THE EFFECT OF ACETAMINOPHEN (PARACETAMOL®) ON TEAR PRODUCTION

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ABSTRACT

The effect of acetaminophen (paracetamol®) on the tear production of 100 young healthy subjects was studied using their right eyes. These subjects with the mean age of 22.5±3.24 years consisted of 40 men and 60 women selected after a thorough case history, IOP measurement and TBUT determination to rule out pathology. Schirmer's test was done in all the selected volunteered subjects before ingestion of 1000mg (2 tablets) of acetaminophen. The test was repeated at interval of one hour after the ingestion for 4 hours. The mean induced tear secretion reduced from the mean baseline tear secretion by as 3.70mm (14.43%), 7.06mm (27.55%), 5.76mm (22.47%) and 5.30mm (20.68%) for the first 1-4hours respectively. The mean baseline tear secretion was found to be 25.63mm. These reductions were found to be statistically significant ($p>0.05$), showing that paracetamol significantly inhibits tear production. Paracetamol® should therefore be used with caution in individuals that have or are predisposed to dry eye syndrome.

KEYWORDS: acetaminophen (paracetamol®), prostaglandins, cyclo-oxygenase, Schirmer's strips, tear production.

INTRODUCTION

Paractetomal® belongs to the group of drugs referred to as non-narcotic (non-opiates) analgesic and antipyretic drugs. This group of drugs is known to relieve pain without depressing the central nervous system (CNS), and also reduce fever due to their antipyretic property. The examples of other drugs in this group are aspirin and Ibuprofen. Paracetamol®, known as acetaminophen in the United States of America, is a painkiller that is popular throughout the world because it is remarkably safe and does not irritate the stomach[1].

It appears Paracetamol has a highly targeted action in the brain blocking an enzyme involved in the transmission of pain[2]. The production of prostaglandins is part of the body's inflammatory response to injury and inhibition of prostaglandins production around the body by blocking the cyclo-oxygenase enzymes known as cox-1 and cox-2 has long been known to be the mechanism of action of aspirin and other non-steroidal anti-inflammatory drugs (NSAID) such as Ibuprofen[3]. The cyclooxygenase is responsible for the biosynthesis of prostaglandins and by reducing the amount of cyclooxygenase available for synthesis, acetaminophen helps to relieve mild to moderate pain[4]. Paracetamol® has no significant action on cox-1 and cox-2, which left its mode of action a mystery but did explain its lack of anti-inflammatory action and also more importantly its freedom from gastrointestinal side effects typical of NSAIDS[5].

Chronic excessive alcohol consumption can induce cytochrome P_{450} enzyme (CYP2E1) thus increasing the potential toxicity of acetaminophen. It is for this reason that other drugs such as Ibuprofen other than Paracetamol® are sometimes recommended for hangovers[6]. Concomitant use of other drugs which induce CYP enzymes such as antiepileptic (including carbamazepine, phenytoin, barbiturates) have also been reported as risk factors[7].

Paracetomol® is extremely toxic to cats as they do not have the necessary qlucuronyl transferase enzymes to break it down and tiny fractions of normal tablet for human may prove fatal. It is also lethal to snakes but safe for dogs[8]. Paracetamol® overdose is particularly dangerous in human because the damage (mostly liver) sometimes is not apparent for 4-6 days after taking the drug.[9]

The tear film coats the external surface of the eye and remains most directly in contact with the environment. It is composed of three layers- the inner mucoid layer (0.50%), the intermediate aqueous layer (98.0%) produced by the main lacrimal gland, glands of wolfring and Krause and the outer lipid layer (1.0%) secreted by glands of Zeis and Moll.

Dry eye is a pathologic condition characterized by a poorly functioning tear film due to compromise to either the quantity or quality of the pre-corneal tear film. This results to symptoms of dry or burning eyes, "sandy" or "gritty" foreign body sensation. Prostaglandin E (PGE) is involved in regulating electrolyte and water secretion in vivo, it acts on erprostanoid receptors EP_2 and EP_4 to activate adenylate cyclase, increasing cyclic AMP which in turn stimulates tear productions[3] Cyclo- oxygenase is responsible for the biosynthesis of prostaglandins.

Systemic ingestion of certain drugs or chemical substances that directly or indirectly affect the autonomic nervous system influences the secretion of the lacrimal gland, causing either a hyper-secretion or hyposecretion. The medications known to inhibit tear production include Beta- adrenergic blockers, anti-histamines, anti-cholinergic, sedatives, anti-depressants and analgesics (Paracetamol®) through different mechanisms.

Paracetamol® inhibits the cyclo oxygenase especially cox-3 which was previously unknown, resulting in a decrease in the output of prostaglandins. In addition acetaminophen blocks (though slightly) the enzyme δ-6-desaturase that is converted to PGE_1, which has been shown to stimulate aqueous tear secretion[4]. There was a strong and highly significant correlation between acetaminophen levels in serum and tears one or two hours after ingestion, possibly acetaminophen could be exerting an inhibitory effect on tear production since its level on tear was reduced by just 1.90mug/ml after 2 hours of ingestion compared to the levels in tear after one hour of ingestion[11].

METHOD

The study was done with 100 healthy volunteers comprising 60 women and 40 men with mean age of 22.50±3.24years. The subjects of this age bracket were chosen to eliminate those likely to have dry eye syndrome, glaucoma and any other disease of the aged that may affect tear production. It excluded those with allergies or hypersensitivity reaction to the use of Paracetamol®. The study involved voluntary students selected from different schools within Owerri municipal council. The instruments and materials used include - Schiotz tonometer by Reister, Germany; millimeter rule; timer; anaesthetics (primax) by Ashford laboratories Nigeria Ltd; cotton wool; Methylated Spirit by Nichben Pharmaceuticals Nigeria; 5 x 35mm Whatman filter paper # 41 (Schirmer's Strips); fluorescein dye by Haag Streit Ag, Switzerland; and Paracetamol® 500mg tablets from Nichben Pharmacenticals Nigeria.

The case history, the intraocular pressure measurement (IOP) and determination of the tear break up time (TBUT) were all carried out on the subjects to screen out the ones that were allergic or hypersensitive to the use of acetaminophen, those with increased intraocular pressure, and those with dry eye syndrome. The Schirmer's test was done on all the 100-screened subjects before ingestion of 1000mg (2 tablets) of Paracetamol®. The test was repeated at interval of one hour after the ingestion of Paracetamol® for four hours. The subjects served as their own control as the initial (baseline) test was compared with subsequent tests after the Paracetamol® intake. The amount of wetting of the Schirmer's strip in one minute was multiplied by three to correspond roughly to the amount of wetting that would have occurred in five minutes. A normal eye wets between 10mm to 25mm during the five minutes. Values between 5mm and 10mm are considered borderline and values less than 5mm are indicative of impaired secretion[11].

The tear secretion rate before and after ingesting Paracetamol® was collected for all the 100 subjects used. The data were analyzed using tables, and statistical test using ANOVA at 0.05 level of significance.

RESULTS

The mean baseline of tear secretion in the study population was 25.63mm. The mean induced tear secretions for one hour, 2 hours, 3 hours and 4 hours after ingestion were 21.93mm, 18.59mm, 19.87mm and 20.33mm respectively. The Percentage mean changes at different periods of re-evaluation of tear secretion were found to be 14.43%, 27.33%, 22.4% and 20.68% respectively.

The analysis of variance (ANOVA) F statistics was employed to test the hypothesis about mean at 95% confidence interval, using the mean square treatment and calculation. The statistics for F_{cal} was 307.96 while F_{tab} was 2.37 at the 95% confidence interval. Since the test statistics (F_{cal}) is much greater than the critical value (F_{tab}), the null hypothesis of equal population mean was rejected and therefore there was a significant difference, ($p>0.05$), between the mean baseline and mean induced tear production due to paracetamol intake.

DISCUSSION

The results obtained in this study showed a mean difference of 3.70mm, 7.06mm, 5.76mm and 5.30mm for one hour intervals after intake of 2 tablets (1000mg) of Paracetamol® as shown in table 1. From table 1, it was observed that the mean difference is greatest (7.06mm) after the 2 hours of Paracetamol® ingestion and the mean difference decreased at the 4 hours later tending towards baseline value.

These findings are in accordance with a previous study that Paracetamol® reaches peak plasma concentration within two hours of ingestion[2]. However, in a few isolated cases, there was marked decrease in tear secretion in the fourth hour from the baseline value. This may be attributed to individual peculiarities in metabolism.

The statistical analysis using the ANOVA table at 95% confidence interval showed that acetaminophen significantly inhibits tear production (P>0.05). This is because Pholpramol[3] found that acetaminophen inhibits prostaglandin synthesis and inhibits the enzyme δ-6-desaturase which invariably reduces aqueous tear secretion[3].

Acetaminophen (paracetamol) therefore has an inhibitory effect on tear production of healthy individuals and it is suggested that it be used with care in patients that have dry eye syndrome or predisposed to it.

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TABLE 1: MEAN CHANGE IN TEAR SECRETION AFTER ADMINISTRATION OF 1000MG OF PARACETAMOL

Mean baseline tear secretion (mm)	Mean induced tear secretion (mm)			
	1hour	2 hours	3 hours	4 hours
25.63	21.93	18.57	19.87	20.33
Induced mean change	3.70	7.06	5.76	5.30
% induced mean change	14.43	27.33	22.47	20.68