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ALLEVIATION OF PROCHLORPERAZINE-INDUCED PRIMARY IRRITATION OF SKIN
BY CYCLODEXTRIN COMPLEXATION

Kaneto Uekama,^{*,a} Tetsumi Irie,^a Miki Sunada,^a Masaki Otagiri,^a
Yoshiki Arimatsu,^b and Shigeru Nomura^b

Faculty of Pharmaceutical Sciences, Kumamoto University,^a 5-1, Oe-honmachi
Kumamoto 862, Japan and Department of Public Health, Kumamoto University
Medical School,^b Honjo, Kumamoto 860, Japan

Cyclodextrins (CyDs) protected human erythrocytes from hemolysis induced with prochlorperazine (PCP) in isotonic solution, depending upon the magnitude of the stability constant of PCP-CyD complexes (β - > γ - > α -CyD). The primary irritation produced by PCP on the skin of guinea pigs was found to be reduced by the addition of β - and γ -CyDs, particularly by γ -CyD, while α -CyD enhanced the irritancy of PCP. The most favorable protective effect observed for the γ -CyD complex was mainly ascribable to the weak irritancy of γ -CyD itself, suggesting a great utility of γ -CyD to alleviate the PCP-induced contact dermatitis.

KEYWORDS — prochlorperazine; α -, β -, and γ -cyclodextrins; stability constant; inclusion complexation; drug-induced hemolysis; primary irritation; alleviation of the contact dermatitis

Although the problems of the prevention of occupational contact dermatitis caused by phenothiazine neuroleptics have received increasing attention from the viewpoint of health care for medical staffs such as pharmacists and nurses,¹⁾ few attempts to reduce this type of dermatitis have been made. Drug-induced hemolysis *in vitro* may be considered as a simple and reliable measure for estimating the membrane damage caused by drugs *in vivo*.²⁾ Recently, cyclodextrins (CyDs) have been found to protect human erythrocytes from hemolysis induced with chlorpromazine *in vitro*,^{3,4)} and the CyD complexation was shown to be useful in alleviating the membrane injury. Thus, this paper deals with the effects of CyDs (α -, β -, and γ -CyDs) on the primary irritation produced by prochlorperazine (PCP) on the skin of guinea pigs. PCP was chosen as a test compound because of its higher hemolytic activity and greater tendency to form inclusion complexes with CyDs, among the ten phenothiazine derivatives used in our previous studies.⁵⁾

PCP dimethanesulfonate, a gift from Shionogi Co. Ltd., was used without further purification. α -, β -, and γ -CyDs were purchased from Nippon Shokuhin Kakō Ltd., and recrystallized from water. Human erythrocytes from freshly-drawn ACD-blood were supplied by the Kumamoto Prefectural Red Cross Blood Center. Drug-induced hemolysis was measured as previously described.⁴⁾ The primary irritation test was carried out using Hartly female guinea pigs, weighing about 400 g. The PCP solutions were patched by Testpflaster[®] for 24 hr on the flank of clipped and shaved guinea

pigs. Their responses were evaluated by the Draize⁶⁾ scoring method immediately after the removal of the patch and 24 hr later.

Figure 1 shows the hemolytic effect of PCP on human erythrocytes in the absence and presence of CyDs in isotonic solution. The hemolysis was evident at 0.15 mM PCP and was complete above 0.3 mM PCP. The hemolytic activity of PCP was significantly decreased by the addition of β - and γ -CyDs, while α -CyD had no appreciable effect. The protective effect of the CyDs on the hemolysis was found to depend upon the magnitude of the stability constant of the inclusion complexes (170 M^{-1} for α -CyD complex, 34000 M^{-1} for β -CyD complex, 6100 M^{-1} for γ -CyD complex; determined from UV absorption changes at pH 7.0 and at 25°C). Moreover, the CyDs decreased the binding of PCP to human erythrocytes along with the reduction of surface activity of PCP in the order of β - > γ - > α -CyD. The above results may be due a decrease

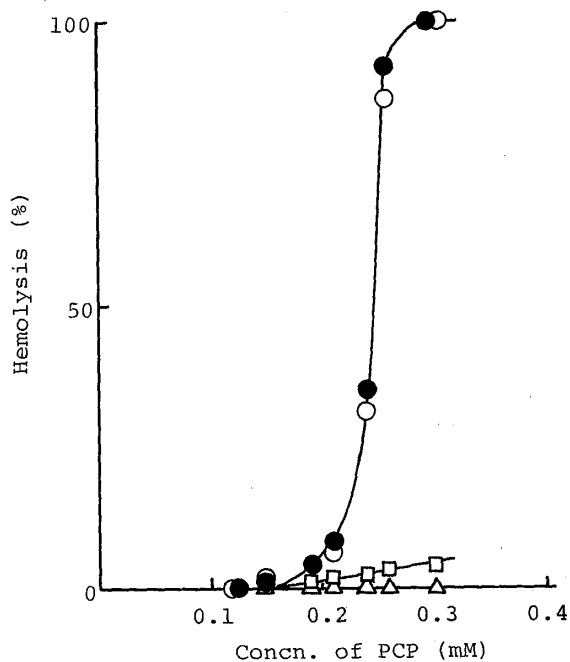


Fig. 1. Hemolytic Effect of PCP on the Human Erythrocytes in the Absence and Presence of CyDs (0.3 mM) in 10 mM Isotonic Phosphate Buffer (pH 7.4) at 37°C
 ○: PCP, ●: PCP + α -CyD, △: PCP + β -CyD, □: PCP + γ -CyD.

Table I. Evaluation Score^{a)} of Primary Irritation Produced by PCP on the Skin of Guinea Pigs in the Absence and Presence of CyDs

System	Concentration (mM)			
	80	16	8	1.6
PCP	1.6	0.5	0.1	0.0
PCP + α -CyD ^{b)}	2.8*	0.3	0.0	0.0
PCP + β -CyD ^{b)}	0.9**	0.3	0.2	0.0
PCP + γ -CyD ^{b)}	0.6***	0.1	0.0	0.0
α -CyD	0.4	0.0	0.0	0.0
β -CyD	0.8 ^{c)}	0.1	0.1	0.0
γ -CyD	0.0	0.0	0.0	0.0

a) Mean obtained from ten animals.

b) Equimolar solution of CyD was used.

c) Suspension.

*: $P < 0.001$ in PCP + α -CyD versus PCP.

** : $P < 0.05$ in PCP + β -CyD versus PCP.

***: $P < 0.001$ in PCP + γ -CyD versus PCP.

in hydrophobicity and membrane permeability of PCP by the formation of inclusion complex rather than the direct interaction of CyDs with erythrocyte membrane. In fact, the CyDs themselves showed little protective or accelerative effect against the osmotic hemolysis.⁴⁾

Table I shows the effects of the CyDs on the primary irritation produced by PCP on the skin of guinea pigs. The irritative effects such as the erythema formation were observed after application of PCP with increasing concentrations. It was found that the irritancy of PCP was reduced by the addition of β - and γ -CyDs, particularly by γ -CyD, where the irritability of 80 mM PCP with 80 mM γ -CyD was almost the same as that of 16 mM PCP alone. On the other hand, α -CyD tended to enhance the irritative reaction of PCP, following the erythema with the eschar formation after application of 80 mM PCP with 80 mM α -CyD. Although these observations are somewhat incompatible with the order of protection of PCP-induced hemolysis by the three CyDs, the discrepancy might be explained by considering the intrinsic irritancy of the CyDs. As shown in Table I, α - and β -CyDs significantly caused the skin irritation of guinea pigs, while no noticeable effect was observed for γ -CyD. It should be noted also that the hemolytic activities of the three CyDs (β - > α - > γ -CyD)⁷⁾ is consistent with their irritative effects on the skin of guinea pigs. Therefore, it is reasonable to assume that the relatively small reductive effect observed for the PCP- β -CyD system may be the result of the intrinsic irritancy of β -CyD. Although the detailed mechanism, including the effect on drug efficacy, should be investigated further, these limited data suggest that γ -CyD is particularly useful to alleviate the contact dermatitis produced by PCP

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