PHENOTHIAZINE PHOTOTOXICITY: AN EXPERIMENTAL STUDY ON CHLORPROMAZINE AND ITS METABOLITES

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Chlorpromazine (CPZ) metabolites were studied for their phototoxic potency with the mouse tail technique. The demethylated metabolites were more phototoxic than CPZ, while CPZ-sulfoxide, 7-hydroxy-CPZ, and 2-chlorophenothiazine were less phototoxic. The phototoxicity of CPZ and desmethyl-CPZ preexposed to UVA was lost, while that of CPZ-sulfoxide was retained. By thin-layer chromatography, CPZ-sulfoxide and promazine were identified as photoproducts of CPZ; the sulfoxide was fairly stable to radiation.

Phototoxic dermatitis is a well-known side effect in patients treated with chlorpromazine (CPZ) and other phenothiazines. The importance of varying molecular structure within this drug group for the phototoxic activity has recently been investigated [1]. The metabolism of CPZ is complicated and little is known about the role played by CPZ metabolites in the phototoxic reaction or about the importance for phototoxicity of radiation effects on CPZ and its metabolites.

MATERIALS AND METHODS

The in vivo method for the study of acute drug phototoxicity has recently been described [2]. Albino mice (Anticimex, Sollentuna, Sweden) were injected intraperitoneally with the test compound immediately before they were irradiated. Groups of at least 5 animals were used throughout. The 7 phenothiazines tested are given in Table I. The dose range was 0.5–80 mg/kg.

The tails of the animals were exposed to long-wave ultraviolet radiation (UVA) for 5 hr with two blacklight tubes (Philips TL 40 W/08) at a distance of 12 cm. The measured average intensity of radiation was 5.0 mw/cm²/sec. The degree of phototoxic inflammation was calculated on the basis of wet weight increase of mouse tail.

Preexposed CPZ, demethylchlorpromazine (DCPZ), and chlorpromazine-sulfoxide (CPZSO) in doses 10, 10, and 40 mg/kg, respectively, were tested by the mouse tail technique; they were also studied by thin-layer chromatography (TLC) and by spectrophotometry (Beckman DB-GT). Solutions were obtained by irradiation with 3 UV sources: (1) exposure for 30 min to nonfiltered light from a 150 W xenon lamp (Osram XBO); (2) exposure for 30 min to the same radiation filtered by window glass excluding radiation below 320 nm (the measured average intensity of radiation was 150 mw/cm²/sec without filter [ultraviolet and visible light] and 150 mw/cm²/sec with window glass [UVA and visible light]); (3) exposure to blacklight as above. Measurements of all irradiation intensities were carried out with an optometer UDT-40X obtained from United Detector Technology.

The test compounds were examined by TLC. Solutions were applied on a precoated silica gel plate (DC-Fertigplatten Kieselgel F₂₅₄, Merck, Darmstadt) and the plate was run for 1 hr in benzene-dioxan-ammonium hydroxide (12:7:1). The plate was inspected in 254 nm and 365 nm ultraviolet radiation.

For statistical evaluation, Student’s t-test was used throughout.

RESULTS

The phenothiazines, when examined by TLC, were all visualized in ultraviolet light as single spots with the exception of 7-hydroxychlorpromazine (OHCPZ). This sample yielded an impurity which was identified by the manufacturer* as 2-chlor-7-hydroxyphenothiazine.

All 7 phenothiazines tested with the mouse-tail technique were found phototoxically active. As may be seen from Figure 1 the minimum reactive dose of CPZ was 2.5 mg/kg. The two demethylated compounds were more phototoxic than CPZ and the minimum reactive dose for didesmethylochlorpromazine (DDCPZ) was 1.0 mg/kg. CPZSO and OHCPZ were also shown to be phototoxic but weaker than CPZ. Least phototoxic of all were 2-chlorophenothiazine (CPHZ) and phenothiazine (PHZ), the chlorinated compound, however, being the stronger of the two. The 3 most potent phenothiazines showed a significant decline of phototoxicity in the highest dose levels.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Abbreviation</th>
<th>Structure</th>
<th>Solvent</th>
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<tbody>
<tr>
<td>Chlorpromazine</td>
<td>CPZ</td>
<td><img src="image" alt="Structure" /></td>
<td>Water</td>
</tr>
<tr>
<td>Desmethylchlorpromazine</td>
<td>DCPZ</td>
<td><img src="image" alt="Structure" /></td>
<td>Water</td>
</tr>
<tr>
<td>Didesmethylchlorpromazine</td>
<td>DDCPZ</td>
<td><img src="image" alt="Structure" /></td>
<td>Methylcellulose suspension</td>
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<tr>
<td>Chlorpromazine-sulfoxide</td>
<td>CPZSO</td>
<td><img src="image" alt="Structure" /></td>
<td>Water</td>
</tr>
<tr>
<td>7-Hydroxychlorpromazine</td>
<td>OHCPZ</td>
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<tr>
<td>Phenothiazine</td>
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<td>Methylcellulose suspension</td>
</tr>
<tr>
<td>2-Chlorphenothiazine</td>
<td>CPHZ</td>
<td><img src="image" alt="Structure" /></td>
<td>Methylcellulose suspension</td>
</tr>
</tbody>
</table>

The compounds were kindly delivered by AB Leo, Helsingborg, Sweden (a), and by Smith Kline & French Laboratories Ltd., Welwyn, Garden City, U.K. (b).
The phototoxicity of CPZ was lost when the drug was preexposed to ultraviolet radiation (Tab. II). This result was obtained with UVA as well as with unfiltered radiation. The wet weight increase of the mouse-tail tissue induced by DCPZ (10 mg/kg) was 22.1% with unirradiated drug; the increase after exposure of the drug for 30 min to UVA from the xenon lamp filtered by window glass was 0.0% (p < 0.001). The wet weight increase by CPZSO (40 mg/kg) was 11.6% with unirradiated drug and 10.6% after exposure to UVA as above (this difference was not statistically significant).

In a CPZ solution exposed to UVA, the CPZ content is gradually decreased. Simultaneously, photodecomposition products appear which may be observed by TLC (Fig. 2). The predominating new spots could be identified as CPZSO and promazine. DCPZ was also degraded by UVA exposure. On the other hand, CPZSO retained its main chromatographic properties after irradiation.

The absorption curves of CPZ, DCPZ, and CPZSO before and after UVA exposure are shown in Figure 3. Unirradiated CPZ and DCPZ showed an almost identical, high peak at 255 nm; CPZSO showed a peak at 245 nm. At higher wavelengths CPZ and DCPZ showed a single peak of about 305 nm, while CPZSO showed 3 peaks at about 278, 302, and 340 nm. After irradiation with UVA, the peak at 245–255 nm of all 3 substances was diminished; the peaks at higher wavelengths were flattened, and absorption extended into UVA and visible light.

**DISCUSSION**

The metabolic pathways of CPZ are complicated and not fully understood. CPZ appears to be metabolized by demethylation in the N-chain, by oxidation of sulfur or nitrogen in the nucleus, and by ring hydroxylation (see [3]). The metabolites thus include DCPZ, DDCPZ, CPZSO, and OHCPZ.

It is not known whether the photosensitizing capacity of CPZ should be ascribed to the drug itself or to one or more of its metabolites. In the present work the phototoxicity in vivo of some known CPZ metabolites was therefore compared to that of CPZ. They were all found to be phototoxic, particularly the demethylated derivatives, which were even more potent than CPZ (Fig. 1). The range of minimum effective doses was wide, 1–40 mg/kg. Actually, the strongest photosensitizing metabolite, DDCPZ, as well as OHCPZ, showed low water solubility. Apparently, the principle of demethylation implies an enhancement of phototoxic potency. This also holds true when systemically administered chlortetracycline is compared to demethylchlortetracyline.

PHZ, the parent compound of CPZ, and its chlorinated equivalent, CPHZ, were also found to be phototoxic. They were, however, less phototoxic.
CPZ lost its phototoxic capacity in vivo after irradiation with ultraviolet radiation. This result was obtained with UVA as well as with unfiltered radiation (Tab. II) in spite of the fact that the main absorption peaks of CPZ are in the UVC and UVB ranges (Fig. 3). The phototoxic capacity of DCPZ also was lost after UVA exposure while that of CPZSO was retained. Accordingly, it was observed by TLC that CPZ and DCPZ were decomposed by UVA while CPZSO was relatively stable (Fig. 2). Among the photodegradation products of CPZ that appeared, CPZSO and promazine, which earlier has been reported [9-11], could be identified.

The absorption curves of CPZ and DCPZ were very similar, but that of CPZSO showed a fairly strong absorption in UVA (Fig. 3). Irradiation diminished the high UVC peak of CPZ, a confirmation of Schwarz's observation [8], as well as that of DCPZ and CPZSO. The difference in absorption peaks in UVB and UVA between the 3 compounds also was markedly reduced after UVA exposure.

With regard to the phototoxic activity of CPZ, recent interest has been focused on its photoproducts [12]. In our experiments, all CPZ metabolites were found phototoxic, active. Of these, CPZSO has the most interesting properties: it is an established CPZ metabolite; it is evidently phototoxic; it has a considerable absorption in UVA; it is a photoprotein of CPZ; and it is itself fairly stable against UVA. Therefore, it may be presumed that CPZSO contributes to the phototoxic effect of CPZ. It is, however, also probable that other CPZ metabolites, such as the sulfoxides of DCPZ and of DDCPZ are phototoxically active since DCPZ and DDCPZ were found to be considerably more phototoxic than CPZ. Without knowing more about the distribution in plasma and skin tissue of the different CPZ metabolites it is impossible to evaluate the clinical importance of the individual metabolites.

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REFERENCES
2. Ljunggren B, Möller H: Phototoxic reaction to chlorpromazine as studied with the quantitative mouse tail technique. Acta Derm Venereol (Stockh) 56:373-376, 1976
6. Clare NT, Whitten LK, Filmer DB: A photosensi-


