

Corticosteroid Therapy in Regional Small Bowel Ischaemia

An Experimental Study in Rats

L. RENTZHOG and S. WIKSTRÖM

From the Department of Surgery, University Hospital, Uppsala Sweden

ABSTRACT

Corticosteroid therapy in pharmacological doses has a well documented positive effect in shock caused by severe intestinal ischaemia. In this study the effect of high doses of corticosteroids on the exchange circulation of the mucosa was analysed in varied, regional small bowel ischaemia. Thirty minutes after establishment of moderate ischaemia the exchange circulation in the mucosa of the ischaemic intestinal segment in animals treated with 100 mg/kg hydrocortisone showed no improvement compared with untreated animals. Higher corticosteroid doses impaired the exchange circulation. On analysis 7 days after establishment of the ischaemia, treatment with 100 mg/kg hydrocortisone during the first 3 days was found to have impaired the exchange circulation. The same treatment in rats with more severe intestinal ischaemia gave a greatly increased mortality. Possible reasons for the impaired mucosal circulation following corticosteroid therapy in pharmacological doses in regional small bowel ischaemia are discussed. One possibility is that corticosteroids induce a "steal syndrome" due to the better vasodilative effect on healthy than on ischaemic intestinal tissue.

INTRODUCTION

In most experimental studies concerning ischaemia of the small intestine the ischaemia has been produced by central, intermittent interruptions of the blood flow. The significance of bacterial endotoxin in this connection has been pointed out by several authors (13, 19). Selkurt et al. (16) discussed the importance of vasoactive substances in intestinal ischaemia. Kobold & Thal (8) identified a vasoactive peptide which was liberated in different types of experimental and clinical ischaemia of the small intestine. Other authors (2, 6, 7) have shown that lysosomal enzymes are released in association with ischaemia in the splanchnic region, and this may well lead to a serious impairment of myocardial function (10, 18).

It seems likely that abnormal bacteria-dependent endotoxin production, ischaemic destruction of lysosomes, release of vasoactive substances and activation of vasoconstrictive reflexes can also be induced in connection with regional small bowel ischaemia. These local factors can affect the collateral circulation and can also probably cause a release of a myocardial depressant factor (10). Lil-lehei et al. (11) pointed out that the ability of the intestine to survive a regional ischaemia is highly dependent upon the collateral flow from adjacent intestinal segments.

Norlén, Rentzhog & Wikström (14) have demonstrated that antibacterial and antithrombotic therapy improve the exchange circulation and chances of survival of the mucosa in regional small bowel ischaemia.

Corticosteroids in gram doses increase the survival in intestinal ischaemic shock (1, 10). The effect of cortisone in pharmacological doses in severe intestinal ischaemia has been discussed. Altura & Altura (1) claim that in these doses corticosteroids unspecifically inhibit the effect of vasoconstriction that may be released in intestinal ischaemia. Lil-lehei et al. (12) assumed that corticosteroids act as alpha receptor blocking agents but provided no definite evidence for this assumption. Bruns & Connolly (3), on the other hand, considered that the effect was a potentiation of the vasoconstrictive action of the catecholamines. Weissman & Thomas (17) and Glenn & Lefer (6) were of the opinion that the main effect of corticosteroids was to prevent lysosomal destruction and thereby the release of deleterious lysosomal enzymes.

The effect of corticosteroids in gram doses in regional small bowel ischaemia does not appear to have been studied previously. We therefore consid-

ered it of great interest to examine the influence of pharmacological doses of corticosteroids on the exchange circulation of the mucosa in standardized, regional small bowel ischaemia both immediately and one week after establishment of the ischaemia.

MATERIAL AND METHODS

Male Sprague-Dawley rats weighing 200–300 g were used. The animals were strictly standardized as regards iodine metabolism and were given iodine in their drinking water both before and during the experimental period.

Standardized small bowel ischaemia was produced by ligation of a defined number of mesenteric end arcades (mes end arc). The ligature material was 5:0 cardiovascular silk (Ethicon). The first ligature was applied on the 6th mes end arc counted from the ileocaecal angle, and a further 11 or 15 mes end arc, in the proximal direction, were then ligated. At the same time a central loop in the devascularized intestinal segment was marked with silk threads. These threads were placed around the intestine without affecting the terminal vessels. The length of the loop thus marked always corresponded to the extent of 2 mes end arc.

The mucosal circulation was assessed by a technique described by Nylander & Wikström (15), based on the fact that the passive absorption, i.e. the diffusion of a given substance from an intestinal loop of defined size, is an expression of the effective exchange circulation in the mucosa of the intestinal segment. A radioactive iodine isotope (NaI^{131}) was used as the test substances. At the time of analysis the previously marked intestinal loop (2 mes end arc) was ligated and the test dose was deposited into its lumen by transmural injection. The pylorus was tied off to prevent gastric contents from passing into the small intestine. After 30 min the animal was killed with ether. The abdomen was opened and the stomach was ligated at the cardia and resected. The isolated intestinal loop into which the test substance had been deposited was also resected. The radioactivity in the stomach, the intestinal loop and the whole body (thus excluding the stomach and the test loop) was recorded.

Two series of experiments were performed. In all animals a catheter was inserted into the vena cava via jugular vein by technique described by Engberg (4), and left *in situ*.

In series I (Table I) small bowel ischaemia comprising 11 mes end arc was produced in four groups of animals. In two groups an intravenous injection of hydrocortisone (Solu-Cortef®, Upjohn) in a dose of 100 mg and 300 mg, respectively, per kg body weight, dissolved in 0.2 ml physiological saline was given immediately before the ischaemia was established. The third group was simultaneously given methylprednisolone (Medrone®, Upjohn), 30 mg per kg dissolved in 0.2 ml physiological saline. The fourth group, as well as a laparotomy control group (no ischaemia) was given 0.2 ml physiological saline alone. The exchange circulation in the ischaemic intestinal segment was analysed 30 min after establishment of the ischaemia.

Series II (Table II) consisted of four groups with intesti-

nal ischaemia—two comprising 11 mes end arc and two 15 mes end arc. In all groups the exchange circulation was analysed 7 days after establishment of the ischaemia. Two of the groups (one 11 and one 15 mes end arc) were treated with hydrocortisone. The first dose (100 mg/kg) was given immediately before the ischaemia was produced, and the next dose (100 mg/kg) 2 h later. A further two doses of 50 mg/kg were given during the rest of the first 24 hours. In the following 2 days four doses of 50 mg/kg were given per day. The other two groups—*ischaemic controls*—were given physiological saline of the same volume as the hydrocortisone doses in the treated groups.

In series II a morphological evaluation of the ischaemic intestinal segment was made (Table II). The material was divided into three different types according to the macroscopical appearance of the small intestine, as follows:

Type 1. The intestinal wall appeared intact, apart from moderate thickening.

Type 2. Varying length of the intestinal wall were considerably thickened. The width of the lumen was normal both above and below the thickened area of the intestinal wall.

Type 3. The intestinal wall was thickened as in type 2, but proximal to the thickened area the lumen was dilated to the extent of an ileus state.

The results of the exchange circulation analyses in the ischaemic segment have been recorded only for type 1 in the respective experimental groups.

RESULTS

In series I, in which the exchange circulation of the intestinal mucosa was analysed 30 min after laparotomy or establishment of regional small bowel ischaemia (11 mes end arc), all animals survived. In Table I it is seen that in the laparotomy control group 26% of the radioactive dose remained in the isolated intestinal loop and at the end of the analytical period. In the untreated ischaemic group the absorption from the isolated loop was considerably impaired 45% of the radioactive dose remaining in the loop. Treatment with 100 mg/kg hydrocortisone did not improve the exchange circulation significantly in comparison with the untreated ischaemic group; in this case 48% of the dose remained in the loop. Following treatment with the higher dose of hydrocortisone (300 mg/kg) and with methylprednisolone (30 mg/kg) the absorption of the radioactive iodine was reduced, 67% and 66% of the dose, respectively, remaining in the loop at the end of the analytical period. Half of the animals treated with the higher dose of hydrocortisone (300 mg/kg) also received 2 ml physiological saline in a continuous intravenous infusion during the experimental period, but these animals showed no differ-

Table I. *Series I. Characteristics of the material and percentage distribution of the radioactive dose 30 min after its deposition in the isolated loop (mean values with S.E.)*

Exp. group	n	Body weight (g)	Percentage of dose in		
			isol. loop	stomach	body
LC	20	231±3.8	26.1±2.2	12.0±0.8	61.9±1.9
11 mes end arc, untreated	18	242±6.8	45.2±3.2	6.7±0.8	48.1±2.7
11 mes end arc, hydrocortisone treated (100 mg/kg)	20	252±1.1	49.1±4.0	10.1±1.3	40.8±3.1
11 mes end arc, hydrocortisone treated (300 mg/kg)	20	240±5.2	66.8±3.2	2.2±0.3	31.0±3.2
11 mes end arc, methylprednisolone treated	10	270±1.0	65.8±5.1	1.9±0.4	32.3±4.8

ence in absorption of the test dose from the animals given hydrocortisone alone (65% and 68%, respectively, of the test dose remaining in the loop). All animals that were given the higher hydrocortisone dose (300 mg/kg) are therefore placed in one group in Table I.

In series II the exchange circulation of the small bowel mucosa was analysed 7 days after establishment of the ischaemia. In Table II it is seen that in the untreated ischaemic group comprising 11 mes end arc 3 of 21 animals died. Morphologically, one of these 3 animals was assigned to type 2. The other 2 animals that died were of type 3, exhibiting acute perforation and peritonitis. Of the surviving animals in this group 2 were assigned to type 3, with severe ileus, and one of them also had perforation. The other 16 animals in this group were assigned to type 1. In the group with ischaemia comprising 11 mes end arc and treated with hydrocortisone, one of 18 animals died. This animal was of type 3. One of the surviving animals of this group was also as-

signed to type 3, with perforation. It is also seen in Table II that in the hydrocortisone-treated ischaemic group the exchange circulation in the ischaemic intestinal segment was significantly impaired compared with the untreated group. Thus 50% of the radioactive dose remained in the isolated loop in the former group, and 35% in the untreated group.

Among the animals with severe bowel ischaemia (15 mes end arc) (Table II), only one could be assigned to type 1. The others were of type 3, and four of these died. Hydrocortisone treatment combined with this severe degree of ischaemia resulted in death in all cases. Morphologically all animals in this group were assigned to type 3.

DISCUSSION

Nylander & Wikström (15) showed that the exchange circulation of the mucosa was greatly impaired immediately following establishment of small

Table II. *Series II. Characteristics of the material, morphological types and percentage distribution of the radioactive dose 30 min after its deposition in the isolated loop (mean values with S.E.)*

Exp. group	n	Mor- tality	Morphological types			Body weight (g)		Percentage of dose in		
			I	II	III	Initial	Final	isol. loop	stomach	body
11 mes end arc, untreated	21	3	16	1	4	284±7.6	285±9.3	34.9±4.2	4.7±0.3	60.4±4.1
11 mes end arc, hydrocortisone treated	18	1	16	—	2	268±1.1	243±4.5	49.8±4.5	4.1±0.6	46.1±5.5
15 mes end arc, untreated	12	4	1	—	11	234±3.4	—	—	—	—
15 mes end arc, hydrocortisone treated	12	12	—	—	12	270±2.9	—	—	—	—

bowel ischaemia. This finding was confirmed in the present investigation. A release of lysosomal enzymes and of vasoactive substances, as well as the influence of bacterial endotoxins, may all presumably influence the collateral circulation and thereby the exchange of the mucosa in the ischaemic intestinal segment. Theoretically it would therefore seem probable that hydrocortisone would improve the exchange circulation, but no effect of this corticosteroid in a dose of 100 mg/kg was found in the acute experiments. Altura & Altura (1) reported, however, from acute experiments in the rat, that the survival in intestinal ischaemic shock was only improved at a dose of 300 mg/kg hydrocortisone or 30 mg/kg methylprednisolone. In our experiments this high dose of hydrocortisone and of methylprednisolone impaired the exchange circulation in the ischaemic intestinal segment, indicating that these steroid doses have a negative effect on the collateral circulation.

One possible reason for this surprising effect of high glucocorticoid dose may be a negative influence on the central circulation. In a pre-experimental study, however, no such influence was observed. In rats with catheters inserted into the femoral artery for continuous pressure recording, a transient reduction of the systemic blood pressure was noted immediately after administration of the glucocorticoid, followed by normalization or a slight pressure increase.

Another possibility is that a strong general vasodilative effect of high doses of glucocorticoids might unmask a hypovolaemia caused by loss of fluid through oedema, for instance, in the ischaemic tissue in these animals. Infusion of physiological saline after administration of the corticosteroid, however, did not affect the results.

A further conceivable explanation is that corticosteroids impair the exchange circulation of the mucosa by inducing a "steal syndrome" due to more effective vasodilatation in healthy than in ischaemic intestinal tissue. It is possible that metabolic factors in ischaemic tissue and any release of certain vasoactive substances may counteract a favourable effect of the corticosteroids on the circulation in an ischaemic intestinal segment. The net effect may then be an impaired circulation in the ischaemic segment.

Folkow (5) has demonstrated that the circulation of the intestinal wall is built up of several parallel vascular systems. Our method measures indirectly

the circulation in the mucosal vascular system. It is possible that high corticosteroid doses do not impair the total circulation of the ischaemic intestine despite a reduction of the exchange circulation of the mucosa. A redistribution of blood to deeper layers of the intestinal wall is conceivable, especially to the vascular system in the muscular layer.

The presence of an adequate circulation during the first days after the development of intestinal ischaemia is of decisive importance for survival and restoration of the intestine. During this initial ischaemic period the available intestinal circulation would seem to be most susceptible to a negative influence of a high sympathetic tone and local release of vasoactive substances, endotoxins and lysoenzymes. High corticosteroid doses during the first 2-3 days might have a positive effect on the local damage and improve the chance of survival. In our second series of experiments, however, there was no definite positive effect of intensive corticosteroid therapy during the first three days following establishment of the ischaemia. In rats with severe ischaemia (15 mes end arc) the high dose of corticosteroid had a distinctly negative effect on the survival.

In untreated animals with ischaemia comprising 11 mes end arc the exchange circulation was considerably better one week after than immediately after establishment of the ischaemia. This is in full agreement with previous results of Nylander & Wikström (15). On the other hand, treatment with a corticosteroid in gram doses during the first 3 days after ischaemia had been produced resulted in no improvement of the mucosal circulation 7 days later. A probable explanation, as in the acute experiments, is that gram doses of corticosteroids impair the collateral circulation in regional ischaemia due to a "steal syndrome". Another possibility is that corticosteroid therapy favours bacterial invasion in this ischaemic intestinal wall, with consequent oedema and fibrosis, leading to an impairment of the mucosal circulation.

ACKNOWLEDGEMENT

This investigation has been supported by grants from the Swedish Medical Research Council (B76-17X-2809-06). Excellent technical assistance was provided by Mrs Inger Fogelberg.

REFERENCES

1. Altura, B. M. & Altura, B. T.: Peripheral vascular actions of glucocorticoids and their relationship to protection in circulatory shock. *J Pharmacol Exp Ther* 190: 300, 1974.
2. Bitensky, L., Chayen, J., Cunningham, J. G. & Fine, J.: Behaviour of lysosomes in hemorrhagic shock. *Nature, London*, 199: 493, 1963.
3. Bruns, D. L. & Connolly, J. E.: Comparative study of the effectiveness of adrenal cortical compounds in hemorrhagic shock. *Surg Forum* 10: 382, 1960.
4. Engberg, A.: A technique for repeated renal clearance measurements in undisturbed rats. *Acta Physiol Scand* 75: 170, 1969.
5. Folkow, B.: Role of nervous system in the control of muscular tone. *Circulation* 21: 760, 1960.
6. Glenn, T. M. & Lefer, A. M.: Protective effect of thoracic lymph diversion in hemorrhagic shock. *Amer J Physiol* 219: 1305, 1970.
7. Janoff, A., Weissmann, G., Zweifach, B. & Thomas, L.: Pathogenesis of experimental chock: IV. Studies on lysosomes in normal and tolerant animals subjected to lethal trauma and endotoxemia. *J Exp Med* 116: 451, 1962.
8. Kobold, E. E. & Thal, A. P.: Quantitation and identification of vasoactive substances liberated during various types of experimental and clinical intestinal ischemia. *Surg Gyn Obst* 117: 315, 1963.
9. Lefer, A. M.: Role of myocardial depressant factor in the pathogenesis of circulatory shock. *Fed Proc* 29: 1836, 1970.
10. Lefer, A. M. & Verrier, R. L.: Role of corticosteroids in the treatment of circulatory collapse states. *Clin Pharm Ther* 11: 630, 1970.
11. Lillehei, R. C., Goott, B. & Miller, F. A.: The physiological response of the small bowel of the dog to ischemia including prolonged in vitro preservation of the bowel with successful replacement and survival. *Ann Surg* 150: 543, 1959.
12. Lillehei, R. C., Longerbeam, J. K., Block, J. H. & Manax, W. G.: The modern treatment of shock based on physiological principles. *Clin Pharm Ther* 5: 63, 1964.
13. Milliken, J., Nahor, A. & Fine, J.: Study of the factors involved in the development of peripheral vascular collapse following release of the occluded superior mesenteric artery. *Brit J Surg* 52: 699, 1965.
14. Norlén, K., Rentzhog, L. Wikström, S.: Experimental ischemia of the small intestine. Effect of antibiotic and antithrombotic drugs on the mucosal exchange circulation. *Acta Chir Scand* 141: 780, 1975.
15. Nylander, G. & Wikström, S.: Propulsive gastrointestinal motility in regional and graded ischemia of the small bowel. An experimental study in the rat. I. Immediate results. *Acta Chir Scand, Suppl.* 385, 1968.
16. Selkurt, E. E., Scibetta, M. P. & Cull, T. E.: Hemodynamics of intestinal circulation. *Circ Res* 6: 92, 1958.
17. Weissman, G. & Thomas, L.: Studies on lysosomes: I. Effects of endotoxin tolerance and cortisone on the release of acid hydrolases from a granular fraction of rabbit liver. *J Exp Med* 116: 433, 1962.
18. Williams, L. F., Jr., Goldberg, A. H., Polansky, B. J. & Byrne, J. J.: Myocardial effects of acute intestinal ischemia. *Surgery* 66: 138, 1969.
19. Witznitzer, T. & Rozin, R.: Bacterial factor in shock following superior mesenteric artery occlusion. *Israel Med J* 22: 4, 1963.

Received July 20, 1976

Address for reprints:
Stig Wikström, M.D.
Department of Surgery
University Hospital
S-750 14 Uppsala
Sweden