Similarities and Differences in the Toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (tetra-CDD) and its Structural Analog, Chlorpromazine

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ABSTRACT

Tetra-CDD and its structural analog chlorpromazine give rise to a number of similar toxic effects. The present investigation of tetra-CDD-specific biologic/toxicologic endpoints revealed similarities as well as differences, both of which require further examination under careful consideration of the profound differences in the toxicokinetics of these two compounds.

INTRODUCTION

Chlorpromazine is a structural analog of the chlorinated dibenzo-*p*-dioxin family of compounds (Fig. 1). It causes a number of toxic effects in laboratory animals, which are identical to the effects seen after administration of dioxins: hypothermia, hypertriglyceridemia, hypoglycemia, glycogenosis (Maickel et al.[1]), immunosuppression (Szeri et al., 1990[2]), body weight loss and reduced feed intake (Maickel et al.[1]). At therapeutics doses, chlorpromazine appears to be anticarcinogenic in chronically treated human subpopulations (Lialiaris et al.[3]). At low doses, tetra-CDD has been shown to reduce dramatically the incidence of mammary tumors in rats (Kociba et al.[4]). Because of this striking similarity, it appeared meaningful to examine some toxicologically relevant effects of tetra-CDD toxicity in chlorpromazine-treated rats.

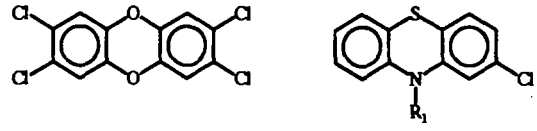
MATERIALS AND METHODS

Thirty male Sprague-Dawley rats (235-250 g) were randomly divided into six groups: group 1, 2 and 3 received 2, 8 and 32 mg/kg injections of chlorpromazine subcutaneously twice a day, respectively. Group 4, 5 and 6 were given injections of saline in a similar manner and served as pair-fed controls. Each rat in these control groups received the same amount of feed as its chlorpromazine-treated ad libitum-fed pair had consumed voluntarily on the previous day. Body weights and feed intake

were recorded daily. After seven days of treatment, rats were sacrificed. Liver and blood samples were collected, immediately frozen in liquid nitrogen and stored at -80°C until analysis.

Phosphoenolpyruvate carboxykinase (PEPCK) activity was determined as described by Petrescu et al.[5] using deoxyguanosine 5'-diphosphate as the nucleotide substrate. Glucose-6-phosphatase (G-6-Pase) activity (Baginski et al.[6]) was measured by the release of inorganic phosphate from glucose-6-phosphate. Ethoxyresorufin-o-deethylase (EROD) activity was measured fluorometrically as described by Dutton and Parkinson[7]. Tryptophan-2,3-dioxygenase (TdO) activity was estimated according to Metzler et al.[8] UDP-glucuronyltransferase (UDPGT) activity was measured as described by Dutton et al.[9] Total T_4 concentration in serum was determined using the Coat-A-Count RIA kit of Diagnostic Products Corporation (Los Angeles, CA, USA).

Analysis of variance (ANOVA) and correlation analysis was used for statistical evaluation of the data obtained by using the NCSS (Kaysville UT, USA) software package on a Zenith 386/33e computer.



Tetra-CDD Chlorpromazine

Figure 1. Structural formula of chlorpromazine and tetra-CDD.

RESULTS AND DISCUSSION

Subacute treatment of rats with chlorpromazine resulted in a perfect dose-dependent decrease of serum T_4 (Fig. 2), as it was reported for tetra-CDD previously (Gorski and Rozman[10]). Similar to the effects of tetra-CDD, G-6-Pase activity was decreased, whereas EROD activity was induced, but neither effect was as pronounced in the dose-range investigated as with tetra-CDD. PEPCK and TdO activities were unaffected in the dose-range studied.

The most interesting finding was that UDPGT activity was significantly reduced, rather than induced as with tetra-CDD. Moreover, both reduced serum T_4 and reduced UDPGT and G-6-Pase activities revealed a strong statistical correlation with feed intake reduction but not with the treatment. These findings suggest that the effect of chlorpromazine on serum T_4 is unrelated to the induction of UDPGT activity, raising the possibility that this may also true for tetra-CDD in spite of claims to the contrary.

Results obtained suggest that a final conclusion about similarities and differences in the toxicity between tetra-CDD and chlorpromazine may not be possible before comparative toxicity studies will be conducted by using dosing regimens resulting in similar AUCs.

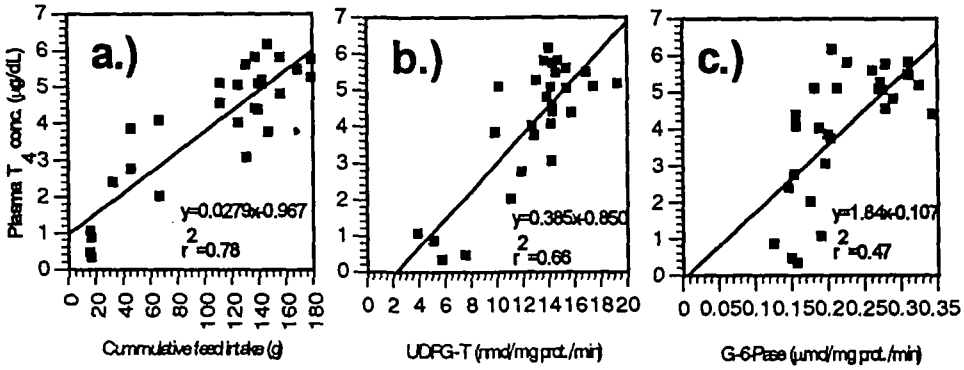


Figure 2. Correlation between decreased serum T_4 and a.) reduced feed intake, b.) reduced UDPGT activity and c.) reduced G-6-Pase activity.

Table 1

Effect of chlorpromazine on serum T_4 and hepatic EROD, UDPGT and G-6-Pase activity.

Cumulative Dose (mg/kg)	Cumulative Feed Intake (g)	Serum T_4 (µg/dl)		EROD (pmole/mg/min)		UDPGT (nmole/mg/min)		G-6-Pase (µmole/mg/min)	
		Treated	Pair-fed	Treated	Pair-fed	Treated	Pair-fed	Treated	Pair-fed
28	157	5.2±0.2[a]	5.4±0.3	9.5±2.1	6.9±2.0	14.2±0.7	15.6±2.4	0.29±0.02	0.30±0.01
112	131	4.0±0.3	5.4±0.2	17.6±5.5	6.9±0.8	14.0±1.2	14.5±2.7	0.21±0.02	0.23±0.02
448	35.8	1.4±0.6	2.5±0.8	30.3±19.8	4.1±1.6	9.1±2.9	7.7±4.3	0.16±0.01	0.17±0.02

[a] Mean ± SE (n = 4 to 5)

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