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New Derivatives of the Vinca Rosea Alkaloids

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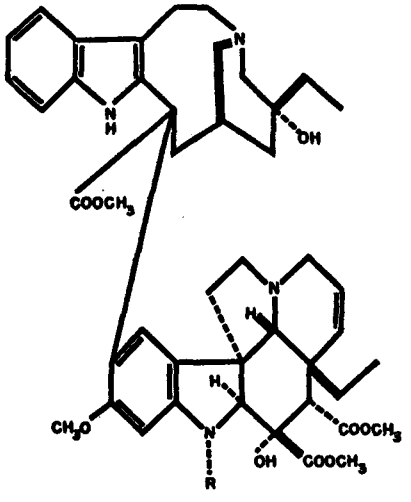
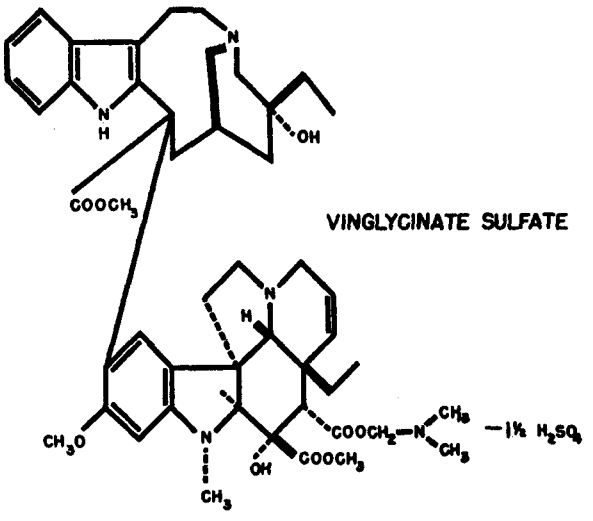
The oncolytic drugs which have been derived from *Vinca rosea*, the flowering periwinkle, are remarkable in that major differences in potency, toxicity and anti-tumor spectrum appear to depend on relatively minor differences in the side chains attached to the skeleton which they share in common (Armstrong *et al.*, 1962; Johnson *et al.*, 1963) as shown in Fig. 1. For example, vincristine sulfate (VCR) has been found useful in the treatment of acute lymphocytic leukemia and lymphosarcoma in contradistinction to vinblastine sulfate (VLB), which is relatively more effective in the treatment of Hodgkin's disease and some other neoplasms (Armstrong *et al.*, 1962). With these differences in mind, it appeared logical to produce more alkaloids of this series by chemically modifying some of the side chains. From the clinical standpoint this seemed to be particularly justifiable in view of the lack of cross-resistance among the active vinca alkaloids.

Several ester derivatives of VLB have been prepared and tested biologically in the Lilly Research Laboratories. Some were found to be more effective than the parent compound (VLB) in prolonging the survival of DBA/2 mice with P-1534 leukemia. The most active ester was desacetyl VLB-4-chloroacetate sulfate. From this, a series of α-amino ester analogs were prepared and also tested in the P-1534 leukemia system. Desacetyl VLB 4-(N, N-dimethylglycinate) sulfate was the most active of these analogs and was therefore selected for further evaluation. Furthermore, in biological studies it appeared to be more selective in anti-tumor spectrum and less toxic than either VLB or VCR.

On the basis of these studies, it was decided to employ this drug, the generic name of which is vinglycinate sulfate (Fig. 1), in a clinical trial at the Lilly Laboratories for Clinical Research. This trial has so far involved 40 patients with various types of malignant disease. Significant objective evidence of a beneficial response has been encountered in Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, carcinoma of the bronchus, malignant carcinoid and chondrosarcoma (Tab. 1). As with the parent compound (VLB), the dose-limiting toxicity is leukopenia. However, while the dosage necessary to produce anti-tumor responses and leukopenia are about in the same ratio, they are approximately ten times greater than those of VLB. As with other clinically active Vinca drugs, no significant effects on the thrombocytes





Tab. 1. Therapeutic results obtained with Vinglycinate sulfate

	Total cases	Number evaluable	Significant improvement	
			Objective & subjective	Objective only
Lymphomas:				
Hodgkin's disease	9	7	3	0
Lymphosarcoma	2	2	1	0
Reticulum cell sarcoma	4	1	1	0
Leukemias:				
Acute childhood	3	1	0	0
Acute monocytic	1	0		
Acute myelogenous	1	0		
Carcinomas:				
Breast	1	1	0	0
Bronchus	6	4	1	0
Fallopian tube	2	2	0	0
Kidney	1	0		
Pancreas	1	1	0	0
Unknown primary	3	3	0	0
Miscellaneous:				
Malignant carcinoid	1	1	1	0
Malignant melanoma	2	2	0	0
Neuroblastoma	1	1	0	0
Teratoblastoma	1	1	0	0
Chondrosarcoma	1	1	0	1
Totals	40	28	7	1

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or the erythrocytes have been encountered. The only other side-effects have been partial epilation in three patients and transient nausea after each dose in one patient.

The following incremental dosage plan has been evolved for vinglycinate sulfate.

Week	Intravenous dose in mg/kg
1	0.50
2	0.75
3	1.00
4	1.25 etc.

until leukopenia has occurred. After the leukocyte count has returned to normal, treatment has been continued for so long as a response could be maintained with weekly doses one increment smaller than that which caused leukopenia.

It was of great interest to find that some patients responded to vinglycinate sulfate after having previously responded to and then become refractory to other Vinca drugs including the parent compound (VLB). This lack of cross-resistance between the Vinca alkaloids adds to the usefulness of the series.

Such findings as these encourage us to produce yet more derivatives of the Vinca alkaloids. Hopefully, structure-activity relationships will emerge to point the way for the development of more specific, more potent and less toxic derivatives of VLB and VCR.

Summary

1. Vinblastine (VLB) and vincristine (VCR) are both naturally occurring alkaloids derived from the flowering periwinkle plant, Vinca rosea, Linn.

2. Both drugs have large molecules and are very similar in chemical structure. They differ only in that VLB has a methyl group ($-CH_3$) while VCR has a formyl group (-CHO) attached to one of the nitrogen atoms in the molecule.

3. In spite of this chemical similarity, VLB and VCR differ greatly in the types of malignancy against which they are effective, their toxicities, and their potencies.

4. With these differences in mind, it appeared logical to produce more alkaloids of the series by modifying one of the side chains of VLB.

5. Vinglycinate sulfate (VGL), the first of these semisynthetic VLB derivatives to undergo clinical trial, has proved useful in the treatment of some patients with malignant disease. There was no cross-resistance between VGL and its parent substance, VLB, or with VCR.

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RIASSUNTO

1. Vinblastina (VLB) e Vincristina (VCR) sono alcaloidi naturali derivati dalla Vinca rosea.

2. Ambedue questi medicamenti hanno grosse molecole a struttura chimica molto simile. Differiscono soltanto perché, legati ad uno degli atomi d'azoto della molecola, VLB ha un gruppo metile (-CH_3), mentre VCR ha un gruppo formile (-CHO).

3. Nonostante la loro somiglianza chimica, VLB e VCR differiscono notevolmente per i tipi di tumori su cui sono efficaci, per la loro tossicità e per la loro potenza.

4. Tenendo conto di queste differenze, è apparso logico produrre più alcaloidi della serie modificando una delle catene laterali di VLB.

5. Il Vinglicinato, il primo di questi derivati semisintetici di VLB ad essere sottoposto ad esame chimico, è risultato utile nel trattamento di alcuni pazienti affetti da tumori. Non vi è stata resistenza reciproca fra VGL e la sua sostanza d'origine VLB, o con VCR.

RÉSUMÉ

1. Vinblastine (VLB) et Vincristine (VCR) sont les alcaloïdes de la Pervenche, Vinca rosea Linn.

2. Les deux médicaments représentent des molécules très similaires au point de vue chimique. La seule différence est que la VLB contient un groupe methyle (-CH_3) tandis que VCR contient un group formyle (-CHO) attaché a un des azotes de la molécule.

3. Malgré cette ressemblance, VLB et VCR montrent une grande différence dans l'abilité de contrôler certaines tumeurs et dans le degré de la toxicité.

4. En considérant ces différences il était logique d'entreprendre un programme de la modification chimique de ces composés.

5. Vinglycinate sulfate (VGL) est le premier de ces composés d'être soumis à un essai clinique. Il a êté démontré d'avoir un bon degré d'activité dans un certain nombre de malades avec des tumeurs. On n'a pas encore observé une résistance entre VGL et VLB ainsi que VCR.

ZUSAMMENFASSUNG

1. Vinblastine und Vincristine sind natürliche, aus der Vinca rosea gewonnene Alkaloide.

2. Beide Medikamente besitzen grosse Molekeln und sind sich in ihrer chemischen Struktur sehr ähnlich Der Unterschied ist, dass bei VLB eine Methylgruppe (-CH_3) und bei VCR eine Formylgruppe (-CHO) an das Stickstoffatom der Molekel gebunden ist.

3. Trotz der chemischen Ähnlichkeit wirken VLB und VCR jedoch nicht bei den gleichen malignen Erkrankungen, und unterscheiden sich in ihrer Toxizität und Potenz.

4. Unter Berücksichtigung dieser Unterschiede, erschien es logisch, mehr Alkaloide der Serie unter Veränderung der Lateralketten des VLB herzustellen.

4. VGL war das erste dieser semisynthetischen VLB-Derivate, das chemisch untersucht wurde und zeigte sich bei einigen Patienten mit malignen Erkrankungen nützlich. Es zeigte sich keine Resistenz zwischen VGL und seinem Ursprungspräparat VLB oder dem VCR.