

Pharmacokinetics of Intraluminally Administered Serum Papaverine for Spasm Prophylaxis of the Internal Mammary Artery

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ABSTRACT

Background: Papaverine (Paveron NTM Linden Arzneimittel Vertrieb GmbH, Germany) is a widely used agent for preventing spasm in mammary artery preparations. The question addressed in this study is whether the intraluminal administration of papaverine can result in detectable absorption of the drug into the systemic arterial circulation.

Methods: In 15 patients (age 65 ± 6 years; body mass index 28.9 ± 3.7), an internal mammary artery (IMA) was prepared during coronary artery bypass grafting (CABG). A maximum of 3 mL of a 1 mg/1 mL diluted papaverine solution was injected intravascularly (intraluminally) for spasm prophylaxis. The IMA was closed proximally and distally with bulldog clamps. Blood samples were taken immediately after administration (T1), after 20 minutes (T2), and at the end of the operation (T3). Samples were measured in a liquid chromatography--tandem mass spectrometry (LC-MS/MS) system consisting of a binary pump from Agilent (Waldbronn, Germany) coupled to a high-throughput screening (HTS) PAL injection system (CTC, Zwingen, Switzerland) and a tandem mass spectrometer (API 4000, AB Sciex, Darmstadt, Germany). Papaverine was analyzed in positive mode using an electrospray ion source. Quantitation was performed using Analyst 1.5 software (AB Sciex, Darmstadt, Germany).

Results: The newly developed LC-MS/MS method was successfully established for the detection of papaverine in plasma samples. The highest plasma papaverine levels were determined at time point T1 (mean 54.7 ± 39 ng/mL, range 16.6-179 ng/mL). The concentration was already halved 20 minutes after administration (T2) (mean 23.3 ± 2 ng/mL, range 4.6-118 ng/mL). Because of the short half-life and the hemodilution in the extracorporeal circulation, at the end of the operation papaverine (T3) had already fallen to just above

the limit of detection (mean 4.1 ± 3.9 ng/mL, range 1.3-16.9 ng/mL). At time point T1, a significant negative correlation was determined between plasma levels and systemic diastolic, but not systolic, blood pressure.

Conclusion: Papaverine was successfully determined systemically in plasma by LC-MS/MS after intraluminal administration in the IMA. Systemic circulatory effects are dependent on the detected quantity. Group size and the absence of a control group are considerable limitations.

INTRODUCTION

Since the first clinical use of aortocoronary venous bypass at the end of the 1960s and the introduction of the left internal mammary artery (IMA) as bypass material, the principle of coronary revascularization by bypass surgery has become established alongside pharmacologic and interventional cardiology as one of the mainstays of the treatment of coronary heart disease. More than 55,000 coronary operations are performed in Germany every year [Gummert 2011]. Early postoperative mortality has been progressively reduced by means of improved surgical techniques and optimized perioperative therapy. Excellent long-term results, with patency rates of more than 90% after 5 and 10 years achieved using the IMA, prompted surgeons to perform complete cardiac revascularizations mainly using arterial conduits [Rastan 2006]. The IMA has been used routinely for years to treat the stenotic left anterior descending artery (LAD). Revascularization with at least 1 IMA is the gold standard in cardiac bypass treatment [EACTS 2010]. The radial artery is also used as an arterial conduit. Complete arterial revascularization is now also regarded as a safe standard method for elderly patients (>70 years old). Problems with arterial coronary revascularization arise mainly because of the limited amount of available graft material, the increased vulnerability of the arteries (compared to a venous graft) with the resulting more difficult preparation, and the risk of vascular spasms. Intraluminal administration of papaverine is now successfully used in coronary surgery to control the increased tendency of the IMA to spasm [Mills 1975; Mulay 1997] and to overcome venous spasm, for example when creating an arteriovenous fistula to prevent postoperative early thrombosis. The dilatation of the vascular graft produced by papaverine simultaneously

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facilitates preparation. Local or intraluminal papaverine is used as a standard method in bypass operations in numerous cardiac surgery departments [Dregelid 1993]. In bypass surgery, papaverine is currently the standard medication used as an intraluminal vasodilator [Sasson 1995]. The topical and intraluminal administration of papaverine has been used successfully to prevent spasm and secondary traumatization during and after the harvesting of venous and arterial vascular grafts and the subsequent surgical anastomosis and to increase the flow rate [Yavuz 2001]. The equivalence, if not superiority, of papaverine over other vasodilators has been demonstrated in several studies. Studies with various vasodilators, in which no significant increases in flow were achieved in comparison to saline, are the exception [Nili 1999]. The vasodilator effects of papaverine are pronounced and clinically relevant. For example, in coronary artery bypass grafting (CABG), intraluminal injection of papaverine was followed by an increase in the flow rate by 285% of baseline [Goldman 1982]. The flow rate can be doubled both with papaverine and with combinations of nitroglycerin plus verapamil [He 1994]. The different routes of administration comprise local, superficial (topical), or intraluminal (intravascular) use of papaverine. Direct, intraluminal administration has been subject to 2 main criticisms. First, injection has been reported to cause endothelial damage to the IMA [Cooper 1995]. Second, with intravascular administration, a systemic effect cannot be ruled out. This takes the form of vasodilation with a possible decrease in blood pressure [Jahr 1995]. If the graft is closed with a bulldog clamp proximally, i.e., close to the origin of the subclavian artery, absorption of the drug into the patient's systemic circulation, while unlikely, is nonetheless possible. This hypothesis was the starting point for the question addressed in the study reported here: Can the intraluminal administration of papaverine lead to detectable diffusion of the drug into the systemic arterial circulation? This question was investigated at 3 different time points.

METHODS

Papaverine Hydrochloride

Papaverine is an alkaloid of opium derived chemically from benzyl-iso-quinoline. Papaverine exerts its effect directly on vascular smooth muscle cells. [Hartmann 1997; HSDB 2002]. Papaverine has vasodilator properties resulting from its direct relaxant effect on vascular smooth muscle. Studies on isolated coronary arteries have shown that the muscle relaxant effect is due to inhibition of phosphodiesterase resulting in an increase in the cytosolic cAMP concentration [Yavuz 2001]. Metabolism takes place very rapidly after hepatic extraction, mainly by demethylation to less- or nonactive metabolites. Excretion is primarily as a conjugate via the renal route. However, elimination is not substantially changed in anuria. Protein binding is 97%. After intravenous administration of 1 mg/kg papaverine, the volume of distribution is 1.52 ± 0.45 L/kg. When a heart-lung machine is used, however, the volume of distribution is significantly increased after intravenous administration. Correspondingly, the half-life of 2.8 ± 0.28 hours

is increased compared to 1.3 ± 0.25 hours without a heart-lung machine. The elimination the half-life of papaverine is reported by other investigators as approximately 2 hours and 0.5-2 hours, with considerable intraindividual variability.

Method of Measurement

We mixed 10- μ L plasma samples with 10 μ L internal standard (codeine-d3, 500 ng/mL in methanol), 90 μ L water, and 200 μ L protein precipitation solution (0.1 mol/L methanol:zinc sulfate 4:1, volume/volume). After vortexing and centrifugation, supernatant was evaporated under nitrogen at 45°C and reconstituted in 50 μ L 0.1% formic acid. Samples were measured in a liquid chromatography–tandem mass spectrometry (LC-MS/MS) system consisting of a binary pump from Agilent (Waldbronn, Germany) coupled to an HTC PAL injector system (CTC, Zwingen, Switzerland) and a tandem mass spectrometer (API 4000, AB Sciex, Darmstadt, Germany). Separation was performed on a Polar RP column (150 \times 2 mm, 4 μ m particle size) using gradient mode and water and acetonitrile, both containing 0.1% formic acid and 1 mmol/L ammonium formate, as mobile phases. Papaverine was analyzed in positive mode using an electrospray ion source. Quantitation was performed using Analyst 1.5 software (AB Sciex, Darmstadt, Germany) and the transition m/z 340.1 to 324.1. The coefficient of variation over the calibration range (0.1 to 150 ng/mL) was 15%.

Dosage

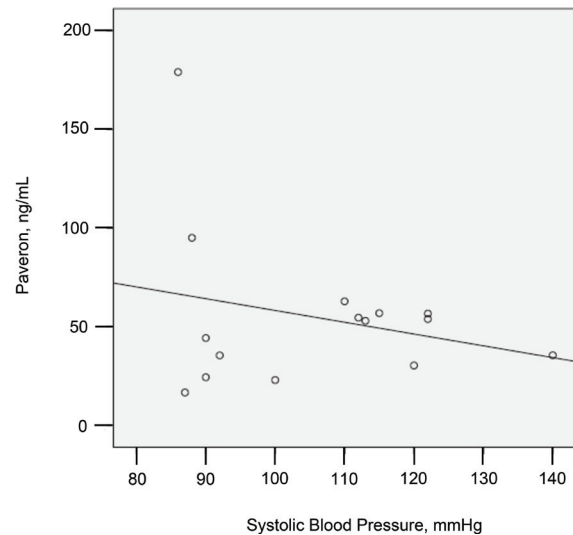
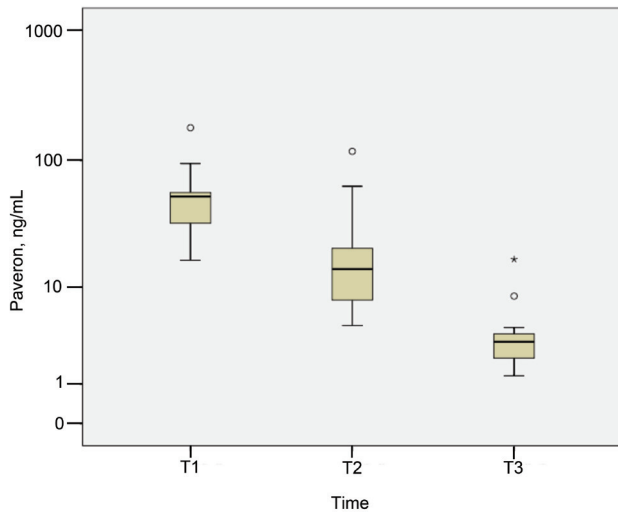
Papaverine is usually diluted in physiological NaCl solution: 1 ampoule of 2 mL Paveron N, equivalent to 50 mg papaverine hydrochloride, is mixed with 48 mL NaCl 0.9% to produce a final dilution of 50 mg/50 mL or 1 mg/1 mL. In most cases, 3 mL (equivalent to 3 mg papaverine hydrochloride) of the final dilution solution is instilled slowly into the distal end of the dissected arterial blood vessel, where it remains intraluminally as a result of the centrally acting arterial pressure. The exposure time to the solution is about 20 to 40 minutes. An assessment of the free flow is then performed. The portion of blood that contains papaverine and that is extravasating again from the vessel is discarded to prevent unnecessary systemic exposure.

Surgical Procedure

Papaverine is administered intraluminally in accordance with the standard surgical procedure. After distal dissection of the IMA, diluted papaverine solution (1 mg/1 mL) is carefully introduced into the vessel by use of a special blunt cannula. The total amount should be 3 mL. The vessel is then temporarily closed at the distal end with a bulldog clamp and the vascular pedicle is sprayed. Excess solution is removed directly from the surgical field using a “dirty sucker.”

Statistical Analysis

The following were calculated for each of the quantifiable parameters: mean, standard error, 95% confidence intervals of the mean, minimum, maximum, variance, and median (Excel 2003, SPSS 20.0 IBM, USA). The conduct of the trial was approved by the Ethics Committee of Johann Wolfgang Goethe



University Frankfurt am Main and the Ethics Committee of the Hessen State Medical Association. The patients were informed in writing about the contents of the study and gave their consent to participate with their signature (ClinicalTrials.gov, no. NCT01436981NCT, Ethics Committee no. 176/11).

T1 (mean 54.7 ± 39 ng/mL, range 16.6-179 ng/mL). The concentration was already halved 20 minutes after administration (mean 23.3 ± 2 ng/mL, range 4.6-118 ng/mL). Because of the short half-life and the hemodilution in the extracorporeal circulation, papaverine had already fallen to just above the limit

Descriptive Statistics of Parameters Recorded at Time Points T1 to T3.

Patient Parameters (n = 15)	Range	Minimum	Maximum	Mean	SD	Variance
Age, years	36	39	75	65.27	6.36	40.49
Body mass index	13.7	23.5	37.2	28.99	3.79	14.37
Weight, kg	54.0	60	114	86.55	15.25	232.69
Height, m	0.4	1.5	1.9	1.72	0.09	0.01
Papaverine at T1, ng/mL	162.4	16.6	179	54.7	39.62	1570.43
Papaverine at T2, ng/mL	113.4	4.6	118	24.38	29.91	894.90
Papaverine at T3, ng/mL	15.6	1.3	16.9	4.18	3.891	15.14
Papaverine at T1, ng/m/kg BW*	2.00	0.18	2.18	0.65	0.5041	0.25
Papaverine at T2, ng/m/kg BW	1.38	0.05	1.43	0.29	0.371	0.13
Papaverine at T3, ng/m/kg BW	0.15	0.01	0.16	0.04	0.038	0.001
Pulse at T1, bpm	59	50	109	68.67	15.47	239.52
RR for diastole at T1	33	50	83	65.33	10.26	105.38
RR for systole at T1	54	86	140	105.80	16.63	276.74

*BW indicates body weight; RR, R wave to R wave interval.

RESULTS

The newly developed LC-MS/MS method was successfully used to determine papaverine in plasma samples collected from patients after IMA preparation in the single-dose pharmacokinetic study. The mean plasma concentration–time profile of papaverine is presented in Figure 1, and the corresponding pharmacokinetic parameters are summarized in the table. The highest serum papaverine values were determined at time point

of detection (mean 4.1 ± 3.9 ng/mL, range 1.3-16.9 ng/mL) after 2 hours (T3). These pharmacodynamics were also demonstrated with body weight–adapted means (papaverine ng/mL/kg body weight) (Table). The blood pressure measured at time point T1 showed a trend toward a reduction of systolic values with increasing serum papaverine levels (Figure 2). However, a significant correlation could not be demonstrated ($P = 0.13$). Papaverine administration was not observed to cause undesirable side effects in the 15 patients.

DISCUSSION

The therapeutic effects of papaverine for the indication “intraluminal use in coronary surgery (coronary revascularization) for prevention of vasospasm when harvesting and anastomosing arterial and venous grafts” was assessed in relation to alternative therapeutic options and other factors. Positive effects similar to those of papaverine can in principle also be achieved with other vasodilators, for example with combinations of verapamil with nitroglycerin or verapamil alone [Cantürk 2010]. Convincing superiority of other vasodilators over papaverine is not described in the literature. Mills and Bringaze emphasize that pericardotomy, cannulation, and other operative steps can be performed in the time up to the onset of dilatation in graft preparation with intraluminal injection of a diluted papaverine solution into the IMA (here: 60 mg papaverine in 40 mL physiological saline as the final concentration) [Mills 1989; He 1994]. The following are regarded as the advantages of using papaverine: enlargement of the vessel to be grafted with a lower probability of technical surgical errors, elimination of spasm with achievement of an increased flow rate, and identification of nonclamped or non-cauterized vascular branches requiring follow-up investigation [Mills 1989]. The literature contains a large number of studies describing the use of papaverine for the indication of intraluminal use for prevention of vasospasm when harvesting and anastomosing arterial and venous grafts. These include a randomized, double-blind, parallel-group comparative study with the medicinal product papaverine in CABG operations [Battaloglu 2007]. One study recommends using papaverine solutions at 37°C to prevent intraoperative spasm [Bilgen 1996]. The intraluminal use of papaverine is superior to extraluminal use, although the latter also produces noteworthy dilations [Mills 1989]. Systemic effects of intraluminal papaverine on patients’ blood pressure have also been described and are also a known phenomenon in the clinical routine [Formica 2006]. With the practiced method involving the application of bulldog clamps at the proximal origin of the subclavian artery and the small, diluted, intravascularly administered quantity of papaverine, it has so far been assumed that no noteworthy amounts of papaverine (<10 ng/mL) enter the patient’s systemic circulation. The use of the novel LC-MS/MS method of measurement [Yan 2005] in this study made it possible to demonstrate for the first time that papaverine administration is followed by detectable absorption of the drug into the patient’s systemic circulation. This effect has not previously been described in the literature. To prevent systemic circulatory effects, in preparation of the mammary artery, papaverine should possibly be administered only topically and locally.

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AUTHOR CONTRIBUTIONS

Dr. Kiessling conceived and designed the study, performed analysis and interpretation of data and coordination of the study and wrote the manuscript. Dr. Romasku participated in

patient and sample recruitment. Drs. Ferreirós and Labocha analyzed the samples and were involved in drafting the manuscript and revising it critically for important intellectual content. Drs. Moritz and Rastan conceived the study and coordinated and reviewed the manuscript and revised it critically for important intellectual content. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

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