INDUCTION OF DRUG METABOLISING CAPACITY IN THE RAT BY DI-(2-ETHYLHEXYL)PHTHALATE

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Numerous chemicals, including certain drugs, when administered chronically cause liver hypertrophy, proliferation of endoplasmic reticulum and induction of the cytochrome P-450 drug metabolising system. These effects have well documented consequences *in vivo* resulting in an enhanced drug metabolising capacity. Di-(2-ethylhexyl) phthalate (DEHP) is a plasticizer which readily leaches out from plastic materials and hence is ingested in significant amounts as a food contaminant and is delivered parenterally to patients on infusion therapy (Thomas et al 1978). DEHP displays many of the classic induction characteristics in the *in vitro* systems and it is believed to selectively induce formation of a specific cytochrome component (P-452) concerned primarily with fatty acid oxidation (Lake et al 1984). The consequences of DEHP on drug metabolising capacity *in vivo* are unclear and hence we have investigated the effects of multiple dosing of DEHP on the pharmacokinetics of antipyrine, a well established marker of drug metabolising capacity (Rhodes & Houston, 1983).

Male Sprague-Dawley rats (n=18) received (N-methyl-^{14}C)-antipyrine (25mg/kg; 10μCi/kg; i.p.) and were housed in all-glass metabolism cages which allowed the continuous collection of $^{14}CO_2$ (derived from N-demethylation) and urine. The half-life of antipyrine was estimated from the $^{14}CO_2$ exhalation rate (CER)-time profile.Animals were divided into 4 groups and each rat tested before, and at varying times up to 15 days while receiving daily oral doses of corn oil (5ml/kg) alone or together with DEHP (0.5, 1 or 2g/kg). On the day after the 15th dose the rats were killed, livers removed for preparation of microsomes by standard differential centrifugation.

The data shown in table 1 demonstrates that at each of the doses studied there is liver enlargement and an increase in two microsomal markers of drug metabolising capacity - cytochrome P450 content and ethoxycoumarin O-deethylase. In contrast the antipyrine CER half-life is affected only at the highest dose. The maximal reduction in half-life following DEHP dosing, which is considerably less than that observed with other classic inducers (Rhodes & Houston 1983) is maximal at 7 days and maintained until day 15. It would appear that cytochrome P-452 and any other cytochromes inducible by DEHP do not show a strong affinity for antipyrine as a substrate. Although additional studies employing other drug substrates are required, the present investigation would indicate limited consequences of DEHP induction on *in vivo* metabolism.

Table 1 Effects of various doses of DEHP on drug metabolising capacity

Dose (g/kg)	CER half-life(min) Day 0	Day 15	Liver weight (% of body weight)	Cytochrome P-450 (nmoles/mg protein)	Ethoxycoumarin O-deethylase (nmoles/min/mg protein)
0	125 ± 7	126 ± 11	3.4 ± 0.2	0.345 ± 0.074	0.657 ± 0.131
0.5	112 ± 10	112 ± 8	4.5 ± 0.2[a]	0.463 ± 0.095[b]	0.881 ± 0.129[b]
1	117 ± 7	110 ± 9	5.4 ± 0.2[a]	0.396 ± 0.154	0.825 ± 0.195
2	128 ± 26	101 ± 17[c]	5.7 ± 0.4[a]	0.496 ± 0.042[a]	1.076 ± 0.105[a]

Mean ± s.d. Statistical significance from control $p<0.01$(a) and $p<0.05$ (b) by one way ANOVA and $p<0.05$ (c) by two way ANOVA.

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