THE ROLE OF ENDOGENOUS OPIOIDS IN THE BAROREFLEX DYSFUNCTION OF DIALYSIS PATIENTS


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Summary

We studied the effect of the opiate antagonist naloxone on the response to Valsalva manoeuvre in nine dialysis patients, in six diabetics with normal renal function whose response to Valsalva manoeuvre was similar to that of dialysis patients and in eight healthy subjects.

Naloxone caused a progressive increase in the subnormal Valsalva ratio in dialysis patients but it did not cause any change in diabetics nor in healthy subjects. The increase in Valsalva ratio observed in dialysis patients was due to restoration of the parasympathetically mediated reflex bradycardia of the release phase of the manoeuvre.

Endogenous opioids may be responsible for the baroreflex dysfunction of dialysis patients.

Introduction

It is well established that baroreflex control of heart rate is often impaired in patients with chronic renal failure [1,2]. However, the factors involved in the pathogenesis of this dysfunction remain unclear.

It has recently been proposed that accumulation of unknown middle molecular weight substances interfering with baroreflex control might account for the baroreflex dysfunction in patients with chronic renal failure [3]. We thought that one of such substances might be the endogenous opioid (Met)-enkephalin, indeed this compound depresses baroreflex sensitivity, has a MW of 576 daltons and is retained in chronic renal failure [4].

The present study was designed to find out whether the retention of (Met)-enkephalin is involved in the baroreflex dysfunction in uraemic patients on chronic haemodialysis. For this purpose we have tested the effect of the opiate antagonist naloxone on the response to Valsalva manoeuvre in a group of dialysis patients, in a group of diabetic patients whose response to Valsalva manoeuvre was similar to that of dialysis patients and in a group of normal subjects.
Methods

Subjects

We studied nine uraemic non diabetic males (age 36–58 years; mean 44), six diabetic males (19–64 years; mean 43) and eight healthy males (31–53 years; mean 41). The uraemic patients had been dialysed three times a week for periods ranging from one to 11 years. They were well at the time of the study with no evidence of heart failure or pericardial effusion. The six diabetic patients had normal serum creatinine and had been treated with insulin (4 cases) or with oral hypoglycaemic drugs (2 cases) for periods ranging from two to 13 years. None of the dialysis or diabetic patients had symptoms of peripheral or autonomic neuropathy. No patient was taking antihypertensive drugs or other medications known to affect the autonomic nervous system. The nature of the study was explained to all participants who gave their informed consent.

Protocol

Each subject was studied on two occasions 48 hours apart, uraemic patients being investigated the day between dialyses. In the first study, at 9 a.m. subjects rested quietly for 15–20 minutes and their supine mean arterial pressure (MAP= pulse pressure/3+diastolic) and heart rate were recorded at five minute intervals with a Dinamap 845 monitor. The response to Valsalva manoeuvre was then tested and the Valsalva ratio calculated as the ratio of the longest RR interval of the release phase to the shortest RR interval of the strain phase [5]. After these baseline measurements (nil time) subjects received intravenously either naloxone (.07mg/kg) or placebo (10ml of saline) in randomised, balanced and single blind fashion. Supine mean arterial pressure and heart rate and the response to Valsalva manoeuvre were reevaluated one, two and three hours after the injection. On the second study the treatments were crossed over and the same experimental sequence repeated.

All results are expressed as mean ± SEM and their changes with time analysed with repeated measures. To compare the effects within the groups of naloxone with placebo the paired ‘t’ test was employed.

Results

Before injection of either naloxone or placebo (Figure 1, nil time) there were no significant differences between the three groups as for supine mean arterial pressure and heart rate. By contrast, Valsalva manoeuvre ratio was significantly less in dialysis and diabetic patients than in normal subjects (p<0.05 or less). In both dialysis and diabetic patients the impaired Valsalva ratio was due to a reduced response during the release phase (p<0.01 or less), the response during the strain phase being no different from that of healthy subjects (Figure 2, nil time).

Naloxone had no effect on supine mean arterial pressure and heart rate in any of the groups. However, in dialysis patients the drug caused a progressive
increase in Valsalva ratio from a baseline value of 1.46 ± 0.09 to a final value of 1.73 ± 0.011 (p<0.0125). Placebo administration did not alter Valsalva ratio in any of the groups. As shown in Figure 2, the improvement in Valsalva ratio observed in dialysis patients after naloxone was almost entirely attributable to a significant lengthening of the RR interval during the release phase (p<0.01), the RR interval being unaffected during the strain phase.

Discussion

Abnormal baroreflex control of heart rate to stimuli such as Valsalva manoeuvre and phenylephrine injection were first reported in chronic uraemics by Hennessy [1] and Pickering [2]. Subsequently several authors [7,8], including ourselves [5], confirmed these observations. This autonomic defect has been attributed to a parasympathetic dysfunction probably resulting from an afferent or central lesion in the baroreflex arc [5]. In agreement with these studies we also found
that the reduced Valsalva ratio in dialysis patients was due to a parasympathetic dysfunction. Indeed this abnormality was sustained mainly by an impaired heart rate response during the release phase which is known to depend on parasympathetic activation.

By restoring the response during the release phase naloxone almost entirely reversed the abnormal Valsalva ratio in dialysis patients. The drug had no similar effect in diabetic patients nor in normal subjects. The favourable effect of naloxone in chronic uraemics most likely results from antagonism of endogenous opioids. Endogenous opioids have been recently measured in uraemic patients by Smith et al [4] who found a slight increase in plasma beta-endorphin and markedly elevated levels of (Met)enkephalin. Enkephalins are important modulators of baroreflex control: in rabbits, intracisternal injection of an enkephalin analogue attenuates the reflex heart rate response to hypotensive and hypertensive stimuli such as sodium nitroprusside infusion and phenylephrine injection while these effects are prevented by intravenous naloxone [9]. That enkephalins participate in the regulation of baroreflex activity in man is suggested by the observation that intravenous infusion of a (Met)enkephalin analogue,
DAMME, has a depressant action on baroreflex sensitivity [10]. Therefore, it appears possible that the improved response to Valsalva manoeuvre in chronic uraemics is due to antagonism of the depressant effect of retained (Met)-enkephalin on baroreflex sensitivity. This possibility is also supported by the fact that naloxone had no effect in diabetic patients who, although displaying an abnormal response to Valsalva manoeuvre, have normal plasma values of (Met)enkephalin, nor in normal subjects. Our observation is in line with the view that naloxone affects circulatory control only in those pathophysiological conditions associated with elevated plasma endogenous opioids.

In conclusion, our results suggest that substances of the enkephalin class, most likely (Met)enkephalin, are responsible for the impaired reflex control of heart rate in uraemic patients.

References

1 Hennessy WJ, Siemsen AW. Clin Res 1968; 16: 385
3 Henderson LW. Kidney Int 1980; 17: 571
6 Wallenstein S, Zucker CL, Fleiss J. Circ Res 1980; 47: 1
10 Rubin PC, McLean K, Reid JL. Hypertension 1983; 5: 535

Open Discussion

RITZ (Chairman) Could you briefly comment on whether there was nausea in your patients on the administration of naloxone? This of course could heighten parasympathetic tone.

ZOCCALI No, there were no side effects.

RITZ Your observations would suggest that there is a reversible functional component to baroreflex dysfunction. There is also some evidence I would like to mention: Dr Röckel’s* paper in the European Journal of Clinical Investigations five years ago stated that even after transplantation there are still subtle abnormalities pointing to autonomic nerve dysfunction. Have you had the opportunity of studying patients after transplantation in order to see whether the abnormality has gone or is still responsive to naloxone?

ZOCCALI Yes, we read the paper about the effect of renal transplantation on autonomic insufficiency and we found that the autonomic dysfunction is at least in part reversed by renal transplantation, but a subtle defect remains although it is a minor one.