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SEPSIS IN RATS: EFFECT OF DIPYRIDAMOLE, ASPIRIN, OR THEIR COMBINATION

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Abstract:

1. Sepsis induced in rats by cecal ligation and one puncture was found to cause a statistically significant hypoglycemia, thrombocytopenia, a decrease in liver cyclic AMP concentrations with a significant increase in the plasma 6-keto-$PGF_{1\alpha}$ concentrations 20 hours following induction of sepsis i.e. during late sepsis.

2. Dipyridamole administered to septic rats in a dose of 50 mg/kg at 30 minutes and 18 hours after induction of sepsis was found to improve significantly the hypoglycemia, thrombocytopenia, significantly increase liver cyclic AMP and decrease plasma 6-keto-$PGF_{1\alpha}$ concentrations at 20 hours following sepsis.

3. Aspirin injected in a dose of 50 mg/kg intraperitoneally 30 minutes prior to induction of sepsis was found to improve the hypoglycemia, thrombocytopenia, decrease the plasma 6-keto-$PGF_{1\alpha}$ concentrations.

4. Combination of dipyridamole with aspirin was found to improve the thrombocytopenia of sepsis only without affecting other parameters significantly.

5. Twenty four hour survival rate was 37.5% in untreated septic rats which was increased to 87.5% in both dipyridamole treated and aspirin pretreated septic rats and to 50% in rats receiving combination of dipyridamole treatment and aspirin pretreatment.

6. Combination of dipyridamole and aspirin was not more effective in treatment of sepsis than either drug used alone.

Introduction:

Septicemia continues to be a major problem in modern clinical practice because of the high mortality associated with septic shock.

It was established that hypoglycemia is a hallmark and an important sign of severe sepsis. [1] Hypoglycemia as manifestation of sepsis have been reported in human [2] and several animal species during sepsis induced by cecal ligation and puncture like rats [3] and mice. [4]

Levels of many hormones that maintain homeostasis and the metabolic processes regulated by these hormones are altered in shock. Since production, release and the cellular activities of many of these hormones are controlled by the cyclic AMP system, so diminished effectiveness of the cAMP mechanism could result in loss of control of critical cellular activities in shock. [5] Peritonitis in rats induced by cecal ligation and puncture was found to cause a significant decrease in hepatic and renal nucleotide levels in late sepsis [3] and a significant decrease in liver cAMP levels was reported in endotoxic mice. [6]

A rapid and marked increase in the synthesis and/or release of prostaglandins were demonstrated in endotoxin shock [7] and sepsis. [8] Thromboxane A_2 and prostacyclin have been implicated as a causative agents in the endothelial damage, increased capillary permeability, and hemodynamic and respiratory dysfunction of septic shock [9] and they play a role in systemic coagulopathies [10] manifested as disseminated intravascular coagulation (DIC) [2] but they are not the mediators of sepsis- induced alterations in carbohydrate metabolism [11] or accelerated proteolysis during sepsis. [12]

Dipyridamole as a phosphodiesterase inhibitor leading to increased level of platelet cAMP [13] was able to protect against DIC in rats and result in correction of all

hematological parameters measured. [14] Moreover it has been recently shown that dipyridamole 50 mg/kg administered i.p. 7 hours postendotoxin in mice improved blood glucose and liver cAMP. In addition it improved platelet count and increase survival rate to 100% when administered soon after endotoxin. [6]

Aspirin was also found to improve survival rate and significantly decreased the endotoxin induced elevation of plasma levels of thromboxane A2 and 6-keto-$PGF_{1\alpha}$ in rats. [10]

Combination of dipyridamole with aspirin in endotoxin shock in baboon have been tried and was found to be not as effective as aspirin alone in achieving the apparent protective effect. [15]

Therefore the aim of the present study was to investigate the effect of dipyridamole, aspirin or their combination on blood glucose, platelet counts, liver cAMP, 6-keto-PGF1 in rats during sepsis induced by cecal ligation and one puncture which represents a picture which is close to peritonitis in humans.

The idea behind the use of dipyridamole was to modify the level of cAMP which might be reflected on blood glucose, liver cAMP and platelet counts which have been known to be altered during sepsis. The use of aspirin was to reduce the level of prostaglandins and modify platelet adhesion and aggregation which occur during sepsis.

Materials and Methods:

Animal model Male, Albino Whister rats weighing 250-350 g were employed. The animals had free access to tap water and standard- pellet diet until 24 hours prior to induction of sepsis when food was withheld. Peritonitis was done by laparotomy under light ether anesthesia. A midline incision was performed and the cecum was located through the incision. After the cecum was filled with feces by milking stool back from the ascending colon, the lower portion of the cecum was ligated with a 3-0 silk ligature. The ligated cecum was punc-

tured once with a 21-gauge needle to allow leakage of the cecal content, then the cecum was replaced into the peritoneal cavity. The abdomen was closed in two layers.[16] Immediately after the operation, the animals were allowed free access to water . Sham operated group of rats undergo laparotomy, only manipulation of the cecum was done and then the abdomen was closed in two layers.[16] On the day of the experiment which was twenty hours following the operation, animals were anesthetised by pentobarbital injected intraperitoneally in a dose of 25 mg/kg for septic rats and 50 mg/kg for sham operated rats. Blood samples were obtained by open chest cardiac puncture. For survival studies other groups of rats used each of 8 using the septic procedure and drug regimes without blood sampling.

Blood glucose estimation 0.1 ml of blood was taken for immediate glucose estimation colorimeterically [17].

Platelet count Blood was collected in EDTA containing tubes for platelet count using formol- citrate red- cell diluent method [18].

Liver cyclic AMP A sample of liver was cut quickly and frozen using liquid nitrogen, weighed and kept at -20 ^{o}C for assay of cyclic AMP using radioimmunoassay kit (^{125}I- cyclic AMP) purchased from Amersham U.K.

Plasma 6-keto-$PGF_{1\alpha}$ 5 ml of blood was transferred into a tube containing 0.475 ml of EDTA and 0.025 ml of 0.04M indomethacin solution (50 mg indomethacin dissolved in 3.5 ml absolute ethanol). Indomethacin will inhibit the subsequent metabolism of arachidonic acid to prostaglandins. Blood samples were centrifuged and plasma was stored at -20 C for the assay of 6-keto-$PGF_{1\alpha}$ using a radioimmunoassay kit (^{125}I-6-keto-$PGF_{1\alpha}$) purchased from Amersham U.K.

Statistical treatment of the results: Results were expressed as mean ± SEM. Comparisons between means were performed using independent t- test for unpaired data. Significant difference was assumed to be present if the calculated value for t was greater than tabulated value for t at the 0.05 level of P.

Drugs used 1. Dipyridamole (Persantin) ampules (Bohringer Ingelheim international GmbH) were used. Each ampule contains 10 mg of dipyridamole in 2 ml solution.

2. Aspirin (Aspegic) vials (Laboratories Synthelabo France) containing 0.5 g acetylsalicylic acid, used after dissolving it in 5 ml distilled water.

Results:

1. Effects of sepsis in rats: Sepsis in rats resulted in a statistically significant hypoglycemia ($P<0.05$), significant thrombocytopenia ($P<0.05$), a significant decrease in liver cAMP concentrations ($P<0.05$) when compared with sham operated control group, with a marked and significant increase in plasma 6-keto-PGF_1 concentrations as compared to sham operated control group ($P<0.02$) (table 1). The 24 hours survival rate was 37.5% in late septic group of rats compared to 100% in sham operated control group (table 2).

Table 1. Effect of sepsis on blood glucose, platelet count, liver cAMP and plasma 6-keto-$PGF_{1\alpha}$ levels in rats.

Rats	Blood glucose (mg/dl)	Platelet count $x10^9$/L	Liver cAMP (pmol/g)	Plasma 6-keto-$PGF_{1\alpha}$ (pg/ml)
-Sham operation	103±23 (6)	873±44 (6)	746±115 (6)	266± 557 (6)
-Late sepsis	51±12* (10)	280±25* (10)	524±25* (10)	1093± 338** (8)

The samples were taken at 20 hours following sham operation or induction of sepsis. Each value is the mean ± SEM. Numbers in brackets are numbers of observations. *$P<0.05$, **$P<0.02$ significantly different from sham operated control group.

Table 2. 24 hours survival rate in sham operated, septic rats or septic rats treated with different regimes of drugs.

Drug used	No. of animals	Surviving animals No.	%
- Sham operated rats	8	8	100
-Septic rats	8	3	37.5
- Septic rats treated with 50 mg/kg dipyridamole at 30 min. and 18 hours following induction of sepsis	8	7	87.5
- Septic rats treated with 50 mg/kg aspirin 30 min. before sepsis.	8	7	87.5
- Septic rats treated with 50 mg/kg dipyridamole and 50 mg/kg aspirin.	8	4	50

2. Effects of dipyridamole, aspirin, or their combination in septic rats: Figure 1A shows that dipyridamole injected alone in a dose of 50mg/kg i.p. 30 minutes and 18 hours after induction of sepsis significantly increased the blood glucose concentrations ($P<0.005$). Similarly aspirin injected in a dose of 50mg/kg i.p. 30 minutes prior to induction of sepsis increased significantly the blood glucose concentrations ($P<0.01$), while combination of dipyridamole and aspirin caused no significant change in blood glucose concentrations.

Thrombocytopenia of sepsis was found to be improved significantly with dipyridamole treatment, aspirin pre-treatment or their combination ($P<0.005$)(Fig.1B).

The liver cAMP concentrations were increased significantly in septic rats treated with dipyridamole when compared with untreated septic rats ($P<0.01$) while no

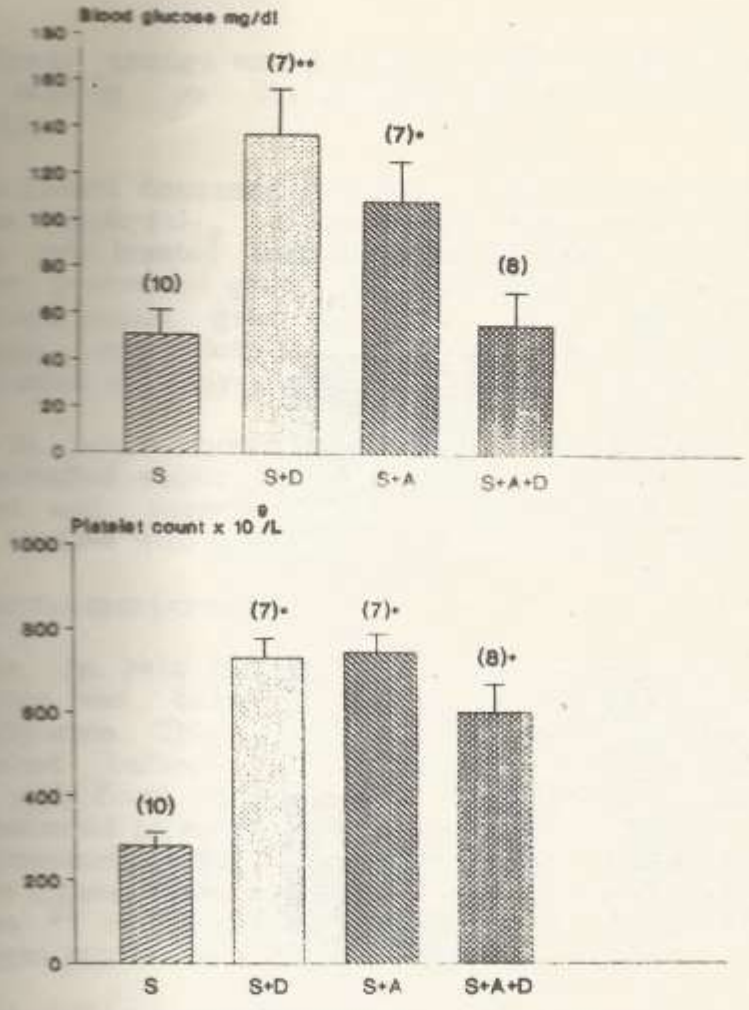

Figure 1.A(upper) Blood glucose concentrations in rats. *P<0.01, **P<0.005 significantly different from untreated septic rats.

Figure 1.B(lower) Platelet counts in rats. *P<0.005 significantly different from untreated septic rats.

S: untreated septic rats, S+D: dipyridamole treated septic rats, S+A: aspirin pretreated septic rats, S+A+D: septic rats pretreated with aspirin and treated with dipyridamole. Each column is the mean ± SEM. Numbers in brackets are numbers of observations.

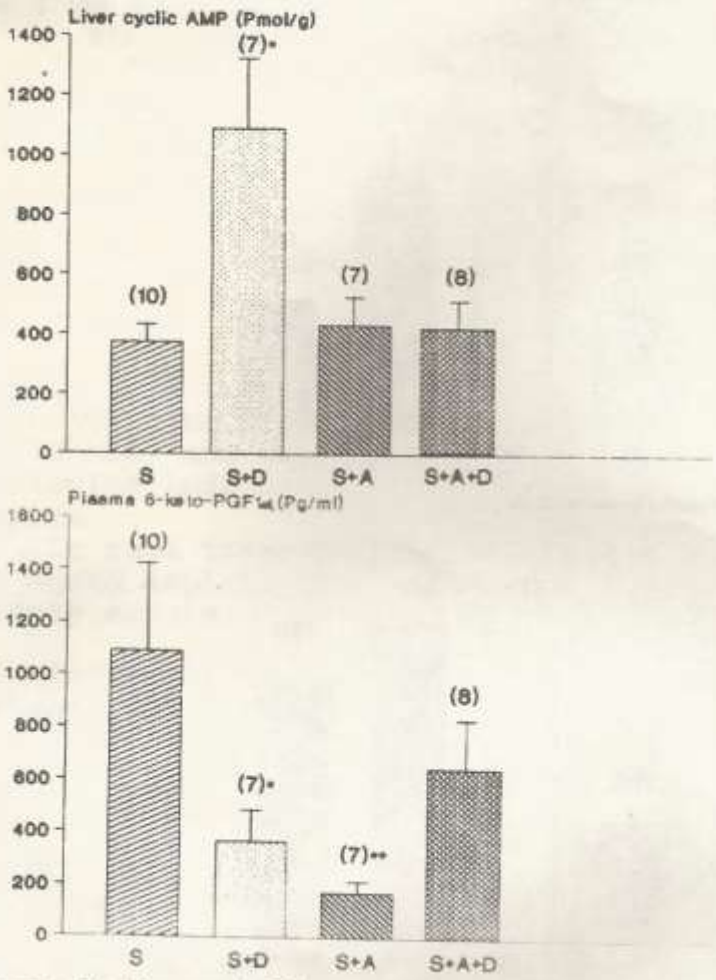

Figure 2.A(upper) Liver cyclic AMP concentrations in rats. *P<0.01 significantly different from untreated septic rats.

Figure 2.B(lower) Plasma 6-keto-$PGF_{1\alpha}$ concentrations in rats.
*P<0.05, **P<0.02 significantly different from untreated septic rats.

S: untreated septic rats, S+D: dipyridamole treated septic rats, S+A: aspirin pretreated septic rats, S+A+D: septic rats pretreated with aspirin and treated with dipyridamole. Each column is the mean ± SEM. Numbers in brackets are numbers of observations.

significant change was detected in septic rats pretreated with aspirin or its combination with dipyridamole (Fig.2A).

A significant decrease in sepsis- induced increase in plasma 6-keto-$PG_{1\alpha}$ concentrations was demonstrated in septic rats treated with dipyridamole ($P<0.05$) and aspirin pretreated group ($P<0.02$) when compared to the untreated septic group of rats. While no significant decrease was detected in septic rats treated with combination of dipyridamole and aspirin (Fig.2B).

The 24 hours survival rate was increased from 37.5% in untreated septic rats to 87.5% in both dipyridamole treated and aspirin pretreated groups, and to 50% in rats treated with combination of these drugs (table 2).

Discussion:

Sepsis in rats induced by cecal ligation and one puncture was found in this study to cause significant hypoglycemia. This finding coincides with what has been published before. [3] Hypoglycemia was also detected in rats with fecal peritonitis. [19] A similar effect was demonstrated in mice subjected to sepsis by cecal ligation and puncture. [4] Such hypoglycemia was explained to be due to either increased glucose utilisation by peripheral tissues [20] or inhibited gluconeogenesis [21] or depleted glycogen stores. [22]

The thrombocytopenia seen in this study coincides with that reported in rats during sepsis. [23] It has been reported that the pathogenesis of thrombocytopenia is related to increased platelet turnover [24] or it may be a direct result of bacterially derived substances [25] or results from pulmonary and hepatic sequestration of platelets. [26]

The decrease in the liver cAMP concentrations in this study agreed with previous findings. [3,6] This decrease may be due to a decrease in hepatic activity of adenylate cyclase [27] rather than a decrease in the level of ATP as it was found that ATP level increased in sepsis and septic shock. [28] The increased destruction of cAMP is

probably not a contributing factor for the decreased cAMP level as it was demonstrated that phosphodiesterase activity was not changed during endotoxicosis.[29]

The marked and significant increase in plasma 6-keto-$PGF_{1\alpha}$ concentrations of this study coincides with already reported findings.[23,30] Such increase has been explained to be due to either increase in the production or a decrease in the enzymatic breakdown of prostacyclin, or to a diminished clearance (hepatic or renal) of 6-keto-$PGF_{1\alpha}$.[31] Others have shown that endotoxin interacts with cellular plasma membrane to activate a phosphodiesterase, which releases arachidonic acid for oxidation by cyclooxygenase or lipoxygenase.[32]

The hypoglycemia and decreased liver cAMP levels were improved in septic rats treated with dipyridamole and such results are in agreement with those reported in endotoxic mice.[6] The phosphodiestrase inhibition by dipyridamole may be the main mechanism for improvement of hypoglycemia and cAMP concentrations.

Dipyridamole was also found to improve thrombocytopenia significantly and this agrees with the results obtained in endotoxic rats[14] and mice[6] using the same dose . So from our results, it might be suggested that dipyridamole, by inhibiting platelet aggregation and improving platelet counts, attenuates intravascular thrombosis and could decrease or probably prevent DIC usually occurring during severe sepsis. Such effect might be important together with improvement of blood glucose concentrations in the increased survival rate to 87.5%.

Significant decrease in the plasma 6-keto-$PGF_{1\alpha}$ concentrations was detected in dipyridamole treated septic rats. As dipyridamole is a potent stimulator of prostacyclin biosynthesis[33] and as plasma 6-keto-$PGF_{1\alpha}$ concentrations markedly increased during sepsis, so we suggested that such increase might exert some sort of feed-back mechanism on prostaglandin synthetase enzyme which in turn will decrease further elevation in plasma 6-keto-$PGF_{1\alpha}$ concentrations.

Aspirin when administered i.p. 30 minutes prior to induction of sepsis resulted in improvement of the hypoglycemia. This agrees with that observed in rats during endotoxicosis. [10] The mechanism of such increase may be due to a decrease in aerobic metabolism of glucose, an increased glucose-6-phosphatase activity which is decreased during sepsis [34] and a promotion of glucocorticoids secretion by aspirin. [35] That thrombocytopenia was also improved with aspirin pretreatment which agrees with that observed in primate model of endotoxicosis. [15] Aspirin pretreatment also decreased the elevated plasma 6-keto-$PGF_{1\alpha}$ concentrations which agreed with that found in endotoxin shock. [10]

The combination of dipyridamole and aspirin resulted only in a significant increase in the platelet count and 24 hours survival rate up to 50%. These findings were explained in that prostacyclin stimulates cAMP formation which becomes evident in the presence of a phosphodiesterase inhibitor[36] and as there was a marked increase in the stable metabolite of prostacyclin during sepsis, this will further increase liver cAMP level. When aspirin was used in combination with dipyridamole, it inhibited prostacyclin production to a certain extent which may not be effective in augmenting dipyridamole in stimulating cAMP formation. The improvement of thrombocytopenia may be due to potentiation between dipyridamole and aspirin in inhibiting platelet aggregation.[37]

The insignificant decrease in plasma 6-keto-$PGF_{1\alpha}$ concentrations may be explained in that aspirin inhibits prostacyclin production and therefore decreases the plasma 6-keto-$PGF_{1\alpha}$ concentrations, but at the same time dipyridamole increases the production of prostacyclin. Dipyridamole was found to increase prostacyclin production even in the presence of prostaglandin synthesis inhibition by aspirin. [38]

From these results, it is concluded that combination of dipyridamole and aspirin was not as effective as either drug alone in achieving the protective effect i.e. improvement of hypoglycemia, thrombocytopenia, decreased cAMP concentrations, elevated plasma 6- keto-$PGF_{1\alpha}$

concentrations and 24 hours survival rate.

References:

1. Miller S.F., Wallace R.J., Musher D.M., Septimus E.J., Kohe S. and Bughan R.E. Hypoglycemia as a manifestation of sepsis. Am. J. Med., 1980, 68, 649.
2. Harris R.L., Musher D.M., Bloom K., Gathe J., Rice L., Sugarman B., Williams T.W. and Young E.J. Manifestations of sepsis. Arch. Int. Med., 1987, 147, 1895-1903.

3. Chaudry I.H., Wichterman K.A. and Baue A.E. Effect of sepsis on tissue adenine nucleotide levels. Surgery, 1979, 85, 205-210.

4. Urbaschek B., Ditter B., Becker K.P. and Urbaschek R. Protective effects and role of endotoxin in experimental septicemia. Circ. Shock, 1984, 14, 209-222.

5. Rutenberg A.M., Polgar P., Bell M. and Egdahl R.H. Adenosine 3,5- monophosphate metabolism in the liver in experimental haemorrhagic shock. Surgery, 1973, 74, 660-665.

6. Al-Jibouri L.M. and Najim R.A. Effect of dipyridamole on blood glucose and liver cyclic AMP levels and platelet count during endotoxemia in mice. Clin. and Exp. Pharmacology and Physiology, 1988, 15, 527-532.

7. Fletcher J.R. and Ramwell P.W. Modification, by aspirin and indomethacin, of the hemodynamic and prostaglandin releasing effects of E. coli endotoxin in the dog. Br. J. Pharmac., 1977, 61, 175-181.

8. Fletcher J.R. The role of prostaglandins in sepsis. Scand. J. Infect. Dis. (Suppl), 1982, 31, 55-60.

9. Slotman G.J., Quinn J.V., Burchard K.W. and Gann D.S. Thromboxane, prostacyclin and hemodynamic effects of graded bacteremic shock. Circ. Shock, 1985, 16, 395-404.

10. Halushka P.V., Wise W.C. and Cook J.A. Protective effects of aspirin in endotoxin shock. J. Pharmacol. Exp. Ther., 1981, 218, 464-469.

11. Lang C.H., Bagby G.J., Bakesley H.L. and Spitzer J.J. Inhibition of Eicosanoid production by BW 755C does not attenuate sepsis- induced alterations in glucose kinetics. Circ. Shock, 1987, 22, 105-113.

12. Hasselgren P.O., Warner B.W., Hummel R.P., James J.H., Ogle C.K. and Fischer J.E. Further evidence that accelerated muscle protein breakdown during sepsis is not mediated by prostaglandin E2. Ann. Surg., 1988, 207, 399-403.

13. Packham M.A. and Mustard J.F. Clinical pharmacology of platelets. Blood, 1977, 50, 555-574.

14. Yoshikawa T., Murakami M. and Furukawa Y. Effect of dipyridamole on experimental DIC in rats. Thtomb. Res., 1983, 29, 619-625.

15. Rao P.S., Cavanagh D. and Gaston L.W. Endotoxic shock in the primate: Effects of aspirin and dipyridamole administration. Am. J. Obstet. Gynecol., 1981, 140, 914-922.

16. Wichterman K.A., Baue A.E. and Chaudry I.H. Sepsis and septic shock. A review of laboratory models and a proposal. J. Surg. Res., 1980, 29, 189-201.

17. Asatoor A.M. and King E.J. Colorimeteric method for true sugar in blood in microanalysis in: Medical Biochemistry, third edition, King E.J. and Walton I.D.P., editors, J. and A. Churchill. London. 1954, p.25.

18. Dacie J.V. and Lewis S.M. Platelet count in practical haematology, 5th edition. Churchill- Livingston- Edinburgh. 1975, p. 53-54.

19. Rink R.D., Short B.L., Van N.V. and Fry D.E. Role of colonic bacteria in the pathophysiology of fecal peritonitis. Circ. Shock, 1987, 4, 259-270.

20. Furr P.A., Peterson T.V., Dale J.E., Hinshaw L.B. and Keyl M.J. Effect of endotoxin on glucose uptake by the isolated forelimb of the dog. Circ. Shock, 1978, 5, 43-50.

21. Kuttner R.E., Sugai T., Yamashita K. and Schumer W.

Inhibited gluconeogenesis greatly intensifies the lethality of endotoxin. Circ.Shock, 1984, 13, 83 (Abstract).

22. Mori E., Hasebe M., Kobayashi K. and Iijima N. Alterations in metabolic levels in carbohydrate and energy metabolism of rat in hemorrhagic shock and sepsis. Metabolism, 1987, 36, 14-20.

23. Fink M.P., Michael G.W., Rothe lR. and Raymond F.J. Plasma levels of 6-ke to-prostaglandin F1α but not thromboxane B2 increase in rats with peritonitis due to cecal ligation. Circ. Shock, 1985, 16, 297-305.

24. Kelton J.G., Neame P.B. and Gualdie J. Elevated plate let- associated IgG in the thrombocytopenia of septicemia. N. Engl. J. Med., 1979, 300, 760-764.

25. Goldbum S.E., Simon T.L. and Thilsted J.P. Pneumococcus induced thrombocytopenia in rabbits. J. Lab. Clin. Med., 1985, 106, 298-307.

26. Gutmann F.D., Murthy V.S., Woijciechowski M.T., Wurm R.M. and Edzards R.A. Transient pulmonary platelet sequestration during endotoxemia in dogs. Circ.Shock, 1987, 21, 185-195.

27. Ghosh S. and Liu M.S. decrease in adenylate cyclase activity in dog livers during endotoxin shock. Am. J. Physiol., 1983, 245, R737-R742.

28. Illner H. and Shires G.T. Changes in sodium, potassium, and adenosine triphosphate contents of red blood cells in sepsis and septic shock. Circ. Shock, 1982, 9, 259-267.

29. Gimpel L., Hodgins D.S. and Jacobson E.D. Effect of endotoxin on hepatic adenylate cyclase activity. Circ. Shock, 1974, 1, 31-37.

30. Butler P.R., Wise W.C., Halushka P.V. and Cook J.A. Thromboxane and prostacyclin production during septic shock. Adv. Shock Res., 1982, 7,133-145.

31. Bult H., Beetens J., Vercrysse P. and Herman A.G. Blood levels of 6-keto-$PGF_{1\alpha}$, the stable metabolite of

prostacyclin during endotoxin- induced hypotension. Arch. Int. Pharmacodyn., 1978, 236, 285-286.

32. Schade U.F. Involvement of lipoxygenase in the activation of mouse macrophages by endotoxin. Biochem. Biophys. res. Commun., 1986, 138, 842-849.

33. Blass K.E., Block H.U., Forster W. and Ponicke K. Dipyridamole: a potent stimulator of prostacyclin (PGI_2) biosynthesis. Br. J. Pharmac., 1980, 68, 71-73.

34. LaNoue K.F., Mason A.D. and Daniels J.P. The impairment of gluconeogenesis by gram- negative infection. Metabolism, 1968, 17, 606-611.

35. Flower R.J., Moncada S. and Vane J.R. Analgesic-antipyretic and antiinflammatory agents in: Goodman and Gillman,s the pharmacological basis of therapeutics, 7th edition. macmillan publishing company. New York, Toronto, London.1985, p. 648.

36. Dembinska A., Ruecher W. and Schoenhoefer P.S. PGI_2 enhanced cAMP content in bovine coronary arteries in the presence of isobutylmethyl xanthine. Naunyn-chmied. Arch. Pharmacol., 1979, 308, 107-110.

37. Rajah S.M., Penny A.F. and Crow M.J. The interaction of varying doses of dipyridamole and acetylsalicylic acid in the inhibition of platelet functions and their effect on bleeding time. Br. J. Clin. Pharmacol. 1979, 8, 483-489.

38. Toda N. and yamamoto M. Modification of angiotensin II-induced relaxation by dipyridamole, phthalzinol and aspirin in isolated dog renal arteries. JPN. J. Pharmacol., 1983, 33, 1027-1034.

١- تم تحريض الإنتان في الجرذان عن طريق ربط الاعور ووخزه مرة واحدة والذي ادى الى حصول انخفاض معتد احصائيا" في تركيز غلوكوز الدم، وتعداد الصفيحات وتركيز احادي فوسفات الإدينوسين الحلقي في الكبد، مع زيادة في تركيز البروستكلاندين -٦- الكيتوني ف الفا (6-Keto-PGF) في البلازما بعد ٣٠ساعة من تحريض الإنتان اي اثناء الإنتان المتأخر.

٢- ان حقن عقار الدايبريدامول (٥٠ ملغم/كغم) في الدقيقة الثلاثين والساعة الثانية عشرة بعد تحريض الإنتان قد ادى الى تحسن وبصورة معتدة احصائيا" في تركيز غلوكوز الدم، وتعداد الصفيحات، وتركيز احادي فوسفات الإدينوسين الحلقي في الكبد مع انخفاض في تركيز البروستكلاندين -٦- الكيتوني ف الفا في البلازما.

٣-عقار الإسبرين (٥٠ ملغم/كغم) بعد حقنه في الدقيقة الثلاثين قبل تحريض الإنتان قد ادى الى زيادة في تركيز غلوكوز الدم، وتعداد الصفيحات مع انخفاض في تركيز البروستكلاندين -٦- الكيتوني ف الفا في البلازما.

٤- ان تجميع عقار الدايبريدامول مع الإسبرين قد ادى الى زيادة في تعداد الصفيحات فقط.

٥-نسبة بقاء الجرذان على قيد الحياة لمدة ٢٤ ساعة خلال الإنتان قد ازداد من ٣٧,٥٪ الى ٨٧,٥٪ بعد حقن الدايبريدامول، والى ٨٧,٥٪ بعد حقن عقار الديبريدامول مع الإسبرين.

٦- ان تجميع عقار الدايبريدامول مع الإسبرين لم يكن مؤشرا" في علاج الإنتان كما لو استخدم كل عقار لمفرده.