

Mechanism of allergic contact dermatitis from propacetamol: sensitization to activated *N,N*-diethylglycine

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In order to confirm the mechanism of skin sensitization to propacetamol, a pro-drug of acetaminophen, 3 patients with allergic contact dermatitis from propacetamol were patch tested with *N,N*-diethylglycine phenyl ester, an activated form of *N,N*-diethylglycine. Positive patch tests were observed in all the patients at 10% in pet., while 20 control patients remained negative. This strongly suggests that propacetamol is acting as an activated form of *N,N*-diethylglycine, transferring this part of the molecule to nucleophilic residues of proteins. This also explains why reactions to acetaminophen have never been observed in patients sensitized to propacetamol.

Key words: allergic contact dermatitis; propacetamol chlorhydrate; acetaminophen; activated *N,N*-diethylglycine; pro-drug; medicaments; occupational; nurses; hospital workers; health care workers.
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Propacetamol **1**, a water soluble *N,N*-diethylglycidyl ester of acetaminophen **2**, is a pro-drug widely used for its analgesic and antipyretic properties. After intravenous injection, either by non-specific esterases or by non-enzymatic mechanisms, propacetamol is readily hydrolysed into acetaminophen **2** and *N,N*-diethylglycine **3** (Fig. 1). Several cases of occupational contact dermatitis from this pro-drug have been reported in nurses handling propacetamol (1–4), with in all cases positive patch tests to propacetamol and negative patch tests to acetaminophen.

The propacetamol molecule contains 3 chemical functions that could potentially be involved in the skin sensitization process (5), *i.e.*, interaction with proteins: (1) the acetamide function present in the acetaminophen part of the molecule; (2) the *p*-aminophenol moiety that could be metabolized into a reactive intermediate; (3) the *N,N*-diethylglycidyl ester function. Previous studies performed to elucidate which part of the propacetamol molecule (6) was responsible for the sensitization have ruled out the first 2 possibilities, as patch tests to acetaminophen **2**, to acetamide-containing analogues (*i.e.*, acetanilide and phenacetin) and to the *p*-aminophenol structure were negative. Potential impurities have also been tested without success (6).

The pro-drug concept is based on easy, enzyme-specific or not, release of the drug from the pro-drug, and we have therefore considered that the *N,N*-diethylglycidyl ester function should be the most reactive part of the molecule toward nucleophilic attacks. This is confirmed by the short half-life time of propacetamol in 5% glucose serum (about 40 min), which indicates that this position is very sensitive to H₂O nucleophilic attack and therefore potentially sensitive to other nucleophilic attacks. In this respect, propacetamol belongs to the phenyl ester family, which are well-known skin sensitizers.

In order to investigate this hypothesis, *N,N*-diethylglycine phenyl ester **4**, an activated derivative of *N,N*-diethylglycine not containing the acetaminophen moiety, was synthesized. Patch tests were then performed with this molecule in 3 nurses with previously recognized sensitisation to propacetamol.

Materials and Methods

Chemistry

All NMR experiments were performed on a Bruker AC 200 instrument at 200 MHz and 50 MHz

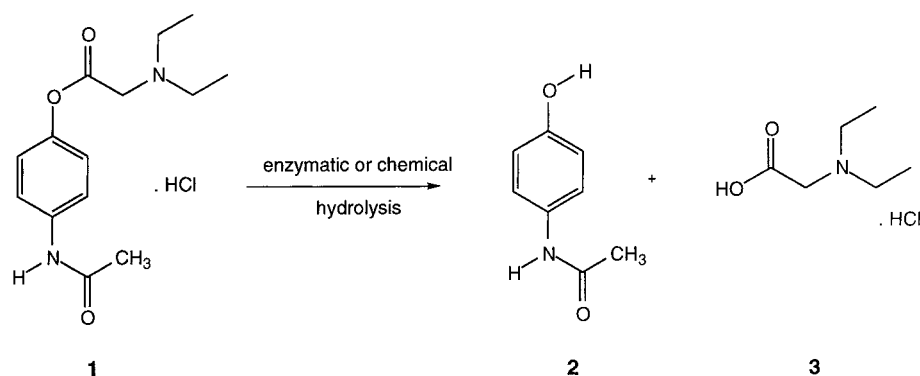


Fig. 1. Hydrolysis of propacetamol **1** into acetaminophen **2** and *N,N*-diethylglycine **3**.

for ^1H and ^{13}C NMR spectra, respectively. Chemical shifts are reported in ppm (δ) with respect to tetramethylsilane (TMS). Residual signals of acetone or methanol were used as internal standard ($\delta=2.05$ ppm and $\delta=3.30$ ppm, respectively) in ^1H experiments. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), and m (multiplet). Melting points were determined on a Buchi Tottoli 510 apparatus and are uncorrected. Dried solvents were freshly distilled before use. Ether was distilled from sodium benzophenone. Pyridine and diethylamine were distilled from KOH. Phenol was dried by azeotropic distillation in benzene and then distilled. All air- or moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of dry argon. Analytical grade organic solvents were used for recrystallization.

Phenyl chloroacetate. To a solution of phenol (12 g, 0.127 mol) in acetone (60 mL) at 0°C were added pyridine (10.8 mL, 0.134 mol, 1.05 equiv.) and $\text{ClCH}_2\text{OCH}_2\text{Cl}$ (10.7 mL, 0.134 mol, 1.05 equiv.). The solution was stirred at room temperature for 2 h. The precipitate was filtered off, washed with ace-

tone and the residue concentrated under reduced pressure. The product was recrystallized from ethyl acetate/hexane to give phenyl chloroacetate (19 g, 0.111 mol, 88% yield) as a white solid (mp $40.5\text{--}41^\circ\text{C}$). ^1H NMR (acetone- d_6 -200 MHz) δ 4.56 (s, 2H, CH_2), 7.50–7.15 (m, 5H, H_{ar}); ^{13}C NMR (acetone d_6 -50 MHz) δ 166.8, 151.6, 130.4, 127.0, 122.3, 41.8.

***N,N*-diethylglycine phenyl ester **4**.** To a solution of phenyl chloroacetate (17 g, 0.1 mol) in acetone (60 mL) was added HNEt_2 (11.4 mL, 0.11 mol, 1.1 equiv.). The solution was stirred at room temperature for 2 h and the precipitate was filtered and washed with acetone. The residue was concentrated under reduced pressure to give an intermediate (19.3 g, 0.1 mol, quantitative yield) as a yellow oil. A solution of this intermediate (5 g, 29.3 mmol) in ethyl ether (60 mL) was treated by HCl(g) for 15 min at room temperature. The solid was filtered, washed with dry ether and recrystallized in a mixture of ethanol/ethyl ether to give **4** (4.5 g, 19.6 mmol, 67% yield) as white needles ($161\text{--}162^\circ\text{C}$). ^1H NMR (CD_3OD -200 MHz) δ 1.4 (t, 6H, $J=7.3\text{Hz}$, CH_2CH_3), 3.38 (q, 4H, $J=7.3\text{Hz}$,

Table 1. Patch test results in 3 patients sensitized to propacetamol **1**

Patch test material	Conc. % (veh.)	Patient no. 1	Patient no. 2	Patient no. 3
propacetamol 1	10 (pet.)^{a)}	++	+	++
	5 (pet.)	++	—	++
	1 (pet.)	+	—	—
	0.1 (pet.)	—	—	—
acetaminophen 2	pure	—	—	—
	50 (pet.)	—	—	—
<i>N,N</i> -diethylglycine $\cdot$ HCl 3	50 (aq.)	—	—	—
<i>N,N</i> -diethylglycine phenyl ester ^{b)} 4	10 (pet.) ^{b)}	+++ ^{c)}	+/+	+++
	1 (pet.)	NT	—	+++
	0.1 (pet.)	NT	—	+++
	10 (aq.)	-/+	NT	+++

^{a)}30 negative controls were performed. ^{b)} 20 negative controls were performed. ^{c)} Patch test results at 2 and 4 days.

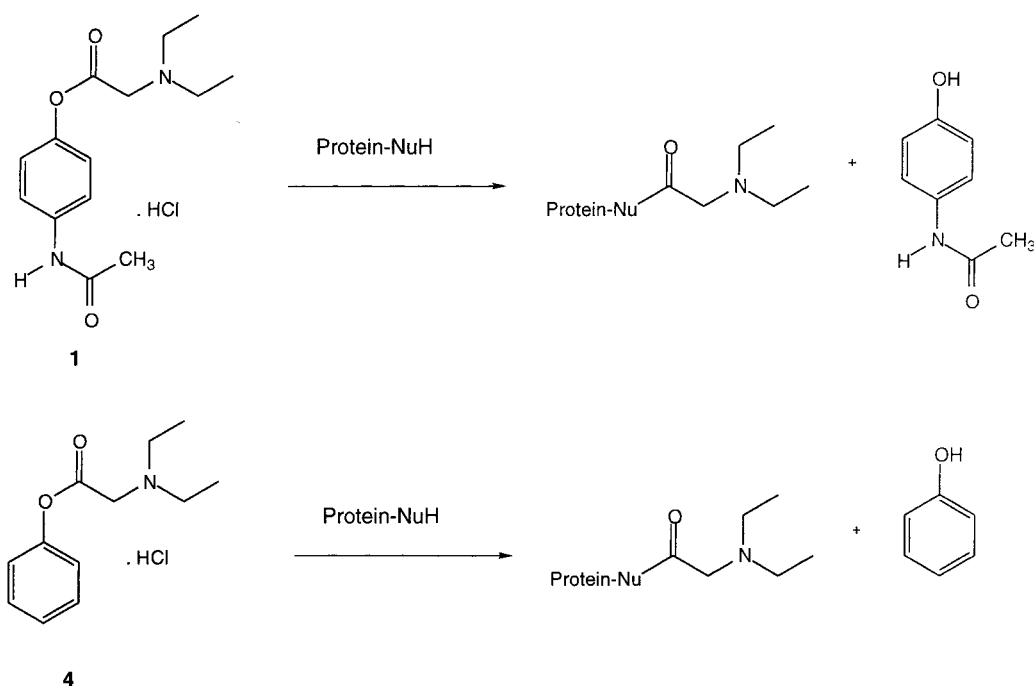


Fig. 2. Potential modification of proteins by propacetamol **1** and *N,N*-diethylglycine phenyl ester **4**.

CH₂CH₃), 7.49–7.22 (m, 5H, H_{ar}); ¹³C NMR (CD₃OD-50 MHz) δ 166.6, 151.5, 130.8, 127.9, 122.5, 53.7, 50.8, 9.5.

Patch testing

3 surgical nurses, aged 28, 31 and 39 years, respectively, developed an occupational propacetamol-induced contact dermatitis. They had no intolerance reaction related to the ingestion of acetaminophen for their own therapeutic purposes. Patch tests performed with propacetamol diluted at 10% in petrolatum (pet.) were positive (30 negative controls), while patch tests to acetaminophen (pure and 50% pet.) and to *N,N*-diethylglycine chlorhydrate (50% in water (aq.)) were negative. The 3 nurses were further patch tested with *N,N*-diethylglycine phenyl ester at different concentrations in pet. and aq. (Table 1). 20 control patients were patch tested with *N,N*-diethylglycine phenyl ester diluted 10% pet. and were negative.

Results and Discussion

N,N-diethylglycine phenyl ester **4** was synthesized according to classical chemical reactions (see experimental section for details on the synthesis) and was patch tested at several dilution in pet. and aq. (Table 1). In all patients, while patch tests performed with *N,N*-diethylglycine **3** were negative, patch tests to *N,N*-diethylglycine phenylester **4**, the

activated form of *N,N*-diethylglycine, diluted, 10% in pet. were strongly positive when read at 2 and 4 days (Table). 20 control patients were patch tested to *N,N*-diethylglycine phenylester **4** and were negative.

Data reported herein emphasize that contact dermatitis due to propacetamol is not related to sensitization to acetaminophen but to sensitization to *N,N*-diethylglycine. At first sight, this might appear to be in contradiction with the negative results observed when patch testing patients with *N,N*-diethylglycine, but one should keep in mind the molecular mechanism of skin sensitization. To form a covalent bond efficiently with nucleophilic residues of proteins, and therefore behave as a sensitizer, the carbonyl function of *N,N*-diethylglycine needs to be activated (the carboxylic acid is a poor electrophile (5)) as a phenyl ester group, for example. This is the case in the propacetamol molecule, which behaves therefore as an activated *N,N*-diethylglycine derivative, transferring the *N,N*-diethylglycine moiety to nucleophilic residues of proteins. This explains the strongly positive reactions observed to *N,N*-diethylglycine phenyl ester **4**, another activated *N,N*-diethylglycine derivative, in patients sensitive to propacetamol, the formed epitopes being the same (Fig. 2).

With regard to the chemical basis of allergic contact dermatitis, this sensitization to a pro-drug, accidentally in contact with the skin, is not surprising, as the ester bond between the drug and the

vector has been specially selected to be chemically reactive. The carbonyl is therefore highly reactive toward nucleophilic residues of proteins and can induce skin sensitization. This also indicates that patients with an occupational propacetamol-induced contact dermatitis should not be in contact with other pro-drugs using a *N,N*-diethylglycine ester as vector. The development of new pro-drugs based on *N,N*-diethylglycine esters should be avoided or commercialized in a package that avoids any contact between the skin and the pro-drug during handling.

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