INTRA-ARTERIAL HISTAMINE IN TREATMENT OF CLAUDICATION AND REST PAIN

BY

W. ARTHUR MACKEY, M.B., F.R.C.Sed., F.R.F.P.S.

Assistant to the Professor of Surgery, University of Glasgow

When the main vessel of a limb is obliterated by thrombosis the blood supply to points more distal depends upon the adequacy of the collateral network. In some cases this is such that the existence of thrombosis may remain unsuspected; in others, signs and symptoms of ischaemia are produced.

Insufficiency of the supply of arterial blood to the capillary network of the skin carries with it the risk of gangrene. Inadequacy of arterial input to the capillary network of the muscles results in claudication. It is useful to separate these two aspects of peripheral arterial insufficiency, since the arterioles feeding the capillary beds concerned are under systems of control which differ quantitatively. The arterioles of the skin are much more completely under control of the sympathetic nervous system, while those of the muscles normally respond mainly to the metabolites produced by muscular action.

The general aim of treatment is to aid and augment the development of the collaterals, since normally the disease of the main vessels is so final and permanent that no recanalization is to be expected. The principle utilized is to produce vasodilatation, either intermittent or permanent.

Most of the methods in current use, however, are either insufficiently potent or insufficiently specific in their point of application (Fig. 1). The latter demerit may constitute

THEORETICAL EFFICACY OF VASODILATOR THERAPIES

AGENT	SYMPATHOLYTIC DRUGS	SYMPHECTOMY	I.A.H
DILATOR EFFECT	ESSENTIALLY CUTANEOUS & ACRAL — GENERAL —	CUTANEOUS & ACRAL — LOCALISED —	LOCALISED BUT CUT- ANEOUS & MUSCULAR
EFFECT ON B.P.	LOWERED	NO EFFECT	NIL TO SLIGHT UNLESS DOSAGE RATE EXCESSIVE

FIG. 1.—Schematic representation of the incidence of vasodilator effect.

a danger. This is particularly obvious in methods of treatment involving the use of drugs which produce general vasodilatation. Such vasodilatation must necessarily occur predominantly in the least diseased portions of the arterial tree. It must, in addition, be accompanied by a lowering of arterial pressure. There is a consequent possibility that the net result may be to deviate blood from the areas most in need. I have observed femoral thrombosis to occur as an immediate sequel of the intravenous injection of a potent vasodilator drug. More local vasodilata-

tion is produced by an appropriate sympathectomy which releases the arterioles from the control of the vasomotor centre. In the case of the lower limb this operation may therefore result in significant improvement in the cutaneous circulation, especially of the feet. It is found to relieve "rest pain," and it unquestionably diminishes the danger of gangrene in cases not excessively advanced. It is less common, however, for reasons noted above, to find a striking improvement in claudication follow sympathectomy.

The ideal method of treatment will be one acting, in the main, upon the small blood vessels of the most affected limb only, and without any particular bias in favour of either the superficial or the deep vessels. The method described by Mufson (1948), in which a dilute solution of histamine acid phosphate is introduced into the lumen of the femoral artery, would seem theoretically to fulfil these criteria. During the past year the method has been used in a series of 14 cases of arteriosclerosis obliterans with arterial insufficiency of the lower limbs. Worthwhile improvement has been achieved in nine, and five have remained unimproved. So far as can be determined, none has been made worse. The results are summarized in Tables I and II, and brief protocols are given.

TABLE I.—Details of Improved Cases

No.	Age	Yards Walked		Rest Pain	
		Before	After	Before	After
1	52	200	400	—	—
2	62	200	500	—	—
3	53	70	200	—	—
4	53	200	No limit	+	—
5	58	100	2 miles	+	—
6	56	100	250	—	—
7	51	200	800	+	—
8	56	80	2 miles	—	—
9	60	200	400	—	—

TABLE II.—Results (14 Cases)

9 cases	..	Average age, 55.7 years	..	Improved
5 "	..	" " 60.2 "	..	Not improved

Technique

Two mg. of histamine acid phosphate is dissolved in 500 ml. of normal saline, which is delivered under pressure into the femoral artery at the groin after percutaneous puncture (Fig. 2). Administration customarily takes 30 to 45 minutes. This dose of histamine introduced direct into the general circulation would have profound systemic effects, but administered intra-arterially it appears to be bound and utilized to a very large extent in the tissues of the limb, and general effects are slight. An ordinary intravenous apparatus is used and air pressure is applied, controlled by means of a sphygmomanometer at a level between the diastolic and systolic pressures of the recipient. Delivery is through a Kaufman syringe and a serum needle of No. 4 gauge. Records are made of blood pressure, pulse rate, skin temperature, and the magnitude of arterial pulsation at calf level. In addition, general effects such as facial flushing are noted. The present cases have been treated in a routine fashion with 10 intra-arterial infusions spaced at intervals of one week.

Observed Effects

Within seconds of the start of the infusion a bright flushing appears in the upper thigh, generally in a patchy fashion, and spreads distally to a variable extent. In some cases the flush is followed by the formation of a thick histamine weal. Commonly, flushing extends no further

FIG. 2.—Method of infusion

than the knee, but as the series of injections progresses at weekly intervals there is a tendency for the flush to extend further down the leg, and in some cases to reach the toes. Skin temperatures run roughly parallel with the flushing. The flushed area shows a rise in skin temperature. In the more successful cases there is a rise in the temperature of the toes. The records of the arterial pulsations at calf level, made with the Boullite oscillometer, run to a curious and interesting pattern. During the infusion there is almost invariably a diminution in the magnitude of oscillation. Immediately following the termination of the infusion there is often a very striking increase in these pulsations. This is to a large extent short-lived, but a small proportion of the increase may be carried forward to the following week. Some patients claim an improvement in walking capacity quite early during the series of injections, and this tends to increase. In others, benefit is delayed and less in degree. In some there is no change.

Discussion

The rationale of the method is that the smaller blood vessels exposed to the solution of histamine undergo full dilatation and that the arterial blood is driven in more abundantly and under greater pressure. If these premises be accepted it is reasonable to expect that repeated treatments will facilitate the dilatation and hypertrophy of the smaller arteries and possibly capillaries on which depends the development of an adequate collateral circulation. This is, of course, the principle underlying other methods of treatment, such as pavaex, intermittent venous occlusion, Buerger's exercises, and sympathectomy.

That histamine is effective in achieving this objective in a proportion of cases is indicated by the progressive

clinical and objective improvement which has been recorded.

The curious behaviour of the oscillometric readings during the administration is difficult to explain. A number of factors may be at work, such as lowering of the systolic blood pressure, damping out of the troughs of the diastolic portion of the pulse wave by entry of the injection fluid principally during this phase, effects upon the blood vessels of the temperature of the fluid injected, and alteration of the viscosity of the blood in the limb by admixture of saline. Since in a "successful" case the injection is commonly associated with rise in temperature of the toes and improvement in their colour, it seems unlikely that the histamine solution produces, in fact, vasoconstriction followed by full vasodilatation. Further controlled investigation is obviously required, and in particular plethysmographic study.

It is of interest that two of the cases (Case 1 and Case 6) had been unimproved by operation (lumbar ganglionectomy and adrenalectomy). It must be pointed out also that, in general, the improvement achieved has been essentially subjective and clinical. In few cases has there been a material improvement in the oscillometric readings. In some there has been evidence of progress of degeneration in other parts of the arterial tree.

Improved Cases

Case 1

A dairyman aged 52, first seen on November 10, 1947, complaining of claudication of six years' duration, limiting walking to 200 yards (180 metres) and compelling him to give up work six months previously.

Examination.—A big, well-built man in fair general condition. B.P. 135/80. There was patchy calcification of arteries.

Treatment.—Left lumbar ganglionectomy and excision of left adrenal gland on November 26, 1947. Following this operation his condition improved only a little and for a short time, and by August 25, 1949, he was rather desperate. He was able to walk only 50 yards (46 metres). He had a moderately severe degree of vascular insufficiency, affecting both legs. Oscillometer reading: right, 1.5; left, 1.5. A course of intra-arterial histamine (I.A.H.) drips, 2 mg. of histamine acid phosphate (H.A.P.) in 500 ml. normal saline—10 infusions given into each femoral artery (20 in all)—between August 26, 1949, and January 24, 1950.

Result.—Fairly marked clinical improvement was produced. When seen on March 24, 1950, the patient was enthusiastic regarding the improvement in his walking. He was then able to walk for 400 yards (360 metres). Oscillometer reading: left, 1.5; right, 2.0. It was noted at this time that there was convincing evidence of fairly severe progressive myocardial damage.

Case 2

A clerk aged 62, first seen October 14, 1948. Had had tiredness in both legs for one year. Recent disabling claudication, right, at 400 yards.

Examination.—A well-preserved man, rather florid. B.P. 185/85. Electrocardiogram showed myocardial damage. Pulses present at both ankles. Oscillometric reading: right, 5.0; left, 5.0. Arteriogram: almost normal vascular pattern in right leg as far as ankle. Some tiny patches of atheroma in the tibial vessels, especially at points of branching.

Treatment.—On the findings it was felt that the symptoms complained of could not be due to the modest degree of vascular damage present, and so a course of physiotherapy was arranged, from which no benefit was derived. Indeed, by March 26, 1949, the symptoms had increased and a thrombotic complication had obviously occurred in the left leg. Oscillometric reading: right, 5.0; left, 1.5. Claudication now severe on the left side at 200 yards. May 26: disability increasing;

poor result from vasodilator tests. A course of I.A.H. infusions, into the left leg, was given between May 31 and August 5.

Result.—There was a temporary improvement in the left oscillometric reading, which by August 5 had risen to 5.0. There was marked improvement in his capacity for walking, but about this time he began to suffer from claudication on the right side, and it was found that the oscillometric reading on this side had now fallen to 1.5. By this time, also, the myocardial condition was giving cause for increasing anxiety. On March 16, 1950, he still had pain in the right calf, and walked 500 yards slowly. Oscillometric reading: left, 3.0; right, 1.5. He was eager to have a course of I.A.H. infusions in the right side. The final result showed improvement in the status of the leg under treatment. Arterial degeneration was progressing elsewhere.

Case 3

A shipyard rigger aged 53 first seen June 2, 1949. Principal complaint, severe claudication in both calves, worse on left, of one year's duration, limiting walking to 60–70 yards (55–65 metres); also palpitation, headache, and giddiness.

Examination.—A very big, heavy, muscular, plethoric man. B.P. 190/100. Condition of feet satisfactory, but pulses not felt. Oscillometric reading: right, 4.5; left, 0.5.

Treatment.—A course of I.A.H. infusions was given between June 5 and September 17, 1949, into the left femoral artery.

Result.—Towards the end of the course these infusions were associated with a significant improvement in oscillometric readings—from 0.5 to 2.5—and, on occasion, with flushing extending as far as the foot. When last seen on November 10 the patient was emphatic in claiming both local and general benefit from the treatment. He was at work and able to walk 200 yards at a moderate pace. Oscillometric reading: right, 5.0; left, 1.5. B.P. was now 165/80. He was no longer having "blackouts," and described himself as "feeling better in every way."

Case 4

A self-employed engineer aged 53, first seen March 31, 1949. Claudication at 200 yards left calf for three months. Left foot cold; marked rest pain at night.

Examination.—A well-preserved man. B.P. 125/80. Marked vascular insufficiency, left leg. Foot pallid—wellnigh cadaveric in appearance. Oscillometric reading at calf level: right, 10.0; left, 0.25. Arteriography: obliteration of the left popliteal artery over a distance of 2 in. (5 cm.), with excellent collaterals and distal refill.

Treatment.—A course of I.A.H. infusions was given between April 5 and June 11, 1949.

Result.—The response to the drips was variable, but in general it was characterized by flushing and warming of the foot, the temperature rising as much as 3.5° C., and the oscillometric reading rising from 0.25 to 2.0. The final result must be classified as good. (1) The rest pain has disappeared. (2) The colour of the toes of the left foot and calf is good. The oscillometric reading is virtually unchanged; right, 8.0; left, 0.25. He is doing a normal day's work. If he walks slowly he can go on indefinitely. He is emphatic regarding the benefit derived from the injections.

Case 5

A tram driver aged 53, first seen June 2, 1949. Had had claudication left calf of three years' duration; now coming on at 100 yards (90 metres). Rest pain severe in left foot.

Examination.—A heavy muscular man, hypertensive. B.P. 260/115. Severe vascular insufficiency, left leg. Oscillometric reading at calf level: right, 5.0; left, 0.25. Arteriogram: obliteration of left superficial femoral.

Treatment.—A course of I.A.H. infusions, into the left femoral artery, was given between June 4 and September 8, 1949.

Result.—At no time was there a very striking objective result from the infusions. Marked vascular reaction occurred in the thigh, but rarely and to minimal extent did this reach the lower leg and toes; the oscillometric reading also remained

unchanged. Despite this, the patient claims some improvement in that he is able to walk about a mile (1.6 km.), and sometimes more, without pain, and rest pain is markedly diminished. On February 18, 1950, he wrote: "Keeping very well; constantly at work. Walked about two miles (3.2 km.) a few days ago without having to stop. Very little pain in foot at night." The result may be assessed as "serviceable benefit."

Case 6

A railway goods yard foreman aged 56, first seen February 17, 1949. Claudication right calf at 100 yards, of three months' duration, associated with numbness and coldness of right foot.

Examination.—A fairly well preserved man. B.P., 180/90. Severe vascular insufficiency right leg. Arteriogram: marked atheroma of femoral artery. Principal damage just distal to bifurcation of popliteal, where the main trunk breaks up into three small inadequate channels. Seen again March 7. During last 10 days or so has developed trouble with the left leg, which is now, if anything, more disabled than the right, claudicating at 80 yards (73 metres), with pain both in calf and in anterior tibial muscles. Oscillometric reading: left, 0.5; right, 1.0.

Treatment.—Ganglionectomy and adrenalectomy, left, on May 2, 1949. The left foot was warm on June 9. Oscillometric reading: left, 1.5; right 0.5. Despite objective evidence of increased arterial input on left side, functional capacity unchanged. A course of I.A.H. infusions—10 in each leg (20 in all)—was given between June 26 and October 9, 1949. These were generally associated with flushing and warming of the toes and increased oscillometric readings.

Result.—Decisive improvement in both legs. Last seen December 12: at work and walking 250 yards (230 metres) without pain; walking three to four miles (4.8 to 6.4 km.) per shift in short stretches at his work. Oscillometric reading: left, 1.0; right, 0.75. Left foot hot and dry; right cool. The result may be assessed as a serviceable improvement in a case unmodified by ganglionectomy and adrenalectomy.

Case 7

A metal worker aged 51, first seen July 7, 1949. Claudication left calf of 10 weeks' duration, limiting walking to 200 yards. Severe rest pain left foot, disturbing sleep.

Examination.—General condition good. B.P. 120/90. Severe arterial deficiency left leg. Left foot cool and pale. Oscillometric reading: right, 7.0; left, 0.1.

Treatment.—Response to vasodilator test, nil. A course of I.A.H. infusions was given between September 3 and December 5, 1949.

Result.—Improvement in walking comfort began early in the course of injections, associated fairly regularly with rise in temperature in the toes of the left foot, as great on occasion as 3° C. There was a slight improvement in oscillometric readings, but probably not significant. At the end of the course he was able to walk half a mile (0.8 km.) at moderate pace, and was relieved of rest pain.

The patient returned to work on December 12, and was still working on February 22, 1950. There was no rest pain and no severe claudication.

Case 8

A boot and shoe repairer aged 56, first seen February 3, 1949. Claudication right calf, of sudden onset seven months previously, associated with the feeling of deadness of the limb and now limiting walking to 80 yards (73 metres).

Examination.—Only fair nutrition. B.P. 170/90. Gross narrowing of the retinal arteries. Severe arterial insufficiency right leg. Oscillometric readings: left, 9.0; right, 1.5.

Treatment.—A course of I.A.H. infusions was given between March 20 and June 21, 1949.

Result.—The infusions, in general, produced flushing as far as the toes and a significant increase in oscillometric readings, on one occasion as great as from 0.5 to 4.0. In parallel with this his walking improved steadily, and when last seen on July 29, 1949, he was able to walk slowly for 30 minutes on

the level. Pain, formerly present in the calf muscles, no longer occurred, its place being taken by an easily bearable aching sensation around the heel and tendo achillis. Oscillometric readings not materially altered: left, 8.0; right, 1.5.

On February 20, 1950, he wrote: "Condition satisfactory. At work. Have walked nearly two miles, with discomfort only."

Case 9

A male telegraphist aged 60, first seen August 5, 1949. Claudication affecting left leg for two years and right leg for six weeks. Walking distance about 200 yards.

Examination.—A reasonably well preserved arteriosclerotic. B.P. 160/90. Oscillation: right, 0.2; left, 0.2. Feet bluish; marked capillary stasis.

Treatment.—As the recently affected right leg seemed to be improving, it was decided to observe the case while a course of vitamin E, 450 mg. daily, was given. This produced no effect, and claudication persisted, limiting walking to 200 yards. A course of I.A.H. infusions was given between November 19, 1949, and January 23, 1950.

Result.—When examined on February 3, 1950, the patient was delighted with his recent progress, and was emphatic that the histamine infusions had resulted in a striking improvement in his walking capacity. He was now able to walk 400 yards and to get to and from his work easily. Despite the subjective improvement, the oscillometric readings were unchanged. On April 14 the improvement had been maintained.

Unimproved Cases

Case 10

A time-keeper aged 65, first seen June 30, 1949, with claudication at 200 yards left calf for one month, and a history of anginal pain.

Examination.—A plethoric, hypertensive male. B.P. 220/120. Marked vascular insufficiency left leg. Commencing atrophy of pulp of great toe. Oscillometric reading at calf level: right, 7.0; left, 0.5.

Treatment.—A course of I.A.H. infusions was administered at weekly intervals into the left femoral artery at the groin between July 7 and October 29, 1949.

Result.—Histamine infusions associated with fairly marked general reaction, but negligible improvement in circulation in calf or in foot. Clinical status at end of course unaltered.

Case 11

A labourer aged 58, first seen January 27, 1949. Claudication left calf for three years; recently much worse, coming on at 100 yards, associated with pallor, coldness of foot, and rest pain.

Examination.—Severe generalized arteriosclerosis. B.P. 210/100. Left foot pallid; very poor reaction to vasodilator tests. Arteriogram: severe atheroma with thrombosis left superficial femoral. Fairly good collateral network.

Treatment.—A course of I.A.H. infusions was given between June 2 and August 23, 1949.

Result.—Occasional slight rise of temperature in foot and temporary increase of oscillometric reading on one occasion only. Last seen September 1, 1949: clinical status unchanged.

Case 12

A man aged 61, first seen June 10, 1949. Five months' history of claudication; sudden onset, now limiting walking to 100 yards. No rest pain.

Examination.—A well-preserved rather plethoric workman. B.P. 180/100. Marked vascular insufficiency right leg. Cutaneous circulation good. Oscillometric readings: left, 6.0; right, 1.5.

Treatment.—A course of I.A.H. infusions was given between June 16 and September 2, 1949.

Result.—In general, although the injections were associated with vasodilatation, on occasion reaching the foot, and slight improvement in the oscillometric readings, there was no striking improvement in functional capacity. On February 20, 1950, he was still at work. Claudication occurred at 100–150 yards.

Case 13

A storeman aged 67 was admitted on July 29, 1949, suffering from arterial thrombosis left leg, on a basis of severe arteriosclerosis. B.P. 200/100; acute ischaemia left leg. A course of heparin injections was given without benefit. On August 16, 1949, he was transferred to the surgical division.

Examination.—Severe arterial insufficiency both legs, worse on right side; pregangrenous stasis; severe rest pain. Oscillometric reading: right, 1.5; left, 0.25.

Treatment.—A course of "padutin" injections was given without effect; this was followed by a course of 10 I.A.H. injections into the left femoral artery, beginning on November 8, 1949.

Result.—Treatment conferred little benefit, and on December 23 the thrombotic process on the right side advanced and became more complete than on the left. Throughout his illness mental changes were severe. He was irritable and depressed, but these symptoms were improved to a striking degree by administration of dextro-amphetamine—so much so that it was possible to allow him to go home on January 16, 1950. His condition otherwise remained unchanged.

Case 14

A clerk aged 50, first seen March 22, 1949. Intermittent claudication right, of six months' duration, now coming on at 200 yards.

Examination.—A well-preserved, heavy muscular man. B.P. 180/100. Oscillometric reading: right, 1.0; left, 10.0.

Operation (April 20).—Right lumbar ganglionectomy. There was a temporary improvement in the circulation of the right leg, but by June 24 exercise capacity was as before operation, and by August 5 was actually less. Oscillations at this time were: left, 9.0; right, 0.5.

Treatment.—A course of I.A.H. infusions was administered between September 9 and December 22.

Result.—There was no improvement whatsoever in walking. The right foot remained warm at all times as a result of ganglionectomy.

Summary

A clinical trial has been made, in a series of 14 cases of arteriosclerosis obliterans, of intra-arterial histamine therapy as described by Mufson (1948). In two of the cases both limbs were treated.

A course of treatment has consisted of 10 infusions, at weekly intervals, of 2 mg. of histamine acid phosphate in 500 ml. of normal saline.

In nine cases capacity for walking has improved and "rest pain," when present, has been diminished. In five cases there has been no improvement. In no case has the treatment done obvious harm.

I have been much indebted to Dr. Sheila Christian, Dr. James Allan, and Dr. John Leitch for help with the tedious work involved in the large number of arterial infusions represented by this brief paper.

REFERENCE

Mufson, I. (1948). *Ann. intern. Med.*, 29, 903.

Some common-sense advice attractively set out on the care and feeding of babies is provided in four pamphlets issued by the Central Council for Health Education. They are intended for mothers, and tell them how to prepare food, about the elements of breast feeding, and when to consult the family doctor. Entitled "Planning Ahead," "The Natural Way," "Mixed Feeding," and "Weaning," they are obtainable for 6d. each from the council at Tavistock House, Tavistock Square, London, W.C.1.