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EFFECTS OF OPIPRAMOL ON HEPATIC GLUTATHIONE LEVEL IN RATS

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ABSTRACT

It was investigated if, opipramol (OPI), a tricyclic antidepressant, which has a corresponding double bond for epoxidation , causes any decrease in hepatic glutathione (GSH) level. This was done by administering rats with OPI and then determining their hepatic GSH levels by means of a spectrophotometric method. Both repeated and single low dose (4 mg/kg), and high dose (50 mg/kg) OPI administration produced statistically significant decreases in hepatic GSH level in rats.

KEYWORDS

Opipramol, glutathione, liver.

INTRODUCTION

Electrophilic substances and electrophilic metabolites formed in the liver, can be detoxified in the body by the conjugation with the hepatic nucleophil glutathione (GSH). Since, the capacity of the hepatic GSH is limited, a depletion may occur in the GSH level, after the conjugation reactions. This may lead electrophiles to react with the nucleophilic macromolecules in the

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cell resulting in toxic effects like losing of cell viability, carcinogenic and mutagenic effects.

Opipramol (OPI), a 5H-dibenzo (b,f) azepine derivative tricyclic antidepressant, has a corresponding double bond to be metabolized to an epoxide, and epoxidation is a general biotransformation of this compound (1). In this study, it was investigated that OPI administration causes any decrease in hepatic GSH level in rats as can be expected from its biotransformation products.

MATERIAL AND METHODS

Wistar albino male rats (200-300 g) were employed as test animals in this study. OPI was dissolved in saline and injected i.p. to test animals, and the solution was freshly prepared for each use. OPI was administered in two dose levels to test animals : Low (4 mg/kg, single, and repeated, 3 days, two times a day), and high (50 mg/kg, single). Animals were killed three hours after the drug administration (in repeated drug administration studies after the last administration). The liver was removed, washed with water, gently blotted and weighed. Tissue homogenisation and subsequent GSH determination was performed using the method of Kaplowitz, N. (2). In this method 5,5'-dithiobis (2-nitro benzoic acid), (DTNB) was used to determine GSH.

RESULTS

Both repeated and single low dose and high dose OPI administration produced statistically significant decreases in hepatic GSH level in test animal groups relative to controls (Table 1). t-Values are, 8,215 for single low

dose, 7,908 for repeated low dose and 9,982 for high dose group in t-Test and all these values are greater than 4,221 (t%0,1, 10).

Table 1

% Hepatic glutathione content and its % depletion after the opipramol administration in rats

Groups	n	mg GSH/100 g liver	Decrease in %
Control	7	156,4 ∓ 3,1	
Single low dose	5	137,3 ∓ 5,0	12,2
Repeated low dose	5	143,4 ∓ 2,3	8,3
High dose	5	107,4 ∓ 12,7	31,3

DISCUSSION

Electrophilic substances and electrophilic metabolites formed in the liver, may undergo conjugation with the hepatic nucleophil GSH, and can be detoxified by this pathway. At this time, hepatic labile GSH-pool is depleted and that makes the cell more vulnerable to electrophilic substances.

In this study significant decreases in hepatic GSH level were observed after low and high dose level OPI administration. Since, observed depletion of GSH has occurred in a short period after the drug administration, it is likely that another mechanisms such the interaction with the synthesis of GSH, did not contribute to this decrease. In our opinion, the decrease in the hepatic GSH-pool that we observed, occurs due to the conjugation of the GSH in the labile pool with the electrophilic metabolite (s) of opipramol.

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