Proc EDTA–ERA (1985) Vol 22

THE EFFECT OF PREVENTIVE ADMINISTRATION OF NIFEDIPINE ON ACUTE ISCHAEMIC RENAL FAILURE IN HYDROPENIC DOGS

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Summary

The effect of preventive administration of nifedipine in experimental acute ischaemic renal failure in two groups of hydropenic dogs was studied. After clamping the renal pedicle on one side (control kidneys), 10μg/kg body weight of nifedipine (NF group) was given intravenously. Fifteen minutes later the renal pedicle on the other side was clamped. Total ischaemic period was 60 minutes and renal function was evaluated for 120 minutes thereafter.

Nifedipine treated kidneys had a much shorter time of starting diuresis while creatinine clearance C_{Cr} at the end of the second hour after revascularisation was 3.5 times greater in comparison with the placebo and the control groups.

This effect could be due to the calcium blocking action of nifedipine in the hydropenic model of acute ischaemic renal failure.

Introduction

The syndrome of acute renal failure remains a common and complex clinical problem. During the past few years there have been many ideas regarding pathogenesis but despite that there are many points not entirely clarified. The mortality rate of the syndrome has not been considerably improved [1,2], therefore interest has been focused on prevention of the syndrome by using certain agents having a favourable influence on the course of acute renal failure in experimental and clinical practice.

Recently there has been interest in the pathogenic role of calcium on the ischaemic and toxic renal cell damage [3,4]. Moreover, the preventive administration of verapamil has produced a favourable influence on the course of experimental ischaemic acute renal failure in dogs [5,6].

This paper examines the effect of nifedipine, another calcium entry blocker agent, on the prevention of acute ischaemic renal failure in hydropenic dogs,

since ischaemia and hydropenia are often combined in clinical cases of acute renal failure.

Materials and Methods

The experiments were performed in two groups of healthy mongrel dogs. The first group (10 animals was used for the study of nifedipine (NF group) and the second (10 animals) (placebo group) for the comparative evaluation with the first group.

Both kidneys were exposed by bilateral flank incisions. Then, the renal pedicle on one side was clamped and 10g/kg body weight of nifedipine or placebo was given intravenously. After 15 minutes, the renal pedicle of the contralateral kidney was also clamped. The total ischaemic period was 60 minutes for both kidneys. Thus the first kidney of each group was used as a control and the second for the study of the effect of the nifedipine or the placebo. At the end of the 60 minute ischaemic period the clamps were removed and blood flow through both kidneys was established. Renal function was studied for two hours after revascularization. For that purpose urine flow rate (U_V) endogenous creatinine clearance (C_{Cr}) and clearances of urea (C_{urea}), osmolality (C_{osm}), sodium (C_{na}), potassium (C_K), fractional excretion of sodium (FENa) and the urine LDH were evaluated. At the end of the experiments histological examination of both kidneys was performed. Student's 't' test for paired data was used for statistical analysis and $p<0.05$ was accepted as statistically significant.

Results

The mean time of initiation of diuresis after recirculation was 20.6 minutes in the nifedipine group and 41.8 minutes in the control group (p=NS). In addition the kidneys of the nifedipine group produced a higher U_V, and at the end of the study the mean U_V reached 113 per cent of the mean control value while it was only 45 per cent in the control group ($p<0.05$).

After revascularization renal blood flow as measured by an electromagnetic flowmeter in nine experiments was superior by 17 per cent in the nifedipine group in comparison with the control group.

C_{Cr} was higher in the nifedipine group, compared with the control group during all studied periods. At the end of the experiment, the mean C_{Cr} reached 73 per cent of the control value in the nifedipine group and around 48 per cent in the control and placebo group ($p<0.05$) (Figure 1).

The other parameters of the glomerular and tubular functions are shown in Table I. There was a rapid fall of the mean FENa in the nifedipine group and it remained lower during the last 30 minutes of the observation compared with the control group (p=NS). In addition, during the last three periods, the mean

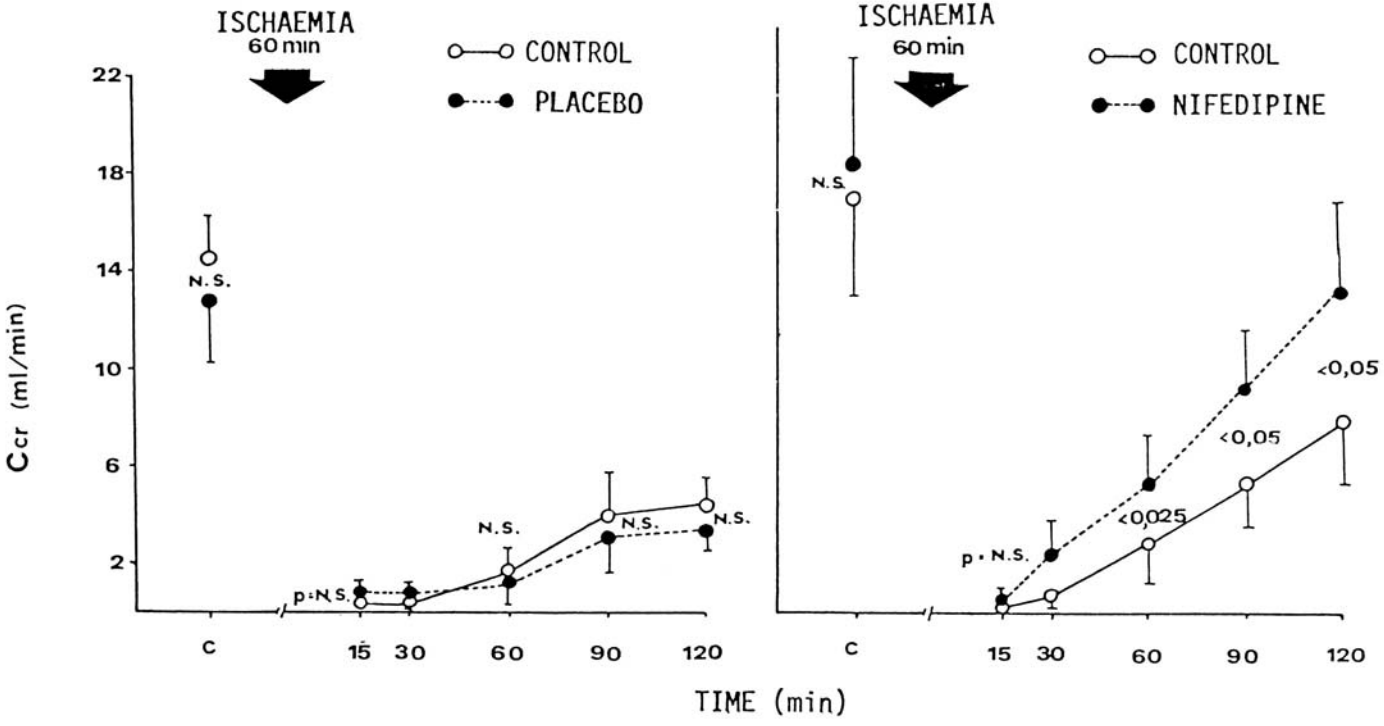

Figure 1. Schematic presentation of C_{Cr} changes after 60 minute ischaemia (M±SE)

TABLE I. Comparison of the glomerular and tubular function before clamping and two hours after revascularization (M±SE)

	Placebo Group				Nifedipine Group			
	Control		Placebo		Control		Nifedipine	
	Before	After	Before	After	Before	After	Before	After
U_V ml/min	0.67 ± 0.18	0.50 ± 0.13	0.58 ± 0.19	0.55 ± 0.13	0.69 ± 0.25	0.31 ± 0.07	0.70 ± 0.25	0.79* ± 0.24
C_{Cr} ml/min	14.64 ± 1.62	4.49 ± 0.84	12.83 ± 2.12	3.40 ± 0.69	17.10 ± 3.83	8.15 ± 2.47	18.36 ± 3.71	13.37* ± 3.72
C_{urea} ml/min	10.82 ± 1.43	1.08 ± 0.24	9.29 ± 1.36	2.08 ± 0.91	13.57 ± 3.57	3.16 ± 0.82	12.39 ± 3.55	5.65** ± 1.21
C_{osm} ml/min	1.38 ± 0.31	0.57 ± 0.11	1.17 ± 0.21	0.67 ± 0.14	1.20 ± 0.41	0.40 ± 0.11	1.31 ± 0.54	0.78 ± 0.34
FENa (%)	5.42 ± 1.62	8.48 ± 1.87	4.94 ± 1.10	9.23 ± 1.42	5.86 ± 1.58	9.08 ± 3.43	4.88 ± 1.36	7.27 ± 1.64
LDH (U/L)	39.30 ± 3.76	384.70 ±109.07	48.87 ± 9.57	385.80 ± 58.69	27.75 ± 3.50	274.30 ± 64.69	33.30 ± 5.80	101.60* ± 21.77

*$p<0.05$; **$p<0.025$

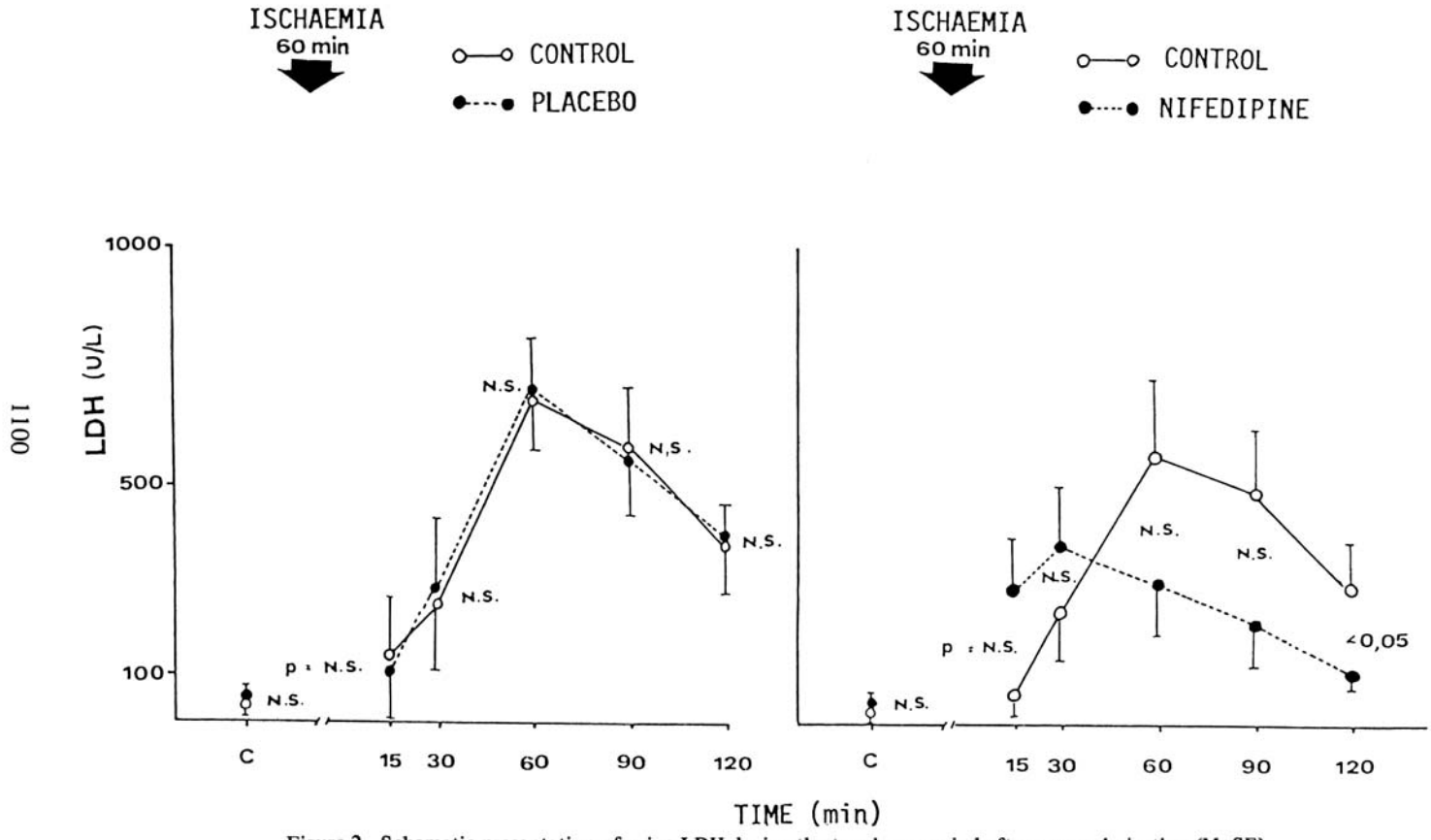

Figure 2. Schematic presentation of urine LDH during the two hour period after revascularization (M±SE)

urinary concentration of LDH was lower in the nifedipine group. In fact, at the end of the experiments the urinary LDH on the nifedipine group reached 305 per cent while in the placebo was found increased up to 789 per cent of the control values. On the other hand, the two control groups of kidneys showed a similar increase in urinary LDH being 978 per cent and 988 per cent respectively (Figure 2).

In general the histological lesions were not different between the two groups, with the exception that the interstitial oedema and tubular changes were milder in the nifedipine group.

Discussion

The effective effect of verapamil in the experimental models of acute ischaemic renal failure is well established. On the other hand there is little data concerning the protective role of nifedipine or other calcium entry blockers on the course of experimental acute ischaemic renal failure [6–8]. In addition, it is well known that hydropenia increases the severity of the renal cell damage after an ischaemic episode and this is often encountered in clinical practice [9].

By using this study protocol, it was shown that the one hour renal ischaemia produced a degree of ischaemic damage in both groups of kidneys (nifedipine-placebo). After revascularization, there was much earlier diuresis in the nifedipine group compared with the control group. In addition renal function (glomerular and tubular) was found to be superior with more rapid improvement during the next two hours in the nifedipine than in the placebo and control groups.

The differences between the two groups may be due to the reduction of vasospasm [10], and mainly to the better viability of renal tissue in the nifedipine group. The mechanism of inhibition of entrance of calcium into the tubular and endothelial cells and the better mitochondrial function induced by nifedipine could be an explanation for that result as has recently been shown by a group of other investigators [6]. Therefore, it is likely that the preventive administration of nifedipine in experimental and clinical practice could favourably influence the course of acute ischaemic renal failure of 60 minutes duration. It is suggested that nifedipine or other less light sensitive agents could be used for prevention of renal failure in all cases of impending acute ischaemic renal failure including renal transplantation as we have shown with verapamil (unpublished observations).

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