REVIEW ARTICLE

THE ACCIDENTAL INTRA-ARTERIAL INJECTION OF THIOPENTAL

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ONE of the potentially serious complications of the use of thiopental occurs following its inadvertent injection into an artery. Though rare, it is an ever-present danger, as long as drugs are administered intravenously. The accidental intra-arterial injection of many unrelated drugs may cause gangrene and loss of an extremity. Many of these drugs have been identified from case reports of such accidents; many others remain unknown because reports are not submitted. It is impossible to say which of the currently used intravenous preparations may produce serious sequelae after injection into an artery, for often this information is unknown even to the drug manufacturers. A safe assumption is that all drugs are potentially dangerous when injection is misdirected.

Several drugs used in anesthesia have produced this complication. Thiopental has caused the greatest number of serious sequelae, but myanesin,[39] ethyl ether,[30] tubocurarine,[15, 45, 46] meperidine-Diparcol,[48] strophanthin,[38] pentobarbital,* blood,[61] and a phenothiazine compound* have also caused tissue damage. A review of the accounts of these accidents reveals how little is really known about them. Though thiopental was introduced clinically in 1934, the first report of its injection into an artery did not appear until 1942. Lundy[34] reported three intra-arterial injections in the first 25,000 patients to whom the drug was administered, an incidence of 1 in 8,000 cases. One of these patients died, the other two recovered uneventfully. Van der Post[55,56] provided the first report of gangrene with the loss of three fingers following the intra-arterial injection of 6 ml. of 10 per cent thiopental.

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Macintosh and Heyworth[36] also stressed the danger of this complication in their report of two cases, one with loss of the arm. During World War II, a warning against this accident with case reports appeared in at least two issues of the *Bulletin of the United States Medical Department*.[53, 54] It was not until 1948, that an excellent, comprehensive study of the accidental intra-arterial injection of drugs was presented by Cohen.[8, 9] While discussing the general aspects of the problem, he devoted greatest attention to the damage resulting from injections of thiopental. Twelve detailed descriptions of this complication are included. Four of them had previously been reported; the remainder were gathered by the author. Since 1948, several additional cases have appeared in the literature—almost all by English authors.[3, 10, 12, 15, 25, 26, 43, 45, 49, 50, 57-59] Most follow the same general pattern—a brief description of the complication, the therapeutic measures employed and an attempt to show that the treatment effected the cure.

INCIDENCE

It is difficult to establish the incidence of this complication. Widely diverse estimates are provided by Lundy (1:8,000),[34] Cohen (1:56,000)[8] and Dundee (1:3,500).[13] It is doubtful whether any of these figures approaches the true situation. During the administration of thiopental, an artery may accidentally be entered. This happens to the experienced as well as the inexperienced. Most recognize what has occurred and remove the needle; when unrecognized, thiopental is injected into the artery. Many factors such as the concentration of thiopental, the volume of the initial injection, the rate of injection and the degree of sedation, determine the response of the patient. Small volumes (4–5 ml.) of dilute solutions (2½ per cent or less) injected slowly may produce no complaint. The very

slow injection of even more concentrated solutions may produce only minimal changes. Thiopental has been injected into an artery without the anesthetist ever being aware of it until after the injection was completed.[8, 57] On other occasions it has produced mild and transient pain and some color change in the extremity without any permanent effect.[57] Seldom are these cases reported in the literature. Cases with a favorable outcome following treatment, may be reported; few accounts, if any, of the failures appear. The incidence of recognized and unrecognized intra-arterial injection of thiopental is probably much higher than is supposed but certainly is much less than the 1:3,500 estimate of Dundee. Too many clinicians whose experience with thiopental, directly or indirectly, exceeds 75,000, have never seen the complication. The permanent sequelae appear to be rare.

Factors Contributing to Accidental Intra-Arterial Injection

Although it is natural to wish to mollify the negligence of those who inadvertently have injected thiopental into an artery, nevertheless, in almost all instances, there has been a break in the standard procedure advocated for safe and controllable venipuncture.[33] There is little excuse to pass off such an accident as "bad luck" or "a bad break." Everyone who assumes the responsibility for the administration of drugs which can cause such serious complications, is bound by a similar responsibility to make certain that drugs labeled for intravenous use are properly injected into well-identified veins. Where doubt exists as to the proper position of a needle within a vein, injection must be withheld, especially if an artery lies close to the area. Arterial puncture is more apt to occur (1) where arteries are anomalously situated and (2) when the arterial pulsations are markedly diminished.

Arterial Anomalies of the Arm. Normally the brachial artery begins at the lateral border of the axilla, passes down the arm medial to the humerus and gradually crosses laterally above the brachialis muscle so that within the cubital fossa, it lies between the two epicondyles. At this site and about one inch below the crease of the elbow, it divides to form the radial and ulnar arteries, which then continue down the arm. The larger ulnar artery as it courses downward, gives rise to the volar interosseous artery and 2 recurrent branches. These arteries normally are deeply situated beneath the superficial and deep fasciae of the forearm and along most of their course are well protected by muscles or tendons.[8, 9, 20]

In some arms (approximately 10 to 13 per cent),[30, 42] division of the brachial artery takes place above the cubital fossa. In 3 per cent of the population, the high division occurs bilaterally. Either the ulnar or the radial artery or both may originate in this position.[23] In almost every case where the ulnar artery has a high origin, it follows a superficial course as it passes down the arm. This superficial course is variable. It may remain entirely subfascial, it may be subcutaneous in the elbow region and then penetrate below the fascia or it may lie subfascial at the elbow, become subcutaneous farther down the arm and finally again become subfascial.[8, 9, 20] When the ulnar artery originates above the cubital fossa and follows a superficial course, its volar interosseous branch originates from the radial artery. Inadvertent injection into the aberrant ulnar artery will not involve the volar interosseous branch which supplies the median nerve. This explains why injection into the superficial ulnar artery is rarely followed by permanent sequelae.

Because of the numerous superficial positions the ulnar artery might occupy, it has often been entered during attempted venipuncture.[8, 10, 34, 35, 50] In 5 of the 12 cases reported by Cohen,[8] injection was made into the superficial ulnar artery. However, the brachial and the radial arteries might also be quite superficial in the elbow region. Injection of thiopental into the brachial artery has occurred where the median basilic vein was directly over an underlying superficial brachial artery. The arterial variations of the arm, especially in and about the cubital fossa, are common and numerous.[43] If venipuncture must be performed in this area, a higher index of suspicion must be maintained to forestall misdirected injections.[33]

Diminished arterial pulsations, could mask

an inadvertent arterial puncture. Most commonly, an excessively tight venous tourniquet partially or completely occludes the artery. Hypotension could make identification difficult. Full abduction of the arm, placing a sand bag between the scapulae, hyperextension or rotation of the head away from the arm extended on an arm board, all may diminish or obliterate normal arterial pulsations.[8, 9]

Prophylaxis of Inadvertent Intra-arterial Thiopental Injection

Many common sense measures have been advocated to prevent this accident and protect against its serious sequelae. It is an avoidable complication. All personnel who administer thiopental must be familiar with the arterial supply of the arm and the anomalies which can exist. The venous distribution of the arm and the sites which most consistently provide the largest and safest veins for venipuncture, should be known. A safe technique of venipuncture should be adopted.[27, 33, 52] Since many accidents have followed attempted venipuncture in the medial aspect of the antecubital space, this area should be avoided when possible.[9, 13] If the median basilic vein is the most prominent or the only usable vein in the arm, it is advisable first to start an intravenous infusion and then, after making sure that the needle is not in an artery, to inject the thiopental into the infusion tubing. Many believe this technique should be followed routinely for all intravenous injections at any site. It is unlikely that accidental arterial puncture would fail to be detected if this practice were adopted. The absence of pulsation does not rule out the presence of an artery but it is a further check. Arterial puncture may be painless especially if a small-caliber, well-sharpened needle has been used. The color of arterial blood may not be bright red as classically described. Many factors can reduce the degree of hemoglobin saturation. Bright blood may not spontaneously spurt back into the syringe or be readily aspirated. This is especially true when the bevel of the needle is only partially through the wall of the artery or if a small gauge needle is being used. The yellowish tinge of thiopental frequently masks the bright color of arterial blood. However, when one or more of the previously mentioned factors is present, arterial puncture must be suspected and the needle removed or the site carefully rechecked.

If evidence of arterial puncture is not observed, a "test dose" of 1 to 2 ml. of thiopental should be slowly injected.[19, 49, 59] Opinions differ as to the purpose of the "test dose." Most frequently it is used to evaluate the systemic response of the patient to the barbiturate. While valuable in this respect, it is equally important as a method of detecting intra-arterial injection. Typically the intra-arterial injection of a small amount of thiopental should immediately produce pain along the distribution of the artery and into the hand, with blanching of the hand and fingers. In a few patients, the test injection has failed to produce this response and subsequent larger doses have been injected with tragic results. The reliability and usefulness of the "test dose" is not absolute. If injected too slowly, even when using 5 or 10 per cent solutions the rapid blood flow sufficiently dilutes the thiopental to make it non-irritating. The patient may not have symptoms suggesting intra-arterial injection. Conversely, the rapid injection of a small test dose may produce considerable arterial injury in some patients.[8] The continued use of the precautionary test dose, followed by a sufficient pause to permit detection of untoward effects, is advocated by the majority of experienced personnel who use this drug. It should not however, replace the use of precise techniques of venipuncture which guarantee against inadvertent arterial puncture.

Clinical Picture

The intra-arterial injection of thiopental produces a classical response of intense, excruciating, burning pain which radiates down the forearm and into the hand and fingers. Macintosh[36] vividly describes this reaction: "The patient writhed in agony, gasping that he felt as if boiling water was being poured over his hands and flames were shooting from his fingers." The onset of pain is immediate. It may continue undiminished, or it may subside somewhat in one or two minutes, leaving a

painful, burning sensation which persists for many hours. With the onset of pain, the distal arm and hand become blanched, the fingers may rapidly become cyanotic. Motor function and sensation are intact at this time. This blanching may be followed by a definite reactive hyperemia of the lower part of the extremity which appears within minutes after the injection. Its appearance is a favorable sign; its absence usually indicates the rapid onset of permanent arterial occlusion.[8, 9, 11, 13, 14, 21, 24, 31, 37, 41]

Loss of consciousness may be slightly delayed, but rarely for longer than 40 seconds. Usually the patient is asleep within 20 seconds. Recovery occurs without delay. The potency of the drug does not appear to be reduced. Depression occurs in spite of the intense pain.[8, 9, 13]

After injection, the radial pulse may remain full, but most often, its volume is reduced or it disappears completely. In the more severe cases, it rapidly becomes imperceptible with the onset of pain and remains absent permanently. The presence of a pulse early does not rule out late thrombosis.

Cohen[8, 9] reports a shock-like state which developed in 2 patients who had received thiopental intra-arterially. Lundy[34] had a similar case. It is postulated that the injection caused vasomotor depression. These reactions are difficult to explain.

Various additional changes may occur within the first two hours depending upon the distribution of the thiopental within the arm. The arm may appear progressively cadaveric. The arm and hand may become hypesthetic or totally anesthetic. Motor weakness or paralysis may develop. The arm and hand may become markedly edematous, with extension of the swelling well above the site of injection.[8, 9] When these changes progress rapidly and little evidence of viability remains in the part, the outlook is poor.

Over optimism, because of early encouraging signs, must be guarded, for the onset of complete circulatory occlusion may be delayed for as long as two weeks.[8]

Pathology

Previously, it was believed that the pathology of intra-arterial thiopental injection was similar to that of traumatic arterial disease.[8, 9] In both conditions, arterial spasm was thought to be the essential change which later caused thrombosis and gangrene.[12, 14, 22, 24, 25, 31, 41, 49] The high alkalinity of thiopental (*p*H 10.6) precipitated intense arterial spasm.[8, 9, 11–14, 21, 22, 24, 31, 49] If untreated, this spasm caused tissue necrosis either directly, by obstructing blood flow, or indirectly by causing thrombosis within the spastic vessel. Arterial spasm also caused trapping of the thiopental in the distal arterial tree,[13, 14, 22, 24, 31, 49] prolonging the exposure of the vessels to the irritant effect of the drug. Treatment was primarily the correction of arterial spasm. Many of the most recent texts[11, 13, 14, 22, 24, 31, 37] continue to support this concept despite the work of Cohen, which in 1948, clearly demonstrated the importance of direct arterial damage and thrombosis in this accident.[8, 9]

Recent laboratory studies[28] support many of the conclusions previously proposed by Cohen. In light of this information, perhaps a different sequence of events follows the intra-arterial injection of thiopental.

Unlike traumatic arterial injury, the essential pathology of intra-arterial thiopental is not arterial spasm.[8, 9, 28, 47] An intense chemical endarteritis develops after injection of the drug, which rapidly destroys the endothelial and subendothelial tissues and in severe reactions, the inner portion of the muscle layer as well.[8, 9] This injury is immediate and requires but momentary contact between the drug and the vessel wall. Its diffuseness is determined by many factors but, in general, the volume injected is most important, provided a concentrated solution is used. As little as 4 to 5 ml. of solution can cause intimal damage of the entire arterial tree down to the capillary level.[8] The depth of penetration of the injury (endothelial, subendothelial, muscularis) appears to vary directly with the concentration of the injected thiopental and the individual susceptibility of the patient's tissues to the drug.[8, 9, 13, 14, 16, 18, 28, 29]

The initial local response in the tissues adjacent to the areas of intimal necrosis, is edema. This develops shortly after destruction of the intima. In the larger arteries, swelling of the inner portion of the muscularis does not encroach upon the lumen of the ves-

sel, but as the caliber of the vessels decrease, this edema assumes increasing importance. In the finer arteries and arterioles, blood flow may be greatly reduced or completely arrested. Stasis and intimal damage together favor thrombosis.[8, 9]

The aggregation and breakdown of blood platelets at the areas of intimal destruction activate tissue thromboplastin and initiate the clotting mechanism. A layer of fibrin is deposited over the sites of injury. It grows thicker if active thromboplastin continues to be released from tissue destruction. Thrombosis is the essential pathologic change of intra-arterial thiopental.[8, 9, 28]

If some blood flow to the vessel wall remains, repair of the arterial wall starts within one to two hours. After this period, inflammatory cells migrate from the wall of the artery into the fibrin layer and the tissues adjacent to the destroyed intima. In the thiopental cases which ended with gangrene, histologic section revealed very few inflammatory elements in the areas, indicating that circulatory arrest occurred rapidly, before healing could start.

Contrary to previous belief, the tissue-destroying effect of thiopental is a property of the drug itself, not its alkalinity. Kinmonth and Shepherd[28] were unable to produce necrosis of the rabbit ear by intra-arterial injection of buffered solutions adjusted to the *p*H of thiopental (10.6). Necrosis consistently occurred when thiopental was used in the same way.

Clinical reports have indicated that gangrene is more likely to follow intra-arterial injection of 10 per cent thiopental than more dilute solutions.[8, 9, 12, 16, 18, 28] Not a single case of gangrene following the accidental intra-arterial injection of 2½ per cent thiopental has been reported.[13, 18, 28] Kinmonth and Shepherd[28] verified the importance of the concentration of thiopental in causing permanent sequelae.

Spasm of various parts of the arterial tree has always been assumed to occur with intra-arterial injections of thiopental. It has never been demonstrated in the human patient nor reproduced in the laboratory animal. The only controlled animal studies which have been done failed to demonstrate arterial spasm.[4, 5, 28] Kinmonth and Shepherd[28] state: "On no occasion has any prolonged contraction been observed, (following intra-arterial thiopental), nor anything at all resembling the spasm which follows mechanical trauma to an artery." In these studies, thiopental was injected into the femoral artery of the rabbit. The typical response was a transient (30 seconds) constriction of the artery followed by a longer period (1 minute) of slight dilation before return to the pre-injection caliber. When thiopental was injected into the central artery of the rabbit ear, signs of inflammation such as edema and redness developed. This lasted for a variable period of time before occlusion of the circulation occurred and the ear became cold. In some, occlusion by thrombosis occurred as late as the third or fourth day. These authors conclude: "The period of vasoconstriction produced by thiopental injection is so short that it could not possibly explain the occurrence of necrosis after such an injections."[28] Burn and Hobbs[4] substantiated this observation. They were unable to demonstrate arterial spasm in the hind leg of the dog or tail of the cat by intra-arterial thiopental. The brief initial constriction was demonstrated. Burns[5] attributes this response to the ability of intra-arterially injected thiopental to release norepinephrine from the arterial wall. Spasm was not demonstrated.

Following the intra-arterial injection of thiopental in man, the final outcome depends upon the degree of arterial destruction produced by the brief contact of the drug with the vessel wall. The concentration of the thiopental may determine this. Another factor is the susceptibility of the tissues of each patient to the destructive effect of chemicals. This is difficult to evaluate but could explain the absence of permanent sequelae without treatment, following intra-arterial injection of 5 ml. of 5 and 10 per cent thiopental,[35, 57] and the extensive damage which has occurred with as little as 1.5 ml. of 10 per cent.[35] This is not an idiosyncrasy.[7, 32, 44] Widespread, penetrating damage to the arterial intima rapidly determines the fate of the extremity. Edema of the muscularis impinges on the lumen of the smaller arteries and arterioles causing acute distal vascular stasis. Spasm does not occur. Thrombosis is progressive and complete.

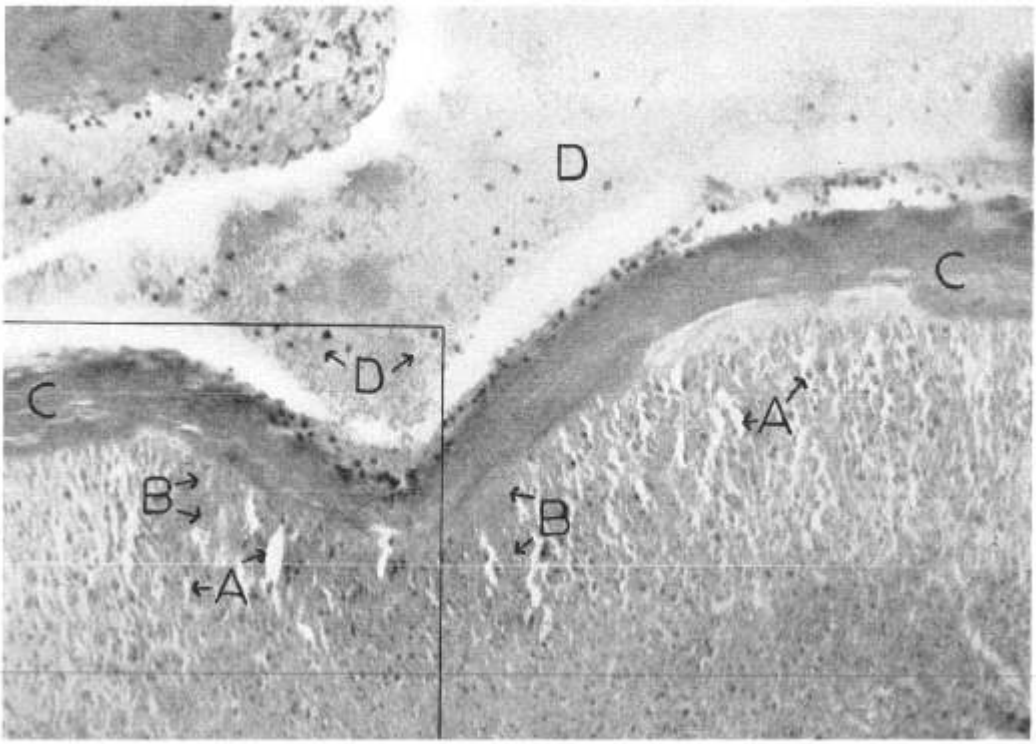

FIG. 1. *Low Magnification.* Section of the left radial artery from an arm amputated two and one half days after the intra-arterial injection of 3 ml. of 5 per cent thiopental. *A.* Edema of inner layer of muscularis. *B.* Degeneration and necrosis of muscle fibers adjacent to destroyed intimal layer. Very few inflammatory cells present. *C.* Thick fibrin layer completely replacing the destroyed endothelial and subendothelial tissues. Almost no leucocytes present in this layer. *D.* Portion of thrombus occluding the artery.

In the larger arteries, extensive intimal damage may be present but here thrombosis does not occur early because of the rapidity of the blood flow.[60] The injured wall is coated by a layer of fibrin which grows by accretion and eventually completely occludes the vessel resulting in delayed thrombosis which takes days to become complete.[8, 9, 35]

Injected thiopental, shunted to different areas of the arm, may cause changes referable to the particular tissue in which the greatest amount of the drug accumulates.[8, 9] If diverted to the skin, multiple areas of superficial necrosis may develop; if shunted to the muscle mass, intense edema of the forearm may result with eventual muscle necrosis. When reaching the hand, the fingers may rapidly become cyanotic and ashen indicating that circulation in the digital arteries is already irreversibly arrested.[8, 9]

Microscopic examination of a gangrenous arm, amputated two and one half days after the intra-arterial injection of 3 ml. of 5 per cent thiopental into the left brachial artery, revealed the advanced changes characteristic of this complication (figs. 1 and 2). "In the major arteries coagulated blood coats the intima which shows areas of rarefaction and destruction. The portion of the muscularis closest to the destroyed intima contain a few degenerated eosinophilic muscle cells without infiltration by inflammatory elements. This indicates a very acute episode of intimal destruction affecting also the muscular layer. In the fingers, fresh thrombi are found in the very small arterial branches and in some of the arterioles. The digital arteries contain thrombi. There is less evidence of intimal damage in the smaller vessels with skip-areas of undamaged endothelium. There is loss of

striation of the muscles of the fingers and hand which indicates early necrosis. No edema is present in the tissues. The changes indicate an acute destructive vascular process." The significant findings are the lack of inflammatory elements in the area of injury and the lack of edema in the degenerated muscle. This indicates the rapidity with which total vascular occlusion occurred. Cohen has noted that the absence of edema was a poor prognostic sign.[8, 9] Normally, inflammatory cells migrate into injured tissue within one to two hours—if the circulation to the part is maintained.

Treatment

Many forms of treatment have been used to prevent the onset of gangrene following the intra-arterial injection of thiopental. It is difficult to assess their value because the complication is so rarely encountered. Any conclusions as to what constitutes the best treatment has little more than clinical impression to support it. Additional information has only recently come from laboratory studies.[28] Many conflicting reports indicate a great variability in the response of the patient to this type of injury. A certain number recover without treatment.[35] Some develop gangrene following the injection of small volumes of concentrated solutions.[8, 35] The immediate treatment of the complication by the methods advocated does not guarantee a favorable outcome.[9, 47] No data are available to indicate how frequently treatment does prevent gangrene. There is some evidence that severe reactions are not benefited by any type of treatment no matter when instituted.[8, 9, 47]

In addition to the pathologic changes within the artery, the outcome depends upon the following:

(1) The concentration of the thiopental solution. Gangrene has never been reported with the 2½ per cent concentration even without treatment.

(2) The volume of solution injected intra-arterially. Injection of 1 to 2 ml. of concentrated solutions (5 per cent or over) may be safely tolerated without treatment; larger volumes are far more dangerous.

Fig. 2. High magnification of section indicated in figure 1. Notations as with figure 1.

(3) The artery into which injection was made. Serious sequelae infrequently follow injection into an aberrant ulnar artery even with concentrated solutions. This is not true of the brachial artery.[8, 9, 13, 14, 35]

(4) The type and time of treatment. The importance of this factor in the final outcome remains to be proven. It may be considerable.

The primary purpose of treatment is to prevent thrombosis.[8, 9, 11, 13, 14] Once it has occurred, efforts to re-establish circulation are rarely successful.[8, 9, 13, 47] Following intimal damage by thiopental, the onset of thrombosis will be influenced by the following:

(1) The amount of active thromboplastin released from sites of arterial damage (depends upon the severity of the injury).

(2) The presence of substances which prevent coagulation or cause dissolution of the thrombus (antithromboplastin, heparin, antithrombin, fibrinolysin).

(3) The reduction of blood flow to the arm and/or circulatory stasis (increased peripheral vascular tone, increased viscosity of blood, edema of injured arterial walls and muscle, hypotension, mechanical obstruction of the subclavian, axillary or brachial artery, *i.e.*, tourniquet, position of arm, etc.).

Therapeutically, little if anything can be done to abolish the release of active thromboplastin. This occurs only with healing, which requires a number of days for its completion. Treatment consists of the use of anticoagulants (heparin and bishydroxycoumarin),[8, 9, 11, 12–14, 22, 24, 28, 31, 47, 49, 51] plus measures to increase and maintain an adequate blood flow through the extremity.

Intra-arterial injection, suspected as well as confirmed, is a medical emergency. All else assumes secondary importance to permit immediate, intensive treatment.[9, 11, 13, 14, 31, 49] As with any other catastrophy, an orderly plan of management should be part of the indoctrination of all anesthesia personnel, to forestall chaos and panic. The surgeon must be told what has happened and made well aware of the possible outcome.[8, 9] Elective operations must be cancelled. The urgency of an emergency operation should be a surgical decision. If operation must continue, treatment of the extremity should be started first.[13, 14] Where this is not possible, treatment should be instituted during operation. The arm should be positioned so that it is visible and easily accessible. Notes should be made of all changes in the arm, time, treatment and personnel involved. Accurate and complete records must be kept in view of the possibility of future legal action.

Anticoagulant Therapy. Heparin should be administered as soon as possible following the accident. This should force cancellation of elective operations. If emergency operation must continue, heparin should be withheld for at least 2 to 3 hours following its completion.[9, 13] This time interval should be adequate to minimize postoperative bleeding but it is not a guarantee against it. Heparinization makes nerve block hazardous and should be withheld until either a brachial plexus or stellate ganglion block is first performed. The former block is preferred.[8, 9, 11, 13, 14, 21, 22, 24, 31, 37, 47, 49]

Since continuous sympathetic block will be needed for an indefinite period, a catheter technique should be instituted to avoid the danger of subsequent blocks in a heparinized patient.

An accepted regime for heparinization should be followed. Beneficial effects are obtained when coagulation time is approximately twice its original value.[9] A suggested dosage schedule is 7,500 to 10,000 units initially followed by 7,500 units every 8 hours. All doses are given intravenously after careful check of daily coagulation time. Anticoagulant therapy must be continued as long as there is any evidence of impaired peripheral circulation. Complete thrombosis may not occur for 2 weeks in these cases.[8, 9, 13]

When prolonged use of anticoagulants becomes necessary, a bishydroxycoumarin type drug which may be given orally, should be substituted for herapin.[8, 9, 13] A daily prothrombin time should be done to follow the anticoagulant effect; a value near 30 per cent should be maintained. A drug such as warfarin may also be used; initial dose: 40 to 60 mg.; maintenance dose: 5 to 10 mg. per day. Heparin should be continued for 24 to 48 hours after the start of bishydroxycoumarin to allow time for the latter to take full effect.[9, 13]

Heparin (20,000 units) has been injected into the damaged artery through the same

needle, left in place, after the thiopental had been given.[13, 14, 24, 31, 49] If the needle has been removed, puncture of the subclavian artery is suggested.[13, 14, 24, 31, 49] Intravenous doses of heparin are immediately effective and probably safer for the person inexperienced in routine subclavian puncture. The advantage of intra-arterial heparin over effective intravenous doses has not been established. The 20,000-unit dose of heparin suggested by Dundee [13] for intra-arterial injection appears to be dangerously high in terms of the heparin preparations in this country.

The anticoagulants, by inhibiting thrombosis, maintain a good active peripheral blood flow which is vital for healing. Kinmonth and Shepherd [28] obtained this effect in the rabbit. Full heparinization reduced the amount of ear necrosis from 14.5 to an average of 9.2 sq. cm. They also demonstrated the value of prolonged heparinization. After two days of heparin, the loss was reduced from 14.5 to 11.7 sq. cm.; after 4 days, this loss was further reduced to 7.8 sq. cm.

It is doubtful whether even dangerously large doses of anticoagulants could prevent thrombosis following extensive arterial damage by thiopental.

Arterial Dilatation. Maximal dilatation of all arm vessels is desirable following intra-arterial thiopental. It increases peripheral blood flow, which decreases edema, dilutes the active thromboplastin and flushes out aggregates of platelets which accumulate in sites of injury. Vasodilatation may be produced by block or inhibition of the sympathetic nerve supply to the arm or by the administration of various agents into or around the damaged artery. Sympathetic nerve block (brachial plexus or stellate ganglion) is one of the best methods of producing dilatation of the arm vessels. Either should be used immediately when intra-arterial injection is suspected. Continuous brachial plexus block is preferable because it effectively relieves the intense pain which is usually present. Pain may cause reflex vasoconstriction of the arm vessels. Continuous sympathetic block should be maintained for days, if necessary.

General anesthesia using cyclopropane and/or ether is also a very effective vasodilator.[1, 2, 9, 13, 14, 22, 24, 31] The immediate availability of the anesthesia machine, which was probably already prepared for use prior to the accident, provides the most direct and immediate method of obtaining vasodilatation and pain relief, equal to that produced by nerve block.[1, 2, 8, 9] General anesthesia with cyclopropane should be used immediately after a diagnosis of intra-arterial injection has been made. The patient is usually semiconscious, writhing with pain and rapidly awakening. General anesthesia is excellent for this situation. First plane anesthesia [1, 2] is sufficient and can be continued until the patient's condition is fully evaluated and other therapy, such as nerve block, instituted. It is especially useful, if heparin has already been given. It may be continued if the surgical emergency demands it.

Kinmonth and Shepherd [28] confirmed the protective value of sympathetic block in the treatment of this complication. Surgical sympathectomy reduced the area of ear gangrene following thiopental from 14.5 to 8.8 sq. cm. This was almost as effective as full heparinization for 4 days (7.8 sq. cm.). Intra-arterial procaine offered no protection.

Other measures have been used to produce vasodilation. Intra-arterial injections of papaverine (40 to 80 mg. in 10 to 20 ml. of normal salt solution) [13, 14, 22, 24, 31, 40, 45, 49] and tolazoline (50 ml., 1 per cent),[12-14, 22, 31] have been enthusiastically advocated because of their excellent spasmolytic effect. Since spasm is not present in this injury, the effectiveness of these drugs could be much less than previously supposed. Their vascular dilating effect has never been measured in this injury. Both are inferior to sympathetic nerve block for producing dilatation.[17]

Local anesthetics [12-14, 22, 24, 31, 49] in various concentrations, have also been used by intra-arterial and peri-arterial injection to produce vasodilation. Procaine has had the widest use. Although it does have a dilating effect on vessels in spasm, it has never demonstrated this effect in thiopental injury. Kinmonth and Shepherd found it without effect.

Attempts to produce reflex vasodilation by the application of heat to the uninvolved extremities, has been unsuccessful.[9]

Intra-Arterial Injection of Various Substances. Direct injection of various substances

into the damaged artery has been proposed to produce the following effects:

(1) Dilution of the thiopental still in the arterial tree.

(2) Vasodilation (papaverine, tolazoline, local anesthetics).

(3) Local heparin effect within the artery.

It had been thought that thiopental could be trapped in the arterial tree after injection by the spasm which developed. Intra-arterial injection of normal salt solution and various volumes of procaine[12–14] were used to dilute the "pooled" drug. Injection was made through the same needle left in the artery or, if the needle had been removed, into the subclavian artery. There is no evidence that arterial spasm or pooling of thiopental exist in this condition. Some benefit of intra-arterial flushing might arise from dilution of active thromboplastin and washing out aggregates of platelets that have accumulated, but this effect could only be transient.

Surgical Treatment. Present-day advances in vascular surgery have very limited application in the treatment of this complication.[9] While thrombectomy and endarterectomy have successfully been performed in the larger arteries of the arm down to the wrist, it is impossible to remove the many thrombi lodged in the smaller arteries and arterioles of the hand and fingers. Thrombectomy may establish good pulsation of the radial and ulnar arteries to the level of the wrist with no improvement in the condition of the hand or distal forearm.[9] In the rare instance where only a segment of a larger artery appears to be thrombosed and presumably damaged, perhaps arterial grafting could be tried.

Other Measures. The intense pain of this complication must be controlled by narcotics if brachial plexus block has not been completely effective. Pain may cause marked reflex vasoconstriction of the arm and reduce peripheral blood flow. Hypotension should be treated by parenteral fluids which also improve hydration and prevent hemoconcentration. Heat or cold should not be applied. The arm should remain elevated to the level of the heart to permit free venous return and thus prevent venous thrombosis which can develop when arterial circulation is sluggish.

Medicolegal Aspects

The medicolegal implications of these cases are obvious.[36] If these cases reach the trial court, the outcome is uniformly bad for the physician. Where a portion of the arm or hand has been lost, the evidence is obviously overwhelming. This was well illustrated by a recent malpractice action in which we had more than a passing interest. A patient, who had entered the hospital for minor elective surgery, was given an injection of 3 ml. of 5 per cent thiopental by an anesthesia resident for induction of general anesthesia. Injection was made into the brachial artery as a result of which, gangrene developed, necessitating amputation of the forearm. Malpractice action was entered against the surgeon and the physician-anesthetist in charge. Neither was present at the time of injection. The resident physician was not involved in the action. After a trial which lasted for 3 weeks, a verdict in favor of the plaintiff was returned awarding $75,000.00 damages. The verdict of the lower court was upheld by the Supreme Court. Both physicians were found negligent. The court could not excuse the intra-arterial injection. This case should never have reached the courtroom. According to the doctrine of *res ipsa loquitur*, it was lost as soon as the trial began and the patient appeared.

It is understandable that physicians are reluctant to report such cases especially if the possibility of litigation still remains. Even after a case has been tried, few physicians wish to stir up its bitter memories. If a trial is pending, it is unwise to publish a case report. Many years may lapse if publication is withheld until the trial is completed. In the case mentioned, the final decision was not obtained for five and one-half years. Yet, failure to record the lessons learned, deprives further patients of tested methods of prophylaxis and treatment. Hence, the report that a certain phenothiazine compound has produced gangrene of the hand and fingers in 3 patients following intra-arterial injection, will never appear in the literature, and the unsuspecting physician will continue to use the drug until he suddenly discovers the injury it can cause.

Discussion and Conclusions

A review of the literature reveals an amazing scarcity of articles devoted to this subject. The majority are brief case reports or comments on these case reports. The comprehensive work by Cohen stands out because of the objective study of all phases of this unusual type of arterial injury. Most authors (the present one included) refer, directly or indirectly, to this article. The only significant contributions which have appeared since Cohen's publication have come from the lab-

oratory studies of Kinmonth and Shepherd [28] and Burn and his associates.[4, 5] For the first time the effects of intra-arterial thiopental were studied under controlled conditions in laboratory animals (rabbit, dog, and cat). These studies revealed a close similarity between the arterial injury and tissue damage observed in the ear of the rabbit and the human arm, following intra-arterial thiopental injection. This may not permit application of the results of animal investigation to the clinical situation, but in the absence of other data, these findings appear significant.

These studies demonstrated that the chemical properties of thiopental, rather than its alkalinity, causes injury to the arterial lining. This is substantiated by the clinical and experimental observations that higher concentrations of thiopental produce greater irritation and tissue loss. The intima of man apparently can safely tolerate thiopental concentrations of 25 mg./ml. or 2½ per cent. When this level is exceeded, thiopental produces a chemical endarteritis and destruction of the inner layers of the arterial wall with eventual thrombosis. The depth of the vascular injury is directly proportional to the concentration of the drug.

The existence and importance of arterial spasm in this type of injury is disproved. The use of spasmolytic agents to treat arterial damage appears to have little physiologic basis.

Animal studies demonstrated the therapeutic benefit of anticoagulants and sympathectomy in the treatment of arterial injury due to thiopental. A rational regime of treatment should employ: (1) brachial plexus block and/or general anesthesia with cyclopropane; (2) adequate and early heparinization; (3) cancellation of elective operations, and (4) local intra-arterial injection of drugs (if needle still remains in artery).

A sufficiently large number of patients have not been treated to permit a clear evaluation of the benefits of one type of treatment over another, or a comparison of the results. Clinicians who have observed the rapidly progressive death of an arm following the intra-arterial injection of thiopental despite treatment, are impressed by the irreversibility of this reaction; those who have seen an arm saved, are much more optimistic.

Despite all precautions and suggestions, unrecognized arterial puncture will continue to occur. Serious sequelae following injection can be greatly minimized or completely prevented by the routine use of the 2½ per cent solutions.

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