Effect of timolol on changes in serum potassium concentration during acute myocardial infarction

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SUMMARY One hundred and six patients with acute myocardial infarction admitted to hospital within four hours after the onset of symptoms were randomised to treatment with intravenous timolol (54 patients) or placebo (52 patients). Serum potassium concentrations were estimated at frequent intervals during the first 24 hours of admission. Patients in both treatment groups, who did not receive subsequent diuretic treatment, had a transient rise in serum potassium concentration, which was maximal after four hours. This rise was abolished by diuretic treatment in the placebo group but not in the timolol group, in which there was a pronounced and prolonged rise in serum potassium concentration. The change in serum potassium concentration in the first four hours after admission correlated with cumulative creatine kinase release in the placebo group, but not in the timolol group. Hypokalaemia (serum potassium concentration $\leqslant 3.5$ mmol/l) occurred in 15 (28.8%) patients in the placebo group and in seven (13%) in the timolol group and was independent of infarct size. The frequency of hyperkalaemia was not increased in the timolol group.

By increasing the serum potassium concentration and preventing hypokalaemia, the use of intravenous timolol early in acute myocardial infarction may have important clinical effects in addition to reducing infarct size.

Low serum potassium concentrations have been associated with an increased frequency of cardiac arrhythmias in acute myocardial infarction,[1-3] and an inverse relation has been shown between serum potassium concentrations <5.2 mmol/l and the occurrence of ventricular fibrillation.[3] If the electrophysiological consequences of a low serum potassium concentration[4] are the cause of the increased frequency of arrhythmias, then prevention of hypokalaemia in the early phase of acute myocardial infarction, when arrhythmias are most frequent,[3] may be of importance. Serum potassium concentrations correlate inversely with catecholamine concentration,[5] which is increased in acute myocardial infarction,[6] and beta blocking drugs impair the potassium response to infused catecholamines in dogs[7] and healthy volunteers.[8] A small rise in serum potassium concentration

has been reported in hypertensive patients treated with beta blockers.[9] Intravenous treatment with beta blockers has been shown to have beneficial effects on infarct size in acute myocardial infarction.[10-12]

The present study was undertaken to examine the effects of intravenous beta blockade with timolol maleate on serum potassium concentration and to determine the incidence of hypokalaemia during the first 24 hours after hospital admission in patients with acute myocardial infarction.

Patients and methods

The study population was a cohort from a randomised, double blind placebo controlled study of the nonselective beta receptor blocking drug timolol maleate in acute myocardial infarction.[10] The complete study included 144 patients, of whom 106 with definite infarcts are reported here. Thirty eight patients were excluded because of protocol violation, incomplete data, death within the study period, or unconfirmed infarction. The protocol for the study and the demog-

raphic data of the patients have been fully reported previously.[10]

The patients were randomly allocated to intravenous treatment with timolol maleate or placebo. Treatment was started within five hours after the onset of symptoms with the injection of 1 mg of timolol or an equivalent volume of saline, and this was repeated 10 minutes later. After a further 10 minutes a constant infusion of timolol, 0·6 mg/hour, or an equal volume of normal saline was started and continued for 24 hours. Drugs, other than diuretics, known to affect the concentration of serum potassium were not used. Blood samples for measuring serum potassium concentration and creatine kinase activity were collected before the start of treatment with placebo or timolol, after two and four hours, and thereafter every four hours for the first 24 hours. The blood samples were immediately centrifuged and the serum frozen until the analyses were performed. Serum potassium concentration was analysed using flame photometry and creatine kinase concentration and cumulative release of creatine kinase as previously described.[10] Hypokalaemia was defined as a serum potassium concentration of ≤3·5 mmol/l and hyperkalaemia as a concentration of ≥5·2 mmol/l.

STATISTICAL ANALYSIS

Statistical tests were two tailed and p values <0·05 were considered to be significant. Student's *t* test was used to compare mean serum potassium concentrations between the treatment groups at comparable time intervals (unpaired *t* test) and also for comparing serum potassium concentrations before treatment with potassium values at subsequent time intervals within each treatment group (paired *t* test). Fisher's exact test was used to analyse categorical data. Linear regression analysis was used to correlate cumulative creatine kinase release and change in serum potassium concentration. Results are expressed as mean (standard error of the mean).

Results

Of the 106 patients in this study, 54 received timolol and 52 placebo. Data are given for all the patients together in each treatment group and according to whether or not diuretic treatment was given. In the timolol group 20 (37%) patients received a diuretic before the start of treatment or during the first 24 hours of the study; of these, 18 received frusemide (mean dose 63·6 (31) mg) and two thiazides. Twenty one (40%) patients in the placebo group received diuretics, of whom 19 received frusemide (mean dose 50·5 (18·1) mg) and two thiazides. The difference between the mean doses of frusemide in the two treatment groups was not significant.

Two patients in each treatment group also received oral potassium chloride supplements (placebo group 11 g and 6 g; timolol group 4 g and 1 g).

SERUM POTASSIUM CONCENTRATIONS

The mean serum potassium concentrations before treatment were comparable in the two groups; placebo 4·12 (0·07) mmol/l and timolol 3·99 (0·08) mmol/l. The mean time from the onset of symptoms of infarction to the start of treatment was 3·7 hours (placebo group) and 3·3 hours (timolol group) (NS). In the timolol group serum potassium concentrations rose to a significantly higher value compared with in the placebo group between four and 12 hours after the start of treatment. Patients treated with timolol had significantly higher serum potassium concentrations at 2, 4, 8, 12, 16, and 20 hours compared with before treatment. No such difference was seen in the placebo group (Fig. 1a).

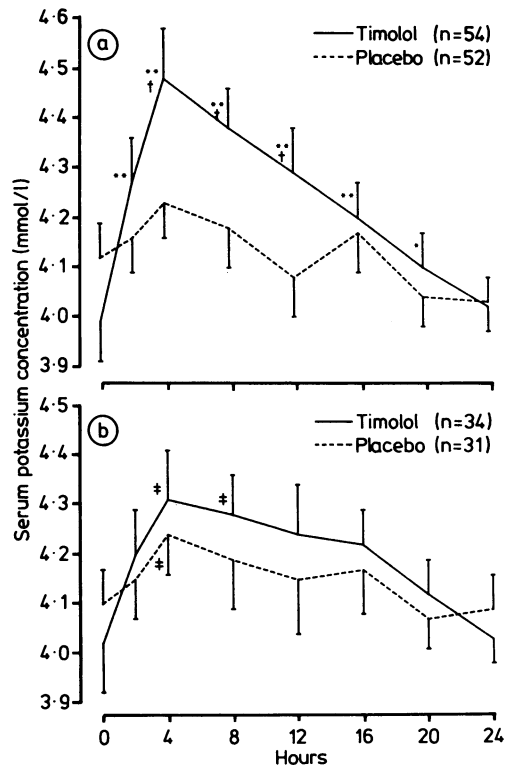In the patients not treated with diuretics before or

Fig. 1 *Mean (SEM) serum potassium concentration during 0–24 hours of drug administration in (a) all patients and (b) patients not treated with diuretics either on admission or during the first 24 hours.* *p<0·05; **p<0·01 comparison with baseline; †p<0·05 comparison between timolol and placebo groups; ‡p<0·05 each time interval compared with baseline.

Table 1   *Mean serum potassium concentrations (mmol/l) for patients treated with intravenous frusemide on admission and during the first 24 hours. Values are mean (SEM)*

Treatment group	Before treatment	After treatment (hours)				
		2	4	8	12	24
Placebo (n=15)	4·22 (0·17)	4·05 (0·14)	4·11 (0·2)	4·08 (0·14)	3·97 (0·15)*	3·89 (0·1)*
Timolol (n=12)	3·71 (0·17)	4·12 (0·2)*	4·63 (0·25)*	4·29 (0·18)*	3·93 (0·14)	3·95 (0·2)

*p<0·05 within group comparison with pretreatment values.

during the first 24 hours there was a significant increase from pretreatment values in mean serum potassium concentration in the placebo group at four hours and in the timolol group at four and eight hours (Fig. 1b). The increase was greatest in the timolol group, but there was no significant difference between the placebo and timolol group at any time. The probability of a difference between treatment groups between two and 24 hours was 0·16 by repeated measures analysis of variance.

The mean serum potassium concentration fell in patients in the placebo group who were treated with intravenous frusemide on admission and during the first 24 hours of the study. Compared with pretreatment values serum potassium concentration rose significantly at two hours in the patients in the timolol group who received frusemide (Table 1). The mean frusemide dosage was identical in the two treatment groups on admission and during the study. The mean cumulative creatine kinase release for these patients was 2290 (406) U/l in the placebo and 2121 (407) U/l in the timolol group (NS).

HYPOKALAEMIA
Timolol significantly reduced the incidence of hypokalaemia during the first 24 hours of treatment. During 2–24 hours after the start of treatment, 15 patients became hypokalaemic with placebo treatment, with a total of 35 hypokalaemic samples, compared with seven treated with timolol, with a total of 18 samples (Table 2). Hypokalaemia occurred more often in patients treated with diuretics in both groups (Table 2), but the lower overall incidence of hypokalaemia was not related to the administration of diuretics (Table 2). The lowest serum potassium concentration was 2·7 mmol/l. Hypokalaemia was transient, and only one patient had hypokalaemia in five consecutive samples during the 24 hour sampling period. In most patients with hypokalaemia this was noted in at most two or three consecutive samples (a duration of 6–12 hours).

Fourteen of 106 (13·2%) patients were hypokalaemic before treatment, three in the placebo and 11 in the timolol group. Only two of the 14 hypokalaemic patients had been treated with diuretics before admission. Of the 11 patients in the timolol

group who were hypokalaemic before treatment, four had hypokalaemia at least once during treatment compared with one of three patients in the placebo group.

HYPERKALAEMIA
Six patients in the placebo and 10 in the timolol group had one or more hyperkalaemic samples during the study period (NS). Hyperkalaemia was transient; one patient in each group had four consecutive high serum potassium values, and one patient in each group had three consecutive high values. The highest value of serum potassium was 6·95 mmol/l. The incidence of hyperkalaemia before treatment was six of 106 (5·7%) patients (three in each treatment group), none of the values being ≥6·0 mmol/l. The number of patients with serum potassium values ≥6·0 mmol/l with treatment were three (5·8%) in the placebo and three (5·6%) in the timolol group.

CUMULATIVE CREATINE KINASE RELEASE AND SERUM POTASSIUM CONCENTRATION
The change in serum potassium concentration before treatment and at four hours (corresponding to the mean peak rise) in each patient not treated with intravenous frusemide was related to infarct size as estimated by cumulative creatine kinase release (Fig. 2). There was a significant correlation in both treatment groups, but a weaker correlation was obtained in the timolol group.

The mean cumulative creatine kinase release for

Table 2   *Patients with hypokalaemia (serum potassium concentration ≤3·5 mmol/l) on one or more occasions during the first 2–24 hours of timolol or placebo administration. Figures are numbers (percentages) of patients*

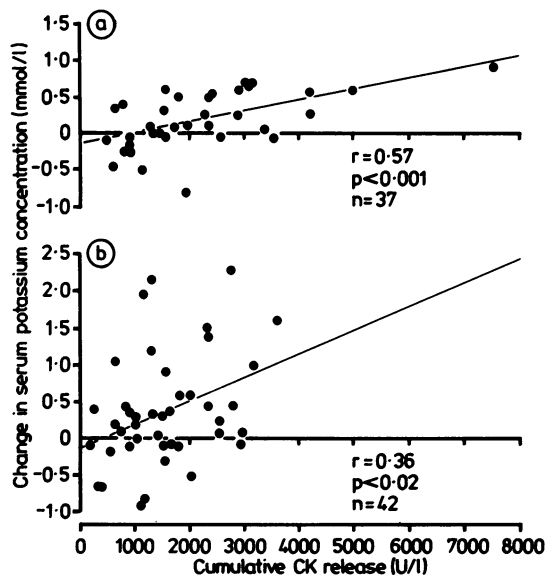|	Placebo	Timolol	p value
All patients	52	54	
With hypokalaemia at:			
2 hours	7 (13·5)	2 (3·7)	NS
2–4 hours	8 (15·4)	3 (5·6)	NS
2–8 hours	9 (17·3)	3 (5·6)	<0·05
2–24 hours	15 (28·8)	7 (13)	<0·05
Patients taking diuretics	21	20	
With hypokalaemia at 2–24 hours	8 (38·1)	4 (20)	NS
Patients not taking diuretics	31	34	
With hypokalaemia at 2–24 hours	7 (22·2)	3 (8·8)	NS

Fig. 2 *Change in serum potassium concentration from before treatment to four hours after treatment in relation to cumulative creatine kinase (CK) release in (a) placebo and (b) timolol patients not treated with diuretics.*

patients not treated with diuretics (Fig. 2) was 2056 (199) U/l in the placebo and 1323 (128) U/l in the timolol group (p<0·01). The mean cumulative creatine kinase release for patients treated with diuretics was 2571 (415) U/l in the placebo and 2181 (264) U/l in the timolol group (NS).

In Table 3 cumulative creatine kinase release is related to potassium concentration. Infarct size was not significantly different between hypokalaemic patients and patients with serum potassium concentrations ≥3·6 mmol/l.

Discussion

This study has shown that early intervention with timolol during the evolution of an acute myocardial infarction increases the serum potassium concentration and reduces the incidence of hypokalaemia. The

Table 3 *Cumulative creatine kinase release (U/l) according to serum potassium concentrations in patients treated with placebo or timolol. Values are mean (SEM)*

	Serum potassium concentration (mmol/l)	
	≤3·5	≥3·6
Placebo	2068 (250) n=15	2344 (272) n=37
Timolol	1675 (728) n=7	1676 (125) n=47

reduction in hypokalaemic episodes in the timolol group occurred despite there being more hypokalaemic patients in this group before treatment. The treatment groups were otherwise well balanced with respect to heart failure[10] and diuretic treatment.

A transient rise in mean serum potassium concentration occurred in both the placebo and timolol groups and reached a maximum four hours after treatment—that is, nearly eight hours after the estimated onset of infarction. The serum potassium concentration returned to pretreatment values in both treatment groups within 24 hours without any change in the regimen of the test drugs.

Treatment with diuretics before or during the first hours after admission abolished the rise in mean serum potassium concentration in the placebo but not in the timolol group (Fig. 1a). Treatment with diuretics alone reduced the mean serum potassium concentration but it still increased in patients treated with diuretics and timolol (Table 1). Diuretics increased and timolol reduced the number of patients with hypokalaemia (Table 2), indicating that timolol and diuretics have opposing effects on the serum potassium concentration.

The mechanism behind the initial rise in serum potassium concentration is unclear. At the onset of ischaemia there is a rapid loss of intracellular potassium in the myocardium, which causes a rise in coronary sinus potassium.[13 14] An average infarction of about 40 g of myocardium with about 0·1 mmol of potassium per gram could add about 4 mmol of potassium to the bloodstream. This mechanism may explain the transient rise in serum potassium concentration and the positive correlation between the ultimate infarct size and the change in serum potassium concentration.

The initial rise in serum potassium concentration is unlikely to have been caused by heart failure with poor peripheral circulation, as clinically overt heart failure did not occur in the patients shown in Fig. 1b. Nevertheless, certain mechanisms leading to increases in serum potassium concentration, as occur during exercise,[15] remain to be elucidated, and these may also contribute to the rise in serum potassium concentration seen during myocardial infarction in our study.

It has been clearly shown in normal volunteers that serum potasssium concentrations fall promptly in response to infusion of adrenaline.[8 16] If there was an outpouring of catecholamines in the immediate phase of evolving infarction then this would cause a fall in serum potassium concentration. This has been clinically described as an acute hypokalaemic syndrome and appears to occur in many acutely ill patients as well as in patients with acute infarction.[17] As the potassium concentrations in our study were not meas-

ured until almost four hours after the onset of symptoms it is quite likely that we missed the early and more pronounced falls in potassium concentration and that the early rise in potassium concentration in the placebo group was a recovery phenomenon from catecholamine induced hypokalaemia. The greater rise seen in the timolol group could be a combination of this recovery effect together with a specific drug effect on potassium movement.

Timolol may affect serum potassium concentration in several ways. A rise in serum potassium concentration is opposed by the adrenaline mediated peripheral uptake of potassium in skeletal muscle.[18] This beta$_2$ receptor effect of adrenaline is blocked by timolol.[8] A rise in potassium concentration in the timolol group may also partly have resulted from unopposed alpha effects of adrenaline.[7] A loss of intracellular potassium is readily reversible after the reversal of ischaemia.[13] A reversal of ischaemia caused by timolol, as occurred according to the accelerated reduction in the electrocardiographic ST segment elevations[10] and the 36% reduction in cumulative creatine kinase release, would be expected to reduce the rise in serum potassium concentration. Thus several mechanisms could have caused the weaker correlation between cumulative creatine kinase release and the change in serum potassium concentration in the timolol group compared with the placebo group. Concentrations of renin, aldosterone, and insulin were not measured in this study, but others have shown the effect of beta$_2$ blockade on serum potassium to be independent of these hormones.[16 18] Urinary potassium output was not measured, but a negative potassium balance has previously been found during beta blocker treatment.[9]

The clinical implications of the alterations in serum potassium concentration during evolving myocardial infarction and the effect of timolol on these alterations are not clear, and electrophysiological studies in non-ischaemic hearts suggest that hypokalaemia may cause cardiac arrhythmias.[4 19] An inverse relation between serum potassium concentration <5·2 mmol/l and the occurrence of ventricular fibrillation in acute myocardial infarction has been reported.[3] This does not, however, imply a definite causal relation. On the other hand, if the relation is causal then even the moderate differences in serum potassium concentration between the treatment groups in this study may be of importance.[3]

Hyperkalaemia is not associated with an increased likelihood of ventricular arrhythmias at concentrations seen during acute myocardial infarction.[1-3 17] In this study, hyperkalaemia occurred mostly at serum potassium concentrations of <6·0 mmol/l and is therefore not a problem in patients selected for treatment with beta blockers during acute myocardial

infarction. More severe hyperkalaemia may, however, be expected in patients with acidosis and renal failure.

Hypokalaemia was not related to infarct size, and the timolol treated patients with a serum potassium concentration ≥3·6 mmol/l did not have significantly larger infarctions than the hypokalaemic patients in the same treatment group (Table 3). The protective effect of timolol on hypokalaemia was therefore not restricted to those with large infarctions.

Although higher circulating catecholamine concentrations are seen in large[6] rather than small infarctions, thus tending to decrease serum potassium concentrations,[5] hypokalaemia is opposed by a rise in serum potassium concentration probably caused by the release of potassium from the ischaemic myocardium. In patients not treated with diuretics the net result, however, is a larger initial increase in serum potassium concentration in the large compared with the small infarctions. Blocking the adrenaline induced peripheral uptake of serum potassium concentration with timolol did not lead to significantly higher serum potassium concentrations compared with placebo, but the comparison is confounded by the significantly smaller infarct size in the timolol group. Patients with the large infarctions are more likely to receive intravenous diuretic treatment, which may initially abolish the rise and subsequently decrease serum potassium concentrations, as was seen in the placebo group. Thus a balance exists between the forces increasing and decreasing serum potassium concentrations, which as a result, when the balance is disturbed, does not confine hypokalaemia to any particular infarct size at least during the early stages of myocardial infarction.

In summary, a moderate and transient rise in serum potassium concentration, which is quantitatively related to infarct size, is seen during the evolution of acute myocardial infarction. The rise is counteracted both by treatment with diuretics, which also cause episodes of hypokalaemia, and by a tendency for hypokalaemia, which is probably caused by sympathetic stimulation. Timolol causes a rise in serum potassium concentration irrespective of diuretic treatment and prevents hypokalaemia. This effect may have important clinical implications for myocardial ischaemia, arrhythmias, and sudden death.

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