Mangafodipir as a cardioprotective adjunct to reperfusion therapy: a feasibility study in patients with ST-segment elevation myocardial infarction

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Sponsor: PledPharma AB

Aim

The aim of the present study was to examine the feasibility of applying the catalytic antioxidant mangafodipir [MnDPDP, manganese (Mn) dipyridoxyl diphosphate] as a cardioprotective adjunct to primary percutaneous coronary intervention (pPCI) in patients with ST-segment elevation (STE) myocardial infarction (STEMI). Both MnDPDP and a metabolite (Mn dipyridoxyl ethyldiamine) possess properties as mitochondrial superoxide dismutase mimetics and iron chelators, and combat oxidative stress in various tissues and conditions.

Design

The study was conducted in a single-blinded manner, included 10 MnDPDP-treated and 10 placebo-treated patients during their first episode of STEMI. Patients were enrolled within 6 hours after onset of chest pain and documented ST-segment elevation and absence of blood flow to the region at risk at angiography (TIMI-flow 0; changed to 0-1 during the study). Just prior to the reperfusion by PCI, patients received either 2 μmol/kg MnDPDP or saline (placebo) as an intravenous slow injection (2-5 min).

The primary endpoint was the plasma biomarkers CK-MB and cTnT measured at 6 hours after reperfusion . The secondary endpoints were (i) CK-MB and cTnT repeatedly over 48 hours. (ii) resolution of ST-segment elevation at 6 hours and 48 hours. And (iii) infarct size and cardiac MRI (CMR) after 6-10 weeks (amended to 7±1 days after 8 patients had been enrolled).

The

Methods

Twenty patients, admitted to the County Hospital of Jönköping, Sweden, were recruited to MANAMI 1-09 between December 2009 and June 2013. They all suffered their first attack of AMI and were apparently free from angina pectoris.

Inclusion criteria were:

1. Males 40-80 and females 50-80 years with first severe coronary attack.
2. Chest pain up to 6 hours.
3. ST segment elevation (≥ 0.2 mV in two neighbouring anterior and inferior wall leads.
4. Decided for treatment by primary PCI.
5. TIMI grade 0 flow in the occluded LAD or RCA artery
6. Written informed consent.

Exclusion criteria.

1. Previous coronary artery bypass operation.
2. Previous AMI.
3. Chest pain more than 6 hours.
4. Angina within 48 hours before admission.
5. Cardiac arrest and cardiogenic shock.
6. Occlusion of the left main stem, circumflex and right coronary arteries at angiography.
7. Known hypersensitivity to mangafodipir (as contrast agent for MRI).
8. Received mangafodipir ≤ 5 weeks before admission
9. History of prior serious allergic or pseudo-allergic reaction

10. Severely reduced liver or renal function
11. Any other serious illness or medical condition
12. Fertile females
13. Phaeochromocytoma

The primary endpoint was peak release at 6 h of high-sensitive cardiac troponin T (TnT) and creatine kinase isoenzyme muscle-brain (CK-MB).

Secondary endpoints included accumulated biomarker release, resolution of STE, and IS and LV ejection fraction (LVEF) assessed by cardiac magnetic resonance (CMR). Baseline characteristics of patients are provided in Table 1.

The study was performed according to the guidelines of the regional ethical review board in Linköping and the Helsinki declaration. Patients received a study number after admission and were preliminary enrolled after the diagnosis of STEMI was made. They were then informed orally about potential participation in the study. Oral and written consent was obtained after angiographic detection of an occluded coronary artery or artery branch. Patients were then allocated into a treatment group (n =10) or a placebo group (n =10) following a randomized enrolment list kept in numbered envelopes in the PCI laboratory. Allocation was blinded for both the patient and the interventionist. However, the interventionist, but not the (well-hidden) patient, might become unblinded after an i.v. infusion of test substance (yellow MnDPDP vs. colourless saline). Investigators of endpoints were only informed about the study number of each patient and were thus blinded to group allocation.

Immediately prior to balloon inflation, the treatment group received a hand-held i.v. infusion of MnDPDP 2.0 mmol/kg b.w. (0.2 mL/kg b.w.) over 2–5 min, whereas the placebo group received saline (0.2 mL/kg b.w.). The pPCI procedure was regarded as satisfactory when a TIMI grade 2–3 was achieved. Further treatment of both groups was given according to the current ESC guidelines for management of STEMI.

Blood samples were drawn for analysis of TnT and CK-MB prior to pPCI and intermittently over 48 h thereafter. Troponin T and CK-MB were analysed by conventional techniques and results obtained according to hospital routine. Maximal STE above the isoelectric line was measured 60 ms after the J point using a computer diagnostic program (Marquett SL-12, GE Healthcare). ST-segment elevation prior to reperfusion and at 6 and 48 h thereafter was expressed in mV.

Table 1 Baseline characteristics

Characteristics	Placebo	MnDPDP
Number	10	10
Age (years)[a]	60.1 ± 10.8	64.1 ± 8.7
Male/female	10/0	8/2
Body mass index (%)[a]	25.9 ± 2.5	27.7 ± 3.3
Previous CHD	1	0
Smoking	2	4
Hypertension	1	3
Haemoglobulin (g/L)[a]	155 ± 11	152 ± 14
Creatinine (μmol/L)[a]	87 ± 22	82 ± 17
Total cholesterol (mmol/L)[a]	4.9 ± 0.7	5.6 ± 0.7
LDL-cholesterol (mmol/L)[a]	2.9 ± 0.7	3.4 ± 0.6
Occluded vessel	LAD 6/RCA 4	LAD 6/RCA 3/LCX 1
TIMI grade 1 before pPCI	3	0
TIMI grade 2 after pPCI	1	0
Ischaemic time (min)[a]	144 ± 72	206 ± 82

Cardiacmagnetic resonance protocol and analysis

Cardiac magnetic resonance with measurements of IS and LVEF was scheduled to be performed at routine clinical follow-up (6–10 weeks) after the coronary attack (late CMR). After eight patients had been included, the time point for CMR was changed to within 1 week (7+1 days) post-STEMI (early CMR). The reason for change of the time point was to gain information about the myocardium at risk (MAR), utilizing a then recently adopted T2-weighted imaging sequence. All 10 patients in the MnDPDP group underwent CMR (six early and four late), but only 8 patients in the placebo group (four early and four late) as two patients refrained from scanning.

Cardiac magnetic resonance was performed on a 1.5-T scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) with use of a six-element phased-array body matrix coil. Ten to 12 short-axis slices were applied to cover the left ventricle from base to apex, with identical positions for all relevant examinations. Left ventricular chamber volumes, LVEF, and LV muscle volume and mass were assessed in short- and long axis images by use of an ECG-triggered balanced steady-state pre-cession cine CMR sequence. Late gadolinium-enhanced (LGE) images for measurement of IS were obtained 10 min after i.v. injection of 0.2 mmol/kg b.w. gadopentate dimeglumine (Magnevist, Bayer Schering Pharma, Berlin, Germany). An ECG-triggered phase-sensitive inversion recovery and a T2-weighted imaging sequence were used to measure the MAR. All CMR sequences were analysed using a computer freeware 'Segment' v 1.9 R2939 (http://segment.heiberg.se).29 One observer analysed all CMR images blinded from clinical data. T2-weighted measurements of the MAR were also undertaken by a second investigator blinded from the other investigator's results.

Myocardial volumes (mL) were converted to mass (g) by using the factor 1.05. Infarct size and MAR were expressed in percentage of the total LV myocardium. The myocardial salvage index (MSI) was calculated as follows: MAR 2 IS/MAR. The presence of microvascular obstruction (MVO) and thrombi in the LV cavity was noted in a yes or no manner without quantification of volumes.

Analysis of data

All data and results obtained were analysed by use of standard nonparametric and parametric programs using the Stat Prism software version 6.03 (Graph Pad Software, Inc., La Jolla, CA, USA). Statistical significance was noted when Mann–Whitney tests reported two-tailed P , 0.05. Results are presented as the median + interquartile range in figures and tables, and as the mean values in the text.

Results

Background characteristics

Patient background was similar in both groups, except for two main factors (Table 1). First, duration of ischaemia (symptom-to-balloon time) was significantly (P =0.037) longer in the MnDPDP group (mean 206 min) than the placebo group (mean 144 min). Secondly, some small residual CBF before pPCI was present in placebo hearts (TIMI grade 1 in three patients), but not in MnDPDP hearts. Also, the placebo group consisted of 10 males, whereas the MnDPDP group included eight males and two females. At admission, two patients in the placebo group were treated with statins for cardiovascular disease and a third patient was treated with corticosteroids for Crohn's disease of the colon. In the MnDPDP group, two patients were on treatment with angiotensin-converting enzyme inhibitors either combined with a calcium antagonist or with a statin and a β-adrenergic antagonist.

Clinical observations

The 2–5 min i.v. infusion of MnDPDP prior to balloon inflation was well tolerated in all patients without any changes recorded in blood pressure, heart rate or ECG. Hypotension or arrhythmias were not encountered during administration of MnDPDP as well as saline placebo. During the stay in hospital after pPCI, no differences in haemoglobin, creatinine, liver enzymes, blood pressure, occurrence of arrhythmias or heart failure were observed. Especially, the incidence of heart failure routinely assessed by echocardiography was similar in both groups as expressed by the scale no/mild/moderate, placebo 2/3/5 and MnDPDP 2/4/4. There were no differences in medical treatment at peri-PCI or at discharge.

Biomarker release

Peak release to plasma of cardiac TnT (cTnT) and CK-MB revealed no differences between groups, whether prior to reperfusion or thereafter (Figure 1). Mean cTnT values were: at 6 h placebo 6063 ng/L and MnDPDP 6473 ng/L; and at 48 h placebo 3532 ng/L and MnDPDP 2906 ng/L. Mean CK-MB values were: at 6 h placebo 258 mg/L and MnDPDP 288 mg/L; and at 48 h placebo 14 mg/L and MnDPDP 13 mg/L. The mean accumulated (0–48 h) releases were also much similar: for cTnT, placebo 211526 ng/L and MnDPDP 207094 ng/L; and for CK-MB, placebo 4850 mg/L and MnDPDP 4730 mg/L.

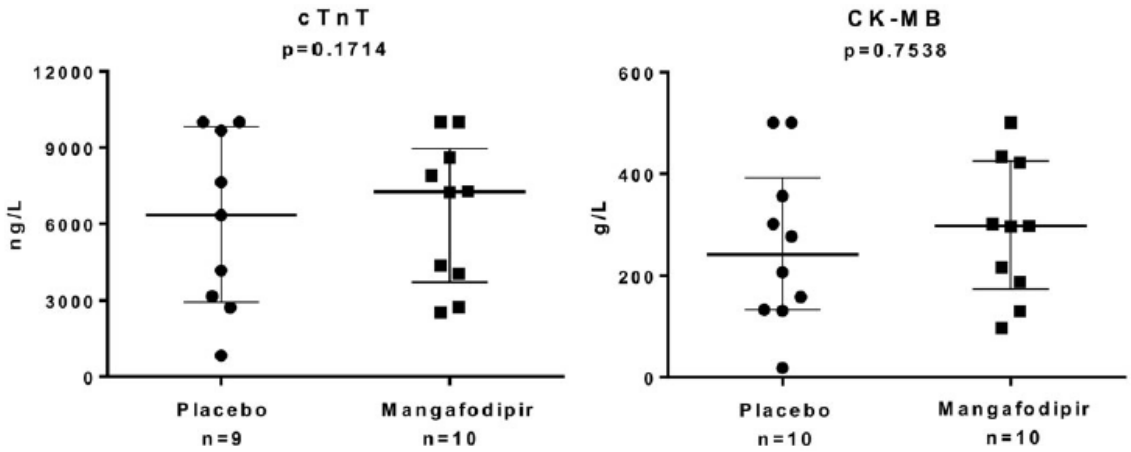

Figure 1 Release of cardiac troponin T (cTnT; ng/L) and creatine kinase isoenzyme muscle-brain (CK-MB; mg/L) at 6 h of reperfusion

ST-segment elevation and resolution

ST-segment elevation was closely similar in both groups prior to pPCI (Figure 2). Following reperfusion, a tendency (n.s.) to a more rapid (6 h) and more complete (48 h) STE resolution might be observed with MnDPDP. Mean STE resolutions were: at 6 h, placebo 69.8% and MnDPDP 81.9% (P =0.138); and at 48 h, placebo 73.1% and MnDPDP 84.3% (P=0.077).

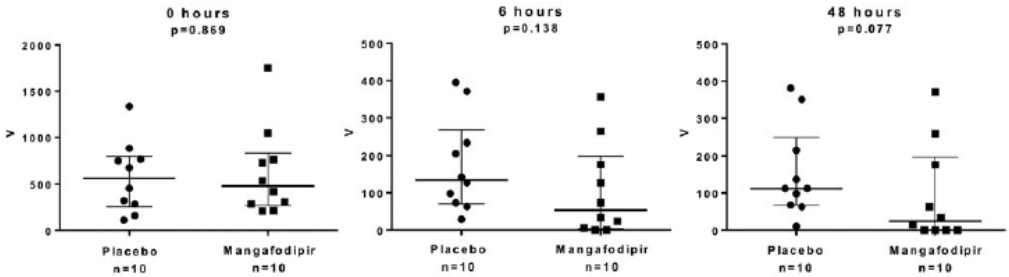

Figure 2 ST-segment elevation (mV) prior to and following reperfusion.

Cardiac magnetic resonance examinations

The mean IS was lower (n.s.) in the MnDPDP group, 26.2%, than in the placebo group, 32.5%, and the mean LVEF was higher (n.s.) with MnDPDP, 47.7%, than with placebo, 41.8% (Figure 3). Left ventricular volume assessments revealed higher (n.s.) mean values of LV end-diastolic volume and LV end-systolic volume in placebo hearts than in the MnDPDP-treated hearts (Table 2). Microvascular obstruction was present in 3 of the 8 placebo hearts and in 3 of the 10 MnDPDP hearts. Thrombi in the LV chamber were significantly more frequent in placebo hearts (5 of 8) than in MnDPDPhearts (1 of 10). Collected data from both groups (n =18) showed a highly significant correlation (P= 0.0009) between IS and LVEF.

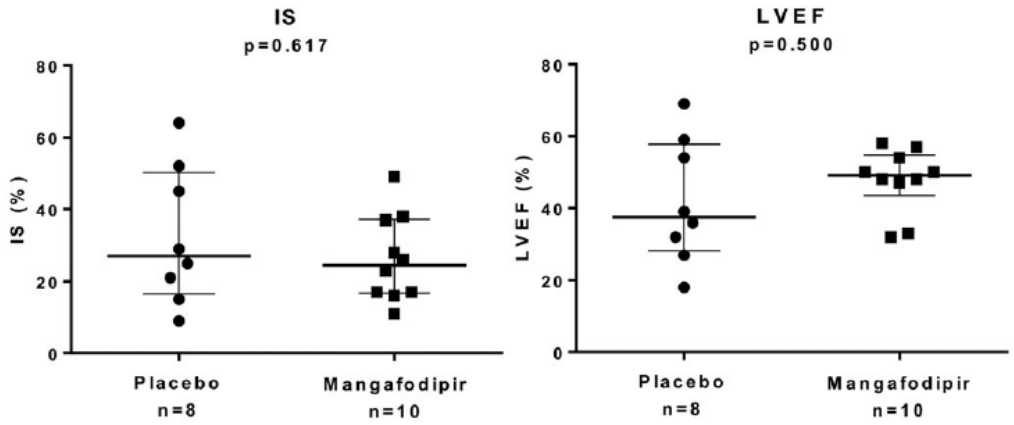

Figure 3 Infarct size (IS) and left ventricular ejection fraction (LVEF). Infarct size was measured by LGE–CMR and expressed as percentage of LV muscle mass.

Table 2 Cardiac magnetic resonance examination

Group	IS (%)	LVEF (%)	LVED (mL)	LVESV (mL)	MAR (%)	MSI (%)	MVO present	LVO Thrombus
Placebo	27.0 (17.1-37.3)	37.5 (28.3-57.8)	210 (158-2349	134 (69-150)	56.5 (42.5-64.5)	33.5 (8.3-44.5)	3	5
	n = 8	n = 8	n = 8	n = 8	n = 4	n = 4	n = 8	n = 8
MnDPDP	24.5 (16.8-37.2)	49.0 (43.5-54.8)	192 (136-212)	95 (65-130)	41.5 (31.0-56.0)	35.0 (22.5-44.3)	3	1
	n = 10	n = 10	n = 10	n = 10	n = 6	n = 6	n = 10	n = 10
P-value	0.617	0.500	0.395	0.372	0.214	0.971	0.999	0.043

IS = Infarct Size; LVEF = left ventricular ejection fraction; LVED = Left Ventricular End Diastolic; LVESV = left ventricular end systolic volume; MAR = myocardium at risk; MSI = myocardial salvage index; MVO = Microvascular obstruction); LVO = Left ventricular opacification

Early CMR measured the MAR to provide a calculation of the MSI while also measuring IS). Despite the small number, a tendency (n.s.) to a higher mean MAR value might be seen in the placebo group (54.5%, n =4) than in the MnDPDP group (42.2%, n = 6). Mean MSI values were almost similar in both groups (MnDPDP 32.2% and placebo 28.8%)

Safety

Patients tolerated intravenous infusion of MnDPDP well without side-effects.
The main finding was that MnDPDP can be safely administered i.v. as an adjunct to pPCI in patients during AMI. This was expected from prior clinical reports, but the study became the first documentation of MnDPDP given safely as a brief i.v. infusion to critically ill cardiac patients. Reported adverse reactions with MnDPDP as a contrast agent releasing paramagnetic Mn ions for MRI are mild and related to NO-induced vasodilation like flushing and headache. Also, the drug may induce hypotension followed by an adrenergic activation (by Mn ions) with transient rise in blood pressure and heart rate. Neither of these possibilities nor allergic reactions were observed. However, the administered dose was lower (2 mmol/kg) than commonly applied for MRI (5–10 mmol/kg).

Conclusion

The median ischemic time prior to PCI was 195 minutes in MnDPDP group, whereas the corresponding time in the placebo group was 144 minutes (p= 0.0387). Furthermore, all patients in the MnDPDP had TIMI-flow o, whereas three in the placebo group had TIMI flow 1.

No significant differences were between groups regarding troponin T or CK-MB at any time point. There was a clear tendency of a better resolution of ST-segment elevation (STR) in the MnDPDP group compared to the placebo group. At 0 hours the interquartile range (IQR) was 270-866 µV in MnDPDP and 256 - 800 µV in the placebo group, whereas the corresponding figures at 48 hours were 0 – 197 µV and 67 – 249 µV respectively. At 48 hours the median STR in the placebo group was 74.5% whereas the corresponding value in the MnDPDP was 90.5% (p=0.0766 two-tailed Mann Witney: P= p=0.0383; one-tailed).

Despite the significant difference in ischemic time, CMR at ambulant control showed a tendency of smaller infarcts in MnDPDP-treated compared to placebo-treated patients 26.2% vs. 32.5% (means), respectively, i.e. corresponding to 19.4% reduction in infarct size) and improved cardiac ejection fraction, 47.7% vs 41.8% (means), respectively. Microvascular obstruction (MVO) and left ventricular thrombus were more common in the placebo group compared to the MnDPDP group.

In conclusion, this small feasibility study provides preliminary proof-of-concept for MnDPDP as an agent protecting against reperfusion injuries in STEMI patients during PCI.