Cardiovascular effects of dipyrone and propofol on hemodynamic function in rabbits

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Objective—To evaluate the short-term cardiovascular effects of IV administration of dipyrone (metamizole) as an intraoperative analgesic during total IV anesthesia with propofol.

Animals—6 healthy female New Zealand White rabbits.

Procedures—Anesthesia was induced with propofol (4.0 to 8.0 mg/kg, IV) and maintained with the same drug (1.2 to 1.3 mg/kg/min, IV). After induction, 3 doses of dipyrone (65 mg/kg each) were administered IV at 25-minute intervals. Before and for 10 minutes after each dipyrone injection, the following vascular and hemodynamic variables were recorded at the left common carotid artery every minute after the first injection: vessel diameter; peak systolic, minimum diastolic, end-diastolic, and mean blood flow velocities; mean volumetric flow; resistance and pulsatility indices; mean arterial blood pressure (MAP); heart rate; arterial oxygen saturation (Spo_2); and end-tidal partial pressure of CO_2 ($PETCO_2$). Echocardiography was performed after the second injection. The same variables were measured at the abdominal aorta (AA) after the third injection.

Results—Dipyrone injections caused a significant, transient decrease in the resistance index at the AA. Also detected were a minor decrease in pulsatility index at the left common carotid artery and a minor increase in end-diastolic blood flow velocity at the AA. The MAP, heart rate, Spo_2, and $PETCO_2$ did not significantly change after injections. A comparison of HR and MAP after the first and third bolus injections revealed only minor changes.

Conclusions and Clinical Relevance—Dipyrone used with propofol anesthesia in rabbits appeared not to significantly impair cardiovascular and hemodynamic function. (*Am J Vet Res* 2009;70:1407–1415)

Dipyrone (metamizole), a potent nonopiate analgesic and antipyretic agent with an additional spasmolytic effect, is widely used in humans to provide perioperative pain relief, whether administered alone or in combination with opioids.[1] In other animals, dipyrone has been used as a postoperative analgesic,[2] but the cardiovascular properties of dipyrone in rabbits, particularly in combination with propofol anesthesia, have not been thoroughly evaluated. The drug is widely used in some countries (eg, France, Germany, Italy, and Spain), whereas in other countries (eg, the United States and Sweden), its use has been restricted or banned because of the risk of adverse reactions in humans, notably agranulocytosis.[1] However, the International Study of Agranulocytosis and Aplastic Anemia[3] revealed that the risk of agranulocytosis attributable to any dipyrone exposure in 1 treatment week is 1.1 cases/million human users. To the authors' knowledge, in veterinary medicine, development of dipyrone-associated agranulocytosis has not been reported.[4]

Propofol is commonly used in rabbits for short-term anesthesia and for induction and maintenance of general anesthesia.[5–7,a] Propofol anesthesia is readily controlled[5,8] because of its short half-life[9,10] and the slight cumulative effects associated with its use. However, the use of propofol alone is considered unsatisfactory for major surgical procedures because the anesthetic has minor, if any, analgesic properties and the dose required to suppress response to surgery induces marked respiratory and cardiovascular depression.[9] Therefore, for surgical procedures, propofol must be combined with an analgesic. In humans, propofol administration re-

Abbreviations

BFV	Blood flow velocity
CRI	Constant rate infusion
MAP	Mean arterial blood pressure
$PETCO_2$	End-tidal partial pressure of CO_2
QTc	Heart rate–corrected QT interval
Spo_2	Arterial oxygen saturation as measured by pulse oximetry

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portedly results in a reduction in the cardiac index and mean arterial pressure.[11] This hypotension can be intensified when fentanyl is used with propofol.[11]

The primary advantage of nonopiate analgesic agents is related to the lack of associated respiratory depression and major adverse effects on the CNS.[4,12] Results from clinical studies in humans and dogs indicate that IV infusion of dipyrone yields marked intraoperative and postoperative pain relief but is not associated with a clinically important impairment in hemodynamic function.[12,b] When administered at 50 mg/kg every 6 hours in rabbits[5] and in dogs,[4] dipyrone can be used effectively in the treatment of postoperative pain, but to provide surgical tolerance, a higher dosage should be used.[4,b]

Because the scientific literature lacks information about dipyrone and the dose required to provide surgical tolerance when administered alone during CRI with propofol, we conducted an explorative study in rabbits. That study revealed that administration of 2 to 3 IV boluses of dipyrone at a dosage of 65 mg/kg (mean total dosage of dipyrone, 158.9 ± 34.3 mg/kg) yields surgical tolerance in propofol-anesthetized rabbits. The purpose of the study reported here was to evaluate the short-term cardiovascular effects of IV administration of dipyrone as an intraoperative analgesic during CRI with propofol in rabbits. A secondary objective was to determine the effects of 3 dipyrone bolus injections on hemodynamic variables during CRI with propofol.

Materials and Methods

Animals and husbandry—Six female New Zealand White rabbits, with a mean ± SD body weight of 3.68 ± 0.56 kg and ranging in age from 10 to 16 weeks, were used in the study. The rabbits were obtained from a colony free of respiratory pathogens[c] and were individually housed in cages on dust-free wooden shavings. Room temperature was maintained at 19° ± 2°C, with a relative humidity of 50% to 60%. A cycle of 12 hours light, 12 hours dark was maintained. The rabbits were fed a commercial pelleted diet[d] and received autoclaved hay and water ad libitum. All rabbits were acclimatized to the new environment for at least 7 days. The study protocol was approved by the local animal care and use committee and carried out in accordance with the German Animal Welfare Act (Deutsches Tierschutzgesetz).

Anesthesia—On the day of the experiment, each rabbit was weighed and clinically examined for behavior, respiration, and cardiovascular variables. Experiments were conducted between 9 AM and noon. A local anesthetic[e] was applied topically to the skin of the left ear of each rabbit, and an arterial catheter[f] (1.1 × 33 mm) was inserted into the median auricular artery for arterial blood pressure measurements. A second catheter[f] (0.9 × 25 mm) was inserted in the lateral auricular vein. Anesthesia was induced with 1% propofol[g] (4.0 to 8.0 mg/kg, IV). After the swallowing reflex was no longer evident, the trachea was intubated (inner diameter of endotracheal tube, 2 to 3.0 mm), which was achieved without direct laryngeal observation. Each rabbit was shaved in preparation for echocardiography and placed on a heating pad to maintain rectal temperature at 37° to 38°C.

Ultrasonographic measurements of the left common carotid artery and 2-D guided M-mode echocardiography were conducted with rabbits positioned in dorsal recumbency. For ultrasonography of the abdominal aorta, the rabbits were positioned in right lateral recumbency. Anesthesia was maintained with a continuous IV infusion of 2% propofol[g] (1.2 to 1.3 mg/kg/min),[5,13] with the infusion initiated at approximately 5 minutes after induction. With this dose, which is commonly used for anesthesia in rabbits, a stable and light plane of anesthesia was maintained, which yielded good muscle relaxation and hypnosis with stable cardiovascular variables (heart rate, MAP, Spo_2, P_{ETCO_2}, and ultrasonographic factors).

Each rabbit was ventilated[h] with 100% oxygen at 29 to 32 breaths/min, with a peak ventilation pressure of 8 to 10 cm H_2O. Monitoring of MAP (invasive MAP), heart rate, P_{ETCO_2}, and Spo_2 was conducted by use of a patient monitor.[i] No rabbit received IV administration of fluids.

Experimental protocol—Three bolus injections of dipyrone[j] (each 65 mg/kg, IV) were administered to each rabbit during CRI with propofol, at 25-minute intervals. For each bolus of dipyrone, the injection volume was adjusted with saline (0.9% NaCl) solution[k] to achieve a total volume of 0.6 mL, and each injection was administered over 20 seconds. Time 0 was defined as the end of each dipyrone injection. After the first dipyrone injection (15 minutes after the CRI with 2% propofol began), changes in vascular and hemodynamic variables were recorded by means of ultrasonography at the left common carotid artery. After the second injection (40 minutes after the CRI began), echocardio-graphy of the heart was used to investigate alterations in cardiac variables. After the third injection (65 minutes after the CRI began), ultrasonographic indicators were measured at the abdominal aorta. Therefore, the ultrasonographic examination was divided into 3 sections.

Each section of the experiment began with measurement of baseline values. Baseline measurements at the various locations were determined once, only after a stable anesthetic plane was evident (ie, values for heart rate, MAP, P_{ETCO_2}, and ultrasonographic variables did not differ from respective baseline values by > 5%). Baseline ultrasonographic data were measured at the carotid artery before the first injection, at the heart before the second injection, and at the abdominal aorta before the third injection.

After bolus injection of dipyrone, vascular (first and third dipyrone injection) and echocardiographic (second dipyrone injection) images were recorded at 30 seconds, at 1 minute, and at 1-minute intervals for up to 10 minutes thereafter. During ultrasonographic evaluations of the carotid artery and abdominal aorta, the vessel images and velocity spectra were recorded for later determination of vessel diameters, peak systolic BFV, minimum diastolic BFV, end-diastolic BFV, and time-averaged BFV.

The resistance index of the blood vessels, which is derived from the peak systolic and end-diastolic

BFVs, is an important index that reflects the vascular resistance distal to the point of Doppler evaluation.[14] It was calculated with the following equation[14]: (psBFV – edBFV)/psBFV, in which psBFV is the peak systolic BFV and edBFV is the end-diastolic BFV. The pulsatility index, which is also used to characterize peripheral vascular resistance, was calculated with the following equation:[15] (psBFV – mdBFV)/V_{mean}, in which mdBFV is the minimum diastolic BFV and V_{mean} is the time-averaged BFV. Mean volumetric flow in the abdominal aorta and the left common carotid artery was calculated with the following equation[16]: $V_{mean} \times \pi \times r^2$, in which r is the vessel radius.

Echocardiography was used in the second section of the study to measure fractional shortening, which was calculated by use of the following equation[17,18]: ([LVEDD – LVESD])/LVEDD) × 100, in which LVEDD is left ventricular end-diastolic diameter and LVESD is left ventricular end-systolic diameter.

For each ECG,[l] a recording speed of 25 mm/s was used. Tracings were evaluated for rhythm disturbances and changes in the general configuration of the complexes. Measurement of interval durations (eg, R-R and QT intervals) was performed by use of lead II data. From ECG data obtained during measurements at the left common carotid artery and the heart, the QTc was calculated by use of the following equation: $QT \times (RR)^{-0.5}$, in which QT is the sum of the durations of ventricular depolarization (QRS complex) and repolarization (ST-T segment) and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex. Hemodynamic data, including heart rate, MAP, Spo_2, $Petco_2$, rectal temperature, and the plethysmographic amplitude,[m] were recorded simultaneously during each section of the ultrasonographic examination.

Ultrasonography of the blood vessels and heart— Vascular imaging was performed with a 10-MHz linear transducer.[n] For echocardiography, a 10-MHz sector transducer[o] was used. Both transducers were used in conjunction with an ultrasonographic system.[p]

Measurements of the carotid artery were obtained by positioning the probe over the ventral cervical region. Measurement of the abdominal aorta was performed by placing the probe over the abdominal region at the caudal aspect of the thorax. The probe was angled to the correct direction and fixed in that position with a clamp. Instrument settings were adjusted to delineate the blood vessel walls from surrounding tissues. Probe position was adjusted until distinct parallel vessel walls were visible. The Doppler sample volume was placed centrally within the vessel, and the sample volume cursor was adjusted to align with the vessel walls and blood flow. The angle between the sample-volume cursor and the ultrasound beam was measured ultrasonographically, and this value was used to correct velocity calculations. An angle between 45° and 60° was consistently achieved between the vessel and the ultrasound beam. Once the sample volume was correctly positioned, Doppler evaluations were conducted in pulse-wave mode. Recorded velocity spectra were assessed for quality on the basis of clarity of the visual and audible signal and then stored for subsequent measurement of peak systolic, minimum diastolic, end-diastolic, and time-averaged BFVs. From these variables, the resistance index, pulsatility index, and mean volumetric flow were derived. Furthermore, 2-D images of the vessel wall were assessed and stored for subsequent measurement of the luminal diameter between the leading edge of the innermost echogenic layer by cursor adjustment.[19]

For echocardiographic assessments, a right parasternal transducer position was used. Two-dimensional M-mode short-axis views at the level of the chordae tendineae were recorded to measure ventricular dimensions (left ventricular end-systolic and end-diastolic diameters). From these variables, fractional shortening of the left ventricle was derived.[17,18,20]

Statistical evaluation—Descriptive statistics (mean ± SD) are reported for all data. Statistical comparisons were made for an exploratory data analysis; thus, no correction of α error rate was considered. A value of $P \leq 0.05$ was considered significant for all comparisons.

To evaluate overall trend in variables of interest, linear mixed regression models with monotonous (linear) or transient (quadratic) time effects were constructed. This modeling approach properly reflects the structure of repeated data and accounts for correlation between measurements within the same subjects. A first-order autoregressive correlation structure as well as random effects for each rabbit was considered in the regression analysis. Effects of time were first specified by graphical assessment and then verified by stepwise model derivation. When a specific effect of time was detected during the analysis, a post hoc Student *t* test for paired samples was used to assess differences between each time point during the 10-minute examination period and the baseline value. Furthermore, a Friedman test followed by paired Student *t* tests was used to separately compare related measured at equivalent time points after the first, second, and third bolus for the variables heart rate, MAP, Spo_2, $Petco_2$, and rectal temperature. All statistical analyses were conducted with commercially available software.[q]

Results

Ultrasonography of the carotid artery—Data were summarized for vascular ultrasonographic measurements obtained at the left common carotid artery after the first dipyrone bolus injection (**Table 1**). At the left common carotid artery, the pulsatility index decreased after this first injection. Changes were transient (minimum pulsatility index obtained at 1 minute after the injection, increasing to 1.98 ± 0.67 mm at 10 minutes after the injection), but because the post hoc tests did not reveal any significant changes, these effects were only minor. Results of the linear mixed regression model indicated the other vascular variables recorded at the left common carotid artery (vessel luminal diameter, peak systolic BFV, end-diastolic BFV, resistance index, and mean volumetric flow) did not change significantly from baseline values.

Ultrasonography of the abdominal aorta—Data were summarized for vascular ultrasonographic measurements obtained at the abdominal aorta after the third dipyrone injection (**Table 2**). End-diastolic BFV of the abdominal aorta significantly increased from

the baseline value after this third injection. Results of the mixed-model regression analysis indicated these changes were transient (first end-diastolic BFV significantly increased until 4 minutes after the injection, then values significantly decreased toward baseline values until measurements ceased), but because results of the post hoc tests did not reveal any significant changes, these effects were only minor. The resistance index significantly decreased relative to the baseline value at 4 minutes after injection. Results of the mixed-model regression analysis indicated this change was transient, and values began to increase at 5 minutes after injection. Results of the linear mixed regression model indicated all other vascular variables recorded at the abdominal aorta (vessel luminal diameter, peak systolic BFV, mean volumetric flow, and pulsatility index) did not change significantly at any point.

Echocardiographic assessment—Selected echocardiographic variables measured after the second dipyrone bolus injection were summarized (**Table**

Table 1—Results of a linear mixed regression model and mean ± SD values for ultrasonographic evaluation of the left common carotid artery in 6 anesthetized rabbits after injection of the first of 3 dipyrone boluses (65 mg/kg each, IV), which was administered 15 minutes after onset of a CRI of propofol (1.2 to 1.3 mg/kg/min).

Variable	Vessel diameter (mm)	psBFV (cm/s)	edBFV (cm/s)	Resistance index	VF_{mean} (mL/s)	Pulsatility index	QTc (ms)
Model*							
Intercept	1.94†	72.50†	18.75†	0.7361†	1.12†	1.82†	287.47†
Time × $coef_1$	–0.0039	0.3726	0.0741	0.0019	–0.0092	–0.0877	1.66†
$Time^2$ × $coef_2$	NT	NT	–0.0128	NT	NT	0.0104†	NT
Time (min)							
Baseline	1.90 ± 0.05	75.10 ± 11.58	18.65 ± 4.68	0.75 ± 0.06	0.97 ± 0.28	2.16 ± 0.60	286 ± 21
0.5	1.95 ± 0.09	70.24 ± 6.14	17.54 ± 3.48	0.75 ± 0.05	1.10 ± 0.23	1.63 ± 0.44	—
1	1.99 ± 0.12	71.51 ± 5.84	19.17 ± 3.77	0.73 ± 0.06	1.19 ± 0.29	1.53 ± 0.27	—
2	1.99 ± 0.08	71.54 ± 4.74	20.89 ± 3.90	0.71 ± 0.06	1.19 ± 0.30	1.57 ± 0.33	294 ± 29
3	1.96 ± 0.08	72.59 ± 7.42	18.48 ± 2.78	0.74 ± 0.04	1.13 ± 0.24	1.59 ± 0.27	—
4	1.93 ± 0.06	73.02 ± 6.70	18.57 ± 2.75	0.75 ± 0.05	1.07 ± 0.27	1.71 ± 0.46	297 ± 26
5	1.94 ± 0.06	75.80 ± 9.54	18.85 ± 2.73	0.75 ± 0.04	1.02 ± 0.11	1.89 ± 0.38	—
6	1.90 ± 0.08	73.19 ± 11.89	19.23 ± 3.25	0.74 ± 0.03	1.06 ± 0.24	1.61 ± 0.23	296 ± 26
7	1.89 ± 0.06	75.30 ± 9.51	17.48 ± 2.77	0.77 ± 0.04	1.09 ± 0.30	1.70 ± 0.45	—
8	1.91 ± 0.07	75.15 ± 9.29	18.80 ± 2.24	0.75 ± 0.03	1.05 ± 0.17	1.82 ± 0.27	301 ± 29
9	1.90 ± 0.07	75.70 ± 13.96	17.89 ± 3.79	0.76 ± 0.04	1.03 ± 0.23	1.82 ± 0.24	—
10	1.91 ± 0.05	76.97 ± 15.09	18.53 ± 3.46	0.76 ± 0.05	0.98 ± 0.16	1.98 ± 0.67	303 ± 33†

*The linear mixed regression model included random effects for each rabbit and an autoregressive correlation structure, which yielded the following equation: intercept + (time × $coef_1$) + ($time^2$ × $coef_2$), in which $coef_1$ is the slope of the predicted value in 1-minute increments and $coef_2$ is the additive change of predicted value in dependence on time squared (ie, $minute^2$). †Value differs significantly ($P < 0.05$) from baseline value.

— = Not determined. ed = End-diastolic. NT = No quadratic trend evident. ps = Peak systolic. VF_{mean} = Mean volumetric flow.

Baseline measurements were obtained before each dipyrone injection, only after a stable plane of propofol anesthesia was evident (ie, values for heart rate, MAP, P_{ETCO_2}, and ultrasonographic variables did not differ from respective initial values by > 5%). Time 0 was defined as the end of each dipyrone injection.

Table 2—Results of a linear mixed regression model and mean ± SD values for ultrasonographic evaluation of the abdominal aorta in 6 anesthetized rabbits after injection of the third of 3 boluses of dipyrone, which was administered 65 minutes after onset of a CRI of propofol.

Variable	Vessel diameter (mm)	psBFV (cm/s)	edBFV (cm/s)	Resistance index	VF_{mean} (mL/s)	Pulsatility index
Model*						
Intercept	3.15†	100.36†	20.17†	0.7925†	2.99†	3.19†
Time × $coef_1$	0.0046	0.3691	1.88†	–0.0187†	–0.0782	0.0685
$Time^2$ × $coef_2$	NT	NT	–0.1640†	0.0018†	0.0069	–0.0061
Time (min)						
Baseline	3.10 ± 0.34	104.37 ± 25.15	18.47 ± 7.08	0.81 ± 0.09	2.80 ± 0.94	3.38 ± 0.89
0.5	3.15 ± 0.28	100.67 ± 23.13	23.15 ± 4.40	0.76 ± 0.06	3.10 ± 0.99	3.00 ± 0.95
1	3.19 ± 0.23	98.77 ± 16.02	22.43 ± 2.92	0.77 ± 0.05	2.84 ± 0.85	3.30 ± 1.02
2	3.18 ± 0.21	101.00 ± 17.64	23.18 ± 4.42	0.77 ± 0.05	3.17 ± 1.39	3.33 ± 1.16
3	3.15 ± 0.28	99.59 ± 17.95	25.32 ± 8.41	0.75 ± 0.07	2.88 ± 0.65	3.13 ± 0.46
4	3.15 ± 0.27	98.44 ± 21.93	27.19 ± 8.03	0.72 ± 0.07†	2.64 ± 0.54	3.38 ± 0.46
5	3.13 ± 0.28	104.86 ± 22.56	24.51 ± 5.72	0.76 ± 0.05	2.81 ± 1.01	3.43 ± 0.64
6	3.14 ± 0.25	101.02 ± 19.80	24.08 ± 4.27	0.76 ± 0.05	2.88 ± 0.66	3.31 ± 0.68
7	3.13 ± 0.22	103.17 ± 23.52	25.64 ± 5.68	0.75 ± 0.06	2.63 ± 0.69	3.59 ± 0.72
8	3.09 ± 0.27	102.66 ± 22.18	22.98 ± 4.52	0.77 ± 0.06	2.62 ± 0.73	3.43 ± 0.50
9	3.10 ± 0.22	103.43 ± 22.39	23.70 ± 4.92	0.77 ± 0.06	2.75 ± 0.63	3.30 ± 0.73
10	3.10 ± 0.25	106.14 ± 21.77	23.36 ± 5.10	0.78 ± 0.05	3.04 ± 0.96	3.18 ± 0.81

See Table 1 for key.

3). Results of the linear mixed regression model indicated the left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and fractional shortening did not change significantly after that injection.

ECG recordings for QTc—After the first bolus injection of dipyrone (when measurements were made at the left common carotid artery), the duration of QTcs increased significantly and linearly from the baseline value (Table 1).

Table 3—Results of a linear mixed regression model and mean ± SD values for echocardiographic variables in 6 anesthetized rabbits after injection of the second of 3 boluses of dipyrone, which was administered 40 minutes after onset of a CRI of propofol.

Variable	LVESD (mm)	LVEDD (mm)	FS (%)	QTc (ms)
Model*				
Intercept	8.66†	14.70†	40.98†	299.39†
Time × $coef_1$	–0.0126	–0.0239	–0.2499	–0.4957
$Time^2$ × $coef_2$	NT	NT	0.0263	NT
Time (min)				
Baseline	8.55 ± 0.71	14.36 ± 1.11	39.77 ± 5.30	299 ± 48
0.5	8.61 ± 0.70	14.80 ± 1.41	41.65 ± 3.92	—
1	8.77 ± 0.47	14.97 ± 0.90	41.27 ± 4.23	—
2	8.48 ± 0.55	14.62 ± 0.91	41.99 ± 2.04	298 ± 38
3	8.65 ± 0.34	14.40 ± 0.51	39.89 ± 3.11	—
4	8.59 ± 0.60	14.75 ± 0.75	41.76 ± 2.85	297 ± 39
5	8.78 ± 0.46	14.79 ± 0.73	40.61 ± 2.72	—
6	8.80 ± 0.85	14.44 ± 0.94	39.09 ± 4.15	297 ± 38
7	8.74 ± 0.62	14.49 ± 1.20	39.48 ± 5.09	—
8	8.73 ± 0.68	14.69 ± 0.98	40.49 ± 4.12	294 ± 40
9	8.52 ± 0.73	14.42 ± 0.73	40.87 ± 4.16	—
10	8.37 ± 0.83	14.36 ± 1.11	41.59 ± 5.83	294 ± 40

FS = Fractional shortening. LVEDD = Left ventricular end-diastolic diameter. LVESD = Left ventricular end-systolic diameter.
See Table 1 for remainder of key.

Clinical hemodynamic variables—Values were summarized for heart rate, MAP, Spo_2, $PETCO_2$, and rectal temperature after each of the 3 boluses of dipyrone were administered (**Tables 4–6**). These variables were recorded simultaneously during all periods of ultrasonographic measurement. Results of the linear mixed regression model indicated there was no significant change from the baseline value for any variable.

When data at equivalent points after the first, second, and third dipyrone bolus injections were compared with the Friedman test, a significant time-adjusted difference in heart rate was revealed between the second and the third injections. Significant time-adjusted differences in MAP were evident when data were compared for the first and third injections and for the second and third injections. A significant difference was also detected between values of Spo_2 for the first and third injections. When a paired Student *t* test was performed after each comparison as part of a hierarchical test procedure, no significant differences were detected.

The recorded plethysmographic amplitude slightly increased within the first 3 minutes after the first injection of dipyrone was administered; this value subsequently decreased to lower than the baseline value. During the measurements at the heart after the second bolus was injected, plethysmographic amplitude did not change. Seven minutes after the third bolus was injected, plethysmographic amplitude decreased to lower than the baseline value.

Table 4—Results of a linear mixed regression model and mean ± SD hemodynamic values in 6 propofol-anesthetized rabbits, recorded after the first bolus injection of dipyrone.

Variable	HR (beats/min)	MAP (mm Hg)	Spo_2 (%)	$PETCO_2$ (kPa)	T (°C)
Model*					
Intercept	220.4†	70.8†	99.5†	5.2†	37.8†
Time × $coef_1$	0.3687	0.2530	0.0067	0.0195	–0.0334
$Time^2$ × $coef_2$	NT	NT	NT	NT	NT
Time-adjusted differences‡					
Bolus 1 vs bolus 3	2.7	7.4†	–0.41†	–0.02	0.53
Bolus 2 vs bolus 3	4.6†	3.9†	–0.05	0.03	0.07
Time (min)					
Baseline	219 ± 15	69 ± 12	100 ± 1	5.2 ± 0.5	37.8 ± 0.8
0.5	224 ± 17	72 ± 11	100 ± 1	5.1 ± 0.4	—
1	225 ± 20	73 ± 11	100 ± 1	5.2 ± 0.5	—
2	225 ± 19	73 ± 10	99 ± 2	5.2 ± 0.4	37.8 ± 0.7
3	225 ± 20	75 ± 9	100 ± 1	5.2 ± 0.4	—
4	226 ± 20	75 ± 9	100 ± 1	5.3 ± 0.4	37.8 ± 0.7
5	225 ± 22	74 ± 8	99 ± 1	5.3 ± 0.4	—
6	225 ± 20	75 ± 7	100 ± 1	5.3 ± 0.4	37.8 ± 0.7
7	225 ± 21	73 ± 8	100 ± 1	5.3 ± 0.4	—
8	225 ± 20	74 ± 7	100 ± 1	5.3 ± 0.4	37.8 ± 0.7
9	224 ± 20	73 ± 6	100 ± 1	5.4 ± 0.4	—
10	225 ± 15	73 ± 8	100 ± 1	5.4 ± 0.5	37.8 ± 0.7

‡Time-adjusted differences between boluses; bolus 1 was considered the reference value.
HR = Heart rate. T = Rectal temperature.
See Table 1 for remainder of key.

Table 5—Results of a linear mixed regression model and mean ± SD hemodynamic values in 6 propofol-anesthetized rabbits, recorded after the second bolus injection of dipyrone.

Variable	HR (beats/min)	MAP (mm Hg)	Spo_2 (%)	P_{ETCO_2} (kPa)	T (°C)
Model*					
Intercept	224.02†	68.08†	99.97†	5.36†	37.39†
Time × $coef_1$	0.168	–0.0080	–0.0092	–0.0085	–0.0285
$Time^2$ × $coef_2$	NT	NT	NT	NT	NT
Time (min)					
Baseline	222 ± 12	62 ± 9	100 ± 0	5.3 ± 0.4	37.4 ± 0.7
0.5	230 ± 16	74 ± 6	100 ± 0	5.3 ± 0.3	—
1	227 ± 12	73 ± 8	100 ± 1	5.2 ± 0.3	—
2	228 ± 10	72 ± 8	100 ± 0	5.2 ± 0.3	37.4 ± 0.7
3	226 ± 9	71 ± 8	100 ± 0	5.3 ± 0.3	—
4	227 ± 8	71 ± 8	100 ± 0	5.4 ± 0.4	37.4 ± 0.7
5	225 ± 10	70 ± 8	100 ± 0	5.3 ± 0.4	—
6	227 ± 9	70 ± 8	100 ± 0	5.4 ± 0.3	37.3 ± 0.7
7	228 ± 8	70 ± 8	100 ± 0	5.4 ± 0.3	—
8	225 ± 8	69 ± 7	100 ± 0	5.4 ± 0.3	37.3 ± 0.7
9	225 ± 10	67 ± 7	100 ± 1	5.4 ± 0.3	—
10	226 ± 10	66 ± 7	100 ± 0	5.4 ± 0.3	37.3 ± 0.8

See Tables 1 and 4 for key.

Table 6—Results of a linear mixed regression model and mean ± SD hemodynamic values in 6 propofol-anesthetized rabbits, recorded after the third bolus injection of dipyrone.

Variable	HR (beats/min)	MAP (mm Hg)	Spo_2 (%)	P_{ETCO_2} (kPa)	T (°C)
Model*					
Intercept	219.75†	65.51†	99.94†	5.35†	37.27†
Time × $coef_1$	0.1896	–0.0874	0.0072	–0.0117	0.0072
$Time^2$ × $coef_2$	NT	NT	NT	NT	NT
Time (min)					
Baseline	217 ± 7	64 ± 10	100 ± 0	5.4 ± 0.3	37.1 ± 0.7
0.5	222 ± 11	67 ± 9	100 ± 0	5.3 ± 0.3	—
1	222 ± 8	66 ± 9	100 ± 0	5.3 ± 0.2	—
2	222 ± 10	67 ± 9	100 ± 0	5.3 ± 0.3	37.3 ± 0.6
3	223 ± 12	67 ± 9	100 ± 0	5.2 ± 0.1	—
4	223 ± 10	67 ± 9	100 ± 0	5.3 ± 0.1	37.3 ± 0.6
5	223 ± 10	66 ± 10	100 ± 0	5.2 ± 0.1	—
6	221 ± 7	66 ± 10	100 ± 0	5.3 ± 0.1	37.3 ± 0.6
7	221 ± 8	66 ± 10	100 ± 0	5.3 ± 0.1	—
8	221 ± 10	65 ± 11	100 ± 0	5.3 ± 0.2	37.3 ± 0.6
9	222 ± 9	64 ± 10	100 ± 0	5.2 ± 0.2	—
10	221 ± 8	64 ± 10	100 ± 0	5.2 ± 0.2	37.3 ± 0.3

See Tables 1 and 4 for key.

Discussion

The objective of the study reported here was to determine some of the short-term cardiovascular effects of IV dipyrone injections in propofol-anesthetized rabbits as measured via ultrasonography. Dipyrone is a water-soluble pyrazolone derivate. Since its introduction in 1922, dipyrone has been recognized as an effective analgesic, antipyretic, and spasmolytic drug.[21] Its use is indicated for severe pain and, particularly, for pain associated with smooth muscle spasm or colic affecting the gastrointestinal, biliary, and urinary tracts.[21] Dipyrone is also useful in the treatment of fever refractory to other drugs.[21] Unlike use of NSAIDs, use of dipyrone is not associated with gastric or renal adverse effects[4,22]; however, parenteral administration may be accompanied by hypotension in rare situations.[4,23] The risk of a sudden decrease in blood pressure is possibly attributable to rapid IV administration because dipyrone use is associated with a low risk of anaphylaxis.[23] Therefore, a slow parenteral injection speed has been recommended to avoid adverse cardiovascular effects in animals.[4]

The pharmacologic mechanism of action of dipyrone remains uncertain. The drug might be an inhibitor of the COX-3 isoenzyme, thereby reducing prostaglandin synthesis in the dorsal horn of the spinal cord.[24] It has been suggested that dipyrone treatment inhibits prostaglandin synthesis in the CNS as well as outside the blood brain barrier.[25] However, because dipyrone is able to yield a significant antinociceptive effect in the absence of an anti-inflammatory response, central mechanisms are believed to be important factors in the analgesic action of the drug.[26,27] The effect of dipyrone

on the CNS has been associated with the endogenous opioid system because its antinociceptive effect is blocked by naloxone.[28]

When administered at a dosage of 50 mg/kg (IV or PO) every 6 hours in rabbits[5] and dogs,[4] dipyrone is also effective in the treatment of postoperative pain; in situations of mild and moderate pain, the drug can be used alone at a dose of 50 mg/kg, thereby avoiding the adverse effects associated with opioid administration completely. More importantly, in situations of severe pain, dipyrone can be an integral component of multimodal analgesia.[4] In such a scenario, dipyrone is not only opioid sparing but can also improve analgesia and potentially reduce the adverse effects of opioids.[4,29] A systematic review[30] of the clinical efficacy of a single dose of dipyrone (500 mg) in the treatment of postoperative pain in humans revealed that dipyrone administered IM had a superior analgesic effect to that of pethidine (100 mg), ketorolac (30 mg), or morphine (10 mg) administered IM. Studies on the effect of dipyrone for multimodal analgesia are limited. In humans, IV administration of dipyrone (1 mg, q 6 h, for 24 hours) resulted in pain reduction and an opioid-sparing effect (reduction of opioid dosage to achieve the pain relief) of 20% for minor orthopedic surgery and of 67% for laparoscopic surgery.[31] Particularly in veterinary medicine, studies on the effect of dipyrone used as an intraoperative analgesic are even more limited. A study[b] in dogs undergoing hip-joint replacement revealed that when 75 mg of dipyrone/kg was administered IV, nearly half (10/22 dogs) of the dogs required additional fentanyl to achieve analgesia.

In the present study, the cardiovascular effects of dipyrone were measured in rabbits by use of ultrasonography of the common carotid artery, the heart, and the abdominal aorta. The combination of Doppler flow technology, which provides high-resolution images of blood vessels, with echocardiography and hemodynamic monitoring can yield extensive information about the cardiovascular effects of drugs.[32] Changes in peripheral vascular resistance within the distribution area of measured vessels can also be determined directly by measurement of end-diastolic BFV and indirectly by calculation of the resistance index and pulsatility index.[14,15,32]

Results of the present study indicated that during CRI with propofol, additional injections of dipyrone at 65 mg/kg caused a short-lasting increase in blood vessel diameter by a maximum of 4.7% in the left common carotid artery (after the first dipyrone injection) and 2.9% in the abdominal aorta (after the third dipyrone injection), compared with respective baseline values. Accordingly, peak-systolic BFV decreased by a maximum of 6.5% in the left common carotid artery (after the first dipyrone injection) and 5.7% in the abdominal aorta (after the third dipyrone injection), compared with respective baseline values. Because the changes were not significant, dipyrone bolus injection appeared not to affect vascular diameters and peak-systolic BFV of the studied vessels.

The resistance index decreased from the baseline value slightly (5.3%) but insignificantly in the left common carotid artery within 2 minutes and significantly (11.1%) in the abdominal aorta 4 minutes after the third dipyrone injection. Correspondingly, after the same injections, the pulsatility index decreased slightly but insignificantly at the left common carotid artery, and end-diastolic BFV increased significantly at the abdominal aorta. These findings indicated that bolus injections of dipyrone had a slight vasodilator effect. Our results are supported by findings in another study[33] in which dipyrone administration appeared to exert a relaxing effect on the smooth muscle of the thoracic aorta in rabbits; this effect might have been caused by a degradation product of dipyrone. However, the effects measured within the present study did not appear to be clinically relevant because values of hemodynamic and cardiac variables did not change significantly after the dipyrone injections.

In contrast, bolus injection of dipyrone slightly increased heart rate and MAP in the present study, indicating that cardiac function was well preserved. Administration of propofol alone results in marked hypotension,[13,34–36] but in our study, when dipyrone was administered in propofol-anesthetized rabbits, a significant decrease in blood pressure was not evident. Accordingly, no significant changes in values of echocardiographic variables (fractional shortening, left ventricular end-systolic diameter, and left ventricular end-diastolic diameter) were detected. These results supported the findings of other investigators[4,12] who found that dipyrone injections did not yield major adverse effects on the CNS and a clinically important impairment in hemodynamic function in dogs and humans.

Changes in plethysmographic amplitude were also recorded in the present study. Plethysmography has been used to measure changes in tissue blood volume. During the cardiac cycle, perfused tissue initially expands as the blood flow into the arterioles exceeds that into the capillary beds. Later in the cardiac cycle, accumulated blood drains into the venous system, allowing the tissue blood volume to return to its presystolic value. Specific changes of plethysmographic amplitude and specific features of the waveform can be used to distinguish healthy perfusion patterns from abnormal patterns in the peripheral vasculature.[36] Peripheral vasodilatation is reportedly associated with an increase of the plethysmographic amplitude.[37] In the present study, we detected this phenomenon after dipyrone was injected into the left common carotid artery over 3 minutes, corresponding to the slight but insignificant increase in blood vessel diameter during this period and a significant decrease in resistance index within the distribution area of the abdominal aorta.

The ECG was recorded before and at defined points after the first and second boluses of dipyrone were injected. The QT interval is affected by electrolyte imbalances, antiarrhythmic drugs, myocardial ischemia or infarction, hypothermia, and myocarditis, among other factors. The QT interval is known to lengthen as R-R interval lengthens (ie, as heart rate slows). Because of this, the QT interval was corrected for heart rate by use of a standard formula.[38] In the present study, a significant increase in the QTc was detected at 10 minutes after the first dipyrone injection, but all rabbits maintained a sinus rhythm and no arrhythmias were detected during the measurements. Prolongation of the QTc has been

proposed as a risk factor for ventricular arrhythmia.[39,40] However, not all drugs that prolong the QT interval are associated with an increased risk of adverse cardiac effects. Because dipyrone is not known to disrupt regulation of I_{Kr} channels, the detected prolongation might have been secondary to the hemodynamic effects. Additional studies are needed to determine the underlying mechanism and the pathophysiologic importance of the prolongation.

In the present study, noncardiovascular reflexes were not measured during anesthesia because it was important to maintain the position of the ultrasound probe, which was complicated by reflexive movement in the rabbits. We examined the effects of injecting 1 to 2 mL of saline solution on vascular volume by use of ultrasonographic evaluation of the carotid artery and abdominal aorta, and conspicuous changes were not detected. Therefore, we did not take steps to account for the possible effect of the 0.6-mL/bolus injection volume when analyzing our findings.

One limitation of the present study is that ultrasonographic measurements were not obtained simultaneously at the various locations. Therefore, cumulative effects had to be assumed when data were compared among the different sections of the study. However, hemodynamic variables were simultaneously recorded throughout the 3 sections of the study, and when changes in variables such as heart rate, MAP, Spo_2, $PETCO_2$, and rectal temperature after the first injection were compared with those of the second and the third injections, only minor changes in values were evident, implying that repeated dipyrone injections are associated with only minor cumulative effects on hemodynamic function. Another limitation is that, to obtain repeated measurements at the heart and the abdominal aorta at a defined probe position, we did not measure these values at the beginning of anesthesia, before the first bolus of dipyrone was injected. Therefore, possible cumulative effects on the baseline values at these 2 positions cannot be excluded.

A Student *t* test for paired samples was used to assess differences between the value for each time point during the 10 minutes after dipyrone injection and the baseline value. Because the probability of detecting a significant difference when one does not exist increases with number of tests conducted, a post hoc test to adjust findings for the number of comparisons made would have increased confidence in the results. Nevertheless, any correction method would have increased the likelihood of a type II error, and a considerably larger sample size would have been necessary to yield sufficient power for a detailed analysis. For that reason, we decided to use nonadjusted value of *P* as statistical measure of importance, and we consider our results explorative.

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c. Asamhof, Bad Kissingen, Germany.
d. Altromin, Lage, Germany.
e. EMLA (lidocaine and pilocaine), Astra Zeneca GmbH, Wedel, Germany.
f. Vasofix, B. Braun Melsungen AG, Melsungen, Germany.
g. Propofol MCT Fresenius, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany.
h. Anesthesia Workstation, Hallowell EMC, Voelker GmbH, Kaltenkirchen, Germany.
i. S/5 Type F-CM1.00 pressure transducers, Hellige Type 4-327-I, Datex Ohmeda, Helsinki, Finland.
j. Novaminsulfon-ratiopharm 2.5, Ratiopharm GmbH, Ulm, Germany.
k. Delta Select GmbH, Pfullingen, Germany.
l. 9790 C, Vitatron GmbH, Cologne, Germany.
m. S/5 Oxi-Sensor, Type F-CM 1.00, Datex Ohmeda, Helsinki, Finland.
n. FLA 1-MHz 1A, GE Vingmed, Horten, Norway.
o. FPA, 10-MHz 2A, GE Vingmed, Horten, Norway.
p. A/S System FIVE/REM, GE Vingmed, Horten, Norway.
q. SPSS, version 15.0, SPSS Inc, Chicago, Ill.

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