SKIN SENSITIVITY TO CETRIMIDE (CTAB)

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CTAB—cetyl trimethyl ammonium bromide—was first introduced as a combined cleanser and skin antiseptic by Barnes (1942). It was subsequently incorporated in the Glasgow No. 9 cream for the treatment of burns (Colebrook and others, 1945). After bacteriological and clinical trial it was advocated for the initial treatment of wounds by Williams and others (1943, 1944). Both Colebrook and Williams reported cases of skin sensitivity to CTAB. The former worker, in a series of 2,000 burns treated with CTAB, noted only three cases of skin reaction; the latter, after patch-testing volunteers, concluded that the risk of skin sensitization to CTAB was slight.

Since 1944, CTAB (now officially known as cetrimide) has been used extensively in this hospital and in the numerous large factories in this area, both for the initial treatment of wounds and also during their subsequent redressing. We wish to record the occurrence of further cases of skin reaction to CTAB. In these cases the skin reaction caused considerable disability although in most instances the initial injury was trivial. In all, fourteen cases have been encountered since 1946. Typical case histories are quoted below.

Case Reports

Case 1.—A man, aged 44, employed as a maintenance worker, sustained a scalp wound while at work, and it was dressed at the factory surgery with acriflavine after preliminary cleansing with cetrimide. The wound did not heal and, after a fortnight's treatment with repeated dressings and cleansings at the factory, he was referred to the Accident Hospital, where again cetrimide was applied as a cleansing agent. When cetrimide was applied once more a week after he was first treated at this hospital, the patient developed a red, irritating dermatitis on the scalp round the injury. There also appeared a red streak running from this area of dermatitis across the temporal region down the cheek to the angle of the mouth and ending in a group of vesicles (fig. 1). The presence of this red streak, conforming to no anatomical structure, appeared to be due to the application of an irritating substance. No further

cetrimide was applied, and the erythema and vesiculation subsided and the wound healed within a week. Subsequent patch tests showed a strong vesicular reaction to 0.1 per cent. cetrimide.

Case 2.—A man, aged 32 years, employed as a die-caster, stated that he frequently sustained minor burns in the course of his work. If he treated the burns at home they healed well but if he had them treated at the factory surgery he got a rash round the burned area.

On this occasion, the patient had multiple small metal splash burns on the arm and back which were treated with 1 per cent. cetrimide and penicillin cream. Two days later he reported because of a rash which had developed on the areas cleaned with cetrimide. The rash consisted of multiple small vesicles with an underlying erythema. No more cetrimide was applied, the dressing of penicillin cream was continued, and both burns and dermatitis were healed in two weeks.

Case 3.—A man, aged 47, employed as a sheet metal worker, had a previous history of dermatitis following a burn which had been treated with Glasgow No. 9 (and probably cetrimide also) in 1946. Two previous burns treated in the same way had healed normally.

On this occasion he cut his left forearm while at work, and the wound was cleansed with cetrimide before suture. When the dressings were removed five days later he had a dermatitis over a rectangular area surrounding the cut. This dermatitis was pustular in nature and swabs yielded *Staph. aureus* (coagulase-positive). The condition had almost healed when, three weeks later, cetrimide was inadvertently applied to the arm. This produced an acute vesicular irritating eruption over the whole forearm, and one week later a secondary rash appeared on the face and calves—this latter site corresponding with an area of friction from Wellington boots which he had been wearing. This vesicular dermatitis became secondarily infected with *Staph. aureus*, and admission to hospital for five days was necessary. The patch test reaction to 1 per cent. cetrimide was violent, and in addition a mild reaction to sulphanilamide occurred.

This patient returned to our care on three further occasions, twice because of the application of cetrimide and once because he had been given sulphonamides by mouth.

During his first attack he lost twelve weeks' working time.

FIG. 1.—Skin sensitivity to cetrimide: erythematous reaction on scalp; red line running down side of face and ending in a group of vesicles.

FIG. 2.—Severe patch test reaction to 1 per cent. cetrimide, photographed ten days after application.

Clinical Findings

Diagnosis.—The clinical appearances of the skin reaction to cetrimide conform to those of any chemical sensitization reaction. The history of previous applications, with or without reaction, and an irritating vesicular dermatitis corresponding with the area of application, provide strong circumstantial evidence of the agent responsible. The main difficulty in detecting the cause of the rash in our patients had been the initial failure to recognize cetrimide as a possible sensitizing agent. In some cases in which early secondary infection has occurred the appearances may be confused with those of an infective dermatitis surrounding a septic abrasion. On occasion the local reaction is accompanied by a generalized vesicular dermatitis affecting areas of skin to which cetrimide has not been applied. Characteristically the areas affected by the secondary reaction are those exposed to friction. This "disseminated reaction" is especially liable to occur when the nature of the local rash is not recognized and the application of cetrimide is continued.

Patch Tests.—The diagnosis can always be confirmed by the patch test. This was performed on all of our patients—each patient being tested with all the likely agents to which he had been exposed. This usually included penicillin, sulpho-namides, flavine, lanette wax, cetrimide, and sometimes adhesive plaster. A control patch of saline was used.

A fine scratch was made in the horny layer insufficiently deep to draw blood. Over this scratch was placed a square of lint soaked in the appropriate chemical. This lint was held in place with a piece of lint 2 inches square coated with melted Unna's paste. All the patches were secured by a bandage. The dressings were removed in twenty-four hours and further observed after forty-eight hours. It was found that in sensitized patients 1 per cent. cetrimide (the strength previously recommended for use) produced a very severe reaction (fig. 2), and consequently 0.1 per cent. solution was used in later cases. The 0.1 per cent. solution produced in the sensitive patient severe itching in eight or ten hours; by twenty-four hours the site of the patch was raised and reddened, and by forty-eight hours a crop of very fine superficial vesicles appeared. The reaction then faded in a few days more. Many other patients tested in this way gave no reaction to cetrimide, and consequently the response cannot be one of simple irritation.

Eosinophilia.—Since in our experience eosinophilia frequently accompanies skin sensitivity reactions, a

study was made of the blood eosinophil counts of these patients. The technique used was the direct count described by Discombe (1946).

Those patients (three in number) who developed a secondary vesiculation on sites to which cetrimide had not been applied had high eosinophil counts (738 to 869 per c.mm. of blood), but those in which the vesiculation was confined to the original area of application showed no eosinophilia. Two patients who had cetrimide applied to an extensive area of skin had eosinophil counts of 425 to 456 per c.mm. of blood. Since the upper limit of normality for the eosinophil count is indefinite (conventionally taken as 320 per c.mm.), the interpretation of these last two results may be left open. In those patients who developed eosinophilia the maximum levels were reached on the eighth to tenth days after the application causing the skin reaction.

Thus the value of eosinophilia as an aid to the diagnosis of cetrimide sensitivity appears to be limited.

Sensitizing Applications and Duration of Sensitivity.—Although an accurate history was not always obtainable it appeared fairly certain that several applications of cetrimide were necessary before sensitization was induced. Most cases gave a clear history of previous applications of cetrimide without ill effect.

Patients patch tested eighteen months after their initial dermatitis gave positive results and so it is obvious that, once induced, the sensitivity is of long standing. Three of our patients had further reactions when cetrimide was inadvertently applied to their skins for subsequent injuries.

Duration of Disability.—With the exception of Case 3 who lost twelve weeks' working time, the usual duration of disability was two or three weeks. Thus of itself the condition is not very serious. But not infrequently the injury necessitating the use of cetrimide was trivial and would not ordinarily have resulted in any lost time. The need to recognize the true nature of the reaction is made greater by the tendency for factory workers to sustain repeated injuries, and consequently to have repeated applications of cetrimide in the factory surgery.

Experiments Designed to Determine the Sensitizing Chemical in Cetrimide

Since cetrimide is a complex mixture of chemicals, and since the formula of pure cetyl trimethyl ammonium bromide shows no relationship with that of other notorious sensitizing substances, the possibility that a contaminating chemical was

responsible for the reaction was investigated. Attempts to sensitize albino guinea-pigs by surface application and intradermal injection of the compound failed, and consequently we had to rely upon sensitized patients to volunteer for further patch tests. This reduced the number of observations that could be made.

A series of negative results with patch tests with potassium bromide indicated that sensitivity to the bromine ion was not the cause of the reaction. Three patients tested with cetyl trimethyl ammonium chloride produced positive patches. This further suggested that either the long-chain radicle or a contaminating chemical was the responsible agent. Accordingly a specially prepared sample of cetrimide was used to test three more patients. This "pure" cetrimide caused reactions equivalent to the impure product. Treatment with alkali (to eliminate organically bound bromine) also failed to destroy the chemical responsible for the reaction. Finally three patients sensitive to cetrimide failed to react to trimethylamine, a possible contaminant of cetrimide which has been recognized as a cause of dermatitis (Horner, 1934).

Thus these investigations were negative. Theoretically it is conceivable that the patients were initially sensitized by a chemical allied to cetrimide and that subsequently the reaction was elicited also by the "pure" compound. But on the other hand a clinical estimate of the severity of the skin responses to the "pure" and the commercial product suggested no difference in response. Although from a scientific point of view this problem has not yet been finally answered, for practical purposes it would appear that cetrimide, as produced commercially, is the agent responsible for the reaction.

Discussion

Although fourteen cases of skin sensitivity reaction to cetrimide have been observed, no further information as to the incidence of this condition can be derived from these figures. Since minor abrasions and burns are frequent in industry, and since cetrimide is used so extensively, it seems likely that the incidence figure of 1.5 per 1,000 reported by Colebrook is not an excessive estimate. But on the other hand where certain workers are repeatedly exposed to minor burns, for example, in die-casting, and consequently are subjected to repeated applications of cetrimide, the chances of inducing sensitivity reactions are increased. Among all the patients in whom we have diagnosed dressing

sensitivity, cetrimide was the most frequent single cause. This may simply reflect the widespread use of this compound, which is often regarded as quite innocuous.

Since the skin reaction may on occasion be severe, it appears to be wise to use cetrimide only for the primary cleansing of wounds. By eliminating multiple applications at subsequent re-dressings the chances of inducing sensitivity are reduced. Cetrimide is sometimes used as a skin antiseptic before penicillin injections. This again involves repeated application, and should be discouraged.

However, since cetrimide has many advantages as a wound cleanser it would seem neither desirable nor necessary to discontinue its use, so long as these precautions are observed. Clearly no cetrimide should be applied to patients who have already exhibited sensitivity rashes from its use.

Summary

1. Skin reactions in fourteen patients caused by the application of cetrimide (CTAB) are reported. The clinical findings and the results of patch tests are described. The rashes are due to skin sensitization.

2. Eosinophilia was found to accompany several of these rashes, particularly when they were extensive or involved body areas remote from the original application of cetrimide.

3. Attempts to find a pure form of cetrimide which did not elicit skin reactions in sensitized patients have failed.

4. Practical recommendations have been made on the basis of these findings.

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