

The effect of tricyclic antidepressive drugs on adrenaline and adenosine diphosphate induced platelet aggregation

SIR,—There is good agreement between the effects of adrenaline, noradrenaline and isoprenaline on the stimulation of the smooth muscle of the nictitating membrane, and on the aggregation of thrombocytes (O'Brien, 1964). Noradrenaline is weaker than adrenaline and isoprenaline has no effect at all. We have examined the effect of the tricyclic antidepressive drugs upon the aggregation of thrombocytes because these drugs inhibit the active uptake of adrenaline by the cells and thus may influence its action on the formation of microthrombi.

A second reason was the statement by Abood, Kimizuka, Rogeness & Biel (1963) that norimipramine probably interferes with the liberation of ATP from muscle cells in the course of depolarization. According to these authors norimipramine strengthens the cellular membrane and maintains the membrane potential.

If both adrenaline and ADP cause aggregation of thrombocytes in the same manner—by depolarizing the cellular membrane—then the tricyclic antidepressive drugs should have an inhibiting effect on the aggregation effect of both substances.

The antidepressive drugs of the tricyclic type were: imipramine, norimipramine, propazepine, amitriptyline and nortriptyline.

The experiments were made with a plasma rich in thrombocytes (Born & Cross, 1963). Using our modification of the method of O'Brien (1964) we found, in addition to the continuous fall in absorbance, another fall after 240 sec, following an additional 1 min of centrifuging at 25 rpm. During this procedure small flakes appeared, the dimensions of which excluded the possibility of plasma viscosity influencing their sedimentation. We also obtained more consistent results. The extent of the reduction, caused by the drugs, in the fall in absorbance with adrenaline or ADP is a measure of the inhibiting effects of the drugs. This is expressed as a percentage of the reduction in absorbance caused by adrenaline, 5×10^{-5} M, or ADP, 5×10^{-4} M, these concentrations being considered to give 100% aggregation.

The effects of the drugs on the aggregation of thrombocytes induced by adrenaline are shown in Table 1. This shows that the drugs at a concentration of 5×10^{-4} M completely block the aggregation of thrombocytes caused by adrenaline. A concentration of 5×10^{-5} M causes an inhibition of some 50%.

TABLE 1. INHIBITION OF THROMBOCYTES AGGREGATION BY TRICYCLIC ANTIDEPRESSIVE DRUGS. Aggregation induced by adrenaline in a concentration of 5×10^{-5} M

Inhibiting substance	conc. M	Inhibition %	s.d.	Number of experiments	Significance of inhibition P
Impramine	5×10^{-4}	100.62	7.16	6	<0.001
Imipramine	5×10^{-5}	45.64	35.56	15	<0.001
Norimipramine	5×10^{-4}	101.51	13.50	8	<0.001
Norimipramine	5×10^{-5}	52.92	7.71	8	<0.001
Amitriptyline	5×10^{-4}	101.39	10.83	4	<0.001
Amitriptyline	5×10^{-5}	41.69	29.22	10	<0.001
Nortriptyline	5×10^{-4}	104.41	4.91	10	<0.001
Nortriptyline	5×10^{-5}	65.88	28.68	11	<0.001

At $5 \times 10^{-6}\text{M}$ the drugs have practically no effect. The differences between the effects of the individual substances are not statistically significant.

The effect of the drugs on the ADP-induced aggregation of thrombocytes is summarized in Table 2. Imipramine, amitriptyline and nortriptyline completely inhibit the aggregation caused by ADP when used in concentrations of $5 \times 10^{-4}\text{M}$. In concentrations of $5 \times 10^{-5}\text{M}$ nortriptyline proved the most effective inhibitor. Concentrations of $5 \times 10^{-6}\text{M}$ of all the drugs still caused an aggregation-inhibiting effect of some 20%.

TABLE 2. INHIBITION OF THROMBOCYTES AGGREGATION BY TRICYCLIC ANTIDEPRESSIVES. Aggregation induced by ADP

Inhibiting substance	Conc. M	Inhibition %	s.d.	Number of experiment	Significance of Inhibition P
Imipramine	5×10^{-4}	93.59	12.62	10	<0.001
Imipramine	5×10^{-5}	25.73	26.50	9	<0.05
Amitriptyline	5×10^{-4}	92.28	10.64	7	<0.001
Amitriptyline	5×10^{-5}	36.89	28.19	11	<0.001
Nortriptyline	5×10^{-4}	95.44	19.22	7	<0.001
Nortriptyline	5×10^{-5}	79.33	20.10	8	<0.001

It seems that the antidepressive drugs of the tricyclic type inhibit the effect of both adrenaline and ADP on the aggregation of thrombocytes in the same way. It may thus be assumed that both adrenaline and ADP have a direct effect on the cellular membrane of thrombocytes. Because of this, adrenaline does not intervene by the liberation of ADP. Imipramine probably strengthens the membrane of the thrombocytes and maintains their potential (Abood & others, 1963).

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