

THE LIMITATIONS OF INTRAVENOUS MEDICATION *

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Therapy, as other branches of medicine, is subject to influences which, temporarily at least, tend to over-emphasize the value of certain procedures. However, the gradual accumulation of new knowledge concerning the value of these procedures usually brings about a clearer recognition of their limitations. Of recent years, the practice of intravenous medication has come to the front to an ever-increasing extent; and, though by no means a new procedure, its application to the treatment of disease has assumed such proportions that it is both timely and important to consider for a moment the real merits and limitations of this form of therapy.

Of course, it is utterly impossible to cover this subject exhaustively in a brief article. All I can hope for is to point out some of the pharmacologic principles involved, illustrating them by a few examples, and to leave you in that healthful state of mind which demands proof in every instance before accepting claims in favor of intravenous medication. First of all, let us inquire into the reasons for this tremendous increase in the popularity of intravenous injections, for, as in other matters, I believe that the historical development of any procedure often throws light on the cause of its introduction and later practice.

HISTORY

Intravenous medication is not of modern origin; on the contrary, it antedates the discovery of the administration of remedies by subcutaneous injection. An English student of this subject¹ attributes the discovery of intravenous medication to Christopher Wren, a professor of astronomy at Oxford University, who, in 1656, made experiments on dogs, and showed that medicines could be introduced directly into the veins without disastrous effect. I believe that these experiments were the natural result of Harvey's discovery (1628) of the circulation of the blood, and they were probably devised to facilitate the rapid distribution of remedies in the body. A year later (1657), the first intravenous injection was made on man, and this was followed by numerous attempts to treat diseases by this method with a great variety of drugs. Crude empiricism characterized this period. All conceivable substances were injected, indiscriminately. A certain Dr. Hale of Boston had even the curiosity to inject into his own veins castor oil in order to test its purgative effect. Strange to say, he survived long enough to write down his experiences. We may look with ridicule on these early attempts; but I dare say that future generations may find amusement in some of our present-day experiments.

The modern application of intravenous medication began with Baccelli's² introduction of the intravenous injection of quinin for the treatment of malaria (1890). He advocated this method as a routine treatment, on the assumption that the drug is brought immediately

into contact with the parasites, whereas, given by mouth, the time required by absorption would necessarily delay the action. This was soon followed by Credé's³ treatment of septicemia by means of intravenous injection of colloidal metals. The reports of this period, as of the former, showed, however, that intravenous medication is not without danger, and consequently it did not come into vogue.

About twenty years later (1910), the discovery and use of arsphenamin in the treatment of syphilis revolutionized medical practice in this respect. Although this drug, given intramuscularly, produced a marvellous effect on the lesions, and caused the rapid disappearance of the parasites, it was soon realized that the local reactions at the site of injection were exceedingly objectionable, so, as a last resort, the intravenous route was chosen; and now, I dare say, millions of such intravenous injections have been given. Hence, the intravenous use of arsphenamin and its substitutes has done more than any other single factor to popularize intravenous treatment. Whereas, in former years, the average physician regarded an intravenous injection as a minor surgical operation requiring considerable practice and preparation, he now had to familiarize himself with this technic; and so it came about that intravenous injections were made on a fairly large scale by the practitioner. Most of the respect for the ever-existing possibility of dangerous reactions resulting from intravenous therapy then vanished, in spite of the fact that careful observers, from time to time, voiced a warning against the careless and indiscriminate use of arsenicals by this route. It is surprising, however, considering the enormous number of arsphenamin injections given, that the reports of untoward reactions have not been more numerous.

THERAPEUTIC EFFECT

This demonstration of the relative harmlessness of intravenous arsphenamin injections has prompted physicians to apply this method within recent years to other drugs and to other diseases, principally on the assumption that intravenous injection is of necessity followed by a more powerful therapeutic effect than is administration of the drug through other channels. The fact was forgotten that the intravenous administration of arsphenamin was simply an attempt to avoid pain and local reaction, and that it was not introduced in order to increase the therapeutic effect. I want to lay particular stress on this point, as this misconception seems to be quite prevalent among physicians and pharmacologists, and it is largely responsible for the present popularity of intravenous medication. I particularly call your attention to the data furnished by Fordyce, Craig, Harrison, Wechselmann and others which add assurance of the therapeutic efficiency of intramuscular and subcutaneous injection; and, during the last three years, we have been able to establish this fact by well-controlled experiments on animals, using a quantitative method. Thus, we showed⁴ that the parasitocidal effect of injections of arsphenamin and neo-arsphenamin given intramuscularly is as good as that of the same dosage given intravenously.

That this should be so is not at all surprising in the light of some recent work of ours⁵ on the mode of action of these arsenicals. Arsphenamin of good qual-

* Chairman's address, read before the Section on Pharmacology and Therapeutics at the Seventy-Third Annual Session of the American Medical Association, St. Louis, May, 1922.

1. Fortescue-Brickdale, J. M.: *Guy's Hosp. Rep.* 58:15, 1904. Eggleston, Cary: *Internat. Clin.* 2:130, 1917.

2. Baccelli, G.: *Tr. Tenth Internat. Med. Cong.* 2:138, Part 5, 1890.

3. Credé: *Berl. klin. Wehnschr.* 38:941, 1901.

4. Voegtlin, Carl, and Smith, H. W.: *J. Pharmacol. & Exper. Therap.* 17:357 (June) 1921.

5. Voegtlin, Carl, and Smith, H. W.: *J. Pharmacol. & Exper. Therap.* 15:475 (July) 1920.

ity we believe to be practically nontoxic per se; but, after its introduction into the animal body, there is gradually formed from it, by partial oxidation, an extremely toxic modification (arsenoxid), which exerts its destructive action on the parasites and, to a lesser extent, on the tissues of the host. Therefore, we must regard arsphenamin as a drug which, after its introduction into the body, forms a depot of a potential drug. When arsphenamin is given intravenously, the depot is more widely spread over the body than when the drug is given intramuscularly, where it remains localized for at least a short time. Nevertheless, in principle, the intravenous injection establishes a depot just as does the intramuscular, and the foregoing experiments clearly prove that it matters little, so far as the therapeutic effect is concerned, whether this depot of arsphenamin is scattered all over the body or is confined to one muscle. The active modification of the drug "arsenoxid" is formed in both cases, and it reaches the parasites continuously by way of the circulation. It is this continuous stream of the active modification, to which the parasites are exposed over many hours, which causes their death.

It having thus been shown that arsphenamin when given intravenously exerts no more powerful parasitocidal effect than when injected intramuscularly, and that the intravenous method was chosen in order to avoid local reactions, the question arises: Are there any drugs which, under certain conditions, give better therapeutic results when injected intravenously? I believe that we must answer this question in the affirmative, as, for instance, when time is an important element in the treatment or when the drug is not sufficiently absorbed by other channels. The intravenous injection of quinin in malignant malaria, of strophanthin in certain cardiac cases, of diphtheria antitoxin in severe diphtheria, is not merely advisable but is absolutely indicated as an emergency measure. Under such conditions, the physician cannot afford the delay incident to the administration of these remedies through other channels.

With regard to the efficacy of intravenous quinin injections, clinical observers agree that the action in extreme cases is more prompt than when the drug is given by mouth, and the patient's life may thus be saved. However, as soon as the critical condition has passed, quinin should be given by mouth for the reason that the available evidence shows that malaria is not more readily cured by intravenous medication;⁶ and this is supported by some recent findings⁷ which indicate that about 90 per cent. of the quinin injected intravenously in man disappears from the blood within one minute, and is stored in the tissues.

Another example of the superior therapeutic effect of intravenous medication is the administration of salt solutions in severe hemorrhage.

With intravenous medication, the dosage required to cause a certain therapeutic effect is, with several drugs, considerably smaller than if treatment is given by other channels. Epinephrin, for instance, produces a much greater rise in blood pressure when injected into a vein than when given intramuscularly. On the other hand, the pressor effect is much more prolonged in the latter case, on account of the more gradual destruction of the drug by oxidation. If, therefore, we wish to counteract the depressing effect of certain drugs on the

blood pressure, such, for instance, as arsphenamin, we choose the intramuscular injection of epinephrin in preference to the intravenous; and this principle holds for certain other drugs with symptomatic or etiotropic action. In other words, gradual absorption counteracts rapid destruction and elimination of the drug, and hence insures prolonged pharmacologic action, which often is a therapeutic desideratum.

COMMERCIALIZATION

What has been said concerning the superior value of intravenous medication with regard to the therapeutic effect is sufficient to raise a question as to the unscientific claims made by certain commercial interests who advertise a great variety of drugs put up in solution for intravenous use. Most of these products have not been included in New and Nonofficial Remedies by the Council on Pharmacy and Chemistry, because they are sold under misleading claims regarding their alleged safety and efficiency.⁸

SAFETY

We have so far considered principally the merits of the curative value of intravenous medication; but it is equally if not more important to inquire into the safety of this method of therapy.

It is perhaps unnecessary to call attention to the various possibilities of injury to the patient which may follow the use of a faulty technic. Asepsis is an essential requirement. It is also perfectly obvious that care should be exercised not to inject any air, solid particles or oil droplets, on account of the danger of embolism. However, this can be avoided by proper technic and, if necessary, filtration of the solution before injection. Furthermore, it is clearly evident that care should be exercised not to allow any of the drug to escape into the perivascular tissues in case such solutions cause local irritation. These untoward reactions are under the complete control of the physician. It sometimes happens that thrombosis occurs in the vein, which usually makes it impossible to use this vein for future injections.

It is, furthermore, of the utmost importance to realize that intravenous medication brings the drug into immediate contact with some vital organs, such as the heart and the central nervous system, and the drug concentration to which these organs are exposed is much greater, at least temporarily, than if the same dose had been given by the usual channels. Now, concentration is an all-important factor in drug action. All drugs, even the purest distilled water, are poisonous in higher concentration, and their beneficial effect is usually restricted to a range far below the toxic dose. Several hundred milligrams of caffeine can be given to dogs with impunity by hypodermic injection; whereas 5 milligrams per kilogram of body weight rapidly injected into a vein will cause death by cardiac failure. It appears to me not at all surprising, therefore, that serious reactions and even deaths sometimes occur from the rapid intravenous injection of such drugs as quinin, arsphenamin and its substitutes and strophanthin.

To be sure, the chances for the occurrence of such deplorable results can be reduced, if not completely avoided, by a full realization of the principles involved, followed by logical procedure. It should always be borne in mind that the rate of injection of any drug must be slow enough to give the blood a chance to dis-

6. Lane, Clayton: *Malaria: A Critical Review*, Trop. Dis. Bull. 19: 93, 1922.

7. Ramsden, W.; Lipkin, I. J., and Whitley, E.: *Ann. Trop. M. & Parasitol.* 12: 223 (Oct.) 1918.

8. Some of Loeser's Intravenous Solutions, J. A. M. A. 76: 1120 (April 16) 1921.

tribute it as effectively as possible. Theoretically, this can be accomplished by giving a relatively concentrated solution very slowly, or by using a very dilute solution. No general rules may be laid down to fit every case; suffice it to say that the number of untoward reactions to arsphenamin have been very materially reduced by the now prevalent use of dilute solutions, given slowly by means of the gravity method. Clinical experience in this matter has fully corroborated previous experiments made by Jackson and Smith⁹ of the Hygienic Laboratory. In these experiments, it was shown that the circulatory phenomena which ensue when an arsphenamin solution is rapidly injected into dogs can be avoided if the solution is given very slowly. That this should be so is not astonishing, if it is remembered that the proper functioning of the animal body depends on a nicely adjusted equilibrium of the body fluids and also of the tissues.

The application of chemistry and physics to the study of these equilibria has taught us much in recent years. We now know that the chemical composition of the blood and its physical chemical properties, such as osmotic pressure, hydrogen-ion concentration and colloidal state, are maintained with remarkable constancy and appear to be essential for physiologic wellbeing. Some of the factors of safety which operate in the maintenance of normal conditions have been recognized. The hydrogen-ion concentration, for instance, is kept at a certain level by means of the so-called buffer value of certain blood constituents, which neutralize any excess of hydrogen or hydroxyl ions introduced into the body. It is this mechanism which protects us under ordinary conditions against alkali or acid intoxication, so that we can take with impunity a considerable amount of alkali and acid with our food. Here again, however, we are forced to consider the rate of introduction. A certain amount of alkali which is well tolerated when given by mouth may prove fatal when injected rapidly intravenously; and, as Jackson and Smith⁹ point out, the acute circulatory reactions following the intravenous injection of alkaline solutions of arsphenamin may be largely due to the excess alkali, which may irritate the myocardium or the blood vessels.

In this connection, I can refer you to some unpublished experiments by Dr. M. I. Smith, which demonstrate the injurious effect of a rapid injection of sodium hydroxid. He found that, in cats, approximately 0.25 c.c. of a normal solution per kilogram of body weight caused a precipitate fall of blood pressure and complete circulatory collapse. These experiments may possibly be of significance in connection with the careless overalkalization of arsphenamin solutions. It would, therefore, seem highly desirable to develop proper buffer solutions to use with arsphenamin.

Again, as regards the colloidal condition of the blood, information is rapidly accumulating pointing to the danger involved from the injection of foreign colloids into the blood stream. Only recently, a death has been reported from the intravenous injection of acacia,¹⁰ a drug which was advocated, during the war, for combating severe hemorrhage and surgical shock. Foster and Whipple¹¹ have also pointed out that acacia injections decrease the coagulability of the blood and the regeneration of blood fibrin; and Hanzlik and Kars-

ner¹² have demonstrated the production of emboli and thrombi in the pulmonary vessels of guinea-pigs.

In the earliest days of the use of arsphenamin solutions, Wechselmann discovered the so-called "Wasserfehler," an acute reaction of the patient due to the presence of bacterial protein in the water used for making the drug solution. Moreover, Hunt¹³ attributes the higher toxicity of freshly prepared arsphenamin solutions, as compared with those which have stood or are heated for a short time, to the physical chemical properties of the former. Colloidal reactions between the drug and certain blood constituents may very well be responsible for these phenomena. Some recent work has shown that arsphenamin solutions approach the true colloidal state; and it is obvious that in a neutral medium, such as the blood, arsphenamin could not exist in true solution, for the reason that the arsphenamin base is completely precipitated at the neutral point. In the case of this drug, therefore, the conditions under which it is used for injection are of the greatest practical importance.

Several instances have come to my attention, even recently, in which the physician used by mistake the hydrochlorid instead of the alkaline solution, with disastrous effect. The injurious action of the hydrochlorid is probably due to the tendency of the hydrochloric acid of the drug to cause intra vitam precipitation of the free base or of a combination of the free base with blood protein. Acids are generally known to cause an aggregation of amphoteric colloids, such as proteins and arsphenamin; whereas alkalis tend to cause dispersion. As a matter of fact, Joseph¹⁴ has actually demonstrated the presence of such arsphenamin precipitates in the blood of animals injected with the hydrochlorid; whereas he failed to find them after the use of alkaline solutions of arsphenamin.

Another possibility for the production of reactions may perhaps be found in the use of large volumes of solutions improperly adjusted as to osmotic pressure. Hypotonic solutions of sodium chlorid given rapidly were shown, by Weed and his collaborators,¹⁵ to cause a great and sudden rise in cerebrospinal fluid pressure. Is it not possible that some of the symptoms which may follow the use of large amounts of drug solutions improperly adjusted in this respect and rapidly injected, especially under pathologic conditions of the central nervous system, could be attributed to sudden changes in cerebrospinal fluid pressure?

To sum up, it appears that a considerable amount of evidence has accumulated in recent years which indicates that the nicely adjusted equilibria of the blood and those of the easily accessible tissues may be temporarily upset by intravenous medication; and this disturbance may give rise to undesirable symptoms and even cause death.

These symptoms are due to various causes, some of which have already been clearly recognized. In many cases, untoward reactions can be avoided by introducing the drug solution at a slow rate, which permits the protective mechanism of the blood and tissues to operate efficiently; whereas, if the injection rate is too fast, this mechanism breaks down, and symptoms appear as visible results of the disturbance of the chemical or physical equilibrium of the blood and tissues.

9. Jackson, D. E., and Smith, M. I.: *J. Pharmacol. & Exper. Therap.* **12**: 221 (Nov.) 1918.

10. Olivecrona, H.: *Acta chir. Scandinav.* **54**: 1, 1921.

11. Foster, O. P., and Whipple, G. H.: *Am. J. Physiol.* **58**: 393-406 (Jan.) 1922.

12. Hanzlik, P. J., and Karsner, H. T.: *J. Pharmacol. & Exper. Therap.* **14**: 379, 425, 449, 479 (Jan.) 1920.

13. Hunt, Reid: *Some Factors Relating to the Toxic Action of Arsphenamin*, *J. A. M. A.* **76**: 854 (March 26) 1921.

14. Joseph, D.: *J. Exper. Med.* **14**: 83, 197, 1911.

15. Weed, L. H.: *The Cerebrospinal Fluid*, *Physiol. Rev.* **2**: 171, 1922.

Under certain pathologic conditions, this equilibrium is more easily disturbed. I shall only refer to the increased possibility of producing reactions in case of diminished functioning of the excretory organs. It is a common practice to test kidney function before and during a course of arsphenamin or its substitutes, for obvious reasons.

In special cases, previous treatment with a drug which produces a cumulative effect has also to be taken into account. In a case of malignant malaria which is treated intensively with quinin by mouth, it is decidedly dangerous to give the intravenous dose of quinin ordinarily recommended for this purpose without first allowing the patient to dispose of the drug previously given; and this is equally true of the arsenical treatment of syphilis, and of the intravenous use of strophanthin in cases which are under treatment with digitalis by mouth.

Having seen that intravenous medication is not necessarily superior therapeutically to other modes of drug administration, and having pointed out the numerous possibilities of injury to the patient inherent in this method, we should strive to simplify the technic of the administration of drugs wherever possible, in order to avoid the necessity of the injection of the medicament directly into the circulation. The subcutaneous injection of morphin and similar drugs is an exceedingly simple procedure, which very often is left to the attending nurse. Would it not be a great step forward if such drugs as arsphenamin or its substitutes could be given subcutaneously?

During the last year, in collaboration with Miss Dyer, Dr. Johnson and Mr. Thompson, I have studied such a preparation experimentally, and so far it meets all the essential requirements. It is prepared from arsphenamin, formaldehyd and sodium bisulphite; its aqueous solutions are very stable and do not increase in toxicity on standing for twenty-four hours or on vigorous shaking. Its parasitocidal effect is extremely constant, and it does not cause any local reactions if injected hypodermically. The chemotherapeutic index or, in other words, the ratio between the curative and the maximum tolerated dose is as good as in the case of arsphenamin. The drug is now being tested clinically, and, should our hopes be fulfilled, I believe that it will have a considerable effect on the practical problem of the control of syphilis; for it stands to reason that such a preparation would make it possible for physicians who have not the required experience with intravenous arsphenamin treatment to give the treatment in this simple manner, if necessary under the general supervision of an experienced syphilologist, as advocated recently by Stokes.

DISEASE CONTROL AND PREVENTION

I believe that it should be emphasized in this connection that intravenous medication, of necessity, places decided restrictions on the treatment as well as on the prevention of certain diseases, on account of the more or less difficult technic inherent in this method. Take, for instance, the problem of the control and eradication of syphilis; it surely stands to reason that a simple technic of treatment, such as the subcutaneous injection, would make it possible to put a larger number of syphilitics under the controlling influence of the arsenicals; and this would unquestionably help in checking the spread of this disease, and it might also assist in its eradication.

Again, the practicability of the prevention of malaria by means of the oral administration of quinin rests exclusively on the fact that it is possible to produce a prophylactic effect by taking quinin tablets by mouth; and I doubt whether anybody would claim that the prevention of this disease could be made a feasible proposition if quinin had to be injected intravenously for this purpose. Therefore, every effort should be made to render the administration of such drugs as simple and safe as possible, without, however, sacrificing their therapeutic efficiency. Intravenous medication, to my mind, will never serve this purpose, and will always have a more or less restricted field of usefulness.

THE REAL THINGS IN MEDICINE *

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The minimum requirements for a career in medicine are a preliminary education, four years in a medical school, and a license to practice. While these requirements are indispensable, they are by no means sufficient. Three higher attributes stand out as real elements that make for a successful physician; without these, real success in medicine is impossible: brains, culture and character.

BRAINS

Brains are the alpha and omega of the man of medicine. We all recall the artist who, when asked what he mixed his paints with, replied: "With brains, sir." Not long ago when I was on the way to talk to college students on medicine as a profession, the wife of one of the faculty said: "Tell them that the one thing they ought to have is brains." She had made my speech. To begin the study of medicine without two good cerebral hemispheres thickly covered with a deep cortical layer is to invite failure. No encouragement should be extended to those about to enter the profession of medicine or to those already in to continue, unless they are supplied abundantly with gray matter. The misfits in medicine, as well as in other occupations, are due largely to a lack of understanding. There are some in the cornfield who ought to be in medicine; there are some in medicine who ought to be in the cornfield.

The study of medicine bestows no more brains and adds not one cubit to the mental stature. It provides only a few more implements of the mind to be used for good or for ill. Unless the roots are deeply planted in the soil of real learning, the study of any science narrowly pursued takes away from the natural resources of the mind more than it puts in. In other words, a finely endowed intellect is needed to carry on in the realm of science, to withstand its temptations toward the illogical, to keep clear headed in the midst of fact and fancy.

Such endowment comes not from science itself; it issues permanently from a mind nurtured in the ways of thinking. The handmaiden of brains, essential for the physician, is common sense, which is simply the ability to put brains to good account. In the words of Holmes, "Science is a first-rate piece of furniture for a man's upper chamber if he has common sense on the ground floor. But if a man hasn't got plenty of good common sense, the more science he has the worse for his patient."

* President's address, read before the Medical Society of the State of North Carolina, Winston-Salem, April 25, 1922.