

## SHORT COMMUNICATION

### EFFECT OF LEAD EXPOSURE ON PLASMA PHENYLBUAZONE LEVELS IN RATS

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**Abstract :** The effect of lead exposure on phenylbutazone kinetics was studied in rats. The biological half-life ( $t_{1/2}$ ) of phenylbutazone was determined from the plasma level versus time curve in 3 groups of rats given (i) 10 mg/kg lead orally for 8 weeks (ii) 100 mg/kg single oral dose and (iii) no lead, after oral administration of 100 mg/kg phenylbutazone to all rats. The  $t_{1/2}$  of the drug was found to be 33% lower on chronic lead exposure and 46% higher on acute exposure than in unexposed control rats. This variation in the  $t_{1/2}$  values of the two different groups of rats indicates that probably phenylbutazone metabolism varies with the period of lead exposure.

**Key words :** phenylbutazone

kinetics

lead exposure

#### INTRODUCTION

Chronic lead toxicity is known to effect several organs of the body (1). Apart from lead nephrotoxicity and hepatotoxicity (2) effect of lead on cytochrome P-450, the hemoprotein responsible for induction of liver microsomal enzymes that metabolise drugs has been reported in rats (3,4). However, drug kinetics after lead exposure has not been studied so far. The present work reports the effect of acute and chronic lead administration on the plasma phenylbutazone levels with time in rats. The study could be of interest for evaluating clinical situations where lead exposed persons require drug therapy for treatment of other underlying diseases.

#### METHODS

Male albino rats (average weight 170 g) inbred in the All India Institute of Medical Sciences animal house colony were divided into 3 groups of 6 each. Rats of Group I were given daily an oral dose of aqueous lead acetate solution (lead 10 mg/kg) for 3 weeks. Rats of Group II and III, were left untreated during this period although animals of all 3 groups were allowed

normal food and water. After 8 weeks, Group II rats were given a single oral dose of lead acetate (100 mg/kg). After 24 hr of lead administration to rats of group II, phenylbutazone (100 mg/kg) in aqueous gum acacia suspension was orally administered to rats of all the 3 groups. Rats were anaesthetized with ether and 1 ml blood was collected at 2,4,8 and 12 hr from the eye (5). A heparinized microhematocrit capillary (broken into 3) was inserted through the outer canthus of the eye into the retro-orbital plexus by rotating the capillary as it is advanced. The ensuing blood was collected in a heparinized centrifuge tube and plasma was separated and stored at 4°C for subsequent phenylbutazone estimation. After 24 hours of phenylbutazone administration, rats were exsanguinated by decapitation and 4-5 ml heparinized blood collected from the heart. One ml aliquot was separated and plasma stored as above while remaining blood was used for lead determination.

Estimation of plasma phenylbutazone was carried out spectrophotometrically at 314 m $\mu$  (6) in a double beam Cecil spectrophotometer. Recovery experiments were carried out by adding known quantities of

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phenylbutazone to 3 blood samples. The concentration versus time curves were plotted on semilog paper and plasma half life ( $t_{1/2}$ ) was estimated by extrapolation of the elimination phase of the curve to 0 hour. Blood lead levels were determined in Pye-Unicam atomic absorption spectrometer (7) after digestion of 1 ml whole blood with nitric, perchloric acid mixture (8).

## RESULTS AND DISCUSSION

In the present study peak plasma phenylbutazone level was attained at 4 hours of drug administration in all the 3 groups of rats. Table I shows that the peak phenylbutazone concentration (PPC) was not related to blood lead level. PPC was almost 23% lower in rats subjected to long term lead exposure than that of control animals. That this lowering was not due to *in vivo* chelation or complex formation between lead and the drug was evident from the results of the acute experiment in which a 36% increase of PPC and 46% increase of phenylbutazone  $t_{1/2}$  values was observed (Table I). It is

TABLE I : Plasma phenylbutazone level of lead exposed rats.

Group	Lead treatment (mg/kg)	Blood lead Mean $\pm$ S.D. ( $\mu$ g/dl)	Phenylbu. Peak conc. Mean $\pm$ S.D. (mg/L)	Phenylbu. $t_{1/2}$ Mean $\pm$ S.D. (hrs)
I	10 daily	68.5 $\pm$ 6.29	225.78 $\pm$ 20.5	4.75 $\pm$ 0.34*
II	100 once	162.4 $\pm$ 7.43	398.3 $\pm$ 32.4	10.25 $\pm$ 0.45*
III	Nil	6.25 $\pm$ 0.62	292.08 $\pm$ 18.2	7.00 $\pm$ 0.50

\*P < .01 than control rats.

conjectured that lead causes a change in phenylbutazone plasma concentration independent of the blood lead level but depends on the length of exposure of rat to lead. The opposite nature of  $t_{1/2}$  values after acute and chronic lead exposure also indicates difference in rate of metabolism or excretion of phenylbutazone under different conditions, particularly the period of exposure to lead.

It was earlier reported (3) that the cytochrome P-450 dependent liver microsomal enzymes were inhibited in rats given a single intraperitoneal high dose (65 mg/kg) of lead acetate. This could explain the increased phenylbutazone  $t_{1/2}$  values in the present acute experiment. On long term exposure lead probably causes an induction of cytochrome P-450 which could have caused the lowering of phenylbutazone  $t_{1/2}$ , 32% in the chronically lead exposed rats. Norpoth et al (9) observed that phenobarbital induced hepatic cytochrome P-450 in rats was not inhibited when lead (30 mg/kg) was orally administered daily for 4 days. Therefore, the present study supports the hypothesis that inhibition of cytochrome P-450 by lead is transient and time dependent (4) and that long term lead exposure might cause induction of the liver microsomal enzymes that are responsible for metabolism of drugs.

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