The Metabolism of Tromantadine

Claus Köppel and Joachim Tenczer
Department of Toxicology, Landesuntersuchungsinstitut für Lebensmittel, Arzneimittel und Tierseuchen Berlin, D 1000 Berlin 21, FRG

Elisabeth Rütten and Franz Klaschka
Department of Dermatology, Klinikum Steglitz, Freie Universität Berlin, D 1000 Berlin 45, FRG

The metabolism of the antiviral drug tromantadine (1-adamantyl-2-(2-dimethylaminoethoxy)acetamide) was studied after an oral dose of 120 mg tromantadine hydrochloride using capillary gas chromatography/mass spectrometry. Most of the dose was excreted unchanged with the urine. Six metabolites could be identified. The main metabolic products were 1-aminoadamantane (amantadine) and 1-adamantyl-(2-hydroxy)acetamide. Further metabolic pathways were demethylation of the dimethylamino function and oxidative desamination to an unstable aldehyde which is oxidized to a carbonic acid or reduced to an alcohol.

INTRODUCTION

Tromantadine (1-adamantyl-2-(2-dimethylaminoethoxy)acetamide) is a commonly used antiviral drug for local therapy in herpes simplex and herpes zoster.[1] Contact dermatitis caused by tromantadine or its metabolites is the most frequently observed side effect (~6%) under this treatment.[2-4] However, no data have been published on the metabolism of tromantadine which might help to understand the etiology of contact dermatitis. Since a high percentage of patients with an established tromantadine contact dermatitis show a positive reaction in the patch test with the structurally related amantadine,[5,6] the question arises whether tromantadine and amantadine might have common metabolites which are responsible for the contact dermatitis. The metabolism of amantadine has recently been studied.[7]

EXPERIMENTAL

Three healthy volunteers received an oral dose of 120 mg tromantadine hydrochloride. Urine was collected for 48 h and stored at −20 °C before analysis.

20 ml aliquots of the urine were extracted twice with 20 ml diethyl ether (nanograde, Mallinckrodt) at pH 2 and pH 9. For cleavage of glucuronides, 20 ml of urine was adjusted to pH 5.5 and incubated with 0.5 ml of glucuronidase/sulphatase (Merck, Darmstadt) at 37 °C for 12 h prior to extraction. The organic solvent was removed with a dry stream of nitrogen. The dried extracts were then dissolved in 200 μl methanol and a 1 μl aliquot was injected into the gas chromatograph of a Finnigan 4021 gas chromatograph/mass spectrometer. The gas chromatographic conditions were: injection port 285 °C; split 1:100; 30 m DB-5 capillary column (J & W Scientific, Rancho Cordova); temperature programme 75–300 °C with 15 °C min^{-1}; direct coupling to the mass spectrometer. The mass spectrometer was run in the electron impact and chemical ionization mode: ion source temperature 250 °C, ion source pressure ~2×10^{-7} Torr (electron impact) and ~4×10^{-5} Torr (chemical ionization with methane), multiplier voltage 2000 V.

Additionally, the urine extracts were subjected to acetylation with acetic anhydride and methylation with diazomethane. Six metabolites could be identified (Table 1). Only tromantadine and its metabolite amantadine

Table 1. Mass spectra and retention times of tromantadine and its metabolites

	Retention time (s)	Mass spectra (*m/z* (intensity %))
Tromantadine	652	$M]^{+\cdot}$280 (0.1), 264 (4), 150 (2), 135 (14), 120 (2), 107 (6), 93 (9), 91 (7), 79 (11), *71* (100), 58 (93)
1 (-acetate)	834	$[M]^{+\cdot}$308 (1), 265 (3), 222 (2), 210 (9), 193 (11), 135 (73), 100 (61), *99* (100), 94 (18), 86 (37), 79 (22), 67 (12), 57 (44)
2 (-acetate)	701	$[M]^{+\cdot}$294 (18), 235 (22), 221 (6), 220 (5), 193 (6), *135* (100), 120 (6), 117 (12), 93 (16), 91 (18), 85 (32)
3 (-methyl ester)	673	$[M]^{+\cdot}$281 (4), 250 (1), 222 (6), 206 (9), 193 (54), 178 (3), 165 (26), *135* (100), 120 (10), 106 (27), 93 (37), 79 (35), 67 (23), 55 (17)
4 (-acetate)	681	$[M]^{+\cdot}$295 (0.5), 235 (10), 193 (3), *135* (100), 120 (2), 118 (6), 93 (12), 79 (13), 67 (7)
5 (-acetate)	563	$[M]^{+\cdot}$251 (13), 208 (4), 192 (7), 191 (6), 152 (16), 148 (18), *135* (100), 107 (8), 93 (14), 79 (13), 67 (10)
6	220	$[M]^{+\cdot}$151 (51), 136 (6), 108 (19), *94* (100), 91 (11), 79 (14), 77 (20), 67 (11), 58 (11), 57 (48)
7 (artefact)	367	$[M]^{+\cdot}$194 (22), 164 (3), 152 (6), 139 (63), *134* (100), 121 (43), 119 (68), 105 (41), 95 (68), 92 (59), 71 (58), 67 (45), 55 (38)

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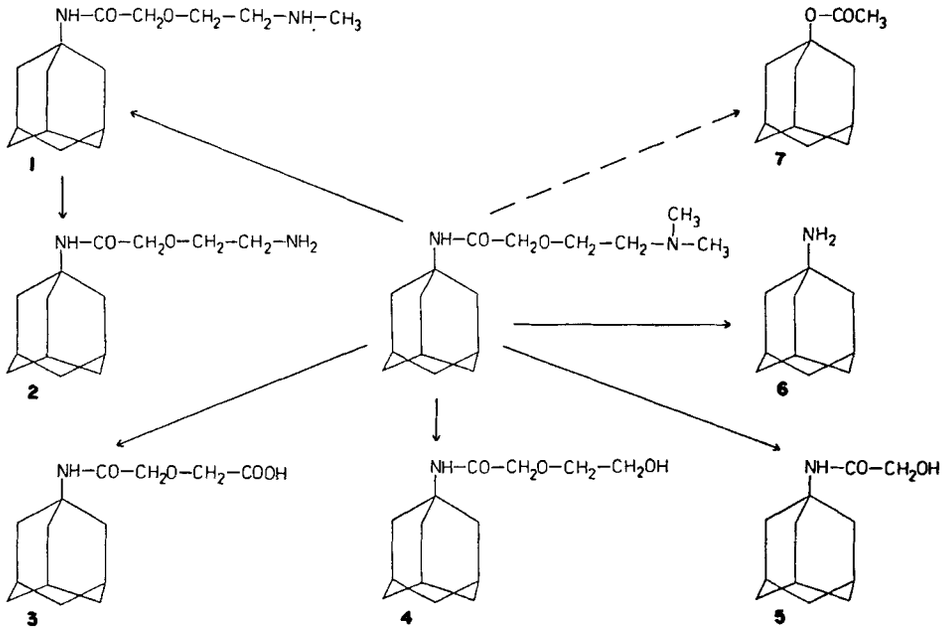

Figure 1. Metabolism of tromantadine.

(**6**) passed the gas chromatographic column underivatized. Trimethylsilylation gave no evidence for the presence of further metabolites.

RESULTS AND DISCUSSION

The fragmentation of tromantadine and its derivatized metabolites occurs via different pathways (Table 1): Loss of the substituted amino function leads to the adamantyl ion m/z 135 which is the base peak in the spectra of **2**, **3**, **4** and **5** (cf. Fig. 1). Cleavage of the oxygen—ethyl bond after hydrogen transfer yields the base peaks at m/z 71 and 99 in the spectra of tromantadine and **1**, respectively. The prominent ion at m/z 58 ($CH_2{=}\overset{+}{N}(CH_3)_2$) tromantadine is formed by α-cleavage. The mass spectrum of amantadine is in agreement with spectra published in literature.[7,8] The main fragmentation is loss of $C_4H_9^{\cdot}$ from the molecular ion.

After acetylation of the urine extracts a further tromantadine derivative **7** (1-adamantol acetate) could be detected. This is most probably an artefact which has already been observed in a previous study of the amantadine metabolism.[7] Under chemical ionization conditions the corresponding $[M+1]^+$ ions of tromantadine and its derivatized metabolites were observed. Metabolites **3**, **4** and **5** were only detectable after enzymatic hydrolysis of the urine extracts, which indicates complete glucuronidation. No metabolites with an alcohol or keto function in the adamantane ring could be detected.

Metabolism of tromantadine occurs via different pathways (Fig. 1): demethylation leads to **1** and **2**. After oxidative desamination an unstable aldehyde is probably formed which may be either oxidized to the carbonic acid **3** or reduced to the alcohol **4**. Cleavage of the ether bond in the side chain yields **5**. Amantadine **6** is formed after cleavage of the amide bond.

More than 50% of the tromantadine dose was eliminated unchanged. The main metabolic products were **5** and **6**. No common metabolites of amantadine and tromantadine, other than amantadine itself, could be detected in the tromantadine metabolism.

Acknowledgement

The technical assistance of Mrs E. Vejmelka is acknowledged.

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Received 18 May 1984; accepted 25 July 1984