation amplitudes before (left points) and after (right points) bencyclane treatment of the ten subjects and the average values. The arrows indicate the two non-responder and their corresponding bencyclane levels of their plasma.

1) We acknowledge with thanks the support of Mr. K. Willmes (Institute for Medical Statistics and Documentation) for the statistical treatment of our data.

The difference between the average maximal aggregation amplitudes before and after bencyclane treatment was significant ($p < 0.005$). Moreover - as shown in Fig. 2 - a positive correlation has been found between plasma concentration of bencyclane in the volunteers and the percent reduction of the spontaneous PA ($r = 0.756$; $p < 0.01$). A single dose of 300 mg bencyclane, however, showed no decrease of the spontaneous PA (not shown).

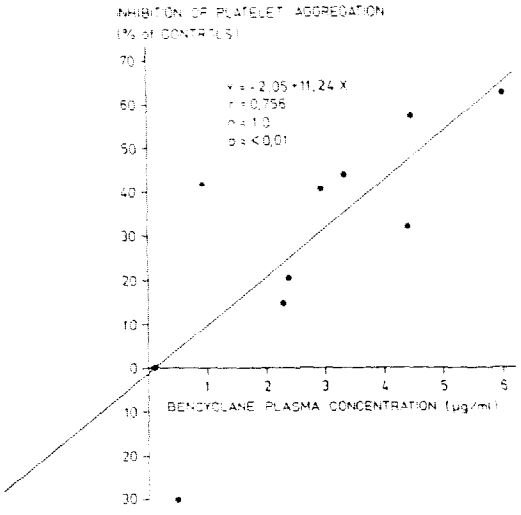

FIG. 2

The positive correlation between plasma concentration of bencyclane in the volunteers and the percent reduction of the spontaneous PA

This study on a small group showed that the oral administration of a clinically suitable dose of 600 mg bencyclane produced a significant reduction in the maximum amplitude of the aggregation curves obtained. For doses up to 600 mg bencyclane per day, corresponding to a plasma concentration up to 6 µg/ml, we have found a linear dose-effect-correlation.

The mechanism of inhibiting action of bencyclane on the spontaneous PA is still unknown. The fact that the inhibition effect of the substance on thrombine induced PA can be found only in presence of plasma proteins supports the view that it is an indirect, protein-mediated mechanism (9). It should be noticed that in the two subjects without detectable changes of spontaneous PA, the plasma concentration of the drug was found 0.53 and 0.18 µg/ml respectively, which are far below the average concentration value of all samples (Fig. 1, see arrow).

Not withstanding this disclosure of an antiaggregating effect of bencyclane under the described in vitro conditions the question of its antithrombotic therapeutical in vivo-effectiveness still remains open. This would be substantiated only through prospective studies at a great number of patients.

Data of DEINHARDT and POLIWODA (10) however, suggest the possibility of an antithrombotic effect: In bencyclane-treated rats they observed in vivo a highly significant decrease of the growth rate of injury-induced wall bound thrombi as compared to the untreated control animals.

Because of side effects 2 out of our 12 cases had to be excluded. We cannot tell whether the symptoms of circulatory disregulation are attributable to the negatively inotropic and negatively chronotropic action of the substance shown in animal experiments (11). However, it does seem possible that there is a synergistic effect on the bencyclane-induced vasodilation with enlargement of the capacity of the peripheral flow channels.

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