Title: PHARMACOKINETICS AND CARDIOVASCULAR EFFECTS OF PIPECURONIUM BROMIDE (ARDUAN) IN C.A.B.G. PATIENTS

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Introduction: Pipecuronium is a competitive steroidal neuromuscular blocking agent, resembling pancuronium not only in its chemical structure, but also in potency and time course of its neuromuscular blocking effects. This new compound is known to cause less cardiovascular side-effects than pancuronium, therefore we investigated the pharmacokinetic profile and hemodynamic effects of high doses of pipecuronium and the influence of perfusion and cooling on the pharmacokinetic variables in C.A.B.G. patients.

Methods: After giving informed consent 11 patients participated in this study, which was approved by the local Medical Ethical Committee. Following premedication with diazepam 10-15 mg orally, all intravascular catheters were inserted and anesthesia was induced with piritramide 0.3 mg/kg followed by an infusion of etomidate 50 µg/kg/min. Patients were ventilated by mask with 100% oxygen and intubated after completion of the cardiovascular measurements. HR, AP, PAP, CVP, WP and CO were measured before and after induction, as well as before and at 3, 6 and 9 mins after administration of pipecuronium (7.68 mg/m^2 ≈0.2 mg/kg). Subsequently anesthesia was maintained with an infusion of etomidate/sufentanyl and a gas mixture of oxygen/air. Plasma and urine samples were taken according to our standard scheme. Additional plasma samples were taken just before and after the perfusion period. Analysis was performed by a fluorimetric method. The parent compound and its putative hydroxy derivatives were separated by TLC. Limit of detection was 25 ng/ml. Pharmacokinetic analysis was performed on individual data using a computer program based on iterative linear least square regression analysis. The data from this study are compared with those from a different study in 9 patients undergoing head and neck (H&N) surgery, who received 3.84 mg/m^2 ≈0.1 mg/kg pipecuronium only. All results were compared by (un-)paired t-test or Wilcoxon rank sum test, depending on the character of the data and differences in variation coefficients.

Results:

Pharmacokinetic analysis: From both studies the pharmacokinetic parameters based on a two compartment model are listed in Table 1. In the C.A.B.G. patients the calculated elimination t 1/2 during perfusion and cooling was 157±47 mins. The recovery of unchanged pipecuronium from the urine approximated 41% and 74% of the administered dose in 24 hrs in the C.A.B.G. and H&N groups respectively.

Cardiovascular effects: The results are listed in Table 2, together with similar data obtained in a matching control group after an equipotent dose of pancuronium. No complications were seen in the pipecuronium group. In the control group one patient developed tachycardia and ST-depression after pancuronium administration.

Discussion: The comparable pharmacokinetic parameters were not significantly different between the two groups except the distribution volume V1, possibly due to differences in sampling place (peripheral vein vs vena cava superior) and equilibration time for different doses. Perfusion and cooling showed no appreciable effect on the elimination t 1/2 of pipecuronium. However, total urinary excretion in the C.A.B.G. patients appeared to be less than in patients undergoing H&N surgery. Pipecuronium, even after the four-fold ED90 dose, did not show drug-related hemodynamic changes. The only effects were those usually seen during induction of anesthesia. These effects were partially counteracted by pancuronium, however, at the expense of a less favorable O_2 delivery/consumption ratio.

Reference:
Pipecuronium bromide (Arduan), Arzneim Forsch/Drug Res 2A, 30(I), 341-394, 1980.

TABLE 1. Mean values - two compartment model.

	Units	CABG patients	H&N patients	significance
Dose	mg/m^2	7.68	3.84	-
C1	µg/ml	1.58	1.07	-
C2	µg/ml	.406	.263	-
T1	min	8.41	10.9	n.s.
T2	min	170	207	n.s.
V1	ml/kg	102	73	p<.005
Vdss	ml/kg	353	270	n.s.
Cl	ml/kg/min	1.76	1.80	n.s.

TABLE 2. Important differences in cardiovascular profile of pipecuronium vs pancuronium.

Parameter	Units	Pipecuronium 0 mins	Pipecuronium 9 mins	P-value
HR	/min	58.5	58.0	n.s.
CO	l/min	4.7	3.8	<.025
AP S/D	mmHg	124/70	107/61	<.025
WP	mmHg	13	10	<.025
LVSWI	N/m^2	43	32	<.05
RPP	-	7300	6200	<.05
LV Power	Wats	.8	.6	<.05

Parameter	Units	Pancuronium 0 mins	Pancuronium 9 mins	P-value
HR	/min	58.5	63.5	<.05
CO	l/min	5.5	5.4	n.s.
AP S/D	mmHg	128/65	115/64	n.s.
WP	mmHg	12	11	n.s.
LVSWI	N/m^2	50	37	<.05
RPP	-	7500	8800	n.s.
LV Power	Watts	.95	.89	n.s.