TOXIC REACTIONS PRODUCED BY THE APPLICATION OF TRINITROPHENOL (PICRIC ACID) *

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Trinitrophenol (picric acid) not only occupies a prominent place in the surgical field, but in its many combinations is utilized extensively in the treatment of diseases of the skin. When applied to the skin it may act in two distinct ways, according to the physical make-up of the subject.

(*a*) In one class, nonsensitive to this chemical, enough may be absorbed to produce severe visceral symptoms and even death. This is especially true when the surface of the skin has been abraded. The reaction from this type is due to the absorption of toxic amounts.

(*b*) Small amounts, which may be considered nontoxic when applied to the normal or abraded skin, will produce certain cutaneous, visceral and central nervous system reactions in the so-called sensitive person. It is in this class that we are particularly interested.

Owing to the wide distribution of ointment bases containing trinitrophenol, the general practitioner and even some specialists are using these preparations not only in the treatment of burns, but as an application for certain conditions about the eyes and the mucous orifices and especially for hemorrhoids and their complications. It is also highly recommended for certain diseases of the skin.

The percentage of persons sensitive to trinitrophenol is approximately 4.

Skin sensitization tests were made on 100 students. On one arm, an area 2 cm. square was painted with a 5 per cent alcoholic solution of trinitrophenol; on the other arm, a similar area was painted with 5 per cent aqueous solution of tannic acid. There were no reactions to the tannic acid, but 4 per cent of the patients showed positive reactions to the trinitrophenol, two reactions being severe and extending far beyond the area of application.

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* Tests for trinitrophenol were made according to Peterson, Haines and Webster: Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1923, vol. 1, p. 707; vol. 2, p. 720.

We have noted that in severe trinitrophenol dermatitis following the application of comparatively small amounts of this substance in sensitive persons, the typical eruptions showing the characteristic yellow tinge will also appear in areas to which the acid has not been applied. We concluded that this dermatitis occurring at a distance was produced by a protein picrinate which was carried by the blood stream or the lymphatics to these areas, where it was split up into its component parts and the trinitrophenol radical or some of its modifications reunited with the epithelial cells. In order to lend evidence to this belief, the following experiments were performed.

EXPERIMENTAL WORK

The skin of a dog that had just died was shaved and painted with a 5 per cent alcoholic solution of trinitrophenol, removed, dried, washed with alcohol to remove the free acid, and then redried. It was cut into small slices with a microtome, since it was impossible to pulverize it by any other method, then washed with saline solution until the results of all tests for trinitrophenol were negative in the washings. One gram of this pulverized skin was placed in a colloidal bag filled with saline solution and placed in a dialyzing chamber—the dialysate was tested for trinitrophenol with negative results. It was shown that a saline solution of trinitrophenol readily passed through this bag. This is evidence of the firm union of the trinitrophenol with the cells of the skin.

A gram of skin prepared as described was then washed with saline solution until the filtrate gave negative reactions for trinitrophenol. The residue was dried, washed with alcohol to make it sterile, redried and mixed with sterile saline solution and injected subcutaneously into dogs. Substances that gave reactions for trinitrophenol were present in the urine on the sixth and seventh days. The blood gave negative reactions. These results gave evidence that the protiopicrinate was split up by the dogs' metabolic processes.

This test for sensitization to trinitrophenol will be of great value to the surgeon. An area of skin 2 cm. square can be painted with trinitrophenol twenty-four hours before an operation is performed. If the patient is sensitive to this chemical, a marked dermatitis will make its appearance within twenty-four hours, giving the operator the opportunity to prevent a severe reaction and the patient the benefit of a more satisfactory convalescence.

REACTIONS

Local.—In our clinical observations we see many cases of dermatitis of the face, hands and feet and of the anal and scrotal regions, due to the local application of ointments containing trinitrophenol. The subjective and objective symptoms are severe, there being no mild types. The majority of these manifestations remain local, but some of them become severely systemic.

Intense itching and burning, accompanied by irritability, are common to nearly all. At some portion of the involvement, the color of the skin leads one to suspect trinitrophenol. Permanent yellow staining of the nails

of the hands and feet is diagnostic. The eruption itself is characterized by irregularly shaped macules, papules, vesicles, blebs, excoriations and edema, and by dried yellow crusts which are the source of reabsorption.

In the maculopapular stage, the purplish yellow is characteristic, even in the distant lesions. The disappearance of the eruption is the same as any acute dermatitis.

Generalized.—These localized reactions may not be considered allergic, but may be followed by generalized cutaneous reactions and constitutional symptoms which are allergic in their nature. In one case, constitutional symptoms of an alarming nature developed.

REPORT OF CASE

A man, aged 35, was superficially burned on his face and hands in a dust explosion. An ointment containing trinitrophenol was applied. In twenty-four hours, vesicles appeared accompanied by severe burning and itching. After each application of this preparation, the symptoms increased until the patient was almost frantic. He became so ill that it was necessary to send him to the hospital. When seen by us he had a generalized exfoliating dermatitis with universal edema. With the exception of the yellowish tinge to the skin the condition resembled that in acute arsphenamine dermatitis. After six weeks he had apparently recovered and was able to resume his work. In a few days he returned to us complaining of difficulty in walking. His speech, which had formerly been rapid and concise, was slow and scanning. In fact, he could not pronounce many words and was unable to repeat short sentences. The pupils were dilated and unequal and reacted poorly to light and in accommodation. A well marked spasticity of the right leg was present, the knee jerk was exaggerated with slight clonus, and the patient was unable to stand with his eyes closed. His gait ended in a mincing step. The blood pressure was systolic 190 and diastolic 120. The Wassermann tests of the blood and spinal fluid were negative. The spinal fluid also gave negative reactions to other standard tests. The blood chemistry was well within normal limits. No albumin, casts or red blood cells were found in the urine. The patient was again hospitalized and put on a milk diet. In three weeks all symptoms referable to the central nervous system disappeared, and the blood pressure was reduced to 130 systolic and 80 diastolic and has remained within normal limits since that time.

We consider that the involvement of the central nervous system in this case was due to the absorption of trinitrophenol.

Malmejac [1] has shown that trinitrophenol is found in the blood serum and even in the spinal fluid in persons who have suffered from the toxic effect of this chemical.

While trinitrophenol was not demonstrated in the spinal fluid of this patient, we could not account for the strange manifestations on any other basis. In two other cases we observed a severe generalized trinitrophenol exfoliating dermatitis due to an abdominal application of this substance. Nervous irritability seems to be a common observation in all severe cases of trinitrophenol dermatitis.

1. Malmejac: Toxicology, Paris letter, J. A. M. A. **68**:923 (March 24) 1917.

In the treatment of burns, trinitrophenol has a twofold purpose: (1) to precipitate the scorched proteins, converting them into a supposedly nonsoluble protiopicrinate or some of its derivatives (we have proved in our animal experiments that these precipitates are absorbed and produce toxic symptoms), and (2) to destroy bacteria by a coagulable process, which it probably does.

We strongly advise the discontinuance of the use of trinitrophenol in the treatment of burns and various dermatoses. We also warn surgeons against its use as a sterlizing agent preceding operations, due to the fact that many persons are sensitive to this chemical and because it is easily absorbed by the intact skin and taken up by the lymphatics and blood stream.

EXPERIMENTS TO DETERMINE THE LETHAL DOSE OF TRINITROPHENOL FOR DOGS WHEN SUBCUTANEOUS INJECTIONS OF THIS SUBSTANCE DISSOLVED IN SALINE SOLUTION ARE GIVEN

Dog 10 was given injections with 0.05 Gm. trinitrophenol in saline solution per kilogram of body weight. The animal became ill within twenty-four hours. In three days the skin was stained a yellowish brown. The blood chemistry was not noticeably influenced by this injection. Albumin, casts and red blood cells appeared in the urine on the seventh day, but disappeared on the sixteenth day. The dog recovered. Tests for trinitrophenol in the blood and urine by potassium cyanide and barium chloride were positive six days after the injection.

Dog 11 was given injections with 0.075 Gm. in solution per kilogram of body weight. The animal became ill on the third day. The blood chemistry was not noticeably influenced. Albumin, casts and red blood cells were found. Both tests for trinitrophenol were positive in the blood urine on this day, but were negative on the twelfth day. The dog recovered.

The same experiment was repeated on dogs 12 and 13, with practically the same results.

Dog 7 was given injections with 0.10 Gm. per kilogram of weight by the foregoing method. The catheterized urine twenty hours later was filled with albumin, casts and red blood cells. The blood was positive for trinitrophenol by potassium cyanide tests. The blood chemistry was normal. The animal recovered.

The same dog was given injections four days later with 0.125 Gm. in solution per kilogram of body weight. Two hours later, the animal had a convulsion, became unconscious—head thrown back, eyes bulging and incessant movement of legs—and died three hours later.

It appears that the lethal dose injected subcutaneously into dogs is between 0.1 and 0.125 Gm. per kilogram of body weight, since larger doses than the latter will kill the animal promptly.

Autopsy on these animals shows that the subcutaneous fat, even at points removed from the area of injection, is stained yellow. The lungs are often stained a brownish yellow. The liver sometimes shows a cloudy swelling, but is not stained. The kidneys show a glomerulitis, and also involvement of the substance, ranging from cloudy swelling to gelatinous degeneration. The intestines are stained yellow. The intima of the great vessels is often stained yellow. (The animals die from respiratory paralysis.)

1. It is shown from these experiments that as the lethal dose of trinitrophenol is approached, the positive reactions for this substance in the blood and urine appear with greater promptness, being positive in one and one-half hours after a lethal dose.

2. The sublethal doses down to 0.05 Gm. will show transitory changes in the kidney; these changes will disappear in a short time.

3. It was demonstrated that the trinitrophenol in the blood stream appeared as a protein combination, since the blood positive for trinitrophenol when passed through a colloidal bag gives a negative reaction to the cyanide method. It was also noted that an aqueous solution of trinitrophenol readily passes through a colloidal bag.

4. Chemical changes in the blood of dogs poisoned with trinitrophenol are slight. The urine of these same dogs nearly always shows albumin casts and red blood cells.

EXPERIMENTS TO SHOW THE AMOUNT OF ABSORPTION OF TRINITROPHENOL WHEN APPLIED TO THE NORMAL SKIN OF DOGS

The dog's skin does not have nearly the same ratio of absorption as the skin of a human being, since it has no sweat glands. Fifty cubic centimeters of a 5 per cent alcoholic solution of trinitrophenol was applied to the intact skin of the dog. The blood showed a positive reaction for trinitrophenol after twenty-four hours.

Tests for trinitrophenol in the blood of human beings who have received applications of trinitrophenol on the skin have not been done, but we are sure that these tests would be positive.

We have proved that a certain percentage of persons are sensitive to the external application of trinitrophenol to the intact skin. We believe that this phenomenon is a true allergic reaction, that the trinitrophenol radical can be broken off from the protein complement and redeposited as a protein picrinate in a new cell, and that this process can be repeated again and again. This repeated absorption can produce changes in other organs, especially of the central nervous system, producing bizarre manifestations which can be mistaken for other conditions of the brain.

We believe that in nonsensitive subjects trinitrophenol applied to the intact skin for surgical sterilization will be absorbed to such an extent that it can be detected in the urine and blood.

The application of a solution of trinitrophenol to burned or abraded skin is dangerous even for nonsensitive persons, since many deaths have been reported from its application.

CONCLUSIONS

1. Trinitrophenol used externally in any form is likely to be followed by disagreeable or dangerous results in a certain percentage of subjects.

2. The percentage of so-called sensitive persons is approximately 4.

3. In experimental work it was shown that in either subcutaneous injection or the external application of trinitrophenol, this substance would appear in the blood and urine of dogs, and while this observation has not been demonstrated in human beings because of the shortness of time in the work, we believe that the same results can be duplicated.

4. We advise against the use of trinitrophenol to sterilize the field of operation and recommend the substitution of tannic acid in proprietary ointment bases.

ABSTRACT OF DISCUSSION

DR. WILLIAM ALLEN PUSEY, Chicago: I merely wish to say that I have seen cases of irritant dermatitis from butesin picrate.

DR. HARRY E. ALDERSON, San Francisco: I have seen a number of cases of dermatitis in patients whose skin was sterilized by solution of trinitrophenol (picric acid), and the dermatitis has extended far beyond the area to which it was applied. In a number of hospitals that I visit regularly this method of sterilization is used exclusively. I was talking to one of our leading surgeons, Dr. John Sperry, last week, and he has had a lot of experience with trinitrophenol. He said that in 255 cases in which he had performed an operation he had had no dermatitis, but in 4 per cent of the women who used a proprietary preparation containing picratol in the vagina an irritation developed extending over the outer surface. I spent two years as resident physician in a railway hospital twenty-five years ago, and it was common practice to cover the burns with a saturated solution of trinitrophenol. At that time no toxic effects were discovered.

DR. WERNER JADASSOHN, Zurich: The great interest in the report of these authors lies, in my opinion, in the fact that 4 per cent of all persons whom they examined were hypersensitive to trinitrophenol. In contradistinction to its use in the United States, we employe this substance very little.

A percentage of 4 is high for hypersensitive subjects. We must, however, take into consideration that a strong concentration was employed. It is nevertheless certain that 4 per cent represents a minimum of those hypersensitive to this concentration. Dr. Staehelin of the Zurich Clinic is now investigating the effect of different methods of testing for eczematous reactions. In my opinion, the reactions observed by the authors are probably of this type. Staehelin's investigations have shown that through simple painting, as has been done in these investigations with trinitrophenol, positive reactions are noted much more rarely than if the test employed is our usual method of functional skin test for eczema. This consists in the laying on of a piece of soaked linen and covering it with oiled silk

and adhesive plaster. These tests are left in place twenty-four hours. A further reason that 4 per cent is probably a minimum is that according to our experience with other substances, reactions are sometimes observed only after more than twenty-four hours have elapsed. We have, therefore, made it a rule to examine the test site during several days. A third reason that 4 per cent represents a minimum number of persons really hypersensitive is that until now the authors have tested only for eczematous reactions. The testing for urticarial hypersensitiveness, through application of the substance to a scratch, would perhaps have revealed more hypersensitive persons through the appearance of a urticarial immediate reaction at the place of testing. In this manner, Stauffer in Zurich in testing with ipecacuanha found, besides the patients with eczematous reactions, a large number who reacted only urticarially. With certain other substances we can find only urticarial reactions as, for instance, with ascaris; or only eczematous reactions as, for instance, with primrose.

I mention these matters because it seems to me that the demonstration of the frequent hypersensitiveness to trinitrophenol is not only of importance practically, but also of interest theoretically, and could perhaps, through further work in various directions, be important in the research of eczema.

DR. ARTHUR J. MARKLEY, Denver: In reference to butesin picrate I think this is one of the most virulent local remedies on the market. It should be borne in mind that butyn itself is capable of producing a violent skin reaction and probably combining it with trinitrophenol makes it even more effective.

DR. JAMES HERBERT MITCHELL, Chicago: I wish to record an experience similar to that of Dr. Pusey's. Last year while I was attending the meeting of this association, an old man whom I was treating ran out of ointment and used butesin picrate. When I returned he was covered with a dermatitis and was ill. I am glad Drs. McBride and Dennie have called attention to the danger of applications of trinitrophenol.

DR. CHARLES C. DENNIE, Kansas City, Mo.: In the majority of our cases the dermatitis was due to the application of butesin picrate and in a smaller number it was due to the use of trinitrophenol alone. The eruption caused by the use of either is indistinguishable from the other. The percentage of sensitive persons is greater following the use of butesin picrate because some persons will be sensitive to both chemicals and some to either one. Our main attempt in this work was to show that the application of trinitrophenol or its compounds to the intact skin was followed by the absorbtion of the trinitrophenol into the blood stream and its deposition into the fixed tissues before it was excreted in the urine; and the redeposition theory which consisted of the union of the trinitrophenol with the fixed cells, its splitting off and transportation by the lymphatics or blood stream to a distant place where it united with a totally different cell, producing a manifestation which resembled the former condition.

We found that 0.125 of trinitrophenol per kilogram of body weight when injected subcutaneously in dogs would produce death. There was practically no change in the blood chemistry, although the urine would contain red blood casts and albumin and the tests for trinitrophenol were positive. In some instances the lining of the blood vessels was stained yellow and the liver showed some pathologic changes. The dogs died of respiratory failure. These observations proved the first contention.

The redeposition of trinitrophenol in cells at a distance from those originally affected was proved by the colloidal bag experiment, and the injection of the picric proteinate under the skin of dogs and the recovery of this substance in the blood and urine of these animals.