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J Clin Invest. 1978;62(3):554-559. <https://doi.org/10.1172/JCI109160>.

Research Article

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When peritonitis was induced with live pneumococci instead of a sterile inflammatory stimulus, 14/18 normal animals survived the infection and were culture-negative when sacrificed at 2 wk. In contrast, 17/18 intoxicated animals died of the infection, in a mean of 2.8 days. 9 of 18 intoxicated animals who also received propranolol survived, and those who died lived a mean of 7.5 days. The survival rates and the time-to-death among the nonsurvivors given propranolol were both significantly greater than in the animals intoxicated without propranolol. Thus, propranolol prevents the granulocyte adherence and delivery defects induced [...]

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ABSTRACT We studied the effects of alcohol and propranolol on the course of peritonitis in rabbits. Induction of sterile peritonitis with normal saline led to a 50% augmentation of granulocyte adherence in normal rabbits, and a mean cumulative granulocyte count of 27,000/mm³ in peritoneal exudate by 8 h. Rabbits intoxicated with alcohol at the time of peritonitis induction maintained a granulocyte adherence below pretreatment values, and only delivered a cumulative mean of 12,000 granulocytes/mm³ into the peritoneal fluid. When intoxicated rabbits received propranolol intravenously at the time of intoxication, adherence increased above preperitonitis levels, and stayed significantly above values for animals given alcohol alone. In addition, the defect in granulocyte delivery was prevented by propranolol, resulting in a mean cumulative granulocyte count in peritoneal fluid of 24,000/mm³.

When peritonitis was induced with live pneumococci instead of a sterile inflammatory stimulus, 14/18 normal animals survived the infection and were culture-negative when sacrificed at 2 wk. In contrast, 17/18 intoxicated animals died of the infection, in a mean of 2.8 days. 9 of 18 intoxicated animals who also received propranolol survived, and those who died lived a mean of 7.5 days. The survival rates and the time-to-death among the nonsurvivors given propranolol were both significantly greater than in the animals intoxicated without propranolol. Thus, propranolol prevents the granulocyte adherence and delivery defects induced by alcohol intoxication, and significantly improves survival from infection.

Presented in part in abstract form. 1977. *Clin. Res.* 25: 373A. (Abstr.)

Received for publication 14 November 1977 and in revised form 24 April 1978.

INTRODUCTION

Acute alcohol intoxication suppresses the inflammatory response (1, 2), which may explain why alcoholics control their infections poorly (3-5). In 1938, Pickrell (1) demonstrated that granulocytes did not appear in normal numbers at the site of subcutaneous pneumococcal infection in acutely intoxicated rabbits and that these rabbits died of overwhelming disseminated infection. In contrast, unintoxicated controls developed intense granulocytic exudation and controlled their infections locally. Recently, Brayton and colleagues (2) have shown that granulocyte migration into skin chambers in human volunteers is profoundly depressed by alcohol intoxication while the ability of these granulocytes to ingest and kill bacteria is not impaired. Previous studies from our laboratory have shown that granulocyte adherence, a necessary step before their diapedesis into tissue, is depressed by alcohol (6). The ability to inhibit adherence is a property shared by most anti-inflammatory agents, and appears to be mediated through a plasma factor (7). The suppression of granulocyte adherence by alcohol may be related ultimately to the cyclic nucleotides. Bryant and Sutcliffe (8) have shown that cyclic AMP and its inducers can inhibit granulocyte adherence, and Atkinson et al (9) has found high cyclic AMP levels in granulocytes exposed to alcohol. We have confirmed Bryant's findings, and have demonstrated that the adherence-inhibiting plasma factor can be antagonized in vitro by cyclic guanosine 5'-monophosphate or by the sympatholytic agent propranolol (10).

The present study was undertaken to determine if propranolol might prevent the suppressant effects of alcohol on granulocyte adherence in vivo, and in so doing might correct the poor delivery of granulocytes

seen in intoxicated animals responding to an inflammatory stimulus. After finding that propranolol did prevent both of these defects, an additional experiment was conducted to determine whether or not these effects of the drug could improve the survival of infected intoxicated animals.

METHODS

Rabbit sterile peritonitis. The rabbit sterile peritonitis model was used to study the effects of alcohol intoxication on both granulocyte adherence and exudate formation *in vivo*. Some intoxicated animals also were given propranolol, to determine if the adherence and exudate defects induced by alcohol could be prevented. Finally, some nonintoxicated animals were given propranolol to study its effects on adherence and exudate formation. For each experiment, groups of four New Zealand White male rabbits weighing 2–3 kg were given sterile peritonitis by the intraperitoneal injection of 120 ml of normal saline through a 16-gauge polyethylene catheter inserted at the beginning of the experiment and left in place for the 8-h study period (11). The saline was not pyrogen tested. Animal I was not treated further; animal II was given 35 ml of a 25% solution of ethanol in normal saline intravenously at the time peritonitis was initiated, and then 20 ml of this solution 4 h later. All intoxicated animals developed nystagmus initially and were ataxic but awake throughout the experiment. Maximum blood levels averaged 295 mg/100 ml \pm SE of the mean of 15.3. Animal III received the same doses of alcohol but in addition propranolol (0.3 mg/kg) was administered intravenously with each alcohol dose. Animal IV received propranolol without intoxication. In a separate experiment, three animals were given 0.3 mg/kg *i.v.* of either the D- or L-isomer of propranolol (kindly supplied by Ayerst Laboratories, New York) and granulocyte adherence was monitored for 2 h thereafter. In all experimental groups peripheral blood granulocyte adherence was measured before, and 2, 4, 6, and 8 h after initiating peritonitis, using the nylon fiber assay system as described (6). Peritoneal fluid was harvested 2, 4, 6, and 8 h after peritonitis and the number of granulocytes per cubic millimeter was counted. Animals were restrained on their backs for 15 min for peritoneal injection, blood drawing, and drug administration. They were then placed in cages until time for drawing of the repeat specimens at 2-h intervals. Thus, animals spent most of the 8-h study period unrestrained, in their cages.

In a separate experiment, body weight, heart rate, and blood pressure were monitored in animals representing the first three treatment groups, to determine whether intoxication, with or without concomitant propranolol administration, affected the animals' cardiovascular response to peritonitis. Rabbits were lightly anesthetized with intravenous pentobarbital sodium (20 mg/kg), and their carotid arteries were cannulated with 19-gauge polyethylene catheters. These were connected to a Statham pressure transducer (Statham Instruments, Inc., Oxnard, Calif.) which made a constant record of blood pressure and pulse on a 5-channel polygraph (Grass Instrument Co., Quincy, Mass.).

Pneumococcal peritonitis. To study the effect of alcohol on the mortality of rabbits given an infectious inflammatory challenge, and to determine whether or not propranolol could reverse this effect, animals were given pneumococcal peritonitis. For each experiment, three rabbits received 120 ml of normal saline intraperitoneally, but now the saline con-

tained 1 ml of an overnight broth culture of a type III pneumococcus with $1-5 \times 10^6$ colony-forming U/ml (organism kindly supplied by Dr. Robert Austrian, Department of Research Medicine, University of Pennsylvania School of Medicine). As before, group I animals were not treated further; group II received 35 ml of a 25% solution of alcohol in normal saline at 0 and 4 h after peritonitis was begun; group III received the same dose of alcohol as group II, but in addition received 0.3 mg/kg of propranolol intravenously at 0, 3, and 6 h after peritonitis was initiated. Peritoneal fluid was cultured 4 h after initiating peritonitis and blood was cultured at 4 and 24 h. Rabbits were observed daily for 2 wk unless death occurred earlier. Survivors in all groups had blood cultures taken at 2 wk.

Blood alcohol and catecholamine levels. In a separate experiment, the effect of propranolol on the rate of alcohol clearance from the blood was determined. One group of 2–3 kg New Zealand White male rabbits was given 35 ml of a 25% solution of alcohol in normal saline intravenously; a second group received the same dose of alcohol, but also received 0.3 mg/kg of propranolol administered intravenously at the same time. Blood alcohol levels were measured at 30 min (peak) and 3½ h (trough) after administration of the drug(s).

Because catecholamines may themselves influence granulocyte adherence, we measured the effect of acute intoxication on total plasma catecholamine concentrations before and 1 h after the intravenous administration of 35 ml of a 25% solution of ethanol in normal saline to three 2½-kg New Zealand White male rabbits. The catecholamines were measured by a radioenzymatic assay.

RESULTS

Sterile peritonitis. None of the animals lost weight during the 8-h study period. (All received 120 ml of normal saline intraperitoneally, and groups II and III also received ≈ 55 ml of a 25% ethanol solution intravenously.) Animals not given peritonitis but restrained briefly for blood drawing at 2-h intervals did not develop any change in granulocyte adherence. Two peritonitis animals died acutely after cardiac punctures for blood specimens; all others survived the sterile peritonitis and had no residua 24 h after the procedure. Base-line mean blood pressure was 95–130 mm Hg in the monitored animals. Peritonitis caused a maximum drop in mean pressure of 10 mm Hg, although several animals did not change at all. Pulse was 240–315/min, with no consistent change over the period of peritonitis. Animals intoxicated at the time that they were given intraperitoneal normal saline, increased their heart rate by 30–60 beats/min for 1–2 h after intoxication. Pressure fell by ≈ 25 mm Hg by 30 min post-intoxication, and rose gradually to normal or near by 2 h. Animals given propranolol at the time of intoxication did not develop tachycardia, but rather decreased their heart rate by 45–60 beats/min for 1–1½ h. Blood pressure fell by the same degree as in animals given ethanol alone, but did not return to normal within 2 h. To summarize: peritonitis caused little change in heart rate or blood pressure, intoxication produced

moderate tachycardia and hypotension for 1–2 h, and propranolol plus ethanol prevented the tachycardia and caused a reduction of blood pressure equal to but more prolonged than with ethanol alone.

Because of technical complications such as malfunctioning peritoneal catheters and death after cardiac puncture for blood specimens, data was not always available for all rabbits in each experiment. Thus, group I rabbits, given sterile peritonitis but not treated further, consisted of 13 animals; group II, those given peritonitis but also treated with alcohol, consisted of 18 animals; group III, those given propranolol in addition to peritonitis and alcohol, contained 9 animals; and group IV, given peritonitis and propranolol, without intoxication, contained 8 animals. Granulocyte adherence was measured in six animals of each group and peritoneal exudate was measured in all animals.

Adherence results are shown in Fig. 1. The mean

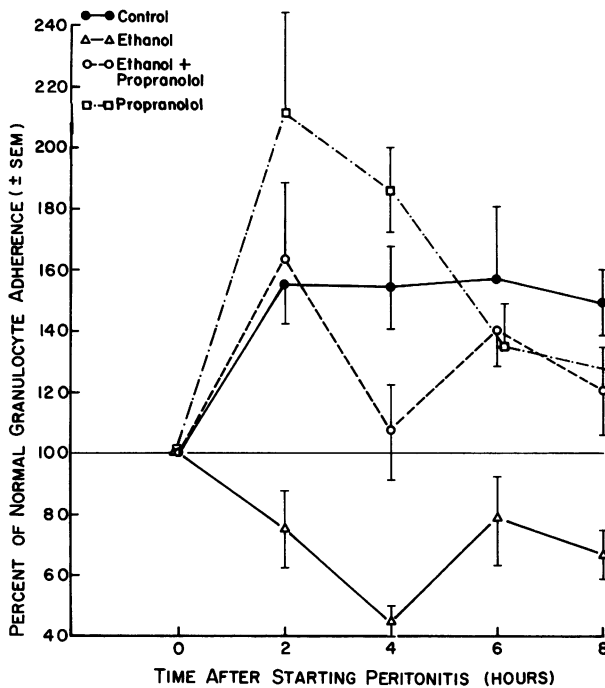


FIGURE 1 Effect of ethanol and propranolol on granulocyte adherence in rabbits with acute sterile peritonitis. Points represent means for six animals, isobars \pm SEM. Normal granulocyte adherence was the value for each animal before initiating peritonitis. Ethanol treatment consisted of 35 ml of a 25% ethanol solution in normal saline given intravenously at time zero, and an additional 20 ml 4 h later. Ethanol plus propranolol-treated animals received 0.3 mg/kg propranolol intravenously with each ethanol dose. Propranolol alone was given to a fourth group of animals at the same time. All values for animals receiving ethanol and propranolol were significantly greater than for those receiving ethanol alone ($P < 0.05$, paired sample t test), and not significantly below values for controls. Propranolol alone did not increase adherence significantly above that in control animals ($P > 0.05$, paired sample t test).

blood granulocyte adherence at 2 h for group I rabbits increased to 156% of the pretreatment value, and stayed elevated throughout the 8-h period, demonstrating that acute inflammation raises granulocyte adherence. In contrast, group II rabbits (those treated with alcohol) had a mean adherence at 2 h of only 75% of the preperitonitis values. It remained below normal for the duration of the experiment and significantly below the values for the control group, despite the fact that both groups received the same inflammatory stimulus ($P < 0.05$, paired sample t test), but significantly higher than values seen in animals treated with alcohol alone ($P < 0.05$, paired sample t test). Thus, propranolol prevented alcohol's inhibition of granulocyte adherence in vivo, allowing adherence to increase to near the level seen in animals given peritonitis without alcohol. Group IV animals (given propranolol without alcohol) developed adherence 216% of preperitonitis values at 2 h and maintained elevated adherence for the duration of the experiment. Values were not significantly different from those in animals with peritonitis ($P > 0.05$, paired sample t test). In the experiment to determine which isomer of propranolol affected adherence, the D-isomer increased adherence to a mean of $164 \pm 7.0\%$ of preadministration levels at 30 min, $220 \pm 38\%$ at 1 h, and $126 \pm 18\%$ at 2 h. In contrast, the L-isomer values were 125% at 30 min, 110% at 1 h, and 126% at 2 h.

How did these changes in granulocyte adherence correlate with peritoneal exudate formation in the four groups? Fig. 2 shows that at 2 h the mean granulocyte count in peritoneal exudate fluid was virtually identical for all groups. At 4 h, the count in the untreated animals was $11,000/\text{mm}^3$, and rose to $27,000/\text{mm}^3$ by 8 h. In contrast, animals treated with alcohol had a mean peritoneal granulocyte count at 4 h of only $3,500/\text{mm}^3$, and at 8 h their counts only reached $12,000/\text{mm}^3$. These counts were significantly lower than the values for the untreated animals at 4, 6, and 8 h ($P < 0.05$, paired sample t test). In the group treated with alcohol and propranolol, the mean granulocyte count in the exudate at 4 h was $6,500/\text{mm}^3$ and by 8 h rose to $24,000/\text{mm}^3$. These values were significantly higher than in the alcohol-treated group ($P < 0.05$, paired sample t test), and nearly at the levels seen in the untreated animals. Thus, in addition to preventing the inhibited granulocyte adherence caused by intoxication, propranolol returned the poor granulocyte delivery to normal. Of interest, even though propranolol alone increased adherence in animals with peritonitis to value above those seen with peritonitis alone, the exudate counts were no higher than in untreated animals.

Blood alcohol and catecholamine determinations. It is possible that propranolol could have prevented the alcohol inhibition of granulocyte adherence and exu-

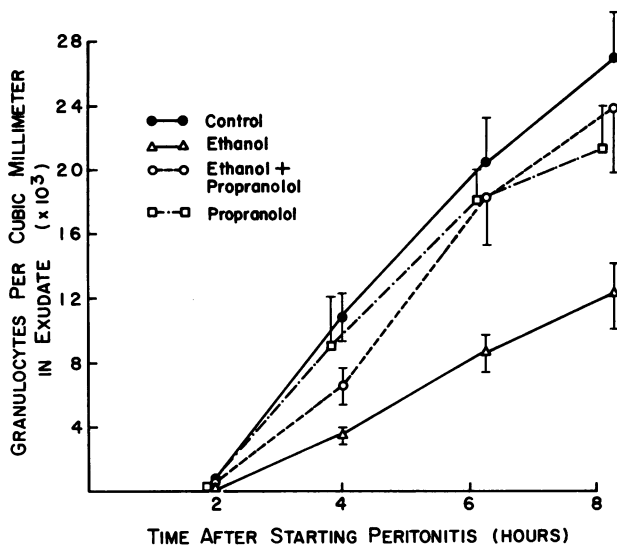


FIGURE 2 Effect of ethanol and propranolol treatment on peritoneal exudate formation in rabbits with sterile peritonitis. Points represent means, isobars \pm SEM. Significantly more granulocytes were exuded at 4, 6, and 8 h in animals receiving ethanol and propranolol than in those receiving ethanol alone ($P < 0.05$, paired sample t test). The values in the ethanol and propranolol-treated animals were not significantly below values in control animals ($P > 0.05$, paired sample t test). Propranolol alone did not increase exudate above control.

date formation by increasing the rate of alcohol clearance from the circulation rather than by affecting granulocyte adherence directly. To evaluate this possibility, blood alcohol levels were measured $\frac{1}{2}$ and $3\frac{1}{2}$ h after animals received either alcohol alone or alcohol plus propranolol. Results are shown in Table I. Peak and trough blood alcohol levels were essentially the same in the two groups, and the percent fall in concentration in 3 h was almost identical (34%).

Because catecholamine administration inhibits granulocyte adherence (12), the question arose as to whether or not alcohol intoxication might be lowering adherence by raising plasma catecholamines. Therefore, levels were measured before, and 1 h after, administration of 35 cm^3 of a 25% solution of intravenous alcohol. Results are shown in Table II. No significant change was found.

Pneumococcal peritonitis. 18 sets of animals were studied. All animals had positive peritoneal fluid cultures 4 h after initiating pneumococcal peritonitis, and positive blood cultures at 4 and 24 h. All survivors had negative blood cultures at 2 wk and appeared healthy. The survival data for these animals are shown in Table III. In group I, those given pneumococcal peritonitis but not treated further, 4 of 18 animals died. In group II, animals given the same infection while intoxicated with alcohol, 17 of 18 died. The difference in survival between the control and alcohol-treated rabbits was highly significant. In contrast, only 9 of 18 group III animals, that received propranolol in addition to alcohol, died of their peritonitis. Thus, propranolol significantly increased the survival rate of infected intoxicated animals ($P < 0.02$, chi square). The number of days until death in intoxicated infected animals who ultimately succumbed was analyzed to answer the question, "Does propranolol treatment prolong time of survival even in the fatal infection?" The mean number of days until death in the alcohol-treated rabbits that died was 2.8 days whereas the group receiving propranolol in addition to alcohol survived a mean of 7.5 days. This difference was highly significant by the Wilcoxon rank sum test ($P < 0.002$).

DISCUSSION

Acute alcohol intoxication has been known to cause poor granulocyte delivery to sites of inflammation since the pioneering work of Pickrell (1). When the inflammatory stimulus is a bacterial infection, the failure to mobilize granulocytes locally to contain the infection leads to its dissemination, and death of the intoxicated subject. The demonstration that granulocytes maintain normal chemotaxis (13, 14), phagocytosis, and intracellular killing (2, 13) in high concentrations of alcohol indicates that alcohol does not prevent granulocyte participation in antibacterial defense simply by narcotizing the cells. This finding led to a search in our laboratory for another explanation for alcohol's exudate-inhibiting effect; the discovery that sublethal concentrations of alcohol significantly inhibited adherence of granulocytes to surfaces *in vitro* offered a plausible mechanism (6). Inhibition of granulocyte adherence was found to be a general property of anti-inflammatory

TABLE I
The Effect of Propranolol Administration on Blood Alcohol Levels and Their Rate of Decay

Treatment	$\frac{1}{2}$ h post-dose	$3\frac{1}{2}$ h post-dose	Percentage of peak
Alcohol alone	295 mg/100 ml \pm 15.3	196.5 mg/100 ml \pm 10.1	66.6
Alcohol plus propranolol given simultaneously	324.2 \pm 10.4	215.2 \pm 21.8	66.4

TABLE II
Plasma Catecholamine Levels in Three Rabbits before and 1 h After Alcohol Intoxication

Pre	Post	Change
pg/ml		
439	537	+22%
405	599	+48%
1,453	1,128	-22%

agents (7), and the intensity of adherence was shown to correlate directly with the rate of granulocyte movement out of the vascular compartment (12). Plasma factors were found which augmented or inhibited adherence in different clinical situations (7, 11, 12) and which could be mimicked respectively by cyclic guanosine 5'-monophosphate or cyclic AMP (10). This suggested that pharmacologic antagonism of alcohol's adherence-inhibiting effect was possible. Because alcohol induces cyclic AMP in granulocytes (9) in a manner similar to beta adrenergic stimulators, propranolol was evaluated and found to augment adherence transiently when given to normal animals (10). This sequence of studies led to the hypothesis that the inhibition of granulocyte adherence by alcohol was responsible for its exudate-blocking action, and that pharmacologic reversal of the inhibited adherence would allow intoxicated animals to deliver granulocytes more normally and thereby control infection more effectively.

The first group of experiments described in this paper demonstrate that acute sterile peritonitis was associated with a marked increase in granulocyte adherence and delivery to the site of inflammation, as reported (11). Acute intoxication completely reversed the increased adherence, resulting in a level below that found in animals without inflammation. This inhibition

TABLE III
Effect of Ethanol and Propranolol on Survival of Rabbits Given Pneumococcal Peritonitis

Group	Treatment	Number deaths/ number animals	Significance by chi square
I	None	4/18	P < 0.0003
II	Alcohol	17/18	
III	Alcohol plus propranolol	9/18	

Mean days until death in nonsurvivors

Treatment	Days	Significance by Wilcoxon rank sum test
Alcohol	2.8	P < 0.0002
Alcohol plus propranolol	7.5	

was associated with a >50% reduction in granulocyte delivery. The treatment of intoxicated inflamed animals with propranolol prevented this inhibition and allowed the development of increased adherence and exudate production, similar to that seen in nonintoxicated animals with peritonitis. Propranolol treatment of unintoxicated animals with peritonitis increased adherence above values seen with peritonitis alone, but did not increase granulocyte delivery to the inflamed peritoneum. This suggests that inflammation already was maximal in the unintoxicated animals, and could not be increased further by an additional increase in granulocyte adherence.

When the pneumococcus was used instead of sterile saline as the stimulus for inflammation, findings were observed similar to those in the groups given sterile peritonitis. As noted by Pickrell (1) and others, the intoxicated animals could not contain the organisms locally and died of overwhelming infection in contrast to the normal animals who usually survived the infection (14/18) and had sterile blood and peritoneum when sacrificed 2 wk after infection. The poor survival rate of infected intoxicated animals was significantly improved by the simultaneous administration of propranolol; moreover, the intoxicated propranolol-treated animals that ultimately succumbed to the infection lived longer than did the animals which only received alcohol. Thus, propranolol prevented alcohol's inhibiting effect on granulocyte adherence and delivery to sites of inflammation, and significantly improved the survival of infected intoxicated animals. Preservation of normal granulocyte delivery would be expected to improve the defense against bacterial infection. In addition, it is possible that other host defense mechanisms which we did not evaluate were also improved by propranolol. The increased survival was accomplished without any change in either peak blood alcohol levels or in the rate of alcohol metabolism. Also, propranolol did not diminish the relative hypotension induced by intoxication, and neither intoxication nor propranolol caused increased volume loss during peritonitis. Thus, it appears that pharmacologic manipulation of granulocyte adherence may be helpful to an infected animal's host defense against bacterial infection. It is possible that antibacterial defense might be improved by the use of adherence-augmenting drugs in other clinical situations associated with impaired adherence such as glucocorticoid therapy (6, 7) and multiple myeloma (15, 16).

ACKNOWLEDGMENTS

We thank Dr. Robert Austrian for providing the pneumococcus used in these experiments, and for his counsel regarding its preparation and maintenance. The experiments monitoring pulse and blood pressure responses of animals with peritonitis were performed under Mr. William Collins'

expert guidance, and with the use of his equipment. Dr. Elias Abrutyn offered helpful editorial comments.

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