Clinical Appraisal of a New Adrenergic Blocking Agent: Effect of Regitine on Digital Blood Flow in Normal Subjects and Patients with Peripheral Arterial Diseases

By CHARLES W. CLARKE, JR., M.D., DAVID RANDALL HAYS, JR., M.D., AND THEODORE B. VAN ITALLIE, M.D., WITH THE TECHNICAL ASSISTANCE OF IRENE M. THOMPSON, R.N.

By means of venous occlusion digital plethysmography, the authors have evaluated the peripheral vasodilating effect on normal and diseased arterioles of a new adrenergic blocking agent, Regitine, 2-[(m-Hydroxy-N-p-tolylanilino)-methyl]-2-imidazoline. Results have been compared with the results of similar studies using Priscoline and indirect body heating to produce vasodilation. The effect of parenteral Regitine on pulse and blood pressure has been noted as well as the clinical results obtained when this drug was used orally for the treatment of certain forms of peripheral vascular disease.

WITH the frequent appearance of drugs presumed to influence peripheral blood flow, it has become increasingly important to have an objective method of appraising such agents clinically. In a previous paper,1 two of the authors (T. B. V. I. and C. W. C.) described such a method, based upon studies of digital blood flow as measured by the venous occlusion plethysmograph.

The following report concerns the application of this method to the evaluation of a new adrenergic blocking agent known as Regitine (preparation C-7337). Chemically, this agent is 2-[(m-Hydroxy-N-p-tolylanilino)-methyl]-2-imidazoline, a congener of Priscoline and of Privine. Meier and his associates2,3 have contributed much of the pharmacologic and toxicologic data on Regitine. More recent studies have been published by Trapold, Warren and Woodbury.4 In man, Longino, Grimson, Chittum and Metcalf5 showed that the drug can be administered orally, intramuscularly and intravenously and that it reduces blood pressure, increases cardiac rate, blocks certain vascular reflexes, abolishes the temperature gradient of the extremities, and may produce such side effects as flushing, ptosis of the lids and nasal congestion. Longino and his associates, among others, also noted that in dogs, Regitine blocks the pressor effect of epinephrine. Plummer6 found that in animals a larger amount (three to five times) of Regitine was needed to reverse the pressor effect of norepinephrine than was required in the case of epinephrine. Walker7 studied the effect of Regitine on the carotid sinus reflex and on the peripheral vascular actions of epinephrine and norepinephrine and showed clearly that the drug is “adrenolytic” in much smaller doses than are needed to produce a “sympatholytic” response.

As might be expected, clinical interest in Regitine has centered on its use in various disorders of the peripheral circulation and in hypertension, including that variety of hypertension caused by chromaffin tumors. This paper reports our experience with this drug, used in the treatment of peripheral arterial insufficiency.

In 1949, Grimson, Chittum and Longino8 reported that Regitine might be useful in the treatment of certain disturbances of the peripheral circulation. Using a previously described
technic,\textsuperscript{1} we have carried out studies in which the effect of Regitine on the digital blood flow of normal subjects and patients with peripheral arterial insufficiency was measured by means of venous occlusion plethysmography. The results were then compared with the results of similar plethysmographic studies done on the same normal subjects and patients (with occasional exceptions to be noted) in which Priscoline and later indirect body heating were used to produce peripheral vasodilatation. Indirect body heating is considered by many investigators to be a convenient and yet effective method of relaxing central vasomotor tone. The resulting increase in peripheral blood flow is said to be comparable to that obtained by paravertebral block and spinal anesthesia.\textsuperscript{9} The highest value for peripheral blood flow measured after body heating has been referred to as the "maximal flow" for that procedure, and is a useful standard of reference with which the effects of other vasodilating agents can be compared.

A concurrent study was conducted in which orally administered Regitine was used in the long-term therapy of ambulatory clinic patients with peripheral arterial insufficiency.

Plethysmographic Studies

1. Subjects

Blood flow and pulse volume studies were performed on five normal subjects and 19 patients with various types of peripheral arterial insufficiency. Among the 19 patients, there were 29 diseased extremities available for examination. The group of normal subjects was composed of five nurses, all in excellent health, with an average age of 23 years. The group of patients with arterial disease was further subdivided into three categories: (1) patients who displayed predominantly vasospastic disease of the peripheral arteries; (2) patients who had primarily organic peripheral vascular disease; and (3) patients who previously had been subjected to lumbar sympathectomy because of peripheral vascular disease. These groups were established in accordance with the response of the patient to indirect body heating.\textsuperscript{1} The patients with vasospastic arterial disorders were four in number, three males and one female, the average age of this group being 35 years. The group exhibiting organic peripheral arterial disease averaged 57 years of age, and was composed of 11 males and two females. The five patients in the post sympathectomy group were all males, and their ages averaged 42 years.

2. Procedure

All subjects visited the Peripheral Vascular Laboratory on at least one occasion, and most of the subjects were examined on three occasions, each separated by two or more days. Examinees were not allowed to smoke, use coffee, tea or liquor, or any drug during the 12 hours preceding examination. Upon arrival at the laboratory, the procedure described in detail in an earlier publication\textsuperscript{1} was followed. Briefly, this consisted of placing the patient in bed, allowing a rest period and performing oscillographic and skin temperature determinations in the locations indicated. Plethysmograph cups were then applied to a toe of each foot or, when only one leg was diseased, to a digit of the involved extremity and the left index finger. In the case of the normal subjects, the left great toe was always used together with the left index finger. The material used to seal the cups to the digits was Kalk-Kord,* a nondrying caulking compound.\textsuperscript{10}

After rest periods varying from 45 to 90 minutes, the blood pressure and pulse rate were determined and resting blood flow and pulse volume determinations were done. A venous occlusion plethysmograph of the transmission type, constructed on the basis of a principle described by Goetz\textsuperscript{41} in 1940 was used. After reproducible resting values for digital circulation had been determined, each subject received an intramuscular injection of Regitine. Persons with peripheral vascular disease received an average dose of 0.75 mg. per kilogram of body weight. Normal subjects received an average dose of 0.6 mg. per kilogram.\textsuperscript{†} The site of injection was uniformly the left deltoid muscle. Plethysmographic tracings were taken at intervals of 5, 10, 20 and 30 minutes following administration of the drug. Blood pressure and pulse rate were measured at the same times, and the patient was observed for untoward effects. Following the last plethysmographic, blood pressure and pulse rate determinations, oscillographic and skin temperature readings again were taken.

With a few exceptions, all the patients returned to the laboratory on two later occasions for comparative plethysmographic studies in which Priscoline and body heating were separately employed for vasodilatation. The procedure followed was similar to the one used for Regitine, except that the dose of Priscoline was always 50 mg. intramuscularly (thus the average patient received between 0.7 and 0.8 mg. per kilogram). When indirect body heating was used, the patient, after the usual period of rest, was asked to submerge his right arm to a few inches above the elbow in water kept at 40 to 45 C. The

\textsuperscript{*} Manufactured by Pressite Engineering Company, 3000 Chouteau Avenue, St. Louis, Mo.

\textsuperscript{†} This smaller dose was instituted after the earlier dose produced severe side effects in two normal subjects.
subject was also covered by blankets to minimize loss of body heat. Plethysmographic studies were done 10, 20 and 30 minutes after the start of body heating.

Results of the plethysmographic studies were corrected\(^{2-4}\) for variations in digital volume and are expressed in cubic centimeters of pulse volume per 15 cc. of digital tissue, and cubic centimeters of blood flow per minute per 100 cc. of tissue. The essential data obtained by means of these procedures are shown in table 1.*

It will be noted that considerable variation normally occurs in the resting blood flow and pulse volume of normal individuals and patients subjected to repeated plethysmographic study. The averages listed below for the group of normal subjects on three separate occasions are illustrative of this fact. It will be seen, however, that the existence of such variations does not in practice prevent the disclosure either of the relative vasodilating ability of the agents under investigation or of the ability of the vessels of the various groups of subjects studied to dilate in response to the agents.

3. Results

Prior to the administration of Regitine, the average resting digital blood flow of five normal subjects was found to be 9 ± 8.3 cc. (per minute per 100 cc. tissue). The average pulse volume at this time was 0.0058 ± 0.0034 cc. After administration of Regitine, the average maximal blood flow was 27 ± 20.2 cc. and the average maximal pulse volume was 0.0150 ± 0.0049 cc.

Prior to indirect body heating, the average resting blood flow among normal persons was 29 ± 23.9 cc. and the average pulse volume was 0.0106 ± 0.0019 cc. After body heating, the average maximal blood flow among normal subjects was 79 ± 31 cc. and the average pulse volume was 0.0204 ± 0.0035 cc.

Prior to the administration of Priscoline, the average resting blood flow in the group of normal subjects was 11.8 ± 10.5 cc. and the average pulse volume was 0.0058 ± 0.0033 cc. After Priscoline, the average blood flow reached a maximal value of 58.8 ± 19.8 cc. and the average pulse volume increased to 0.0198 ± 0.0016 cc.

Thus, in the normal subjects Regitine produced a threefold increase in blood flow, indirect body heating produced approximately a threefold increase and Priscoline was followed by a fivefold increase. The increases in pulse volume were approximately threefold after Regitine, twofold after body heating, and threefold after Priscoline.

In the patients with vasospastic arterial disorders, the average resting blood flow of the four patients examined prior to administration of Regitine was 2.8 ± 2.9 cc. (per minute per 100 cc. tissue). The average pulse volume at this time was 0.0043 ± 0.0038 cc. After the administration of Regitine, the average blood flow increased to 14 ± 10.2 cc. and the average pulse volume increased to 0.0082 ± 0.0035 cc.

Before indirect heating, these same patients with vasospastic disorders had resting blood flow and pulse volume values averaging 5.3 ± 5.2 cc. and 0.0058 ± 0.0041 cc. respectively. After heating, these values increased to 37 ± 18.7 cc. and 0.0166 ± 0.0070 cc. respectively. Before Priscoline, the group with vasospastic arterial disorders showed an average resting blood flow of 2 ± 0.7 cc. and resting pulse volume of 0.0022 ± 0.0016 cc. After administration of Priscoline intramuscularly, the average blood flow reached a maximal value of 20 ± 6.9 cc. and the average pulse volume reached 0.0138 ± 0.0030 cc.

Thus, in the group of patients with spastic peripheral vascular diseases, Regitine produced a fivefold increase in digital blood flow, indirect body heating produced more than a sevenfold increase and Priscoline was followed by approximately a tenfold increase. The average increases in pulse volume in these patients produced by each agent were respectively twofold, threefold and sixfold.

The thirteen patients with organic occlusive peripheral vascular disease had an average resting blood flow of 11.4 ± 10.5 cc. (per minute per 100 cc. tissue) prior to administration of Regitine. Their average pulse volume at rest was 0.0031 ± 0.0020 cc. After Regitine, the average maximal blood flow increased to 21.7 ± 15.3 cc. and the average pulse volume increased to 0.0046 ± 0.0041 cc.

Because of subsequent amputations or deaths, it was possible to study only 9 of the 13 patients with organic peripheral vascular
disease by means of indirect body heating and Priscoline. The average resting blood flow for these nine prior to body heating was 14 ± 12.2 cc. (per minute per 100 cc. tissue). The resting pulse volume was 0.0024 ± 0.0030 cc. After body heating, the average maximal blood flow was 24 ± 12.4 cc. and the pulse volume averaged 0.0038 ± 0.0041 cc.

Prior to injection of Priscoline, the average resting blood flow in the organic peripheral vascular disease group was 10.6 ± 5.6 cc. Pulse volume at this time was 0.0020 ± 0.0019 cc. After administration of Priscoline, the maximal blood flow increased to an average of 24 ± 12.1 cc. and pulse volume increased to 0.0054 ± 0.0049 cc. Therefore, in the group of patients with organic peripheral vascular disease, Regitine produced an increase in digital blood flow which was less than twofold. Indirect body heating also increased blood flow less than twofold, and Priscoline brought about a slightly more than twofold increase. Average increases in pulse volume resulting from the administration of these three agents were also less than twofold in the case of Regitine and body heating and somewhat more than twofold following Priscoline. A graphic comparison of the effects of Regitine, Priscoline and indirect body heating on digital blood flow and pulse volume in normal subjects and patients with vasospastic or organic peripheral vascular disease is shown in figure 1.

In an effort to determine the effect of Regitine upon the sympathectomized limb, five patients who had been subjected to lumbar sympathectomy were studied. In these subjects the average resting digital blood flow prior to administration of Regitine was 15.7 ± 17.6 cc. (per minute per 100 cc. tissue). Pulse volume at this time averaged 0.0028 ± 0.0019 cc. After intramuscular Regitine, the average blood flow decreased to 14 ± 12.6 cc. and the average pulse volume increased to 0.0045 ± 0.0017 cc. Decreases in blood flow in sympathectomized limbs following the administration of vasodilating agents affecting the entire circulation probably occur as a result of dilatation of the vascular bed elsewhere in the body with subsequent shunting of blood away from the unresponsive limb. This finding has obvious therapeutic corollaries.

**Effect of Regitine on Pulse and Blood Pressure**

Regitine has been found to be one of the few adrenergic blocking substances with essentially no cholinergic effect.\(^5\) It differs markedly from Priscoline in this respect. Priscoline is known to produce quite unpredictable changes in pulse rate and blood pressure; moderate decreases to marked increases in each may occur. Regitine, on the other hand, appears to follow a rather definite pattern in its overall effect on cardiovascular dynamics. Generally, it produces a fall in blood pressure and a rise in pulse rate. Our findings were largely in conformity with this pattern, but exceptions in certain individual cases were noted and are described below.
Blood pressures of the five normal subjects averaged 117/72, at rest. When the maximal changes in each subject after the administration of Regitine were averaged, a figure of 109/61 was obtained. The maximal fall (of four cases) was from 130/80 to 108/64 and the maximal increase (one case) was from 114/60 to 130/60.

A similar hypotensive response occurred in the patients with peripheral vascular diseases. The resting blood pressures of all 19 patients averaged 142/89. Following intramuscular Regitine, the blood pressure in persons with peripheral vascular disease fell to an average of 135/84. In this group, seven patients had rises in blood pressure after Regitine; the remainder had varying degrees of fall in blood pressure. The maximal fall was from 164/104 to 128/90, and the greatest rise was from 126/60 to 170/90.

The average resting pulse rate among the five normal subjects was 76 beats per minute. All normal subjects exhibited a rise in pulse rate after intramuscular Regitine. When the greatest increment in each case was used, the average pulse rate after the drug was found to be 86. The greatest individual increase was from 68 to 84.

Among patients with peripheral vascular disease, the average resting pulse rate was 77. Again, in terms of the greatest change after Regitine in each case, the average pulse rate after the drug proved to be 91. Three patients showed no change in cardiac rate as a result of Regitine. The remaining 16 showed varying increases; the largest increase was from 76 to 120 and the least from 70 to 72.

In the 24 persons studied, the following side effects were observed within 30 minutes after injection of the drug: nasal congestion in 14 patients, conjunctival injection in 12, tachycardia in 10, flushing in 8, diaphoresis, piloerection and chills in 3 each, complaints of precordial constriction and anxiety in 2, and nausea in 1 case. Ptosis of the lids was noted rarely. An unexpected side effect observed in a majority of subjects was local pain and tenderness at the site of injection. This sometimes lasted 7 to 10 days, and was undoubtedly due to local irritation of the tissues by the injected substance.

**Clinical Observations on the Outpatient Treatment of Peripheral Vascular Disease with Oral Regitine**

Many of the patients studied plethysmographically were given a trial on oral Regitine and followed in the Peripheral Vascular Clinic. The results of this study are of interest, but cannot be regarded as conclusive since use of adequate controls was not possible.

1. Procedure

Of the 18 patients studied, 6 were females and 12 were males. Their ages ranged from 19 to 74 and averaged 56 years. Fifteen of the patients suffered from organic peripheral vascular disease and three had some form of vasospastic disorder of the peripheral arteries. The specific diagnosis and a summary of relevant clinical information in each case are in table 2.

History and physical examination of these subjects revealed that of the 18, 11 suffered from intermittent claudication, 10 had night cramps of the legs and 16 reported less specific pains in the lower extremities, which were believed by the examiners to be due to arterial insufficiency. Thirteen complained of chronically cold extremities, seven had discoloration of the involved limbs, five displayed trophic changes of the skin and nails or had outright ulceration, and 15 had absent pulsations of the popliteal, dorsalis pedis or posterior tibial arteries, or all three. Seventeen of these patients had abnormally low oscillometric readings in the involved extremities.

During the period of therapy with Regitine, all other drugs with vasodilating properties were discontinued. However, some of these patients were allowed to continue leg exercises and to use heat and massage as part of a previously established therapeutic program.

Because of sensitivity to Priscoline, three persons were started on 60 mg. of Regitine three times per day. Most of the others received 60 mg. five times per day. One patient tolerated 120 mg. three times per day and another was given 120 mg. five times per day. The average dose was approximately 300 mg. per day. Duration of treatment varied from one day to nine months. Average duration of treatment was 44 days.

2. Results

During therapy with Regitine, 6 of the 11 patients with intermittent claudication reported improvement, 7 of the 10 patients...
<table>
<thead>
<tr>
<th>Name, Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Aver. Dose</th>
<th>Dur. Treat.</th>
<th>Clinical findings before Reg.</th>
<th>Clinical findings after Reg.</th>
<th>Side Effects</th>
<th>Comment</th>
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<td></td>
<td></td>
<td></td>
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<td>Classification</td>
<td>Pain</td>
<td>Cold</td>
<td>Poor Color</td>
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<td>62</td>
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<td>60 mg., 5 i.d.</td>
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<td>2 weeks</td>
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<td>60 mg., 5 i.d.</td>
<td>2 months</td>
<td>+ + + + 0</td>
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<tr>
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<td>120 mg., 5 i.d.</td>
<td>9 months</td>
<td>+ + + + 0</td>
<td>0</td>
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<td>60 mg., 5 i.d.</td>
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<td>60 mg., 5 i.d.</td>
<td>1 month</td>
<td>0 0 + 0 0</td>
<td>0</td>
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<td>0</td>
</tr>
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</table>

* + = Present; 0 = Absent; * = Tachycardia; † = Extrasystoles; F = Palpititation; ‡ = Anorexia; § = Fainting.
with cramps had varying degrees of relief, and 9 of the 16 subjects with poorly localized pain experienced improvement. However, only 3 of 13 patients with cold extremities described relief of this symptom, 1 of the 7 patients with discoloration showed improvement, 1 of the 5 persons with trophic changes obtained bene-
fit, and 1 of the 15 patients with absent peripheral pulses developed a palpable dorsalis pedis. Oscillometric studies done at intervals during treatment showed increases in only one case (E. W.).

Regitine by mouth produced toxic side effects in 11 of the 18 patients. Five patients developed nausea and/or vomiting, two had chills, four complained of dizziness or faint-
ness, four had tachycardia and two developed anorexia. Precordial pain, diaphoresis and extra systoles occurred once, each in a different patient. By far the most frequent and most troublesome toxic effect of oral Regitine was diarrhea. Ten persons developed this symptom and diarrhea was a factor in forcing discon-
tinuance of the drug in five instances. Several persons were given tincture of belladonna by mouth in an effort to block this effect of Regi-
tine; however, only one improved and this person only temporarily. This finding supports the contention that Regitine is without choli-
nergic effect. The diarrhea probably occurred as a result of direct irritation of the intestinal mucosa.

The size of the dose seemed to have little to do with the occurrence of toxic side effects. This was particularly true with respect to the diarrhea. Thus, one patient developed loose stools after the first few doses of the drug; another person received 120 mg. five times per day for over nine months and showed no toxic effect whatever.

Of the 18 patients given oral Regitine, 9 reported no benefit from the drug and of these, 5 had diarrhea. Of the remaining nine who did benefit, one finally had to stop the drug because of severe diarrhea, one stopped because of numerous extrasystoles and one because of attacks of syncope. Therefore, only 6 of the original 18 patients benefited from oral Regi-
tine and at the same time had either no toxic effects (four) or else side effects of only mini-
mal severity (two).

**Comment**

Administered in sufficiently large amounts, Regitine is a potent vasodilating agent for man. Compared with indirect body heating, intramuscular Regitine produced roughly an equal increase over resting values of digital blood flow in normal persons, as shown by ve-

uous occlusion plethysmography. However, maximal flow after Regitine was considerably less than maximal flow after body heating and somewhat less than maximal flow after Priscole
de. In persons with vasospastic peripheral vascular disorders, Regitine increased digital blood flow somewhat less than did body heat-
ing. In persons with organic peripheral vascular diseases, the two agents had approximately an equal effect on resting digital blood flow.

Compared with Priscoline, Regitine in comparable doses was found to cause somewhat smaller increases in digital blood flow in normal persons and patients with vasospastic or organic peripheral vascular disease. Thus, intramuscular Regitine appears to be some-
what inferior to Priscoline in its vasodilating effects.

The effect of intramuscular Regitine on cardiovascular dynamics is somewhat unpre-
dictable in individual cases. However, this adrenergic blocking agent in the doses used has a hypotensive effect on most normal sub-
jects and patients with peripheral vascular disease. Pulse rates are moderately accelerated after administration of the drug in these sub-
jects.

Toxicologically, Regitine is similar to many other adrenergic blocking agents when it is given parenterally. Rather severe side effects were seen in two cases, one a normal subject and the other a patient. Each had such a marked degree of tachycardia, flushing and anxiety that further use of the drug in these subjects was not feasible.

By comparison with the generally favorable results obtained with parenteral Regitine, the efficacy of the drug when used orally for the long-term treatment of peripheral vascular disease was a disappointment. As mentioned previously, only 6 of the original 18 patients given the drug were helped and at the same time were able to tolerate the preparation.
CLINICAL APPRAISAL OF REGITINE

SUMMARY

Studies on the clinical use of a new adrenergic blocking agent known as Regitine or preparation 7337 and chemically as 2-[(m-Hydroxy - N - p - tolanilinilino) - methyl] - 2-imidazoline are described. The effect of this drug on digital blood flow was compared with the effect of indirect body heating and of Priscoline by means of venous occlusion digital plethysmography. The effect of Regitine on blood pressure and pulse rate was studied. The long term oral use of this drug in patients with peripheral vascular disease also was studied. The data obtained support the following conclusions:

1. Intramuscular Regitine is somewhat inferior to Priscoline in its ability to increase digital blood flow over resting values in normal subjects and patients with peripheral vascular diseases.

2. Intramuscular Regitine provokes side effects such as nasal and conjunctival congestion, tachycardia, and flushing. It also has a local irritative effect at the site of injection. Generally, administration of the drug is followed by a decrease in blood pressure and acceleration of the pulse rate.

3. Administered by mouth to persons with peripheral vascular diseases, Regitine is found to be of benefit in only a small percentage of cases. A variety of side effects occur, the most severe and common of which is diarrhea.

4. The importance of having an objective method for appraising the effect of new drugs on peripheral blood flow in man is stressed.

REFERENCES


SUMARIO ESPAÑOL

Por medio de pletismografía de oclusión digital venosa, los autores han evaluado el efecto vasodilatador periférico en arterias normales y patológicas de un nuevo agente bloqueador adrenérgico, Regitine, 2-[(m-Hydroxy - N - p - tolanilinilino) - methyl]-2-imidazoline. Los resultados han sido comparados con los resultados de similares estudios usando Priscolina y calor indirecto al cuerpo para producir vasodilatación. El efecto del Regitine parentérico en el pulso y presión arterial fue observado así como los resultados clínicos obtenidos cuando la droga se usó oralmente para el tratamiento de ciertas formas de enfermedad periférica vascular.
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