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The Effect of Pre- Exposure to Caffeine on the Onset of Action of Pancuronium - A Neuromuscular Blocking Agent in Rat

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This study investigated the effect of pre- exposure to caffeine on the onset of action of Pancuronium, a non depolarizing neuromuscular blocking drug. Using intraperitoneal(ip) administration, a graded dose of caffeine was administered to the albino rats before giving Pancuronium, and onset(time) of paralysis was measured. Twenty matured albino rats used for this study were randomly divided into four groups (Group i-iv). Group (i), control was given 0.1mg/kg pancuronium and onset of action was recorded., while group(ii-iv) serves as the experimental groups. Rats in groups (ii-iv) were exposed to 15mg/kg, 30mg/kg, and 45mg/kg of caffeine Thereafter, 30min before pancuronium o1img/kg was administered. The results obtained in this study indicated a dose-dependent increase in the onset of action of Pancuronium upon pre- exposure to caffeine, an effect that is more prominent at the medium and high doses (30mg/kg and 45mg/kg). The result also show that pre- exposure to caffeine delays the action or increases the onset of action of Pancuronium (a non depolarizing blocking drug) at neuromuscular junction and that effect of caffeine is dose dependent. However, from the result of this study,it may be suggested that the dose and time of last intake of caffeine should be considered before determining the dose of Pancuronium to be administered as adjunct to anesthesia in surgical process .

Key words: Exposure, Caffeine, Neuromuscular, Blocking, Activity, Pancuronium, Rat.

Caffeine intake is a daily occurrence for many people all over the world Caffeine is widely known to be a central nervous system (CNS) stimulant, and is commonly used in therapy to treat, migraines and asthma. It is also known as 1, 3, 7-Trimethylxanthine, caffeine ($C_8H_{10}N_4O_2$), is a bitter, white alkaloid commercially derived from tea and coffee.

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The effects of caffeine on neuromuscular transmission have been studied by a number of scientists but specific actions of this agent on the transmission process are unclear. It has been reported that caffeine increases the amount of transmitter released by the nerve terminal during nerve stimulation. Hofmann et al suggested, that this is due primarily to increase in the mobilization rate and an increase in the amount of releasable store (vesicle). Elmqvist and Feldman however examined the effect of caffeine and spontaneous transmitter release and their results suggest an effect on the its release.

Previous studies suggests that caffeine increases synaptic transmission. Wilson (1973) studied the effect of 1.0mM caffeine solution on

an end plate potential when applied to the rat diaphragm. By comparing the effect of caffeine to that of increased Ca2+ concentration. He concluded that caffeine acted on internal calcium stores in the presynaptic cell and also increases the mobilization rate of neurotransmitter.

It has since been shown that caffeine activates the endoplasmic recticulumCa2+ release channel by increasing the frequency and the duration of open events (Meissner *et al.* 1989). Specifically, caffeine is an agonist of the ryanodine-sensitive endoplasmic reticulum Ca^{2+} release channel, enhancing Ca^{2+} induced Ca^{2+} release in rat osteoclasts (shankar *et al*.1995) and rat ventricular myocytes (O"Neill *et al.*1990). More recently, Jacobson (1998) reviewed six of his previous studies on human reactions to ingesting caffeine. The result suggested that caffeine stimulates certain neurotransmitters, both inhibitory and excitatory. This manifest itself in affected muscle groups by either strengthening or weakening the action.

Pancuronium was the first and the most widely used steroid-based neuromuscular blocking drug and belong to the class of non depolarizing neuromuscular blocking drugs. it has a long duration of action which is prolonged in the presence of renal impairment, as 60% of the drug is excreted unchanged through the kidney, it does not release histamine but has direct vagolytic and sympathomimmetic properties. It has a side effect profile than tubocuraine (Martyn and Standaert, 2000).

Most of the investigations were carried out to confirm the facilitating effect of caffeine on the release of neurotransmitters; however, in this study used the basic knowledge of the neurotransmitter-release facilitating effect of caffeine to investigate the effect of pre- exposure to caffeine and see the effect on the onset of action of Pancuronium (a non depolarizing neuromuscular blocking drug)

MATERIALS AND METHOD

Drugs

1) Pancuronium (a non depolarizing neuromuscular blocking drug)
2) Caffeine (a common CNS stimulant.

EXPERIMENTAL

Twenty matured albino rats used for this study are of both sexes and were obtained from the animal house of Babcock University, Ilishan, Ogun state. They were housed in clear plastic cages, which were well ventilated with free access to water and food in a room that was kept at a normal temperature 37^0c.The rats were acclimatized for two weeks to the laboratory conditions after which they were weighed and marked for easy identifications; their average weight was 155gram . The rats were later divided into four groups of five each. The groups (i-iv) . Group (i) was the control group while the other groups(i-iv) were used as the Experimental groups.

Procedures

Animals in **Group(i)** the control group were given 0.1mg/kg of Pancuronium intraperitoneally and the onset of action of the drug and paralysis was recorded. **Group (ii)** animals were given I5mg/kg of caffeine 30minutes before

Table 1. The dose of drugs (Pancuronium(P) and Caffeine (C)were) given to each group and the onset of action of Pancuronium (mins)

Group	Doses mg/kg	N	Onset of action(mins)
Control I	0.1mg P	5	5.78 ± 0.13
II	15mgP and 0.1mgC	5	6.39 ± 0.18
III	30mgP and 0.1mgC	5	8.45 ± 0.19
IV	45mg P and 0.1mg C	5	10.75 ± 0.2

N- Number of animals in each group
The result is expressed as mean ± S.EM $p<0.05$
P= Pancuronium mg/kg, and C= Caffeinemg/kg.

administration with 0.1mg/kg of Pancuronium and the onset of action of Pancuronium was also measured.

Group (iii) animals were given 30mg/kg of caffeine 30minutes before administration with 0.1mg/kg Pancuronium and the onset of action of Pancuronium was recorded. **Group (iv)** animals were given 45mg/kg of caffeine 30minutes prior to being administered with 0.1mg/kg of Pancuronium and the time of onset of action of the drug was determined.

The time of onset of action of Pancuronium was determined by measuring the time of neuromuscular junction blockade taking into consideration the onset of paralysis which is determined by an open field test.

RESULTS

Table 1 shows the dose of drugs (Pancuronium(P) and Caffeine (C)were) given to each group and the onset of action of Pancuronium (mins) were recorded.

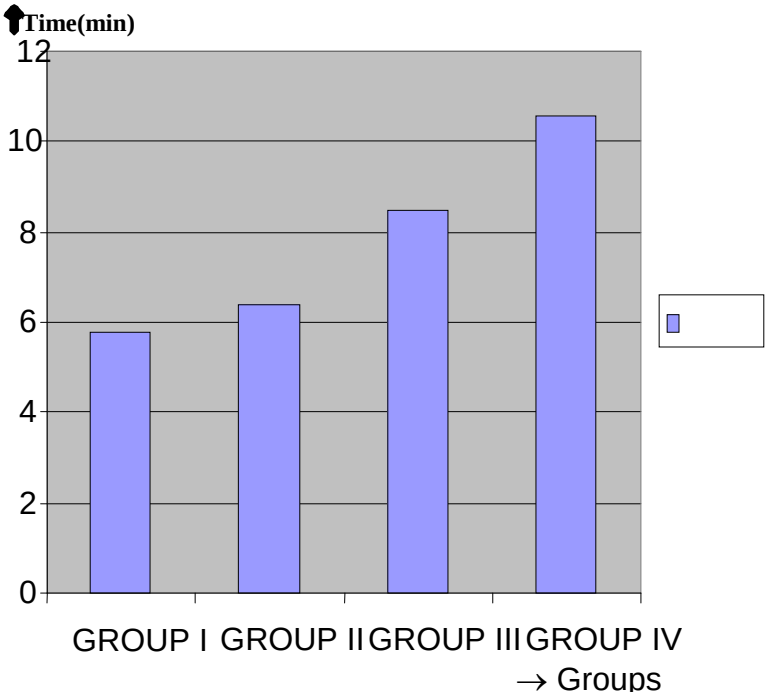

Fig. 1. A Dose-dependent Increase in the Onset of Pancuronium Upon Pre- Exposure to Caffeine
X-axis, indicates the groups (I- Iv); Y-axis, indicates time (min)

DISCUSSION

The present study was conducted to investigated the effect of pre- exposure to caffeine-methylxanthine on the onset of action of Pancuronium. It has been reported that methylxanthnes especially caffeine has the ability to increase the amount of neurotransmitter release at moderately high dose by increasing the Ca2+ (calcium) sensitivity of the ryanodine receptors (Rang *et al.*, 2007). Apart from being an unselective adenosine receptor antagonist in the CNS, caffeine at moderately high dose at the neuromuscular junctions act as an agonist of the ryanodine-sensitive endoplasmic reticulum and it therefore activates the endoplasmic reticulum Ca2+ release channel(Meisnner et al. 1989) and enhances Ca2+-Ca2+ release of neurotransmitter(Shankar et al.1995) .

The result in this study showed that pre-exposure to caffeinein the concentration used in this work,delays the onset of action of

neuromuscular blocking activity of Pancuronium and that this effect is prominent dose dependently. At a dose of 15mg/kg of caffeine (the low dose) the increased in the onset of action of Pancuronium is not too significant compare to the increase caused by a prior exposure to 30mg/kg (medium dose) and 45mg/kg (high dose) of caffeine. This further shows that the increased in onset of action of Pancuronium due to prior exposure to caffeine is more prominent and more significant at a moderately high doses of caffeine

The delay in the onset of action or the increase in the time of onset of action of Pancuronium upon pre- exposure to caffeine as noticed in the result is due to or believed to be as a result of increased amount of neurotransmitter (ACh) released at the rat neuromuscular junction in accordance to Wilson (1975), who suggested that caffeine would cause more neurotransmitter (ACh) release by increasing the rate of mobilization of neurotransmitters at the neuromuscular junction and since Pancuronium(the same dose given to the control group) which act as a receptor antagonist will require more time to displace or overcome the increased amount of ACh compare to the time it takes to elicit the same response(paralysis) in a rat that was not given caffeine. The neuroprotective effect of caffeine can also be a reason for this.

The result and the discussion of the result of this study, clearly show that prior exposure to caffeine especially at moderately high doses/concentration delays the action of **or** increases the onset of action of Pancuronium. It also shows that this effect of caffeine on the onset of action of Pancuronium is dose dependent. This further confirms the neurotransmitter (ACh) release facilitating effect of caffeine at neuromuscular junction

REFERENCES

1. Jacobson, Bert H. 1998. Caffeine ingestion and performance. Perceptual and motor skills **86**(1): 66.
2. O'Neill, S.C.,and D.A. Eisner. 1990 A Mechanism for the Effects of Caffeine on Ca2+ Release During Diastole and Systole in Isolated Rat Ventricular Myocytes. The Journal of Physiology 430: 519-536.
3. Rousseau E.; Meissner G. 1989. Single cardiac sarcoplasmic reticulum Ca2+-release channel:activation by caffeine. AmJ Physiol **256**(2) Pt 2: H328-33.
4. Shankar, Vijai, Michael Pazinas, Christopher Huang, Bruce Simon, Olugbenga Adebanjo, and Mone Zaidi. Caffeine modulates Ca2+ receptor activation in isolated rat ostoclasts and induces intracellular Ca2+ release. 1995 Am J Physiology 268(3) Pt 2:F447-54.
5. Wilson, David F. 1973. Effects of caffeine on neurotransmission in the rat. Am. J. Physiology **225**(4): 862-5.
6. Rod Flower; Humphrey P. Rang; Maureen M. Dale; Ritter, James M. (2007). *Rang & Dale's pharmacology*. Edinburgh: Churchill Livingstone.