EFFECTS OF VINBLASTINE AND VINCRISTINE ON PLATELETS AND LEUCOCYTES

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Summary: The effects of different doses of vinblastine and vincristine administered over varying periods were investigated on total leucocyte and platelet counts in rats. Depending upon dosage, the drugs caused either thrombocytosis with no effect on leucocytes or thrombocytopenia with leucopenia. Thrombocytosis persisted even after prolonged treatment when the drugs were given in proper dosage.

Key words : vinblastine vincristine total platelet and leucocyte counts thrombocytosis throm bocytopenia leucopenia

Vinca alkaloids, vinblastine and vincristine are recently introduced in the treatment of leukemias and Hodgkin's disease. Leukopenia is the commonest side effect of vinblastine therapy and though a fall in leucocytes is liable to occur during treatment with vincristine, this drug causes less bone marrow depression.

Thrombocytopenia can also be produced by either drug, but this is observed as an infrequent side effect in thier clinical use (9,12). An unexplained thrombocytosis associated with either therapy has also been reported (3,6,12).

It is paradoxical that a myelotoxic drug should promote a thrombocytosis. Therefore, the effects of vinblastine and vincristine were studied on total leukocyte and platelet counts in rats.

MATERIALS AND METHODS

The experiements were carried out on male rats weighing 200-300 *g*. Blood samples were collected by tail cuts. Platelet and leucocyte counts were done by the methods of Brecher and Cronkite (5) and Dacie and Lewis (8) respectively. The effects of varying and repeated doses were also studied.

The animals were divided into groups of 5 rats each and initial leucocyte and platelet counts were performed. On the third day, 4 groups received vincristine (ip) and another 4 groups received vinblastine (ip) in single doses of 0.1, 0.2, 0.4, 0.8 *mg/kg* dissolved in 0.5 *ml* of normal saline solution. Two groups received 0.5 *ml* of normal saline (ip) and served as control. Blood counts were performed five days after the injections.

Starting on the 3rd day after the initial counts, eight other groups received the drugs once daily for 7 days; two groups served as controls and received 0.5 *ml* of normal saline for 7 days. Counts were done on 5th day after the last injection i.e. on 14th day after the initial count.

The effects of repeated weekly doses of vinblastine and vincristine were also studied. Following the initial blood counts two groups of 10 rats each were given vinblastine or vincristine

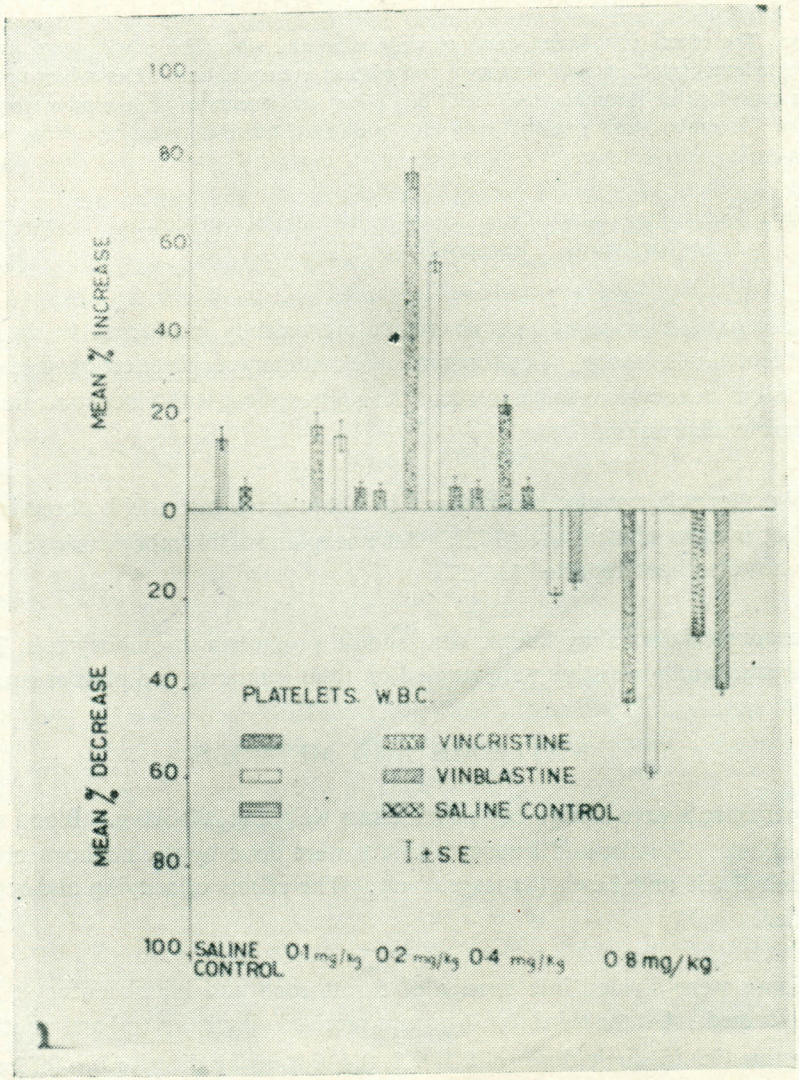

Fig. 1 : Effect of varying doses of vinblastine and vincristine administered once on total platelet and leucocyte counts in rats.

(0.2 *mg/kg* ip) at weekly intervals for 6 weeks. At the end of 6 weeks the administration of vinblastine or vincristine was discontinued in 5 rats from each group and blood counts were done 5 days after the last injection. The remaining five rats from each group continued to receive the drugs for another six weeks. The blood counts were performed 5 days after the 9th and 12th injections. Ten other rats served as control and received 0.5 *ml* of normal saline (ip).

In some animals the intraperitoneal injections of the drugs produced an irritant action menifested by mild peritonitis. In some of these secondary infections, sloughing and necrosis

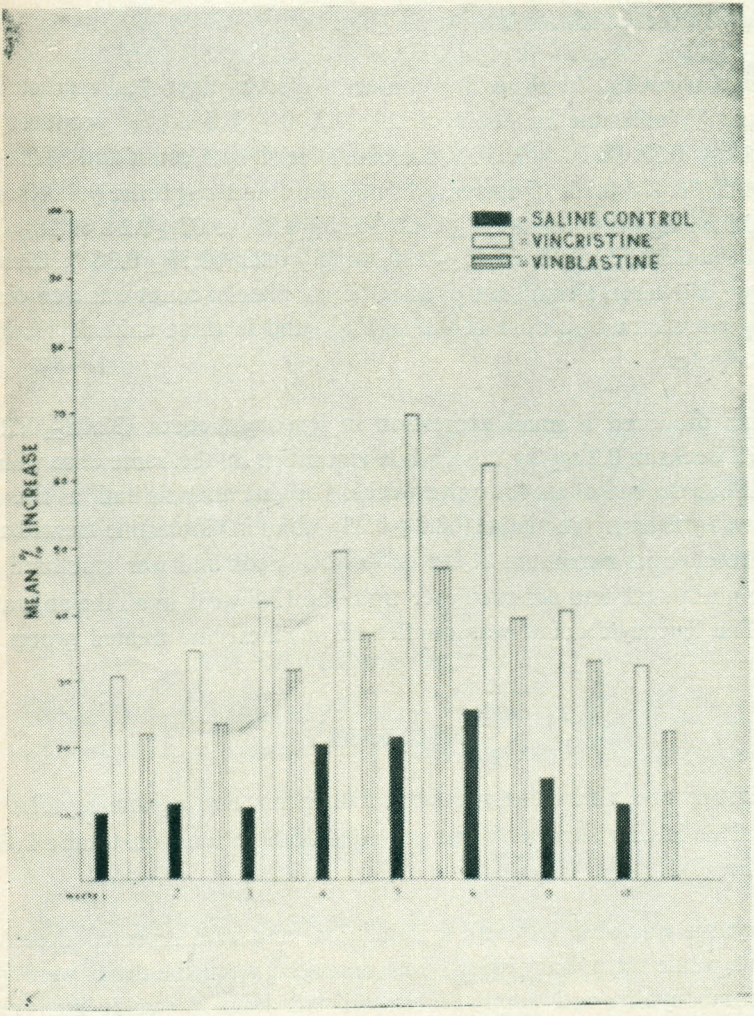

Fig. 2 : Effect of weekly administration of 0.2 *mg/kg* of vinblastine and 0.2 *mg/kg* vincristine on total platelet counts in rats.

was observed after higher doses. These animals were not included in the study.

RESULTS

Single doses of 0.2 *mg/kg* of vinblastine and 0.2 *mg* and 0.4 *mg/kg* of vincristine produced an increase in platelet count in all the test animals. This effect was most marked in rats receiving 0.2 *mg/kg* dose of drugs 0.4 *mg* and 0.8 *mg/kg* of vinblastine and 0.8 *mg/kg* of vincristine caused a decrease in the platelet count. 0.1 *mg/kg* of both the drugs had no appreciable effect, the count being identical with that in control animals which had a small rise in their platelet count. The leucocyte count was not affected by 0.1, 0.2, 0.4 *mg/kg* of vincristine and 0.1, 0.2 *mg/kg* of vinblastine while higher doses produced leucopenia (Fig. 1).

The animals receiving the drugs for consecutive seven days had marked leucopenia and thrombocytopenia. Vinblastine in doses of 0.1, 0.2, 0.4, 0.8 *mg/kg* produced 45.50 $\pm$ 0.32, 68.95$\pm$0.28, 89.15 $\pm$ 0.33, 98.20 $\pm$ 0.38% decrease in leucocyte count and 36.28 $\pm$0.22, 48.50$\pm$ 0.22, 63.52 $\pm$ 0.25, 78.40$\pm$0.35 % decrease in platelet count respectively. Vincristine in doses of 0.1, 0.2, 0.4, 0.8 *mg/kg* produced 26.30$\pm$0.12, 34.76$\pm$0.18, 65.02$\pm$0.24, 89.28$\pm$0.22% decrease in leucocyte count and 20.50$\pm$0.12, 28.65$\pm$0.20, 46.55$\pm$0.23, 62.50$\pm$0.36 % decrease in platelet count respectvely. However, a small rise of 25-50% in platelet count was also observed in some animals receiving vincristine in a dose of 0.2 *mg/kg* and in these animals the leucocyte count also was not affected.

Vimblastine produced a small depression in leucocyte count (32.08$\pm$0.22) when given weekly for 6 to 12 weeks in 0.2 *mg/kg* dose, while vincristine in the same dose without any effect on leucocyte count at the end of six to twelve weeks. The test animals had a rise in their platelet counts which was greater in vincristine (68.0$\pm$0.23) than in vinblastine treated animals (48.6$\pm$ 0.28), The rise reached its maximum at the end of 5th week and was stabilized at lower levels by the end of the ninth week and persisted even upto the 12th week in all the animals receiving the drugs (Fig.2). The leucocyte count was unaffected in vincristine treated group at the end of 12th week.

DISCUSSION

Vinblastine and vincristine produced leukopenia and agranulocytosis after repeated administration. This is consistent with our previous observations on total alkaloids, fraction A and vinblastine (7).

Thrombocytosis was observed with a single dose and with repeated doses of these drugs at weekly intervals, while thrombocytopenia was produced when the drugs were given daily for seven days. Thrombocytosis with single doses, repeated doses at weekly intervals and also by the daily administration (0.2 *mg/kg* ip) of vincristine has been reported by Robertson *et al.* (10, 11). Our observation are in agreement with theirs; in addition we have observed thrombo-

cytopenia with higher doses of vincristine (0.4 *mg* and 0.8 *mg/kg*) administered daily for seven days. This may be due to hypoplasis of the bone marrow as leucopenia and agranulocytosis was concomitantly seen in these animals.

The increase in the circulating platelets could occur due to stimulation of platelet production by bone marrow (11), or by release of platelets from a reserve pool. Such an extra-circulatory reserve is present in the rats and is increased in hypersplenic rats (2). The rise may partly also be due to reaction to the previous bleeding, as seen in the control groups.

White *et al.* (14), have shown that vincristine causes damage to the microtubules of platelets. This might alter their adhesiveness or aggregating properties. leading to a reduction in their reactivity and increased life span (13).

The dosage is important in determining whether thrombocytosis or thrombocytopenia is produced. The smaller doses cause thrombocytosis with no leucopenia, while higher doses or frequent administrations lead to thrombocytopenia with leucopenia. These observations are in agreement with those of Robertson *et al.* (11) with vincristine since depression of bone marrow with busulphan obliterated the thrombocytosis promoting response to the drug. The decrease in the platelet and the total leucocyte count with the higher doses may be due to cytotoxic effect of the drugs.

Though vinblastine and vincristine differ in their mechanism of cytotoxic effects, toxicity, different antitumour spectrum and show no cross resistance in tumours where both are active (1, 4) yet it seems that they possess common thrombocytosis-promoting effect which is quite independent of their oncholytic action. If so, it would be advantageous to study the possibilities of an alteration in their chemical structures with the object of developing agents useful in the therapy of thrombocytopenic states.

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REFERENCES

1. Armstrong, J. G. Vincristine (NSC-67574), symposium-summary and prospectives. *Cancer Chemother. Rep.*, **52** : 527-535, 1968.
2. Aster, R. H. Studies of the mechanism of "hypersplenic" thrombocytopenia in rats. *J. Lab. Clin. Med.*, **70**: 736-751, 1967.
3. Beier, F. R., L. G. Thatcher and M. E. Lahey. Treatment of reticuloendotheliosis with vinblastine sulfate. *J. Pediat.*, **63** : 1087-1092, 1963.
4. Boesen, E. and W. Davis. *Cyotoxic Drugs in the Treatment of Cancer*. Arnold, London, 1969, p. 152-157
5. Brecher, G. and E. P. Cronkite. Morphology and enumeration of human blood platelets. In : *Clinical*

Laboratory Metthods and Diagnosis ed. S. Frankel and A. C. Sonnenwirth. The C. V. Mosby Co. Vo 1963, p. 1198.

6. Carbone, P.P., V. Bono, E. Frei. III and C.O. Brindley. Cilinical studies with vincristine. *Blood.*, 21 : 647, 1963.
7. Chandorkar, A.G. Effect of Vinca rosea alkaloids on peripheral blood cells in rats. *J. Shiv.* U 5 (10), 1972 (Under publication).
8. Decie, J.V. and S.M. Lewis. *Practical Haematology.*, 3rd edn. Churchill, London, 1963, p. 51.
9. Johnson, I.S. Symposium Vincristine. *Cancer Chemother Rep.*, **52** : 455, 1968. Quoted by Robe J.H. & G.M. McCarthy. Periwinkle alkaloids and platelet count. *Lancet, ii*, 353-355, 1969.
10. Robertson, J.H. and G.M. McCarthy. Periwinkle alkaloids and platelet count. *Lancet, ii*, 353-355,
11. Robertson, J.H., E.H. Crozier and B.E. Woodend. The effect of vincristine on the platelet count in *Br. J. Haematol.*, **19** : 331-337, 1970.
12. Selawry. O.S., J.P. Holland and I.J. Wolman. Symposium Vincristine. *Cancer Chemother. Rep.*, 52 : 1968. Quoted by Robertson J.H. & G.M. McCarthy. Periwinkle alkaloids and platelet count. *Lanc* 353-355, 1969.
13. Soppitt, G.D. and J.R.A. Mitchell. Periwinkle alkaloids and platelets (Letter) *Lancet ii;* 539, 1969.
14. White, J.G. Effect of colchicine and vinca alkaloids on human platelets 1. Influence on platelet microtu and contractile function. *Am. J. Path.*, **53** : 281-291, 1968.