TOPICAL ANAESTHETICS IN SKIN DISORDERS

A Survey of the Literature

By W. R. BETT, M.R.C.S., L.R.C.P., F.R.S.L., F.C.S.

The story begins in 1899 when Alfred Einhorn[1] reported the synthesis of procaine, for this stimulated a concentrated and prolonged search for the ideal topical anaesthetic. Particularly interested in the esters of benzoic and *p*-aminobenzoic acids, with procaine as the basic prototype molecule, research chemists were quick to note that alteration in any part of the three main constituents—acid, ester, and tertiary amino groups—altered anaesthetic potency and toxicity and that a more potent anaesthetic could be produced only at the cost of increased toxicity.

Topical anaesthetics are prescribed by the dermatologist, the proctologist, the gynaecologist, and the obstetrician for the relief of pruritus. Until recently, however, the majority of those in common use had certain drawbacks, particularly the production of sensitization and of contact dermatitis. These risks are frequently referred to in the literature. ' It must be kept in mind', D. M. Pillsbury and his colleagues[2] wrote in 1942, ' that many of the external and internal medicaments used to control itching are in themselves sensitizers, and prolongation of the itching may be unwittingly produced by their use. These substances include *local anaesthetics*. . . . '

J. H. Sequeira and co-authors[3] state that in pruritus ani ' Anaesthetic ointments should be avoided ' and that in pruritus vulvae ' the use of anaesthetic ointments is unwise.' ' Topically applied drugs such as . . . *cocaine derivatives*', according to R. Turell,[4] ' are potential allergens and may cause increased irritation or pruritic hyperexcitability', and, according to *Eden and Holland's Manual of Obstetrics*,[5] ' Applications containing benzocaine are strongly contraindicated (in pruritus) owing to their marked tendency to cause eczematous dermatitis, a state of affairs far worse than an uncomplicated pruritus.'

H. J. Wallace[6] admits that ' local anaesthetic preparations, such as carbolic acid 2 per cent., with or without the addition of 1 per cent. menthol, in zinc cream or in calamine lotion, and benzocaine, 2 per cent., in zinc cream . . . are sometimes useful during an acute phase of irritation (of pruritus ani)', but issues the warning that ' the risk of causing a secondary dermatitis must be fully appreciated.'

H. R. Vickers,[7] reviewing the causes of contact dermatitis, mentions 'various proprietary ointments containing local anaesthetics', and F. F. Hellies recommends that in the treatment of ' intolerable local itching ' ' Local anaesthetic ointments are as a rule best avoided as their effect is only temporary and they may lead to sensitization.' R. D. Sweet writes that in the treatment of anogenital pruritus ' Preparations containing benzocaine are dangerous if used for any length of time, because some people become sensitised to this with disastrous results.'

According to an annotation in *The Lancet*,[9] ' Local anaesthetic-ointments of the benzocaine class often sensitise the skin, and the contact dermatitis so provoked may become very severe before the doctor or the patient realises that it is being caused by the supposed remedy for the itching. Such a patient may be sensitised to related chemicals such as the sulphonamides, *p*-aminosalicylic acid, and hair dyes.'

New and Nonofficial Remedies, 1954, warns that ' All local anesthetic agents are toxic and the tolerance of patients varies ' (p. 35) and that ' Many, if not all, local anesthetics occasionally give rise to dermatitis ' (p. 37).

C. G. Lane and R. Luikart *ii*[11] review 107 cases from the literature of epidermal hypersensitivity to local anaesthetics, especially when these were used to relieve pruritus in the presence of an already irritated skin. Of these 78 (73 per cent.) were confirmed by positive patch test. They write: ' The paucity of case reports of the frequent sensitizers among the local anesthetic drugs is surprising. Such cases occur frequently.' In their experience collateral sensitivity among similar organic compounds ' is not infrequent and may be wide.' In the subsequent discussion Luikart expressed the opinion that ' Not only are

local anesthetics dangerous, but frequently the prescribing of a local anesthetic in an ointment base (as is usually done) exaggerates the patient's pruritus.'

Discussing the treatment of neurodermatitis, L. A. Brunsting[12] writes: 'A mistake is often made in prescribing ointments containing a local anesthetic agent, such as dibucaine hydrochloride (nupercaine) or benzocaine, for the relief of itching. Sooner or later, sensitivity to these agents develops and the original condition becomes aggravated and widespread.'

In the experience of R. L. Baer[13], 'local anaesthetics, as a group, cause a higher incidence of allergic contact dermatitis than any other group of compounds used in dermatological therapy at the present time.' In a recent article in the *British Dental Journal*, B. Russell[14] describes dermatitis as a greater hazard for dentists than for any of their professional colleagues. It may be due to primary irritants or to sensitizing substances, the commonest sensitizers being local anaesthetics, particularly those applied on the surface.

Derivatives of cocaine, such as benzocaine, according to E. Hunt[15] exercise a temporary anaesthetic effect, 'but their ultimate action may be disastrous and lead to the development of an acute dermatitis venenata. *Benzocaine* may cause an acutely inflamed erythematous eruption with bullae, which is often slow in resolving.'

Multiple Sensitivity

R. L. Baer[16] defines cross-sensitization as 'the phenomenon where the allergic sensitization, engendered by one compound, extends to one or more other compounds.' These other compounds are related chemically to the sensitizing compound.

The 'caine' anaesthetics, which are all derivatives of benzoic and *p*-aminobenzoic acids, differ from one another in the character of the side-chains attached to the benzene ring. Epidermal allergic responses to substances containing the benzene ring, such as the aniline (aminobenzene) dyes and the sulphonamides, are familiar phenomena. Sensitivity to one member of the group is often accompanied by a positive skin response to all other structurally related compounds.

Many instances are reported of cross-sensitivities to procaine. On these the most important relates to the *para*-amino grouping. Substances containing this grouping include novocaine, orthoform, stovaine, benzocaine, the sulphonamides, and *p*-phenylenediamine.

A. Tzanck and his colleagues[17] found that 90 per cent. of those sensitive to local anaesthetics were sensitive to *p*-phenylenediamine, while only 15 per cent. of those sensitive to *p*-phenylenediamine were sensitive to local anaesthetics. *p*-phenylenediamine is of practical importance because most hair dyes contain it.

It is generally appreciated that, unless itching is controlled quickly, a scratching habit develops which leads to trauma, so that infection is superimposed upon the original condition. In the past, however, many dermatologists have been reluctant to use topical anaesthetics in itching dermatoses for fear of masking symptoms and because of the risk of local reactions or generalized sensitivities.

At one time the introduction of histamine antagonists suggested that these might prove useful in the control of pruritus, but it became soon evident that 'anti-histamines can also cause sensitisation dermatitis after repeated local applications.'[18] In B. F. Russell's[19] experience 'Sensitization to antihistaminic drugs applied outwardly (for their antipruritic effects) is moderately common.' A good review entitled 'Dermites aux pommades antihistaminiques' is presented by E. Sidi, G. R. Melki, and R. Longueville.[20]

'Eurax'

The acaricidal properties of crotonyl-*n*-ethyl-*o*-toluidine ointment ('Eurax,' Geigy) have been known since 1946. In that year W. Burkhardt and R. Rymarowicz[21] reported that a 10 per cent. ointment applied twice with an interval of twenty-four hours without a preliminary bath produced prompt cure in 326 patients with scabies. No side-effects were noted. The ointment was useful also for accompanying pyoderma.

Antipruritic properties of 'Eurax' were described three years later. A. J. Tronstein,[22] successfully treating 109 scabetic patients (48 with accompanying pyoderma), remarks on the 'definite antipruritic value' of the ointment, and M. Couperus,[23] using 'Eurax' in 124 patients for control of pruritus in neurodermatitis, pruritus ani, pruritus vulvae, and dermatitis venenata, reported complete relief, lasting 6 to 10 hours, in 66.2 per cent., considerable relief in 27.4 per cent. and little or no relief in 6.4 per cent. In 121 patients with pruritic dermatoses treated by S. A. M. Johnson and J. W. Bringe,[24] 'Excellent to moderate relief was obtained in 74.3 per cent. Local reactions were noted in 4 per cent. 'Use of the drug for over a year did not decrease its usefulness as an antipruritic agent or cause local reaction.'

In a series of 120 scabetic patients treated by R. L. Patterson[25] with 'Eurax,' 'A definite antipruritic effect was noted by all patients, usually within an hour after application of the ointment.'

J. M. Hitch[26] finds 'Eurax' useful for emergency treatment, for temporary relief while a diagnosis is being made, and as an adjunct to

specific treatment. It possesses a low index of irritation and sensitization. ' Its sustained period of effectiveness and tendency not to " wear out " are definite assets', but ' Its field of usefulness for all physicians is limited by its strictly symptomatic effectiveness. It will not establish a correct diagnosis nor act as a specific remedy except in the parasitic dermatoses.' In a further paper Hitch[27] describes ' Eurax ' as ' an excellent antipruritic (in various pruritic dermatoses), essentially non-irritating except in acute eruptions, without systemic toxicity, and of low sensitizing index', and as ' probably especially efficacious as a symptomatic remedy in the neurodermatoses, chronic eczematoid dermatoses and toxic and allergic erythemas.'

P. Grüneis[28] confirms the good results obtained with ' Eurax ' in the treatment of pruritus in some 150 patients and its freedom from side-effects and toxicity, both local and general. His cases included pruritus vulvae in diabetes, pruritus ani, pruritus senilis, jaundice, penicillin allergy, bromide allergy, and chronic eczema.

The extensive literature on ' Eurax ' has but two reports of sensitization to the active ingredient, and several cases of sensitization to the base. S. M. Peck and T. J. Michelfelder[29] found one instance of sensitization to the active ingredient among 400 patients, and E. S. Bereston[30] reports another case of contact dermatitis from ' Eurax ' ointment, which was due to the active principle. (' Because of the rarity of this finding I felt that it should be reported.') A woman with long-standing pruritic recurrent eczema of the external auditory canals within 24 hours of applying ' Eurax ' to the external ears and to the surrounding skin during an exacerbation of her eczema complained of burning, itching, and swelling of these areas, extending down the cheeks to the chin and front of the neck. When seen on the following day, she had an erythematous vesicular and oedematous dermatitis of the external ears, cheeks, chin, and front of the upper neck. This subsided in a week with cold compresses of 1:30 aluminium acetate and a simple lotion. Reaction to patch tests with ' Eurax ' ointment was 4 + within 48 hours. Patch tests with the ointment base and the active chemical of ' Eurax ' elicited a 1 + reaction to the base in 48 hours and a negative reaction to the active chemical. A delayed 4 + reaction to the active chemical, with erythema and vesicle, appeared 24 hours after the patch test was removed.

M. J. Couperus,[23] commenting on the general absence of local or systemic reactions to ' Eurax', observes that the only unusual sensation noted by some patients is ' a transitory feeling of warmth upon application of the ointment to certain areas of the body, especially the inner thighs, scrotum, vulva, and eyelids. This sensation of warmth appeared a few seconds after application, and lasted for several minutes. None of the patients felt that this sensation was particularly objectionable.' Of 124 patients treated with ' Eurax ' for relief of pruritus three showed a local reaction which was a mild erythema and proved to be due to the washable ointment base.

B. Phillips[31] reports two cases of sensitivity to ' Teevex ' (' Eurax ' 5 per cent., *n*-dimethylaminoethyl-*n*-*p*-chlorbenzyl-α-aminopyridine hydrochloride 1 per cent.), in which patch tests were positive only for the cream base and not the antihistamine content of the cream.

' Quotane '

J. W. Wilson *iii* and his co-workers,[32] reporting the local anaesthetic activity of eight new 1-(β-dialkylaminoethoxy)-3-alkyl*iso*quinolines and one secondary amine of the same type, found that the most effective agent in this series was 3-butyl-1-(β - dimethylaminoethoxy) - *iso*quinoline. E. J. Fellows and E. Macko,[33] testing the local anaesthetic activity of a series of aminoalkoxy*iso*quinolines, noted that 1-(β-dimethylaminoethoxy)-3-*n*-butyl*iso*quinoline monohydrochloride ('Quotane') was outstanding in that an average of 75 minutes anaesthesia resulted from the application of 0.001 per cent. solution. The same authors[34] compared ' Quotane ' with cocaine, procaine, and dibucaine (' Nupercaine ') as regards toxicity and anaesthetic potency. Testing anaesthesia by absence of the winking reflex on touching the rabbit cornea with the rounded end of a fine glass rod, they found ' Quotane ' to be 1,000 times more active than cocaine, and 10 times more potent than dibucaine. Given intradermally to guinea-pigs, anaesthesia to electrical stimulation lasted one and a half times as long with ' Quotane ' as with dibucaine, and seven times as long as with procaine, in the same concentration. Intraperitoneally in rats ' Quotane ' was twice as toxic as cocaine and half as toxic as dibucaine. Massive doses given daily by mouth to rats and guinea-pigs produced no weight loss, toxic symptoms, or demonstrable tissue damage histopathologically. Intravenous administration in dogs caused a transient fall in blood-pressure.

E. F. Corson and his colleagues[35] treated 128 cases of chronic itching eruptions with ' Quotane', which they found effective in relieving itching, even in some types which had proved especially stubborn in past experience. They noted but one instance of evidence of irritation and none of sensitization. In a series of 250 patients, many of whom had shown irritation and/or sensitization reactions to previously applied medicaments, C. S. Livingood[36] found not one single true

sensitization reaction to 'Quotane.' F. W. Lynch and O. E. Ockuly[37] obtained most satisfactory results in anogenital pruritus, pruritus vulvae, and localized dry neurodermatitis (lichen chronicus simplex). In their experience the ointment can be applied safely to dry or moist inflamed skin for many months without sensitivity developing. D. Pillsbury[38] obtained relief of itching in 88 per cent. of some 700 patients, some of whom were treated for as long as 18 months with no evidence of sensitization. R. Gilman[39] used 'Quotane' in herpes zoster to relieve itching, pain, and burning, with 'surprisingly good' results even in those cases in which ointments are generally avoided.

W. H. Ramsey[40] treated 100 patients complaining of anorectal itching, burning, or pain with 'Quotane' in an effort to provide symptomatic relief of their discomfort; 37 of these were treated conservatively, i.e. with the ointment alone, and 67 with the ointment applied to post-operative wounds. In the first group the degree of relief from discomfort was fair in 3, good in 18, and excellent in 12, while in the second group it was fair in 5, good in 45, and excellent in 17. No undesirable side-effects could be attributed to the ointment, and no evidence was noted of development of drug sensitivity despite prolonged use, or of interference with healing of surgical wounds. The author concludes that 'because it appears to be a non-sensitizing yet effective anaesthetic ointment, the preparation should prove useful for the treatment of discomfort in proctologic practice.'

The literature contains only two reports of contact dermatitis due to 'Quotane.' In a patient treated by M. Grolnik[41] for two months, when patch-tested, 'Quotane' gave a 2 to 3 reaction (erythema, oedema, and scattered tiny vesicles). It is interesting to note that other local anaesthetics and related chemicals gave positive reactions (benzocaine 3°). The second case is reported by J. F. Daly.[42]

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