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Comparative analgesic effects of paracetamol with paracetamol-caffeine formulation

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Abstract

This study was designed to evaluate the contribution of caffeine to analgesia in paracetamol-caffeine preparation. Analgesic properties were evaluated in mice using acetic acid-induced writhing and hot plate methods. In the acetic acid method, the test drugs were administered orally to the mice. After 30 min. all the mice received 0.7% aqueous solution of acetic acid (10ml/kg i.p) and writhing was counted for 30 min. after acid injection. The percentage inhibition was then determined. In the case of hot plate method, the mice were placed singly on a hot plate maintained at 45±0.5^{0}C before and at 15, 30, 45, 60 and 90 min. after administration of the tested drugs orally. The latency of nociceptive responses (time taken before the mouse jumped out of the hot plate) was measured each time the mouse was placed on the hot plate. The mean percentage maximum possible effect (% MPE) was determined. The results revealed dose dependent analgesic activities in both paracetamol alone and paracetamol-caffeine combination. The activities were significantly higher compared to the control which received normal saline ($p<0.05$). There was a sharp increase in activity between 15-30mins by paracetamol-caffeine combination, with maximum activity setting in as from 30mins. But paracetamol alone had maximum effect at 45mins. It could be concluded that caffeine could enhance analgesic activity of paracetamol. However further pharmacokinetics and pharmacodynamic evaluations are needed to strengthen this view.

Keywords: Analgesia; Paracetamol; Caffeine; Anti-nociceptive activity; Over-the-counter (OTC) drugs

Introduction

Pain may occur alone or with some disease conditions, depending on the etiology. Pain remains a substantial problem for many patients presenting in the clinical setting. Substantial evidence are available in support of combining analgesics for the management of pain, and have shown, in some instances that they possess improved pharmacological effects (Fiebich *et al.*, 2000). A preparation that is commonly encountered is paracetamol-caffeine preparation. Unsupervised consumption of over-the-counter (OTC) drugs offers clinical challenges to both the patients and health care providers, because of the possibility of drug-drug or drug-food interaction.

In Nigeria, various brands of over-the-counter analgesic preparations exist containing either paracetamol alone or in combination with caffeine or other ingredient. Since they are consumed unsupervised, it is possible to consume two or more (OTC) preparations, OTC drugs with prescription drugs or with

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food preparations containing similar ingredients in them. OTC analgesics may be subjected to inappropriate use or misuse. This occurs when these drugs are used in situation in which they are not indicated or used in overdose. These various consumption patterns may be of serious concern if adverse effects occur, especially when used on chronic basis.

The most likely adverse effect in these situations is renal effects. The two renal lesions that may be encountered are papillary necrosis and cortical interstitial nephritis. Together they represent the syndrome identified as chronic tubulointerstitial disease (CTID). Of patients who develop this form of renal failure, approximately 23% have continued deterioration of renal function and 12% either die or receive maintenance dialysis within 6 months of diagnosis (Knapp and Avioli, 1982; Schrein *et al.*, 1981., Nanra, 1983; Goldberg, 1986 and Perneger *et al.*, 1994). The present work is designed to evaluate the contribution of caffeine to analgesia in this preparation, in order to conduct further studies.

Experimental

Drugs. Paracetamol 500mg caplet: Batch No:0500; Manufacturing Date:08/03, Expiry Date: 08/06. Manufactured by Glaxo SmithKline Nigeria Plc, Lagos. Tested doses mg/kg body weight of paracetamol: 7.14, 14.29 and 21.43. Paracetamol 500mg + caffeine 30mg caplet. Batch No.: 003N; Manufacturing Date:01/05, Expiry Date: 01/08. Manufactured by Glaxo SmithKline Nigeria Plc, Lagos . Tested doses mg/kg body weight of paracetamol-caffeine: 7.57, 15.14 and 22.71.

Animals. Adult mice weighing 18-23g of both sexes were used. They were obtained from the animal house of the Department of Pharmacology and Clinical Pharmacy A.B.U. Zaria, Nigeria. They were kept under standard environmental conditions and fed with a standard diet and drinking water *ad libitum.*

Acetic Acid – induced writhing. The method described by Koster, *et al.* (1959) and adapted by Vongtau *et al.*, 2000, was used. This method was postulated to partly involve local peritoneal receptors and responsible for peripheral action (Bentley, *et al.*, 1981). Mice of either sex were divided into four groups of six mice each and fasted for 18h. Group 1, serving as control, received normal saline. The remaining 3 groups received the tested preparation at different doses. All the drugs were administered orally. After 30min all the mice received a 0.7% aqueous solution of acetic acid (10ml/kg i.p.) and writhing was counted for 30min after acid injection. Percentage inhibition of writhes was calculated as:

$$\% \text{ inhibition} = \frac{\text{Mean number of writhes (control)} - \text{Mean number of writhes (test)}}{\text{Mean number of writhes (control)}} \times 100$$

Hot plate method. The method of Eddy and Leimbach (1953) was used. The method has been shown to involve both peripheral and central effect through polymodal nociceptors. Plymodal nociceptors are characterized by their content of neuropeptides which play role as both central neurotransmitters and peripheral mediators of neurogenic inflammation (Dray and Wood, 1991).

Mice of both sexes were fasted for 18h and divided into four groups of six mice each. Group 1, serving as control, received normal saline. The remaining 3 groups received tested preparations at different doses. All the drugs were given orally. The mice were placed singly on a hot plate maintained at 45 ± 0.5^0C before and at 15, 30, 45, 60 and 90 min after administration of the tested drug. The latency of nociceptive responses (time taken before the mouse jumped out of the hot plate) was measured each time the mouse was

placed on the hot plate. Only mice that showed nociceptive responses within 20s were used and a cut-off time of 60s was selected, to prevent tissue damage. The mean percentage maximum possible effect (% MPE) was calculated as:

$$\% \text{ MPE} = \frac{\{(\text{post-drug latency}) - (\text{Pre drug latency})\}}{(\text{cut off time}) - (\text{pre drug latency})} \times 100$$

Statistical analysis. All data were expressed as the mean ± SD. Statistical analysis was carried out using the student's t-test and the differences considered significant when $p<0.05$.

Results and Discussion

Paracetamol alone (P) and paracetamol-caffeine preparation (PC) showed dose dependent decrease in the number of acetic acid-induced writhes in mice. The decrease was significant ($p<0.05$) compared to the control in both cases. The highest percentage inhibition (56.14%) was shown by paracetamol-caffeine at the dose of 22.71m/kg body weight (Tables 1 and 2).

In considering the latency of nociceptive responses, using hot plate method, the two preparations showed similar dose dependent increase in % maximum possible effect (Tables 3 and 4). In the hot plate method, between 15 and 30min, there was a sharp increase in effect due to paracetamol-caffeine preparation. This increase was not sharp with paracetamol caplet alone. For paracetamol, maximum effect was obtained at 45min.

This evaluative study has shown that the paracetamol alone and paracetamol-caffeine preparation had effects on the number of acetic acid-induced writhes and latency of nociceptive responses using hot plate method in mice. The methods employed in the anti-nociceptive studies were very sensitive, and able to detect effects, which may not be possible in other methods such as tail-flick method. The acetic acid-induced writhe was postulated to partly involve local peritoneal receptors (Bentley *et al.*, 1981). The hot plate method has been shown to involve both peripheral and central effects through polymodal nociceptors. Polymodal nociceptors are characterized by their content of neuropeptides which play a role as both central neurotransmitters and peripheral mediators of neurogenic inflammation, (Dray and Wood, 1991).

Paracetamol is a poor inhibitor of peripheral prostaglandin synthesis, but it has been suggested that it may inhibit brain prostaglandin synthesis and somehow produce an analgesic effect centrally. Also it may be involved in inhibition of central pain recognition mechanism. Due to the fact that paracetamol is a weak inhibitor *in vitro* of both cyclooxygenases (COX), the possibility exists that it inhibits a so far unidentified form of COX, perhaps COX-3 (Botting, 2000).

The sharp increase in effect between 15 and 30min, following administration of paracetamol-caffeine preparation could be viewed from two perspectives; one, because of the potentiating effect and secondly because of prompt and increased absorption of paracetamol-caffeine combination. Studies conducted by Fiebich, *et al.* (2000), revealed that caffeine dose-dependently inhibit microglial PGE_2 synthesis. This is mediated by inhibiting COX-2 protein synthesis. It has been reported that caffeine increases the oral and rectal absorption of ergotamine (Laurence *et al.*, 1997). And it is widely believed that this accounts for its enhancement of therapeutic effects. The same reason may be postulated in part for the enhanced effect of paracetamol-caffeine preparation.

These positive contributions by caffeine remain a subject of further investigation, because caffeine has the potential of causing gastric secretion, which may lead to gastric disorder; and promotion of dependence. Also

there may be cardiac disorders (Laurence *et al.*, 1997). These may constitute a serious problem, when a form of drug-drug or drug-food interaction is involved. It is a well known fact that coffee consumption is a common habit among some Nigerians. Since over-the-counter drugs are consumed most of the time unsupervised, these forms of interaction may constitute a serious health hazard which may not be detected early enough. However further toxicological and clinical evaluative studies are required to strengthen this view.

Table 1: Percentage Inhibition of Paracetamol on acetic acid-induced writhing in mice after oral administration with various doses of Paracetamol.

Dose mg/kg	Number of writhes (mean± SD; n=6)	Percentage inhibition (%)
Control	24.67±1.64	
7.14	16.16±1.18*	34.50
14.14	14.17±0.76*	42.56
21.40	11.50±1.05*	53.38

* Statistically significant ($P<0.05$) compared to the control.

Table 2: Percentage Inhibition of Paracetamol-Caffeine on acetic acid-induced writhing in mice after oral administration with various doses of Paracetamol-Caffeine .

Dose mg/kg	Number of writhes (mean± SD; n=6)	Percentage inhibition (%)
Control	24.33±1.74	
7.75	14.67±0.81*	39.70
15.14	15.50±1.05*	48.62
22.71	10.67±1.2	56.14

* Statistically significant ($P<0.05$) compared to the control.

Table 3: Effect of paracetamol caplet at various doses on the latency of nociceptive responses in mice using hot plate method. (n = 6)

Dose (mg/kg)	Percentage maximum possible effect (% MPE)				
	15min	30min	45min	60min	90min
Control	0.9	0.00	1.55	0.63	0.31
7.14	8.04	12.68	22.29	20.45	22.59
14.14	14.20	18.20	26.24	25.61	26.54
21.43	1.65	20.73	29.72	30.2	29.03

Table 4: Effect of paracetamol-caffeine caplet at various doses on the latency of nociceptive responses in mice using hot plate method. (n = 6)

Dose (mg/kg)	Percentage maximum possible effect (% MPE)				
	15min	30min	45min	60min	90min
Control	0.9	0.00	1.55	0.63	0.31
7.57	12.57	22.09	25.78	38.96	24.54
15.14	20.18	29.67	32.11	30.59	30.28
22.7	23.70	32.93	35.39	33.86	33.54

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