Rauwolfia serpentina in the Treatment of Angina Pectoris

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Fifteen subjects with coronary artery disease and angina pectoris were given alternate courses of the alseroxylon fraction of *Rauwolfia serpentina* and placebo. Fourteen improved on the drug as determined by independent clinical evaluations and the "Daily Report Card" data. Seven developed normal electrocardiograms, 2-step tests or ballistocardiograms, that previously had been abnormal. Alseroxylon appeared to induce an unusually prolonged therapeutic effect that was revealed only by an individual "sequential" analysis of each course of drug and placebo. The nature of the underlying mechanism is not clear. Serious hypotensive responses and acute depressive reactions are infrequent at the dosage levels used, but do occur.

IN A recent report of the therapeutic spectrum of *Rauwolfia serpentina*,* we included some preliminary observations on its use in the anginal syndrome.[1] This paper is a more detailed evaluation of the therapeutic responses of 15 ambulatory subjects with coronary artery disease and angina pectoris whom we have now studied for an average period of 42 weeks each.

Case Material

There were 13 men and 2 women in the study group (table 1). Their mean age was 59 years. As a group, they had experienced frequent, severe anginal attacks for an average period of 26 months. Four subjects had historical and electrocardiographic evidence of previous myocardial infarction that had occurred at a mean time of 27 months before admission. Ten subjects presented abnormal electrocardiograms, 9 of whom also had abnormal ballistocardiograms.[2] Of the 5 with normal admission tracings, there were 4 with positive 2-step exercise tests[3] and 3 with abnormal ballistocardiograms. The fifth subject, who had a negative 2-step test, showed ballistocardiographic abnormalities. Seven subjects gave a history of arterial hypertension and had entrance blood pressures in excess of 150/100 mm. Hg. All subjects had been doing poorly or had ceased to improve on conventional therapy. During this study they received no medication other than nitroglycerin as needed and either alseroxylon or placebo.

Study Plan

In accordance with the double blind technic, one physician examined the subject at each visit and recorded an independent clinical evaluation. A second physician then saw the patient, collected the "Daily Report Cards," which we will describe shortly, and prescribed by code number either the active drug or an identical placebo tablet. These agents were given in alternate courses of 6 or more weeks. In all but 2 cases, the placebo was prescribed first to provide an initial baseline period and to assess any psychologic response.

Various laboratory procedures were performed on admission and at each return visit. These included 12-lead electrocardiograms, 2-step exercise tests, velocity-type ballistocardiograms, and teleroentgenograms for cardiac size and contour. These were interpreted by physicians who had no additional contact with the subjects.

The "Daily Report Card" is a special chart for subjective evaluations and is a modification of the type devised by Greiner and his associates.[4] This card makes but 2 simple demands (fig. 1). First, the subject must grade his angina each day in comparison with his average pretreatment level, by marking an "X" in the appropriate section and second,

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* Riker Laboratories, Inc., supplied the alseroxylon (Rauwiloid) used in this study and aided in its support.

TABLE 1.—*Case Material*

Number of subjects:	15 (13 men, 2 women)
Age:	
mean	59 years
range	35–68 years
Duration of angina (mean)	26 months
Severity of angina:	
severe	5 subjects
moderately severe	10 subjects
Prior myocardial infarction	4 subjects
Time of infarction (before admission):	
mean	27 months
range	5–46 months
Admission electrocardiogram:	
abnormal	10 subjects
normal	5 subjects
Positive "2-step" test	4 subjects
Abnormal ballistocardiogram	12 subjects
Duration of observation (mean)	42 weeks
Incidence of hypertension (B.P. 150/100 mm. Hg or more)	7 subjects

he must record his nitroglycerin intake and actual number of anginal attacks for each 24-hour period. Each card thus provides a daily account of the frequency and severity of the angina over a 31-day interval.

These "Report Cards" have the virtues of simplicity and tangibility. They supply a large volume of data for statistical analysis. In contrast to most subjective evaluation technics, the "Daily Report Card" tends to prevent errors from memory lapses, from undue emphasis on temporary fluctuations in symptoms, and from misleading statements made to the doctor.

RESULTS

Table 2 is an analysis of all the combined "Report Cards" for the entire group. Here, the results of all courses on drug are compared with those of all the placebo periods. The

"DAILY REPORT CARD" FOR HEART PAIN

BRING THIS REPORT CARD WITH YOU EACH VISIT

NAME JOSEPH N. DATE TREATMENT STARTED 3/15/54

HOW MUCH HEART PAIN DID YOU HAVE EACH DAY?	DAY OF WEEK																												
	MON	TUES	WED	THUR	FRI	SAT	SUN	MON	TUES	WED	THUR	FRI	SAT	SUN	MON	TUES	WED	THUR	FRI	SAT	SUN	MON	TUES	WED	THUR	FRI	SAT	SUN	MON	TUES	WED
SAME HEART PAIN AS USUAL		X								X																				
LESS HEART PAIN THAN USUAL GOOD DAY	X		X	X				X	X			X		X		X				X	X	X	X			X	X	X			
MORE HEART PAIN THAN USUAL BAD DAY					X	X					X		X											X							
NO HEART PAIN AT ALL							X								X		X	X	X						X						
NUMBER ATTACKS OF HEART PAIN PER DAY	1	2	1	1	3	3	0	1	1	2	3	1	4	1	0	2	0	0	0	1	2	1	1	4	0	2	2	1			
NUMBER NITROGLYCERINE TABLETS PER DAY	1	2	1	1	3	3	0	1	1	2	3	1	4	1	0	2	0	0	0	1	2	1	1	4	0	2	2	1			

BEFORE GOING TO BED EACH NIGHT, WRITE A MARK (X) IN THE SPACE THAT DESCRIBES YOUR HEART PAIN FOR THE ENTIRE DAY AND WRITE IN THE NUMBER OF HEART ATTACKS AND NITROGLYCERINE TABLETS TAKEN THE ENTIRE DAY.

FIG. 1. Example of Daily Report Card used for subjective evaluations

data on frequency of angina and nitroglycerin intake correlated very closely and have been omitted. On the basis of this combined analysis the total group responses to these 2 agents appear strikingly similar. The minor differences here are not statistically significant.

Table 3 is an individual analysis of the "Report Card" data of each subject (again based on a comparison of the combined drug courses and the pooled placebo periods). The purpose here was to detect any subjects who might have improved on one or the other agent but whose results were obscured by others who did poorly. On the left half of the table, it will be seen that, whereas 3 subjects did better on drug, 2 seemed to improve on placebo, and the majority responded similarly to both agents. From this individual analysis there again appears to be no evidence of any significant therapeutic superiority for alseroxylon.

We did not expect, therefore, to have the independent clinical evaluations indicate unequivocal improvement in all but 1 subject, but such was the case. The basis for these apparently divergent results became clear on re-examination of the "Report Card" data. When we analyzed separately each successive observation period of each subject, we noted a curious sequence of therapeutic events. In essence, after the initial baseline period on placebo, 11 of the 15 subjects had distinctly improved when given alseroxylon. Then, and this was the unexpected finding, these subjects maintained their improvement when placebo was substituted and thereafter exhibited a stepwise pattern of progressive improvement during the subsequent courses of drug and placebo.

The bar graphs in figure 2 illustrate this therapeutic pattern in 2 representative subjects. The light bars represent the percentage of days free of angina, the upper shaded areas are the "Good Days" (i.e., less angina than usual) and the lower black zones are the "Bad Days" (i.e., when the angina was unusually severe). The "Unchanged Days" (i.e., angina same as usual) contribute no differential information and have been omitted from these graphs. For this reason the individual bars usually total less than 100 per cent. The progressive improvement on alseroxylon is now quite apparent, as is its curious persistence during the following placebo periods. This phenomenon was masked in our initial analyses because we had combined the data of all alseroxylon courses and compared them with the pooled placebo results.

A final evaluation of the "Report Card" data is based on these individual "sequential" analyses (table 4). We now find that 14 subjects had improved with treatment. Three of the 14 regressed during placebo administration

TABLE 2.—*Comparison of Rauwiloid and Placebo by "Daily Report Card" Method, Analysis of Group Data*

Agent	No. of days reported	Percentage of days in which angina was reported as:			
		Unchanged (same)*	Increased (bad day)	Reduced (good day)	Absent (no pain)
Rauwiloid	2167	18	11	35	36
Placebo	2232	16	9	31	44

* Terms in parentheses used on "Daily Report Cards."

TABLE 3.—*Comparison of Rauwiloid and Placebo by "Daily Report Card" Method, Analysis of Individual Data*

Group	No. of patients	No. of days reported		Percentage of days in which angina was reported as:					
				Increased (bad day)*		Reduced (good day)		Absent (no pain)	
		R	Pl	R	Pl	R	Pl	R	Pl
1. Rauwiloid "Superior"	3	524	477	9	14	40	30	40	33
2. Placebo "Superior"	2	261	218	21	5	33	38	10	35
3. Rauwiloid and placebo equal	10	1382	1537	10	8	34	30	39	49

* Terms in parentheses used on "Daily Report Card."

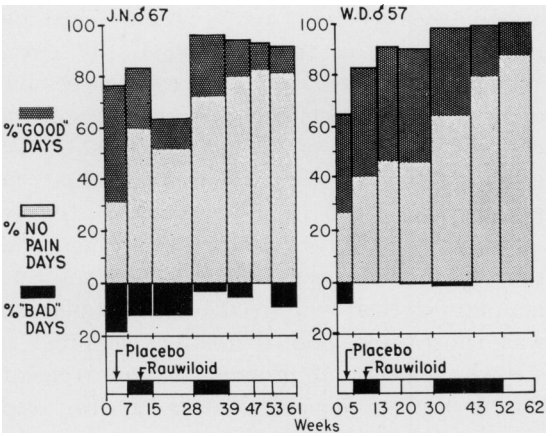

FIG. 2. Bar graphs demonstrating the progressive and sustained therapeutic response pattern after Rauwiloid.

TABLE 4.—*Evaluation on Basis of Sequential Use of Rauwiloid and Placebo*

Therapeutic response pattern	No. of subjects
Improved with Rauwiloid—worse with placebo	3
Improved with Rauwiloid—maintained with placebo	11
No benefit from either Rauwiloid or placebo	0
Worse with Rauwiloid	1
	15

TABLE 5.—*Comparison of Therapeutic Results as Determined by Clinical and "Daily Report Card" Methods*

Method of evaluation	Degree of improvement			Unchanged	Worse
	Marked	Moderate	Mild		
Clinical	9	3	2	1	0
"Daily Report Card"	3	6	5	0	1

but, as we have seen, the other 11 sustained their improvement on this agent. Only 1 subject experienced more angina with alseroxylon, and a possible factor here was the marked fall in blood pressure, presumably induced by the drug.

Table 5 compares the clinical and "Report Card" estimates of the degree to which each subject improved. These evaluations are quantitatively quite dissimilar. Though we can not be sure which is the more accurate, we suspect that the clinical opinions may have been unduly influenced by the general enthusiasm and optimism the subjects exhibited.

LABORATORY RESULTS

Seven subjects demonstrated noteworthy improvement in their serial laboratory tests during the course of this study. Four developed normal electrocardiograms but on occasion, during the intervening placebo periods, 2 of these again became abnormal. In 5 cases positive 2-step tests were converted to negative, with only 1 reverting on placebo. One subject achieved a normal ballistocardiogram while receiving alseroxylon and another exhibited marked though incomplete improvement; when placebo was administered the tracings of both regressed. These laboratory changes tended to follow an alternating pattern, becoming normal with alseroxylon, reverting with placebo, and becoming normal again with the active drug. The x-ray studies failed to reveal any notable changes in heart size or contour.

We do not mean to imply that these laboratory changes were the direct results of therapy. There is insufficient evidence to support such a conclusion. We are well aware of the role of time and spontaneous change in patients with coronary artery disease and wish to note only that these laboratory findings did occur and were coincidental with the administration of alseroxylon.

Figure 3 presents the pretreatment and posttreatment 2-step tests of a subject whose tracings became normal on drug and then reverted on 3 occasions with placebo.

There was little correlation between these laboratory fluctuations and clinical status. After initial improvement, these subjects continued to feel well, even when their tracings deteriorated on administration of placebo.

Alseroxylon reduced the arterial blood pressure and, more consistently, slowed the heart rate of all 15 subjects. The 7 subjects with improved tracings demonstrated an average decrease of 18 mm. Hg in mean arterial blood pressure and 13 beats/min. in heart rate.

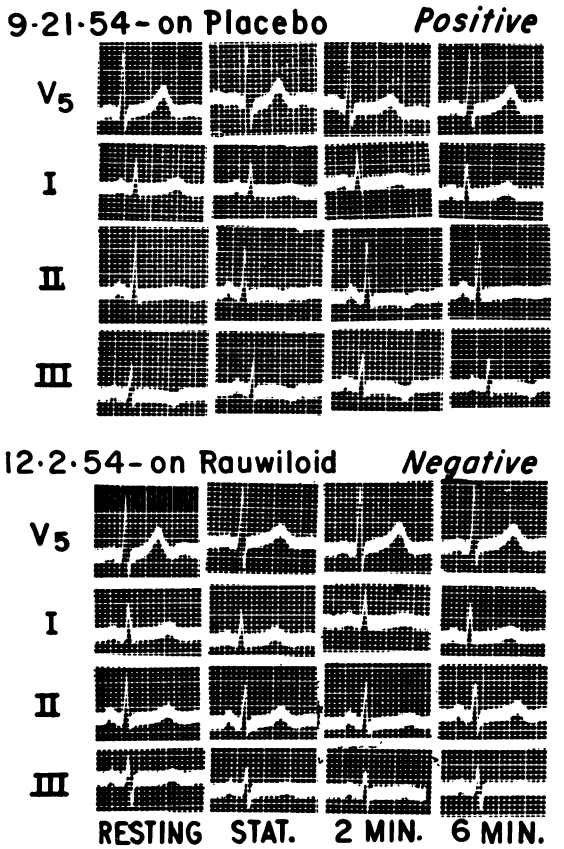

FIG. 3. Example of conversion of positive 2-step test to negative after Rauwiloid therapy.

For the 8 without laboratory changes, the results were almost identical—mean reductions of 16 mm. Hg and 12 beats/min., respectively. There was a similar lack of correlation between these changes in pressure and rate and the relative degree of improvement in anginal status. The possibility is not excluded, however, that these reductions were importantly related to the therapeutic results.

DISCUSSION

In certain respects, these results raise more questions than they answer. It is clear that, with a single exception, all subjects improved on treatment. None developed myocardial infarction or cardiac decompensation during the study. Their characteristic course was one of progressive reduction in frequency and severity of angina and steady increase in effort tolerance.

It does not seem likely that 14 of the 15 subjects spontaneously improved to this degree without relation to therapy. Nor do we believe that iatrogenic factors played a significant role here. The study plan that divided the subject's care among several physicians tended to prevent any close doctor-patient relationships. All subjects were aware of the experimental nature of the program. All physicians tried to maintain impersonal attitudes and deliberately "treated the disease, not the patient." These factors militate against any potent psychotherapeutic role by the members of the research team.

The nature of the prolonged therapeutic effect after alseroxylon is a puzzling feature. It persists well beyond the range of direct pharmacologic action that we had defined in our earlier studies.[1] Undoubtedly alseroxylon's so-called tranquilizing effect may have helped some subjects who were unduly apprehensive about their heart disease, with benefit to their anginal state. In addition, however, we believe it likely that a more efficient and apparently relatively self-sustaining physiologic balance between coronary supply and myocardial demand was pharmacologically established. Whether this effect was mediated directly through the drug's cardiovascular action or indirectly through the central nervous system is not clear. The recent studies[5, 6] by Brodie and his group on the relationship of serotonin and rauwolfia derivatives may shed further light on some of the basic mechanisms involved.

Despite the satisfying results achieved by these subjects, a note of therapeutic caution should be introduced. Rauwolfia preparations must not be employed indiscriminately. Untoward reactions do occur. Some individuals may experience a fall in arterial blood pressure of sufficient magnitude to increase dangerously their preexisting coronary insufficiency. This may well have been the case in our subject whose angina worsened on the drug. A similar sequence of events has been reported elsewhere.[7] Although this has occurred infrequently in our experience, we have nonetheless proceeded very cautiously with hypertensive and arteriosclerotic patients. We have not

observed such reactions in normotensive patients.[1]

Psychologic factors provide another potential problem. Many patients become emotionally disturbed on learning of their coronary artery disease. For those with states of anxiety and tension we have found alseroxylon most effective. Contrariwise, subjects with depressive features, with or without vascular disease, do not do well. A deepening of the depression tends to occur, and suicide becomes a real threat. We believe it mandatory, therefore, to evaluate the psychologic climate before prescribing rauwolfia preparations and to avoid their use when a significant depressive component is present.[1]

We have found that these and other undesirable effects are more likely to develop as the dosage level increases. We have tried various schedules and believe that 4 mg./day of alseroxylon will achieve a maximal therapeutic response about as rapidly as larger amounts. The minor side-effects at this level have been well tolerated by our patients and potentially serious reactions have been rare.

The very nature of the anginal syndrome and the spontaneous variations in its course have always made therapeutic trials most difficult to undertake and assess. Our evaluating technics have not overcome these inherent difficulties but we believe this combination of objective, subjective, and laboratory methods has minimized them. Certainly this multiple approach was, for us, superior to any single method of assessment.

Summary

Alseroxylon appeared to be an effective adjunct to the management of the subjects with angina pectoris in this study, although its mode of action remains unclear.

Summario in Interlingua

Dece-cinque subjectos con morbo de arteria coronari e angina de pectore recipeva in alternation cursos del fraction alseroxylona ab Rauwolfia serpentina e de un medication fictitie. Dece-quatro se meliorava sub le effectos del droga secundo independente evalutationes clinic e le datos del "Carta de Reportage Diurne." In septe casos, previemente anormal electrocardiogrammas, tests a duo passos, o ballistocardiogrammas deveniva normal. Alseroxylona pareva inducer un inusualmente prolongate effecto therapeutic que esseva revelate solmente per individualisate analyses "sequential" de omne curso del droga e del medication fictitie. Le natura del mechanismo involvite in le action del droga non es clar. Serie responsas hypotensive e acute reactiones depressive es infrequente al nivellos de dosage usate, sed illos non es absente.

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