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Plasma nicotinic acid level in chloroquine treated rats

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Summary

The effect of chloroquine phosphate on plasma nicotinic acid levels in adult male albino rats was investigated. Pyrogen free chloroquine phosphate in physiological saline was administered subcutaneously to rats in a dose of 15mg/kg body weight daily for eleven succeeding days in the treatment group. A control group was given equal volume of physiological saline daily for eleven succeeding days. Nicotinic acid concentration in the plasma was determined [1] Plasma nicotinic acid level was found to be significantly reduced ($P < 0.01$) throughout the duration of treatment. No change was observed in the control group. The significant reduction of plasma nicotinic acid level observed in this study may not be unrelated to competitive inhibition of the enzyme tryptophan dioxygenase by chloroquine phosphate.

Keywords: *Nicotinic acid, chloroquine*

Résumé

L' effect de la chloroquine phosphate sur le taux plassuique de l'acide nicotinique chez les rats abino adultes a ele investiguq. La chloroquine phosphate avait été adminstré de facon nous-cutané chez ces rats a does de 15mg/kg poids-du crops pendant 11 jours consecutif dous le groupe des ani aux trailés. Le groupe control avait élé troulé avec Alu liquide physioloque d'acide nicoti nique avait dé deteroninér par la methode [1]. Le taux plassuque do acide nicotinique avait trovve été reduite signi ficativement ($P < 0.01$) pendant toute la dureé du traitement. Il nyavait pas eu de charojement tur la concentraction phasunquine d'acide Nicotini que chez les. La rdeduction significative du taux plasuniqine d'acide nicotinquie observe dans etude ne pourrait pas etre en relation a une ihnibition competitoue de l'enzyme tryptophan dioxygenase par la chloroquine phosophate.

Introduction

Chloroquine, an anti-malaria drug, is commonly used in a malaria endemic region as Nigeria. It has been reported to be concentrated in the kidney, liver and heart muscles following its administration [2]. Its appreciable cellular damage in some tissues has also been reported. [3] There have been reports that the structural resemblance of chloroquine to trytophan and consequently, the toxic effect of chloroquine on liver cells affect the activity of tryptophan dioxygenase. [4,5] Nicotinic acid is a product of the biotransformation of tryptophan in a series of step involving tryptophan dioxygenase[6]. It is implicated in many processes in the body including oxidation –reduction process[7]. Its deficiency may lead to pathological conditions such as dermatitis diarrhea and dementia [8]. The recent report by Kukoyi *et al* [8], that the level of biosynthesis of nicotinic acid, via tryptophan – niacin pathway in chloroquine treated rats, may be reduced prompted the design of this study.

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Materials and methods

Forty adults male alibino rats (Ife Sprawley strain) weighing 200 to 300 mg each were used. They were bred in the animal holding of the College of Health Sciences, Ile-Ife, Nigeria. These animals were divided into 8 groups, each containing 5 rats. Groups 1 to 4 served as control while 5 to 8 constituted the treatment group. The animals were housed in a metabolic cages exposed to a 12 hour light/dark cycle and were allowed free access to water and to animal feeds (Livestock Feeds) containing 20% protein, 10% fat and 2% crude fibre. Choloroquine phosphate 15 mg/kg body weight (Imarsel Chemical Co. Ltd. Chinion, Hungary) was dissolved in sterile physiological saline and administered subcutaneously, daily for eleven successive days to the treatment group, while the control group received daily, subcutaneously, injections of physiological saline for the same period.

The treatment group (5-8) were stunned, decapitated and exsanguinated on days 1, 3, 7 and 12, respectively, and matched with their appropriated control (1-4). The blood samples were centrifuged (3,000 r.p.m.) for 10 minutes at 4 °C. Plasma was precipitated with 40 ml 3.5% (w/v) ice-cold trichoroacetic acid in 0.125M phosphate buffer, pH 7.4. The precipitate was separated from the supernatant by centrifugation (3,000 r.p.m) at 4°C and hydrolyzed in sealed evacuated tubes containing 2 ml of 4M NaOH at 100 °C for 6 h. Nicotinic acid concentration in the supernatant was determined [1]. Statistical analysis of results was by student's t-test. [9].

Results

Table 1 illustrates the levels of nicotinic acid in the plasma of the rats treated with chloroquine. The level of nicotinic acid in control

Table 1: Plasma nicotinic acid level in chloroquine treated rats

Days after Injection	Nicotinic acid concentration in plasma (ug/100 cm³)	
	Test animal	Control
1	13 ± 6*	18 ± 4
3	11 ± 3*	18 ± 6
7	8 ± 5*	19 ± 1
12	6 ± 8*	18 ± 5

**Indicates significant difference from the control.*
Each value is the mean of five observations ± SD.

rats after the first day was 18 ± 4 ug/100 cm^3. Whereas in the treatment group, the level was significant reduced ($P < 0.01$) from the first treatment and remained progressively reduced throughout the succeeding treatment.

Discussion

The results of the present studies clearly demonstrated that chloroquine phosphate produced a significant decrease ($P < 0.01$) in the plasma concentration of nicotinic acid in the treatment group in comparison with control group. The decrease was progressive with the duration of the assault.

Nicotinic acid is produced in the liver through the biotransformation of tryptophan in a series of reactions mediated by tryptophan dioxygenase. The structural similarity of tryptophan and chloroquine has been implicated in its effect on the activity of tryptophan dioxygenase [4,5].

The significant reduction of plasma nicotinic acid level observed in this study may not be unrelated to competitive inhibition of the enzyme tryptophan dioxygenase by choloroquine phosphate. There is evidence suggesting that many pharmacologically active substances alter metabolic process by virtue of their action on the activity of enzymes systems [10]. Formation of the co-enzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide dinucleotide phosphate (NADP) is the major role of nicotinic acid. NAD contains nicotinamide, an important dietary constituent for mammals. These co-enzymes are involved in many reactions in the body including oxidation-reduction reaction processes. The exact mechanism by which nicotinic acid is reduced in the treatment group is not clear and needs further elucidation.

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