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Hemostasis with adrenochrome and its derivatives

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HEMOSTASIS WITH ADRENOCHROME AND ITS DERIVATIVES

A Review of the Literature with Experimental Observations

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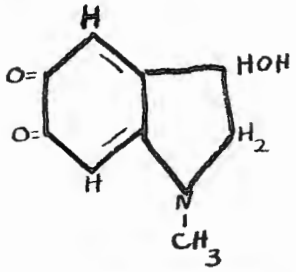
Adrenochrome is a substance formed by the oxidation of adrenalin. It seems to retain the hemostatic properties of adrenalin without its sympathomimetic effects. The lack of knowledge of its mode of action and effectiveness as a therapeutic hemostatic agent have prompted this investigation.

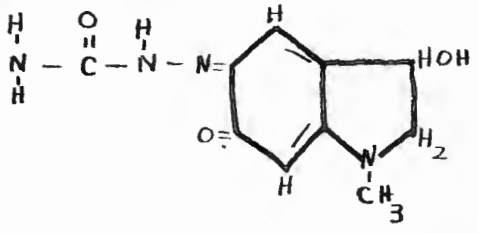
Chemistry

In 1929 Bruno Kisch (1) and his pupils began the first thorough investigations of the catalytic and metabolic properties of a red oxidation product of adrenalin which he called "omega". Weinstein and Manning (2) in 1935 first crystallized the substance. In 1937 Green and Richter (3) verified this work. They gave the substance the name "adrenochrome" and proposed its structure which has since been proven correct by numerous workers. A rather extensive report on the chemistry of adrenochrome and its derivatives was made by Bu'Lock and Harley-Mason (4) in 1951.

Since adrenochrome is relatively unstable and insoluble it was necessary that some derivative be found before it could be utilized clinically. Several have been developed but the most satisfactory seems to be the monosemicarbazone



ADRENOCHROME



ADRENOCHROME MONOSEMICARBAZONE

of adrenochrome. No basic differences between the action of adrenochrome and its monosemicarbazone have been reported. This is the only form available to the clinician at the present time.

Actions

Considerable study has been made of adrenochrome as an oxidative catalyst in an effort to determine the exact mechanism of its action in the human body. In reviewing the work of several investigators, including much of his own, Kisch (1) summarized the effects of omega (adrenochrome). He stated, in brief, that it catalyzes (a) oxidation of adrenalin, (b) oxidative processes which are due to the lactic and malic dehydrogenase system of various tissues and cells, and (c) decarboxylation and deamination of amino acids under certain conditions. He showed that it would increase oxidative processes in living tissues completely independent of adrenalin. Relative to this Parrot (5) showed that the over-all consumption of oxygen in man is increased by adrenochrome.

In animal experiments certain cholinergic effects have been noted. Plotka and Jacquier (6) cite its slowing effects on the frog heart and stimulating effects on rabbit intestine. Kuschinsky (7) showed that atropine would not block this action but, strangely enough, antihistaminics would. No definite relationship between histamine and adrenochrome has been demonstrated.

The exact mode of this activity has not been made clear.

Minz and Plotka (8) feel that adrenochrome has a catalytic action in the synthesis of acetylcholine. The failure of inhibition of the cholinergic effects of adrenochrome by atropine would suggest that its action is distal to the action of atropine and thus at the effector cell. The suggestion by Waelsch (9) that it inhibits cholinesterase seems most reasonable and has received considerable support.

The only definite adrenergic effect of adrenochrome which has been reported is its epinephrine-like hemostatic action. There is some evidence that it may have a mild adrenocorticotropic action similar to that of epinephrine according to Srinivasan (10) and Lecomte and his group (11). However there is insufficient evidence at this time to show that this action is of significant degree.

Considerable investigation of effects of adrenochrome on the cardio-vascular system has been carried out but no definite sympathomimetic action has been observed. Raab and Lepeschkin (12) and Marquardt and Oettel (13) as well as numerous others have shown that in patients who have been given adrenochrome there is a mild bradycardia even after atropine. They also found that its effect on the blood pressure is variable but causes no marked change. Oster and Sobotka (14) showed no blood pressure effects in normal animals but they did describe a definite hypotensive effect in experimentally hypertensive rats. Bacq and his co-workers (15) reported up to 70% increase in cardio output with relatively large doses in dogs. It also has been shown (12) that adrenochrome does

not cause excessive oxygen consumption and resultant hypoxia of the myocardium as epinephrine does. They also observed no extrasystoles or other irregularities of conduction with relatively large doses. Pulaski et al (16) found that the administration of adrenochrome has no effect on skin temperatures or vasomotor responses in human subjects.

Derouaux and Roskam (17) showed that adrenochrome has adrenalin-like hemostatic properties in that it shortens the bleeding time for several hours. On the basis of their own extensive investigations and those of others they conclude (18) that apparently adrenochrome, or a closely related substance, acts as a chemical promediator of sympathin. Thus if it were stored in cells supplied by post-ganglionic fibers it could be converted to sympathin and thus lead to constriction of small vessels and capillaries and thus bring about hemostasis.

Thus we see that adrenochrome exhibits evidence of both cholinergic and adrenergic activity in isolated instances. Plotka and Jecquier (6) have shown that this difference in action may be related to the oxidation-reduction state of the substance. That is, in the oxidized state it is cholinergic and in the reduced state it is adrenergic in effect. However there seems to be no explanation at this time of why its action is apparently confined to only certain specific tissues.

The actual metabolism and excretion of adrenochrome also are not completely known. Fischer and de Lamdtsheer (19) have shown that adrenochrome disappears rapidly from the blood and

may be found in liver and kidney as an indole derivative. Nihoul, Fischer, and Lecomte (20) found that certain strains of intestinal and urinary bacteria destroy adrenochrome semicarbazone with resulting formation of indoles. Fischer and Lecomte (21) also showed that, when given intravenously to dogs or rabbits, 50-70% of it was excreted unchanged in the urine and 25-30% as indole. They (22) found that when it was given orally to human subjects 20% was excreted unchanged in the urine and 20% as indole. When the intestinal tract was freed from bacteria none was excreted as indole. Thus, apparently the body itself alters the substance very little before it is excreted.

Hemostatic Activity

As was previously stated Derouaux and Roskam (17) first noted the hemostatic activity of adrenochrome. Beaudet and his group (23) showed it would cause 33-43% decrease in bleeding time in rabbits. This was in accordance with the findings of Roskam et al (24) who found 0.1 mg. Adrenoxyl* (adrenochrome semicarbazone) in human subjects decreased the bleeding time 33% with maximum effect 60 minutes after injection. Similar results were demonstrated by Sobotka and Adelman (25) who showed that bleeding time immediately after tonsillectomy and adenoidectomy in 32 patients given Adrenoxyl was reduced an average of 38%. Only individuals with short preinjection bleeding times failed to respond.

Hagerty and his co-workers (26) showed marked decrease

* E.R. Squibb and Sons, New York City

in bleeding times in dogs and humans given Adrenoxyl, the maximum effect appearing at 90 minutes in humans. They also showed it would cause marked decrease in hemorrhage from incisions in the liver of dogs except where other than the smaller vessels were cut.

The fact that blood coagulation mechanisms are not affected by adrenochrome was shown by Pulaski, Reichel, and Voorhees (16). Roskam (27) supported this fact when he demonstrated that the hemostatic action of the substance is still present in heparinized rabbits.

Adrenochrome has also been shown to decrease capillary permeability and capillary resistance. Clark (28) found it to be a more potent inhibitor of the spreading effect of hyaluronidase than flavinoids, salicylates, or ascorbic acid but less potent than epinephrine. Prevost, Cotereau, and Parrot (29) showed that 4-6 mg. of Adrenoxyl given intramuscularly to human subjects gave an increase in capillary resistance lasting 24 hours and decreased the bleeding time for approximately 48 hours. Parrot (30) also showed adrenochrome to be capable of decreasing capillary permeability by observing its ability to decrease the spreading of trypan blue dye injected intravenously.

Further support of this action on capillaries was presented by Herve (31) who showed that Adrenoxyl, following x-ray to mouse skin, would reduce the purpura due to the x-ray. Herve and Lecomte (32) also showed that the injection of Adrenoxyl before irradiation would prevent the appearance

of petechiae.

Some work (33) reported to have been done by Dr. M.D. Fulton at the Department of Biology of Boston University appears to confirm the ability of adrenochrome to decrease capillary permeability. After irritating the mucous membrane of the cheek pouch of the hamster with snake venom, he observed and photographed the appearance of many large petechiae and the escape of red blood cells from the capillaries. In the mucous membrane of a similarly treated animal which had received Adrenosem* (adrenochrome monosemicarbazone sodium salicylate) no escape of red blood cells was noted.

Reports on clinical trials with adrenochrome products are few. This is understandable when one considers the many factors which must be accounted for in such a study. Some of these are listed below:

(1) Extent of hemorrhage in each individual patient varies so much that grouping patients is inaccurate without considering each case separately.

(2) Measurment of the exact amount of bleeding with and without the drug is impossible in most cases.

(3) There is always a possibility that bleeding may have stopped just as readily without the drug.

(4) Bleeding from other than small vessels and capillaries is unaffected by the drug.

* S.E. Massengill, Bristol, Tennessee

(5) It is very improbable that the conditions of the hemorrhage in a control case will be identical to those in a treated case.

(6) All the other known factors which might affect hemostasis must be accounted for.

Hagerty, Zavertnik, and Grimson (26) attempted to measure blood loss from surgical patients. A total of 45 patients were studied, approximately one half serving as controls and the other half receiving 0.1 mg. Adrenoxyl. Of these patients 18 underwent tonsillectomy and adenoidectomy, 11 radical mastectomy, and 16 inguinal herniorrhaphy. They felt that their findings were inconclusive as the variation in surgical technique, patients, and extent of operation in each individual case was too great to permit valid evaluation of the drug.

Sherber (34) attempted a clinical evaluation using Adrenosem in a great variety of both medical and surical patients with bleeding manifestations, reporting a total of 72 cases. He recognized the impossibility of establishing definite controls in such a study so made no attempt. He discussed each case separately so far as practical. His results, though incomplete, would seem to indicate that adrenochrome compounds were of considerable value in a great variety of cases of bleeding. It apparently was ineffective in a number of the cases described but this was probably because of involvement of relatively large vessels.

Experimental Studies

A. PURPOSE

The impossibility of carrying out a well controlled, accurate clinical evaluation of the ability of adrenochrome derivatives to produce hemostasis has been discussed. For this reason the author felt that a carefully controlled group of experiments using animals might provide a more accurate indication of the actual effectiveness of this agent. By doing so the bleeding may be produced in an identical manner in areas in which only smaller vessels and the capillaries are interrupted. Also this makes possible a comparison of the amount of bleeding at nearly identical sites before and after injection of the drug.

B. METHODS

Adult mongrel dogs were anesthetized with intravenous Nembutal (approximately 1 gm./5 lbs. body weight). The abdomen was shaved and cleaned with one of the surgical soaps. A full thickness of skin exactly 4x4 cm. square was removed and then the bleeding surface was blotted lightly until all bleeding had ceased. The bloody sponges were placed in an air-tight weighing bottle and weighed immediately, the dry weight of sponges and bottle being determined just prior to the time they were to be used. The difference between the weight of the dry sponges and bottle and the weight of the bloody sponges and bottle was taken as the total blood loss. Then 0.1 cc. of Adrenosem was injected

intramuscularly and similar procedures performed on the opposite side of the abdomen 30 and 60 minutes after the injection.

C. PROTOCOL AND RESULTS

Experiment #1. January, 22, 1955.

(Dog #1, a black and white spotted female, weight 22 lbs.)

A full thickness of skin exactly 4x4 cm. square was removed from the abdomen. Using untreated filter paper as sponges the blood oozing from the surface was blotted until bleeding ceased.

1. Control:

No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 2.8240 gm.

2. 30 minutes after injection of 0.1 cc. of Adrenosem I.M.:

No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 1.3237 gm.

Decrease from control : 1.5003 gm. or 53%.

3. 60 minutes after injection of 0.1 cc. Adrenosem I.M.:

No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 0.7212 gms.

Decrease from control : 2.1028 gms. or 75%.

Experiment #2. January 26, 1955

(Dog #2, a brown female, weight 17¼ lbs.)

A full thickness of skin exactly 4x4 cm. square was removed from the abdomen. Using untreated filter paper as sponges the blood oozing from the surface was blotted until bleeding ceased.

1. Control:

No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 5.2050 gms.

2. 30 minutes after injection of 0.1 cc. Adrenosem I.M.:

No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 4.6665 gms.

Decrease from control : 0.5385 or 10%.

3. 60 minutes after injection of 0.1 cc. of Adrenosem I.M.:

No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 1.9365 gms.

Decrease from control : 3.2665 gms. or 63%.

Experiment #3. January 29, 1955.

(Dog #1, a black and white female, weight 23 lbs.)

A full thickness of skin exactly 4x4 cm. square was removed from the abdomen. Using fine mesh gauze as sponges the blood oozing from the surface was blotted until bleeding ceased.

1. Control:

No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 1.0450 gms.

2. 30 minutes after injection of 0.1 cc. of Adrenosem I.M.: No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 1.5714 gms.

Increase over control : 0.5264 gms. or 50%.

3. 60 minutes after injection of 0.1 cc. of Adrenosem I.M.: Active bleeding from a relatively large subcutaneous vessel was observed.

Blood loss : 5.5984 gms.

Increase over control : 4.5534 gms. or 436%.

Experiment #4. February 1, 1955.

(Dog #3, a brown and white female, weight 21¼ lbs.)

A full thickness of skin exactly 4x4 cm. square was removed. Using plain guaze sponges the blood oozing from the surface was blotted until bleeding ceased.

1. Control:

No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 3.7260 gms.

2. 30 minutes after injection of 0.1 cc. of Adrenosem I.M.: No active bleeding indicating severance of a relatively large vessel was observed.

Blood loss : 3.1150 gms.

Decrease from control : 0.6110 gms. or 16%.

3. 60 minutes after injection of 0.1 cc of Adrenosem I.M.;

Active bleeding from a relatively large subcutaneous vessel was observed.

Blood loss : 7.2201 gms.

Increase over control : 3.4941 gms. or 94%.

D. TABULATION OF RESULTS

Amount of Blood Loss After Administration of 0.1 cc. of Adrenosem Expressed As Percentage of Blood Loss in Control:

Exp't. #1	30"	53% decrease
	60"	75% decrease
Exp't. #2	30"	10% decrease
	60"	63% decrease
Exp't. #3	30"	50% increase
	60"	436% increase*
Exp't. #4	30"	16% decrease
	60"	94% increase*

* interruption of relatively large vessel was noted in these cases.

E. EVALUATION OF RESULTS

From the limited data which have been presented two conclusions may be drawn:

1. when no large vessels were involved the adrenochrome compound appeared to exert a hemostatic effect.
2. when full thicknesses of skin were removed the

resulting bleeding was too variable to permit a valid study of this type.

Thus it is apparent that the occaisonal interruption of large vessels was the one factor in these experiments which prevented entirely valid results. For this reason a similar study is being undertaken in which split thicknesses of skin will be removed by means of the Paget dermatome. By this means only capillaries and precapillaries will be disturbed.

Summary

A review of the literature concerning the actions of adrenochrome and its derivatives and their effectiveness in supporting hemostasis has been presented. A trial of the effectiveness of one of these compounds in bleeding produced in dogs was described.

Adrenochrome acts as a catalyst in certain vital metabolic processes. It has a cholinergic effect on the heart and intestines which is not altered by atropine but is blocked by antihistaminics. It has no appreciable adrenergic effects except its epinephrine-like hemostatic action.

Several explanations are offered for its mode of action, each with considerable valid support. Evaluating all this material collectively we find that by some poorly understood mechanism adrenochrome seems to act at the effector cells of the autonomic nervous system. It seems reasonable to suspect that its action is in some manner related to its

catalyic activity. The most reasonable explanation offered for its action seems to be that it acts either as a cholinesterase inhibitor or as a promediator of sympathin, possibly depending on whether it is in the oxidized or reduced state. Another possible explanation might be that it in some way alters or potentiates the action of acetylcholine or sympathin upon the effector cell. In other words perhaps its action is peripheral to that of acetylcholine or sympathin. At present there is not adequate explanation for its apparent specificity for only certain tissue rather than all those affected by autonomic stimulation.

Adrenochrome is converted by the liver and kidney, as well as certain bacteria, into indole and excreted in this form and in the unchanged form.

Bleeding time determinations in animals and humans indicate that a decrease of approximately 33% or more could be expected with maximum activity of the drug seen 60-90 minutes after administration.

No effect has been noted on the medium and larger size vessels. There is definite evidence of decrease in capillary permeability and increased capillary resistance.

It is readily apparent that accurate reports of clinical trials are impossible. This was pointed out by those who attempted evaluation of the ability of the drug to decrease bleeding during and after surgery. Even when cases of medical and post-operative surgical bleeding are treated with these

drugs and examined individually one cannot conclusively say that this agent has definite hemostatic properties since accurate controls are not possible. However it is difficult to refute the consistently good results reported in the clinical studies and the definite experimental evidence to support it.

My own experiments in which blood loss was measured after removal of full thicknesses of skin from dogs was inconclusive due to the variability in size of vessels encountered from one area to the next. However it appears that when large vessels were not encountered the adrenochrome compound exerted a hemostatic effect.

No significant toxic effects from these agents have been reported. No studies have been made showing the amount of the drug necessary to produce toxicity. This should be done before large doses can be given safely.

There apparently are no contraindications to its use. However one should keep in mind the blocking action of antihistamines and the necessity for larger oral than parenteral dosage due to the large percentage broken down into indoles by intestinal bacteria.

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in the experimental procedures.

CONCLUSIONS

1. The mode of action of adrenochrome and its derivatives is not known but appears to take place at the effector cells.

2. Adrenochrome and its monosemicarbazone significantly decrease the bleeding time in man and animals.

3. Adrenochrome monsemicarbazone appears to be effective as a hemostatic agent in animals and man.

4. No toxic side effects have been reported from use of this drug.

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