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**Short Communications**

# Effect of single and short-term multiple exposure to honeybee venom on the disposition of antipyrine in the rat

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More than 50% of drugs metabolized in the liver are substrates for the cytochrome P-450 system (Vessey, 1982). A variety of immunological stimulants are known to inhibit the P-450 system. Specifically, several vaccines (Farquhar et al., 1976, 1983; Kramer and McClain, 1981; Meredith et al., 1985; Renton, 1979), products of micro-organisms (Gorodischer et al., 1976; Hojo and Hashimoto, 1977; Yoshida et al., 1982), viruses (Ragland et al., 1971; Renton, 1981), and synthetic interferon inducers (Mannering et al., 1980; Renton and Mannering, 1976a and b) are potent inhibitors of drug metabolism. A particularly interesting finding is the recent demonstration that the daily administration of honeybee venom for 24 days depresses microsomal drug metabolism in the rat (Eisman et al., 1982). Whether or not a single exposure to honeybee venom alters drug metabolism has not been examined. While beekeepers and patients receiving venom immunotherapy are exposed to venom chronically, the most widespread exposure to honeybee venom results from a single insect sting. Therefore, the effect of single and short-term multiple exposure to honeybee venom on drug metabolism in vivo was examined.

Male Sprague–Dawley rats weighing 160–250 g had an indwelling cannula implanted in the right jugular vein (Weeks and Davis, 1964) 2 days prior to the administration of antipyrine. Animals were housed in individual plastic metabolism cages and antipyrine (20 mg/kg) dissolved in normal saline (10 mg/ml) was administered via an infusion pump (Harvard Bioscience) through the cannula at a rate of 0.34 ml/min. Serial blood samples (0.25 ml) were obtained through the cannula over a 6-h period. Blood was transferred to heparinized glass capillary tubes and plasma separated by centrifugation. Plasma was stored at $-20\,^{\circ}C$ until assayed. Food and water were withheld during the period of blood sampling.

In one study, animals received a single dose of 1 mg/kg honeybee venom (dissolved in normal saline to 1 mg/ml), or saline, administered s.c. in the medial surface of the upper right hind limb 24 h prior to the administration of antipyrine. Honeybee (*Apis mellifera*) venom (electrically collected extract) was purchased from Vespa Laboratories (Spring Mills, PA). Venom and saline administration were performed with the animals under very light ether anesthesia. In a second study,

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another group of animals received the above treatment for 4 consecutive days prior to antipyrine administration. In all studies, venom solutions were prepared within 1 h of administration.

Antipyrine concentration in plasma was determined using an HPLC method described elsewhere (Svensson, 1986). The plasma concentration vs time data were analyzed utilizing the PCNONLIN program (Statistical Consultants, Inc., Lexington, KY). The pharmacokinetic parameters between control and treatment groups were compared using an unpaired $t$-test. A value of $P < 0.05$ was considered statistically significant. All values are given as mean ± 1 S.D.

The mean antipyrine plasma concentration–time curves for venom and saline treated animals in the single dose study are shown in Fig. 1. Antipyrine plasma concentrations declined monoexponentially. Mean pharmacokinetic parameters for venom and saline-treated animals are presented in Table 1. The disposition of antipyrine

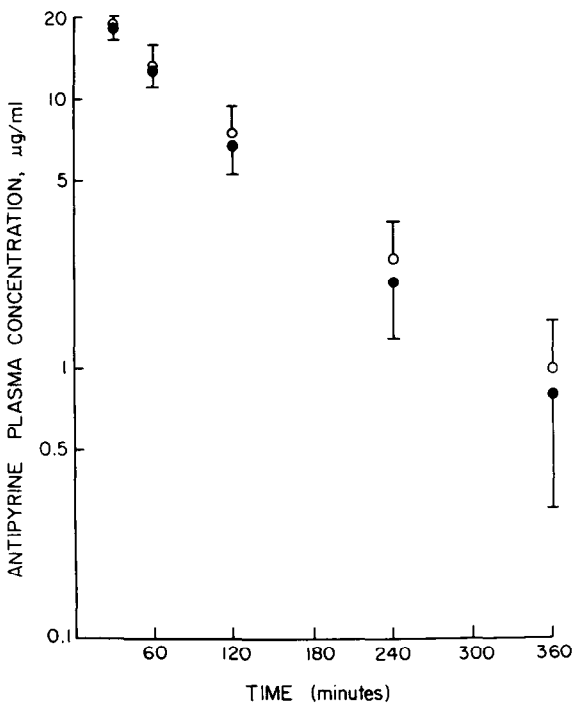


Fig. 1. Mean antipyrine plasma concentration–time profile in control (●) and single exposure venom pretreated (○) rats. Bars represent 1 S.D.

TABLE 1

*Effect of single exposure to honeybee venom on antipyrine elimination*

Results are expressed as mean (±1 S.D.).

| Treatment group | Pharmacokinetic parameter | | |
|---|---|---|---|
| | $Cl$ (ml/min/kg) | $t_{1/2}$ (min) | $V_d$ (ml/kg) |
| Control ($n = 5$) | 8.88 (1.72) | 62.3 (9.0) | 782 (53) |
| Honeybee venom ($n = 5$) | 8.25 (1.72) | 70.1 (16.5) | 801 (34) |

was not significantly affected 24 h after the administration of honeybee venom.

In an effort to test for a possible delayed effect and/or multiple exposure effect, we subsequently examined the effect of 4 days pretreatment with honeybee venom on antipyrine disposition. The mean pharmacokinetic parameters for short-term multiple exposure to honeybee venom or saline are presented in Table II. Pretreatment with honeybee venom for 4 days had no significant effect on the disposition of antipyrine.

These data indicate that single or short-term multiple exposure to honeybee venom does not significantly alter drug metabolism in vivo. While our sample size was not large enough to statistically detect a less than 10% change in antipyrine clearance, it is unlikely that such a small change would be of biological or clinical relevance (even if statistically significant). The dose of venom to which these animals were exposed is substantially higher than that which normal subjects receive following an insect sting. Animals in the present

TABLE 2

*Effect of short-term multiple exposure to honeybee venom on antipyrine elimination*

Results are expressed as mean (±1 S.D.)

| Treatment group | Pharmacokinetic parameter | | |
|---|---|---|---|
| | $Cl$ (ml/min/kg) | $t_{1/2}$ (min) | $V_d$ (ml/kg) |
| Control ($n = 6$) | 8.82 (1.20) | 67.1 (8.6) | 843 (58) |
| Honeybee venom ($n = 8$) | 8.13 (1.81) | 73.7 (13.9) | 837 (70) |

study received ca. 200 μg of venom, while the average insect sting is estimated to be about 50 μg (Lichtenstein et al., 1979). Thus, it appears unlikely that subjects who receive a single, or even multiple, insect sting are at significant risk for altered drug metabolism and its consequences. The significance of the effect of long-term exposure on microsomal drug metabolism noted by Eisman et al. (1982) to humans chronically exposed to venom remains to be determined.

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