Schmidt, R.J. 1987

Dermatologica *174:* 272–279 (1987)

0011-9075/87/1746-0272 $ 2.75/0

Allergic Contact Dermatitis from Proprietary Topical Analgesic Sprays Containing 3-(Aminomethyl)-Pyridyl Salicylate

Richard J. Schmidt, Luis Fernández de Corres

Welsh School of Pharmacy, UWIST, Cardiff, UK; Servicio de Alergología, Hospital General Santiago Apostol, Vitoria, Spain

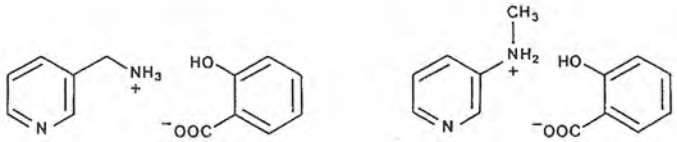
Key Words. Allergic contact dermatitis · Topical analgesic sprays · 3-(Aminomethyl)-pyridyl salicylate · 3-(Methylamino)-pyridyl salicylate · 3-(Aminomethyl)-pyridine · Aminopyridines

Abstract. Eleven cases of allergic contact dermatitis following the use of proprietary topical analgesic sprays (Algiospray® and Pangesic®) are described. Patch testing revealed that the adverse reactions were attributable to 3-(aminomethyl)-pyridine, which is present in these products as an ion pair with salicylic acid. The similarity between the two products investigated is not immediately apparent from the chemical nomenclature used by the manufacturers to describe the ingredients of their sprays.

Introduction

The investigation of an allergic contact dermatitis (ACD) that is evidently produced by the topical application of a proprietary analgesic spray should normally present few problems given a cooperative attitude by the manufacturer of the spray. Our attempts to obtain samples for testing in several such cases of ACD were, however, unsuccessful. Inspection of the container revealed that the product, Algiospray®, contained a compound described as 'piridil-3-metilamina, salicilato'. Because of the unavailability of this compound from the normal commercial sources, 3-(methylamino)-pyridyl salicylate[1] was synthesised and its identity compared with that of the compound present in the proprietary analgesic spray. It thus became apparent that the compound present in the spray was in fact 3-(aminomethyl)-pyridyl salicylate[1]. As a result of this observation, it was realised that the active ingredient of a second proprietary topical analgesic spray (Pangesic®), described as 'sali-

[1] Current IUPAC nomenclature for these compounds is as follows: 3-(aminomethyl)-pyridyl salicylate is 1-(3-pyridinyl)-methanamine 2-hydroxybenzoate (1:1) or 2-hydroxybenzoic acid compd with 1-(3-pyridinyl)-methanamine (1:1); 3-(methylamino)-pyridyl salicylate is N-(3-pyridinyl)-methanamine 2-hydroxybenzoate (1:1) or 2-hydroxybenzoic acid compd with N-(3-pyridinyl)-methanamine (1:1).



[1] [2]

Fig. 1. [1] 3-(Aminomethyl)-pyridyl salicylate. [2] 3-(Methylamino)-pyridyl salicylate.

cilato de beta-picolinamina', was chemically identical with that of the first since β-picoline is the term used to describe 3-(aminomethyl)-pyridine. (The structures these amines are shown in fig. 1.) The investigation described below was carried out in order to clarify the ambiguity we had found in the terminology used to describe the active ingredients of the two proprietary topical analgesic sprays. Moreover, ACD to topically applied amine/salicylate analgesics does not appear to have been described previously. We now report 11 cases of adverse skin reactions to two such analgesic products which are essentially identical with one another. The clinical studies were carried out in northern Spain where the two proprietary sprays are available for purchase from pharmacies.

Case reports

Case 1

A 46-year-old housewife with no history of either personal or familial atopy, but having an arthrosis and intact sensitivity to cobalt and nickel, presented with an exudative eczema on the knees after application of Algiospray. Her face and thighs were also affected.

Case 2

A 63-year-old male developed an exudative eczema of the right thorax after application of Pangesic to a thoracic trauma. The eruption healed after 1 month following topical and parenteral corticosteroid therapy.

Case 3

A 46-year-old female shop assistant was first referred to the clinic in December 1978 with redness and swelling of the arms and forearms after application of Algiospray. She had tolerated the spray 2 months previously; she later suffered a relapse after applying the spray to another person.

Case 4

A 46-year-old male mechanic presented with an exudative and itching dermatitis of the left forearm after application of Algiospray. The right forearm was also affected later.

Case 5

A 39-year-old housewife experienced a microvesicular eruption with a great deal of pruritus and profuse oozing on the dorsolumbar area 8–10 h after the application of Algiospray for dorsalgia. The dermatitis spread to the neck and buttocks, and healed after 1 month with topical and oral corticosteroid therapy.

Case 6

A 48-year-old housewife suffered great itching with erythematous vesicular lesions in the lumbar area 12 h after application of Algiospray. She had never used the product before. The eruption disappeared in 1 month following treatment with oral and topical corticosteroids.

Case 7

A 68-year-old housewife presented with an exudative and itching eczema on the right shoulder after the use of Algiospray for 4 months on a contusion. The dermatitis spread to the neck, both arms, and the eyelids. Four months later, an immediate anaphylactic reaction occurred after an intramuscular carbenicillin injection; she also suffered a flare of the dermatitis on the right shoulder.

Case 8

A 55-year-old male cabinetmaker with both a familial and personal history of atopy was admitted with a generalised dermatitis after the use of a suppository containing the piperazine salt of phenylbutazone (Carudol Rectal®). He reported the previous occurrence of contact eczema from an unidentified anti-inflammatory ointment, and a facial dermatitis lasting 3–4 days after applying Algiospray to another person.

Case 9

A 47-year-old postman reported having a bandage applied to a contusion on his ankle after spraying it with an unidentified topical analgesic. When the bandage was removed 3 days later, a vesicular, exudative, and pruritic dermatitis was observed. The lesion healed in 2 months. During consultation he had a hyperpigmented area measuring 5×10 cm on the dorsal aspect of his foot.

Case 10

A 26-year-old housewife developed an itching of her hands the day after applying Algiospray to her husband. She presented with a micropapular dermatitis on the lower half of her face and on the flexor aspects of her left hand. She recalled that she had suffered contact dermatitis from the same spray several years previously.

Case 11

A 52-year-old housewife with a familial but not personal history of atopy experienced a great itching with an erythematous and papular eruption on the 5th day of application of Algiospray to her back. The dermatitis spread beyond the area of application and in spite of parenteral and local corticosteroid treatment, it persisted for 6 weeks.

Materials and Methods

Algiospray® (Laboratorios Robert, SA, Barcelona, Spain) was purchased locally from a pharmacy in northern Spain, as was Pangesic® (Laboratorios Novag, SA, Barcelona, Spain).

3-Aminopyridine and 3-(aminomethyl)-pyridine were purchased from the Aldrich Chemical Co., Gillingham, UK. 3-(Aminomethyl)-pyridyl salicylate, 3-(methylamino)-pyridyl salicylate, 3-(methylamino)-pyridine, 3-(N-methylacetamido)-pyridine, and 3-(acetamido)-pyridine were synthesised as described below (see also fig. 2). Other chemical substances were laboratory grade reagents obtained from BDH Chemicals Ltd., Poole, UK.

Patch Testing

Algiospray or Pangesic was tested 'as is' in open (1 case) or closed (3 cases) patch tests, but because of the strong reactions produced the use of this test was discontinued. Nine further substances were tested at concentrations shown in table I or as described under Results. 3-(Aminomethyl)-pyridine produced very strong reactions in the first 4 cases tested hence the concentration was lowered from 10% w/v to 1% w/v. A 10% w/v solution was used, however, in control subjects. Patch tests with the European standard battery were also performed. Methyl salicylate (2% v/v in olive oil) was tested in only 3 cases (cases 3, 5 and 11).

Volumes of 0.05 ml of each solution were applied. Open patch tests were attemped first and, if readings at 24 h were negative, then a closed patch test with Al-test (Imeco AB, Sweden) was made in accordance with ICDRG recommendations. Readings were made at 20 min, 24 h, 48 h, and 96 h.

Forty control subjects were patch tested with substances 1, 3 and 4 (see table I), and their responses to components of the para-amino group from the standard battery also recorded.

Synthesis of 3-(Acetamido)-Pyridine

3-Aminopyridine (10 g) was acetylated in a mildly exothermic reaction following the addition of excess acetic anhydride. The crude product was obtained by the addition of excess xylene, boiling to expel acetic acid and excess acetic anhydride, and allowing to cool whereupon it separated from the xylene and crystallised on cooling. The crystalline material was washed with benzene and recrystallised from 1,4-dioxane.

Yield: 68% (9.8 g); pale pink prismatic needles; melting point 133–135 °C [133 °C, in ref. 1].

Synthesis of 3-(N-Methylacetamido)-Pyridine

Methylation of 3-(acetamido)-pyridine was achieved by an adaption of the monoalkylation procedure described by Bowman [2] for α-amidoketones.

Sodium hydride (50% dispersion in oil; 3.53 g = 0.07 *M*) was covered with dimethylformamide (30 ml)

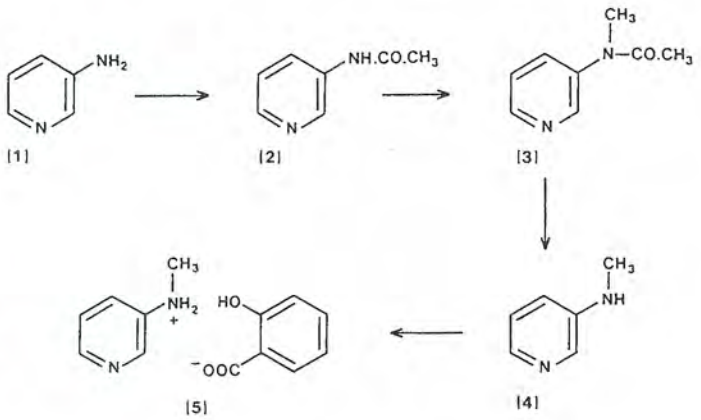


Fig. 2. Synthetic route to 3-(methylamino)-pyridyl salicylate. [1] 3-Aminopyridine. [2] 3-(Acetamido)-pyridine. [3] 3-(N-Methylacetamido)-pyridine. [4] 3-(Methylamino)-pyridine. [5] 3-(Methylamino)-pyridyl salicylate.

under nitrogen and a solution of 3-(acetamido)-pyridine (10 g=0.07 *M*) in dimethylformamide (50 ml) was added slowly with stirring, keeping the temperature below 40 °C. When evolution of hydrogen had ceased, methyl iodide (10.43 g=0.07 *M*) was added cautiously and the mixture kept at room temperature for 0.5 h. The resulting solution in dimethylformamide was washed 3 times with petroleum ether (40–60 °C) and the dimethylformamide removed under reduced pressure. The residue was taken up in absolute ethanol and silver nitrate (0.07 *M*) added. The precipitate of sodium nitrate and silver iodide was filtered off. The ethanolic filtrate was evaporated, taken up in chloroform:dichloromethane (2:1), and filtered and evaporated again. The product was distilled under high vacuum.

Yield 4.6 g; boiling point (<6 mm Hg) 140–144 °C [boiling point 145 °C at 11 mm Hg, in ref. 3]; melting point 64 °C; pale yellow liquid which later crystallised. Proton magnetic resonance (PMR): δ8.6, 1H+1H broad singlet (C-2 & C-6); δ7.75, 1H perturbed double doublet (C-5); δ7.5, 1H perturbed double doublet (C-4); δ3.35, 3H singlet (N-CH_3); δ2.0, 3H singlet (O-CO-CH_3).

Synthesis of 3-(Methylamino)-Pyridine

3-(N-methylacetamido)-pyridine (4.4 g) was hydrolysed by refluxing in hydrochloric acid (20 ml) for 1 h. An excess of potassium hydroxide pellets was added and the mixture extracted with chloroform (3×15 ml). The chloroform extracts were bulked and dried over anhydrous sodium sulphate. The crude amine remaining on evaporation of the chloroform was distilled under high vacuum.

Yield 2.2 g; boiling point (<6 mm Hg) 100 °C [118–120 °C at 12 mm Hg and 96 °C at 4 mm Hg, in ref. 3 and 4, respectively]; pale yellow liquid. PMR: δ7.95, 1H doublet (C-1); δ7.85, 1H double doublet (C-6); δ7.0, 1H double doublet (C-5); δ6.8, 1H perturbed double doublet (C-4); δ5.3, 1H broad singlet exchangeable with D_2O (-NH-); δ2.7, 3H singlet (N-CH_3).

Preparation of 3-(Methylamino)-Pyridyl Salicylate

Salicylic acid (0.65 g=0.0047 *M*) was added to 3-(methylamino)-pyridine (0.51 g=0.0047 *M*), in which it dissolved without significant evolution of heat. After several days, the salicylate salt crystallised out and was used without further purification.

The identity of the product was confirmed by PMR spectroscopy (CD_3OD). No unexplainable signals were observed.

Preparation of 3-(Aminomethyl)-Pyridyl Salicylate

Salicylic acid (1.28 g=0.0092 *M*) was added to 3-(aminomethyl)-pyridine (1.0 g=0.0092 *M*) in which it dissolved with evolution of heat. The salicylate salt crystallised on cooling and was recrystallised from absolute ethanol prior to use.

The identity of the product was confirmed by PMR spectroscopy (CD_3OD). No unexplainable signals were observed.

Extraction of Amine from Algiospray

The alcoholic solution of 'piridil-3-metilamina, salicilato' in the proprietary product Algiospray was evaporated to remove the alcoholic excipient. An excess of a concentrated aqueous solution of potassium hydroxide was added to the residue and the mixture extracted 3 times with chloroform. The chloroform extracts were bulked and dried over anhydrous sodium sulphate. Preparative thin-layer chromatography (see below) was used to prepare a pure sample of the amine thus isolated.

Preparative Thin-layer Chromatography

Preparative chromatography was carried out on kieselgel GF_{254} (Merck) layers (0.75 mm thick), developing in chloroform:methanol:diethylamine (70:25:5). The amine was visible under shortwave UV light (254 nm) as a black zone on a green fluorescent background. The zone corresponding to the amine was scraped from the plates and eluted from the silica using absolute ethanol containing 1% diethylamine. Evaporation of solvent afforded the purified amine.

In its PMR spectrum, the isolated material exhibited the following signals: δ8.5, 1H perturbed doublet (C-2); δ8.4, 1H perturbed doublet (C-6); δ7.6, 1H perturbed double doublet (C-5); δ7.2, 1H perturbed double doublet (C-4); δ3.85, 2H singlet ($-CH_2-NH_2$); δ1.85, 2H singlet exchangeable with D_2O ($-NH_2$). The spectrum was identical with that exhibited by purchased 3-(aminomethyl)-pyridine.

PMR Spectroscopy

Spectra were recorded on a Perkin Elmer R12 spectrometer (90 MHz) from $CDCl_3$ solution (unless otherwise stated), using tetramethylsilane as internal reference standard.

Table I. Substances tested

Material tested	Concentration
Algiospray or Pangesic	as is
(1) 3-(Methylamino)-pyridyl salicylate	10% w/v
(2) 3-(Aminomethyl)-pyridyl salicylate	10% w/v
(3) 3-(Methylamino)-pyridine	1% v/v
(4) 3-(Aminomethyl)-pyridine	1% v/v[c]
(5) 3-Aminopyridine	30% w/v
(6) Salicylic acid	1% w/v
PPD	0.5% w/v

All negative results indicate that no reaction in either open or closed tests was observed. NT= Not tested; petr. = white petrolatum.

Results

Of the 11 cases described, 4 are males and 7 are females. Their ages range between 26 and 68 years. In only 2 of the cases was there either a familial or personal history of atopy, but in 5 of the cases there was a history of another contact dermatosis.

In the cases of ACD described here, an exudative exzema appeared at the site of contact between 4 and 48 h after the application of Algiospray or Pangesic. In 6 of the cases there was oozing. In 3 cases the face was involved, presumably following contact with the aerosol particles. In all of these 3 cases, the patients had applied the spray to another person. In cases 8 and 10 the lesions healed in 7 and 10 days, respectively, but in the remaining cases the eruption persisted for a period of 1–2 months despite treatment. Patch testing was carried out between 1 week and 12 years after resolution of the last occurrence of ACD.

All patients were patch tested with ethyl salicylate (2% v/v in olive oil) but no reac-

Vehicle	Patch test results in the 11 cases										
	1	2	3	4	5	6	7	8	9	10	11
as is	3+[a]	NT	NT	NT	3+[a]	3+[b]	NT	NT	NT	NT	NT
water	–	–	–	–	3+[a]	–	–	–	–	–	–
water	2+[a]	2+[b]	–	–	3+[a]	2+[b]	2+[a]	–	2+[a]	2+[a]	2+[a]
olive oil	1+[a]	–	–	–	3+[a]	–	–	1+[a]	–	2+[a]	–
water	2+[b]	3+[b]	3+[b]	2+[a]	3+[a]	2+[b]	3+[a]	2+[a]	2+[a]	2+[a]	3+[a]
water	–	–	–	–	–	–	–	–	–	–	–
petr.	–	–	–	–	–	–	–	–	–	–	–
petr.	1+[a]	2+[a]	2+[d]	–	2+[a]	2+[a]	–	+[a]	+[a]	1+[a]	3+[a]

[a] Closed patch test; 96 h.
[b] Open patch test; 96 h.
[c] In cases 1, 2, 3 and 4 the concentration was 10% v/v.
[d] Result read at 120 h.

tions were observed. Those patients tested with methyl salicylate (cases 3, 5 and 11) similarly showed no reaction.

The intermediate compounds produced during the synthesis of 3-(methylamino)-pyridine (namely 3-[acetamido]-pyridine and 3-[N-methylacetamido]-pyridine) were ·o patch tested (30% w/v in water) : failed to elicit a reaction either in open or closed tests in any of the 11 patients tested.

Positive patch test reactions to other amines were observed in 9 of the 11 patients investigated. Paraphenylenediamine (PPD; 0.5% w/w in petrolatum) elicited positive reactions in 7 cases; an aniline dye (2% w/w in petrolatum) in 5 cases, with a doubtfully positive reaction in a 6th case; 'caine-mix' (7% w/w in petrolatum) in 4 cases; aminoglycoside antibiotics (neomycin, kanamycin, and aminosidin=paromomycin) evoked strong reactions in case 2; case 8 reacted strongly to both piperazine and phenylbutazone; case 11 reacted strongly to triethanolamine, and promethazine elicited reactions in both case 8 and case 11. Further results are recorded in table I.

In 40 control subjects tested, ten positive (1+) reactions to 3-(aminomethyl)-pyridine (10% v/v in water) were observed. Five of these were retested with a 1% v/v solution and failed to react. Only one of the control group reacted (1+) to the 1% solution of 3-(methylamino)-pyridine; another reacted to 3-(methylamino)-pyridyl salicylate. Seven of the control subjects reacted to PPD, 3 of whom also reacted to 3-(aminomethyl)-pyridine.

Discussion

The chemical analysis of the Algiospray indicated that the product contained 2-(aminomethyl)-pyridyl salicylate and not 3-(methylamino)-pyridyl salicylate. It was important to clarify this matter since a cursory translation of the declared active ingredient of the spray proved to be misleading. As a consequence of clarifying this matter, it became apparent that the product Pangesic was essentially identical with Algiospray and this was further confirmed by the observation that a patient who recalled the use of Pangesic exhibited patch test reactions that were indistinguishable from those exhibited by patients who had become sensitised to Algiospray.

It is clear from the patch test results that the ACD elicited by Algiospray and Pangesic may be ascribed to the 3-(aminomethyl)-pyridine moiety of the amine-salicylate ion pair present in these products. No reactions to salicylic acid were observed, nor to ethyl salicylate. This latter compound was included in the test battery since, theoretically, it may be produced from the reaction of free salicylic acid with the alcoholic excipient present in the products.

It was interesting to observe that 3 of the patients with ACD failed to react to the amine salicylate (compound 2 in table I) although they reacted to the free amine (compound 4 in table I). Likewise, the synthesised 3-(methylamino)-pyridine elicited reactions in 4 of the 14 patients tested whilst its salicylate salt (the active ingredient suggested by the label of the Algiospray) elicited a reaction in only 1 patient. One interpretation of these observations is that the metabolic fate of the amine salicylates in the skin varies between people – in some the amine and the salicylate are apparently dissociated from one another whilst in others the ion pair remains intact, thus impeding the haptenic activity of the amine. This scenario would suggest that the proprietary sprays contain small quantities of free amine to which the patients concerned have become sensitized. The existence of free amine in the sprays was not investigated.

The occurrence of co- or cross-sensitivity to various other amines (including the aminoglycoside antibiotics, piperazine, triethanolamine, promethazine, as well as the para-amino group components) in many of the patients and in some of the controls deserves comment. In 1977, Camarasa [5] reported that the incidence of PPD sensitization among patients attending contact clinics in Spain was almost 10% (which compares with figures of 8% for North America in 1972 [6] and 15% for Poland in 1970 [7]). The Spanish Contact Dermatitis Research Group identified black rubber gloves rather than hair dyes as the principal agents responsible for inducing PPD sensitivity. We believe that the observed PPD sensitivity may also be a reflection of a high background contact sensitivity to sulphonamides. The structural similarity between 3-(aminomethyl)-pyridine and components of the para-amino group (which includes PPD, sulphonamides, and 'caine' anaesthetics) is sufficient to suggest that cross-sensitivity reactions could occur. From the structural variety of the other amines involved in the patients investigated here, it would seem that cross-sensitivity is not the cause in those cases, but rather that the amines are in themselves more potent contact allergens than might generally be believed, especially in persons already sensitised to other amines.

Schmidt, R.J. 1987

Acknowledgement

Dr Fernández de Corres is grateful to the Labour, Health, and Social Security Department of the Basque Government for financial assistance.

References

1 Maier-Bode H. Darstellung von 3-Amino-Pyridin und 3,5-Diamino-Pyridin. Ber dt chem Ges 1936; 69B:1534–1537.
2 Bowman RE. Experiments towards the synthesis of ergot alkaloids and related structures. II. New alkylations on α-carbon and nitrogen in α-amidoketones. J chem Soc 1980:2126–2133.
3 Płażek E, Marcinków A, Stammer Ch. Badania nad 3-aminopirydyna. II. (Pochodne metylowane, acetylaminopirydyna, formyloaminopirydyna.) Roczn Chem 1935;15:365-377.
4 Clark-Lewis JW, Thompson MJ. Methylation of 3-aminopyridines and preparation of 2-amino-3-methylaminopyridine and 2:3-diaminopyridine. J chem Soc 1957:442–446.
5 Camarasa JMG. First epidemiological study of contact dermatitis in Spain – 1977. Acta dermvener 1979;suppl85:33–37.
6 Rudner EJ, et al. Epidemiology of contact dermatitis in North America: 1972. Archs Derm 1972; 108:537–541.
7 Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. Br J Derm 1970;83:543–545.

Received: September 26, 1986
Accepted: December 19, 1986

Richard J. Schmidt,
Welsh School of Pharmacy,
UWIST
PO Box 13,
Cardiff, Wales CF1 3XF (UK)