PROTECTION AGAINST THE PHOTOSENSITIZED SKIN IRRITANC

Y OF CHLORPROMAZINE BY CYCLODEXTRIN COMPLEXATION

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(Received June 27, 1985)

The efficacy of three types of cyclodextrins (CyDs) to reduce skin irritation in guinea pigs caused by photoirradiated chlorpromazine (CPZ) was in the order of \( \beta > \gamma > \alpha \)-CyD, depending upon the magnitude of the stability constant of the CPZ-CyD complexes. The inhibitory effects of CyDs may be attributable to the alteration in the photochemical reactivity of CPZ through inclusion complexation. By the photoirradiation of CPZ in the presence of CyDs, promazine, which is less toxic than CPZ, was produced and the yield decreased in the order of \( \beta > \gamma > \alpha \)-CyD. These results clearly indicate that \( \beta \)-CyD complexation is particularly useful to reduce the CPZ-photosensitized damage to skin.

Keywords — skin photosensitization; photodechlorination; chlorpromazine; \( \alpha \)-cyclodextrin; \( \beta \)-cyclodextrin; \( \gamma \)-cyclodextrin; inclusion complexation; stability constant

Chlorpromazine (CPZ), a typical antipsychotic agent, has been known to frequently cause cutaneous phototoxic and photoallergic responses in patients being treated with prolonged and high doses.\(^1\)\(^2\) In addition, personnel engaged in health services, such as pharmacists and nurses, may develop occupational photocutaneous dermatitis.\(^3\)\(^4\) In spite of the prevalence of the CPZ-induced skin photosensitization, little attention has been given to reduce this type of dermatitis from the pharmaceutical and toxicological points of view.\(^5\) \( \alpha \)-, \( \beta \)-, and \( \gamma \)-cyclodextrins (\( \alpha \)-, \( \beta \)-, and \( \gamma \)-CyDs) are cyclic oligosaccharides consisting of six, seven, and eight glucopyranose units, respectively. One of their characteristics is the formation of inclusion complexes with various drug molecules and this phenomenon has recently received much attention because of its potential application for forms of dosage.\(^5\)\(^7\) In our previous studies,\(^6\)\(^9\) CyDs were found to modify the photochemical reactivity of CPZ through inclusion complexation, suggesting that CyDs have a potential to reduce the phototoxic activity of CPZ \textit{in vivo}. Thus, the present paper deals with the cavity size effects of CyDs (\( \alpha \)-, \( \beta \)-, and \( \gamma \)-CyDs) on the photosensitized skin irritation associated with CPZ in guinea pigs.

CPZ, a gift from Yoshitomi Pharmaceutical Industries Ltd. (Fukuoka, Japan), was used without further purification. \( \alpha \)-, \( \beta \)-, and \( \gamma \)-CyDs were kindly donated by Nihon Shokuhin Kako Co. Ltd. (Tokyo, Japan) and recrystallized from water.

The photoirradiation was performed using a Toshiba metal halide lamp DR 250T/1 (Tokyo, Japan). Irradiation at 305 and 365 nm was 0.05 and 2.5 mW/cm\(^2\), respectively. The test solutions in normal saline were irradiated through a pyrex filter for 90 min at 30 \(^\circ\)C under an air-saturated condition. CPZ and its photoproducts were quantitatively analyzed by gas chromatography.\(^8\)

The skin irritation studies were carried out using Hartley female guinea pigs, weighing ap-

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proximately 400 g. The concentration of CPZ (0.2 μmol) was selected after determining the dose at which no noticeable irritation was observed for non-irradiated CPZ solutions. The irradiated solutions were injected into the dorsal skin of clipped and shaved animals. Their responses were evaluated by the modified Draize scoring method. Some of the skins were used for histological examinations using a procedure described previously. Statistical analysis was performed using the Student’s t-test and Cochran–Cox test.

Figure 1 shows the time-course of the skin irritating reactions following an intradermal injection of photoirradiated CPZ in the absence and presence of CyDs. As can be seen in Fig. 1 (A), the photoirradiated CPZ elicited distinct erythema and edema, followed by eschar formation around the injection site. From histological examinations, the inflammatory cells such as polymorph and macrophage were found to infiltrate into the dermis and subcutaneous fatty tissues. These inflammatory responses persisted for at least 7 d after the injection. It was also noted that there was only a slight loss of phototoxic activity of the irradiated CPZ solution when stored in the dark at 25 °C and tested at intervals over 4 d. These results clearly indicate that the photosensitized irritancy of irradiated CPZ observed in these studies is mainly due to stable photoproducts rather than to transient species such as CPZ and active oxygen radicals. It is evident from Fig. 1 (B)–(D) that the photosensitized irritancy of CPZ was significantly reduced by the addition of β- and γ-CyDs. However, appreciable reduction of irritancy was observed with

![Figure 1](https://via.placeholder.com/150)

**FIG. 1. Effects of CyDs on the Irritating Reactions Produced by Intradermal Injection of Photoirradiated CPZ in Dorsal Skin of Guinea Pigs**

(A), CPZ alone; (B), CPZ + α-CyD; (C), CPZ + β-CyD; (D), CPZ + γ-CyD. The initial concentrations of CPZ and CyDs were 0.2 and 0.4 μmol, respectively. Each result represents the mean ± S.E. of 10 guinea pigs.
\(\alpha\text{-CyD. The order of the inhibitory effect of CyDs correlated with the magnitude of stability constants of the CPZ-CyD complexes, as shown in Table I.}

It is possible that CyDs reduce the tissue toxicity of the CPZ photoproducts by encapsulation into the CyD cavity in a manner similar to that described previously.\(^{11}\) However, when CyDs were added to preirradiated CPZ solutions, the inhibitory effects of CyDs were not demonstrable. For example, in the case of \(\beta\text{-CyD, the average irritation score was 25.8 \pm 1.6 which is almost the same value as in the absence of CyDs (24.7 \pm 2.1). Therefore, it is reasonable to assume that the inhibitory effects of CyDs are mainly due to the alteration in the phototoxic reactivity of CPZ rather than to the direct interaction of the photoproducts of CPZ with CyDs. This hypothesis is supported by the photolysis data of Table I. Although CyDs had little effect on the disappearance of CPZ, the dechlorination of CPZ occurred in the presence of CyDs. Promazine (PZ), which is less toxic than CPZ,\(^{13,14}\) was produced in the presence of CyDs and the yield decreased in the order of \(\beta > \gamma > \alpha\text{-CyD. The use of CyDs, which was found to significantly inhibit the formation of numerous oxidation and polymerization photoproducts, may be of importance to prevent membrane disruption and skin sensitization caused by photoproducts of CPZ.}\(^{13}\)

Although detailed investigations including the inhibitory mechanism of CyDs at the cellular level are yet to be carried out, the present data suggest that \(\beta\text{-CyD is particularly useful in alleviating the phototoxic damage of skin caused by irradiated CPZ.}

**Acknowledgements** The authors wish to thank Prof. M. Otagiri, Kumamoto University and Prof. Y. Arimatsu, Ginkyo College of Medical Technology for their help and valuable suggestions. We are also grateful to Mr. T. Sugi for his helpful assistance throughout the study.

**REFERENCES**


**TABLE I. Relationship between the Results of the Photosensitized Skin Irritation Studies and the Photolysis Data for the CPZ–CyD Systems\(^a\)**

<table>
<thead>
<tr>
<th>System</th>
<th>Irritation score (^b)</th>
<th>Decomposition of CPZ (%)</th>
<th>Formation of PZ (%)</th>
<th>Stability constant (M(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPZ</td>
<td>24.7 ± 2.1</td>
<td>66.8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CPZ + (\alpha\text{-CyD} )</td>
<td>21.0 ± 2.1</td>
<td>72.7</td>
<td>15.6</td>
<td>200</td>
</tr>
<tr>
<td>CPZ + (\beta\text{-CyD} )</td>
<td>1.5 ± 0.3 (e,f)</td>
<td>53.8</td>
<td>67.3</td>
<td>12000</td>
</tr>
<tr>
<td>CPZ + (\gamma\text{-CyD} )</td>
<td>4.4 ± 0.5 (e)</td>
<td>70.0</td>
<td>51.3</td>
<td>1000</td>
</tr>
</tbody>
</table>

\(^a\) Experimental conditions were the same as those in Fig. 1. \(^b\) The sum of the evaluation scores up to 7 d. The value represents the mean ± S.E. of 10 guinea pigs. \(^c\) Based on the decomposed CPZ after 90 min photolirradation. \(^d\) Determined from UV absorption change (pH 7.0, 25°C), see ref. 8. \(^e\) Statistically significant (\(p<0.001\)) when compared with the CPZ alone. \(^f\) Statistically significant (\(p<0.001\)) when compared with the CPZ-\(\gamma\text{-CyD system.} \)
Protection from CPZ Photosensitization