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Effects of Thioxanthene Containing Anti-Psychotic and Anti-Platelet Drug Combination on Mean Platelet Volume and Platelet Distribution Width in Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author MIB did conceptualization, experimental work. Author US did the drafting. Author FA did graphical and statistical analysis and author BA supervised and did proof reading of this article. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To evaluate the combined and individual effects of thioxanthene containing antipsychotic and anti-platlet drug on Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) in rats.

Methods: This investigational study comprised of 100 albino rats of both sexual orientation, they were of 300 g to 350 g. We got ten groups, in which each group consisted of 10 rats (n=10).Ozagrel was used as anti-platelet and Zuclopenthixol was used as thioxanthene containing antipsychotic. Rats were treated with defined doses of Ozagrel and thioxanthene containing anti-psychotic (Zuclopenthixol) alone and in joined for three weeks (21 days). Blood test at 0, seventh, fourteenth and last day of study were taken. Mean Platelet Volume and Platelet Distribution Width were estimated from blood tests by using standard research center procedure. Results were accumulated and abridged by applying statistics. Correlation was framed between all days incentive to zero day values.

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Results: Anti-psychotic drug and antiplatelet drug both showed decrease in MPV with both doses highly significantly (*p < 0.001)* decrease associated with maximum doses alone and with combination group. In case of PDW all individual and minimum combination group showed increase in PDW values but significantly (*p < 0.001)* increase in maximum combination groups.
Conclusion: Combination of both drugs can cause more decrease in MPV as compare to the individual and in case of PDW combination with maximum doses may cause decrease in values by opposing the results individual therapy. It indicated any Drug-Drug interaction between these two drugs regarding Mean platelet volume and Platelet distribution width.

Keywords: Thioxanthene; anti-platelet; anti-Psychotic; mean platelet volume; platelet distribution width.

1. INTRODUCTION

Zuclopenthixol is atypical antipsychotic and its essential activity is dopamine (D2) blockage [1]. Thioxanthene Antipsychotic drugs are generally utilized in medication of psychiatry. Since their presentation, the fresher atypical antipsychotic drugs have turned out to be all the more usually recommended, regularly supplanting traditional medications. Therefore, enthusiasm for their symptom profiles has developed. Most consideration has been paid to unfriendly impacts, for example, Agranulocytosis, which has been related with Clozapine use, and increasingly regular unfavorable neurological reactions. Little consideration has been centered around the possibly lethal antagonistic medication response of venous thromboembolism, which incorporates embolism and deep vein thrombosis [2]. Antipsychotic medicine show may variations in post-stroke mortality by effecting on Platelets activity, yet examines are not many and questionable. We meant to research the post-stroke impacts of anti-psychotic use [3].

Ozagrel sodium, the thromboxane A2 synthase inhibitor is a sort of intravenous antiplatelet medicine. It might expand 6-keto-PGF1alpha in different segregated cells and tissues maybe by means of gathered PG endoperoxides coming about because of the restraint of thromboxane A2 synthase. Ozagrel was right off the bat acquainted with the market in Japan. Ozagrel was likewise found to extend the veins, and hinder the fits of cerebral supply route regardless of the capacity of restraining the collection of platelet enactment in the clinical practice.6 Moreover, intravenously controlled antiplatelet operators offer the possibility of a fast beginning of antiplatelet impact. Hence, ozagrel was utilized to anticipate cerebral vasospasm. Stroke is the second commonest reason for death and the main source of inability globally. Approximately 87% strokes are of ischemic type, because of a blockage of a course in the brain. Platelets in this manner are actived in the intense stage, which discharges neurotoxic and thrombogenic. it is important to investigate different medications with the possibility to improve the cerebral blood stream and secure cerebrum work [4]. Therapeutic properties of ozagrel are observed as to restraint of TXA2 synthase by Ozagrel on human [5].

MPV represents Mean platelet volume which is an auto machine determined estimation of the normal size of platelets, that are found in blood and it is a significant piece of blood tests. Mean platelet volume is higher when the body makes an enormous quantity of platelets. The MPV test estimations can be utilized to mention objective fact identified with platelet creation in bone marrow or platelet obliteration disorders [6]. PDW represents Platelet Distribution width which is the estimation performed via mechanized blood analyzers. PDW shows that how uniform the platelets are regarding their size [7]. Mean platelet volume (MPV) has been demonstrated to be a marker of platelet initiation that assumes a vital job in the pathophysiology of atherosclerotic disease [8].

In any case, a few reports have shown that there is a cozy connection among MPV and cardiovascular hazard factors, Platelet dissemination width (PDW) straightforwardly measures the fluctuation in platelet estimate and has been utilized to separate issue of platelets, for example, basic thrombocythemia from responsive thrombocytosis. Subsequently, its high qualities could propose bigger generation of bigger reticulated platelets [9]. Antipsychotic medications can apply immediate consequences for the vascular system, conceivably prompting serious confusions, for example, thromboembolism. In this way, information of vascular reactions of antipsychotic medications is significant for clinicians. This clinical orientated survey article covers immediate and roundabout

impacts of antipsychotics on the vascular system [10] atypical neuroleptic treatment is directed to hospitalized patients, all conceivable hazard factors for thromboembolism ought to be considered to permit the use of lower hazard drugs. Likewise, other preventive measures ought to be considered, including hydration, low-atomic weight heparin infusions [11]. There was an important to screen out the combined as well as individual effects of both drugs including thioxanthene derivative Zuclopenthixol which is used to treat the post stroke mental illness and anti-platelet/anticoagulant drug Ozagrel which is used to cure the stroke. It is totally a novel work in which first time combined effects of these drugs are evaluated for PDW and MPV. This study will be helpful to survive the patients from any possible Drug-Drug interaction regarding Platelets and thrombosis formation.

2. MATERIALS AND METHODS

2.1 Ethical Approval

All steps of this investigation and animal handlings framework were done in like way EEC board which were supported by Ethical approval committee of Riphah international university, through an affirmed number of REC/RIPS-LHR/2017/005 directed under the rule of Institute of Laboratory Animal Resources, Commission on Life Sciences University, National Research Council (1996) which were for constraining the animal persevering regarding pain.

2.2 Drugs

Zuclopenthixol (Z.P) injection (Clopixol) was of lundbrook Pharma, Ozagrel (OZL) injection was from (Ozac by Graton Pharma), Saline (Merck), Isoflurane, Vegetable thin oil, (Akhai) were purchased from market.

2.3 Animals Subjects

We utilized one hundred rats of both gender. They were of 300 g to 350 g, we formed 10 experimental groups in which each unit contained ten rats (n=10. Seven days preceding begin treatment they were housed at 22 ± 2ºC temperatures, 45– 55% temp and 12h day and light cycle in dark space of Riphah Institute of Pharmaceutical Science [12]. They were fed on free access to food and water. Duration of treatment was 21 days (three weeks) [13]. Animals were divided into 10 groups (n=10).

2.4 Experimental Groups

Z.P shows (Zuclopenthixol) and OZL shows (Ozagrel)

Group I : Control oil treated group (base of Z.P)
Group II : Control normal saline treated group (base of OZL)
Group III : Z.P-treated group by 7.14 mg / Kg
Group IV : OZL-treated group by 11.42 mg / Kg.
Group V : Z.P-treated group by 28.57 mg / Kg dose
Group VI : OZL-treated group by 22.85 mg / Kg dose
Group VII : Z.P + OZL treated group by7.14 mg / Kg (Z.P) +11.42 mg / Kg(OZL)
Group VII : Z.P + OZL treated group by 28.57 mg/ Kg (Z.P) +22.85 mg / Kg(OZL)
Group IX : Z.P + OZL treated group by 28.57 mg / Kg (Z.P) +11.42 mg / Kg(OZL)
Group X : Z.P + OZL treated group by 7.14 mg / Kg (Z.P) +22.85 mg / Kg(OZL)

Route of (Z.P) was I/m route of drug administration and Ozg (OZL) was delivered by I/p route

2.5 Blood Sample

Rats were anesthetized by using the Isoflurane [14]. Blood samples were collected at 0, 7^{th}, 14^{th} and 21^{st} days during experiment. 1 mL of blood was withdrawn at each sampling day.

2.6 Blood Analysis

Mean Platelet Volume and Platelet distribution width were measured by using hematology analyzer (NORMA) with standard laboratory procedures.

2.7 Statistical Operation

With respect to zero day value of every group, percentage increase or decrease and mean with S.D for Red blood cell distribution width was calculated. Two way ANOVA was used for inferential statistics. Graphs were made by using Graph Pad Prism version 5.0. Pattern of Significant was as * $P < 0.05$, moderately significant was represented as ** $P < 0.01$, and

highly significant was represented as *** P < 0.001.

3. RESULTS

3.1 Effects of Thioxanthene Containing Anti-Psychotic and Anti-Platelet Drug Combination on Mean Platelet Volume MPV (Fl) in Rats

Table 1 presents Normal oil treated group showed no significance change during treatment and Normal saline treated group also did not show any significance change on MPV values within total duration of treatment as compare to zero day values. This table also presents that Z.P(min) treated group showed gradually decrease in MPV values by P <0.001 at 21st day ,OZL (min) treated group showed significant gradually decrease in MPV values by P < 0.001 at 21st day, Z.P(max) treated group showed significantly decrease with P < 0.001 at 21st day, OZL(max) treated group showed decrease in MPV values gradually with P < 0.001 at 21st day , Z.P(min)+ OZL(min) treated group showed gradually decrease in MPV values with significance level P < 0.001 at 21st day, whereas Z.P(max)+OZL(max) combination group showed gradually decrease in MPV values with P < 0.001 at 21st day, Z.P(max)+OZL(min) combination showed gradually decrease in MPV values by P < 0.001 at 21st day and Z.P(min)+OZL(max) showed decrease in MPV values gradually by P < 0.001 at 21st day in comparison to zero day values. Fig. 1 shows graphical expression of percentage variation in MPV as compare zero day values.

3.2 Effects of Thioxanthene Containing Anti-psychotic and Anti-platelet Drug Combination on Platelet Distribution Width (PDW) in Rats

Table 2 presents Normal oil treated group showed no significance change during treatment and Normal saline treated group also did not show any significance change on PDW values within total duration of treatment as compare to zero day values. This table also presents that Z.P(min) treated group showed gradually increase in PDW values by P <0.05 at 21st day ,OZL(min) treated group showed significant gradually increase in PDW values by P < 0.001 at 21st day ,Z.P(max) treated group showed significantly increase with P < 0.001 at 21st day, OZL(max) treated group showed increase in PDW values gradually with P < 0.001 at 21st day , Z.P(min)+ OZL(min) treated group showed gradually increase in PDW values with

Table 1. Effects of thioxanthene containing anti-psychotic and Anti-platelet drug combination on Mean platelet Volume MPV (fL) in Rats

Groups with treatment	Days of Treatment			
	0 day	7 day	14 day	21 day
Normal Oil	8.5 ± 0.2	8.4 ± 0.08	8.3 ± 0.1	8.4 ± 0.1
Normal Saline	7.4 ± 0.3	7.4 ± 0.3	7.5 ± 0.2	7.5 ± 0.4
Z.P (Min)	8.5 ± 0.2	8.3 ± 0.2 ↓(2.5)	8.1 ± 0.2 ↓ (6.1) ***	7.5 ± 0.23 ↓(11.6) ***
OZL (Min)	8.4 ± 0.53	7.9 ± 0.3 ↓(6.1) ***	7.9 ± 0.6 ↓(5.3) ***	7.8 ± 0.7 ↓(6.8) ***
Z.P (Max)	8.4 ± 0.23	8.1 ± 0.1 ↓(3.7)*	7.8 ± 0.2 ↓(7.3)***	7.6 ± 0.2 ↓(9.4)***
OZL (Max)	8.6 ± 0.11	8.3 ± 0.1 ↓(4.1) **	8.1 ± 0.3 ↓(5.7) ***	7.8 ± 0.1 ↓(9.4)***
Z.P (Min) + OZL (Min)	8.7 ± 0.3	8.3 ± 0.3 ↓(4.1) *	8.1 ± 0.2 ↓(7.0)***	7.9 ± 0.2 ↓(9.2)***
Z.P (Max) + OZL (Max)	9.2 ± 0.24	8.4 ± 0.2 ↓(8.7)***	7.7 ± 0.3 ↓(16.3)***	7.4 ± 0.3 ↓(19.5) ***
Z.P (Max) + OZL (Min)	8.5 ± 0.24	8.14 ± 0.2 ↓(4.2)**	7.74 ± 0.4 ↓(8.9) ***	7.86 ± 0.1 ↓(7.4)***
Z.P (Min) + OZL (Max)	8.42 ± 0.22	8 ± 0.32 ↓(5.0)***	7.74 ± 0.32 ↓(8.1)***	7.66 ± 0.11 ↓(8.9)***

The values in parentheses indicate percentage change. ↑ increase ,↓ decrease

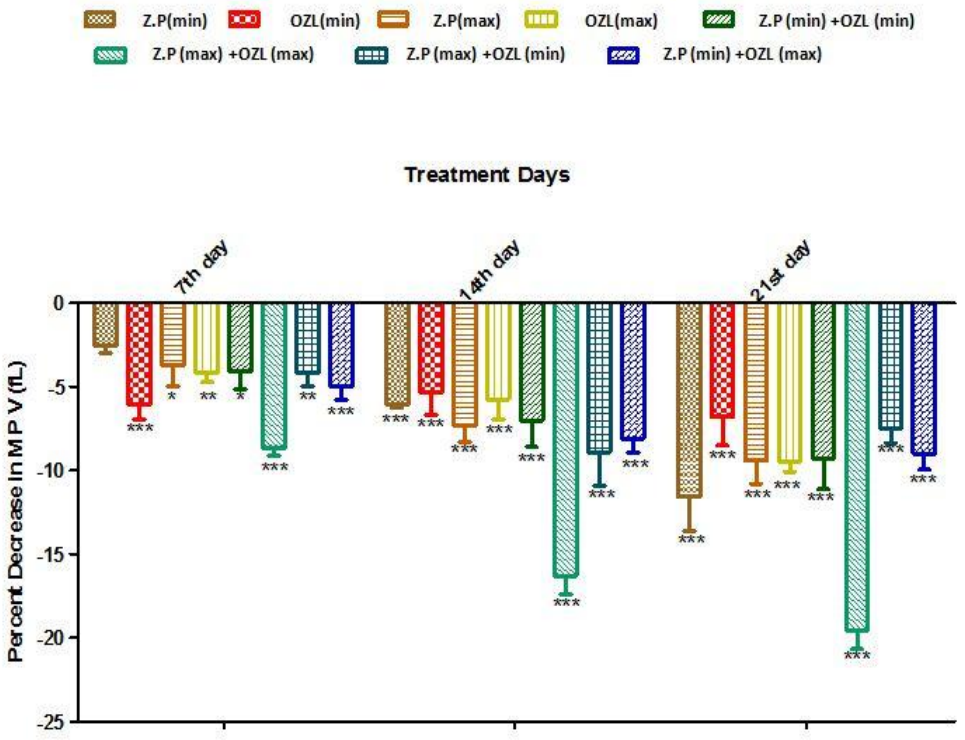

Fig. 1. Effects of thioxanthene containing anti-psychotic and Anti-platelet drug combination on Mean platelet Volume MPV(fL) in Rats

** P < 0.05, ** P < 0.01, *** P < 0.001 as compared to their zero day values*

Table 2. Effects of thioxanthene containing anti-psychotic and Anti-platelet drug combination on Platelet distribution width (PDW) (fL) in Rats

Groups with Treatment	Days of treatment			
	0 day	7 day	14 day	21 day
Normal Oil	9.5 ± 0.3	9.4 ± 0.4	9.5 ± 0.4	9.4 ± 0.2
Normal Saline	8.8 ± 0.2	8.7 ± 0.3	8.7 ± 0.3	8.8 ± 0.2
Z.P (Min)	8.9 ± 0.2	9.1 ± 0.2 ↑(2.7)	9.2 ± 0.1 ↑(3.8)	9.2 ± 0.2 ↑(4.0) *
OZL(Min)	9.04 ± 0.2	9.3 ± 0.3 ↑(3.5)	9.7 ± 0.3 ↑(7.5) ***	9.9 ± 0.3 ↑(10.3) ***
Z.P(Max)	8.7 ± 0.2	8.9 ± 0.2 ↑(2.3)	9.1 ± 0.2 ↑(5.1)**	9.4 ± 0.3 ↑(8.7) ***
OZL(Max)	10.3 ± 0.2	10.6 ± 0.2 ↑(3.3)	11.3 ± 0.18 ↑(9.9)***	12.0 ± 0.2 ↑(16.7) ***
Z.P (Min) + OZL(Min)	9.9 ± 0.2	10.1 ± 0.1 ↑(2.0)	10.4 ± 0.1 ↑(4.8)**	10.6 ± 0.1 ↑(7.1)***
Z.P (Max) + OZL (Max)	10.2 ± 0.8	9.28 ± 0.5 ↓(9.2)***	8.6 ± 0.4 ↓(15.7) ***	8.4 ± 0.4 ↓(17.1)***
Z.P (Max) + OZL (Min)	10.1 ± 0.2	9.72 ± 0.3 ↓(4.3)*	8.96 ± 0.5 ↓(11.7) ***	8.6 ± 0.5 ↓(14.6) ***
Z.P (Min) + OZL (Max)	9.6 ± 0.2	8.9 ± 0.3 ↓(6.6) ***	8.4 ± 0.4 ↓(11.6) ***	8.28 ± 0.3 ↓(13.7)***

The values in parentheses indicate percentage change. ↑ increase ,↓ decrease

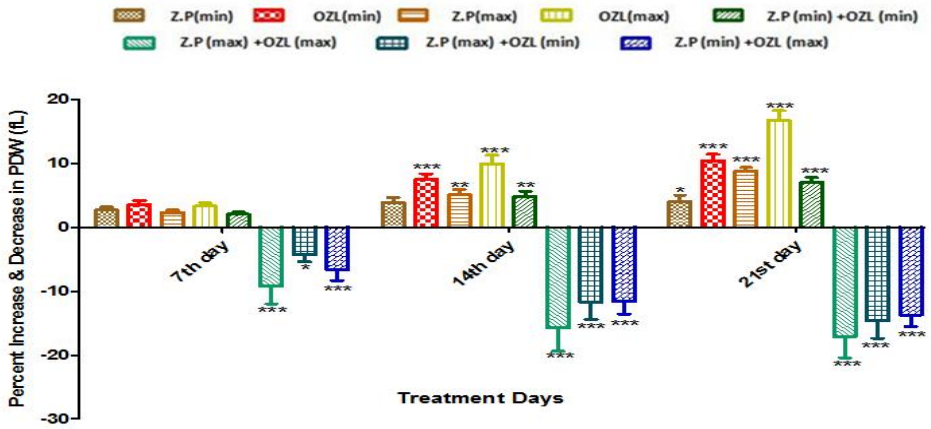

Fig. 2. Effects of thioxanthene containing anti-psychotic and Anti-platelet drug combination on Platelet distribution width (PDW) (fL) in Rats

** P < 0.05, ** P < 0.01, *** P < 0.001 as compared to their zero day values*

significance level P < 0.001 at 21st day, whereas Z.P(max)+OZL(max) combination group showed gradually decrease in PDW values with P < 0.001 at 21st day, Z.P(max)+OZL(min) combination showed gradually decrease in PDW values by P < 0.001 at 21st day and Z.P(min)+OZL(max) showed decrease in PDW values gradually by P < 0.001 at 21st day in comparison to zero day values. Fig. 2 shows graphical expression of percentage variation in PDW as compare zero day values.

4. DISCUSSION

Z.P treated groups showed significant decrease in MPV values and Ozagrel also showed decrease in MPV value which is supported by a previous study [15]. But the double decrease had been showed by Combination therapy with maximum dose as compared to individual treatment with Zuclopenthixol and Ozagrel but near to same results with minimum dose combination in comparison to individual therapy. Previously done studies suggested that a decreased MPV value in active cancer patients was associated with the highest risk of diagnosing thrombosis. These results support an inverse association between MPV and the risk of venous thrombosis at diagnosis [16]. PDW value was increased by Z.P and OZL treated groups with all doses significantly by P < 0.001. An Increase of PDW due to Ozagrel was supported by another study in which PDW had observed minimum increased with unknown mechanism [17]. But decreased in combined therapy significantly with maximum dose whereas slightly increase with minimum dose combination of both drugs. According to previous study PDW shows differences in the size of platelets in circulation, an increase in the PDW level indicates that there are more different sizes of platelets in circulation, while a decrease in PDW indicates that there are more similar sized, old platelets in circulation [7]. Monitoring during treatment either alone and in combination is very important for avoidance of any risk due to such like therapy regarding platelet disorder associated serious diseases.

5. CONCLUSION

Combination of both drugs can cause more decrease in MPV as compare to the individual and in case of PDW combination with maximum doses may cause decrease in values by opposing the results individual therapy. It indicated any Drug-Drug interaction between these two drugs regarding Mean platelet volume and Platelet distribution width.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All steps of this investigation and animal handlings framework were done in like way EEC board which were supported by Ethical approval committee of Riphah international university, through an affirmed number of REC/RIPS-LHR/2017/005 directed under the rule of Institute of Laboratory Animal Resources, Commission on Life Sciences University, National Research Council (1996) which were for constraining the animal persevering regarding pain.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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