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Endobronchial *versus* intravenous application of the vasopressin derivative glypressin during diagnostic bronchoscopy

H-W.M. Breuer, S. Charchut, H. Worth, H.J. Trampisch*, K. Glänzer**

Endobronchial versus *intravenous application of the vasopressin derivative glypressin during diagnostic bronchoscopy. H-W.M. Breuer, S. Charchut, H. Worth, H.J. Trampisch, K. Glänzer.*

ABSTRACT: Glypressin is a vasopressin derivative which is used in the present study to stop pulmonary bleeding. The effects of endobronchially *versus* intravenously applied glypressin were examined during diagnostic fibreoptic bronchoscopy in 27 patients. Transcutaneously measured blood gases and haemodynamics were analysed after 1 mg glypressin was given. The glypressin plasma level was 251 fold higher after the intravenous than after the endobronchial administration. After endobronchial application no significant changes were observed for blood pressure, heart rate or blood gases. Following the intravenous glypressin application there was a significant increase in diastolic blood pressure. The bronchial mucosa pallor appeared earlier after topical than after systemic glypressin application. The haemostyptic effect was similar for both routes of application.

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Department of Cardiology Pneumology and Angiology and *Department of Statistics, University of Düsseldorf, 4000 Düsseldorf, FRG.
**Medical Department, University of Bonn, 5300 Bonn, FRG.

Correspondence: Dr. H.W.M. Breuer, Abt. für Kardiologie, Pneumologie und Angiologie Universität Düsseldorf, MNR Klinik, Moorenstraße 5, D-4000 Düsseldorf, FRG.

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The incidence of severe haemorrhage (>50 ml) during bronchoscopy and transbronchial biopsy ranges from 1 to 4% in the normal host, up to 25% in the immunocompromised patient and 45% in the uraemic patient [1]. Several methods have been proposed for managing pulmonary bleeding. Proper position of the patient with the bleeding site dependent and suctioning the trachea [2] or tamponade of the bleeding source with the bronchoscope may be applied in cases of serious bleeding. A Fogarty catheter for tamponading the bleeding area may be used for bleeding within bronchial segments [3]. The cold saline lavage [4], lung isolation with double lumen endotracheal tubes [3], and bronchial artery embolization [5] should be reserved for massive haemoptysis.

Stimulated by positive experiences with topically applied ornipressin [6] and systemically given vasopressin [7], we inaugurated treating massive haemoptysis in intensive care patients with the vasopressin derivate [8] glypressin (tri-glycyl-8-lysine-vasopressin; Ferring).

As we have experienced good management of lung bleeding by endobronchial application of glypressin, the present study, investigating the drug's effects on haemodynamics and transcutaneously measured blood gases during diagnostic fibrebronchoscopy was performed.

The six minute interval for analysing the observed effects was chosen to be practicable concerning the whole time course of bronchoscopy on one hand and being probably long enough to detect relevant side effects on the other hand.

The endobronchial and the intravenous route of glypressin application were compared.

Methods

Patient characteristics

Twentyseven patients selected for diagnostic fibrebronchoscopy were enrolled in the study. Written informed consent about the risks of bronchoscopy and the possible ways to manage complications was obtained from all subjects before starting the procedure.

The studied group comprised 6 women and 21 men; the mean age of the subjects was 59.3±2.4 yrs (range 22–81 yrs). Twenty-one of them were smokers. About 10 minutes before intubation of the bronchoscope and just before premedication, 10 showed raised systolic artery pressure (>140 mmHg), 4 raised diastolic artery pressure (>90 mmHg). Mean heart rate was 85±3 beats per min. Mean body mass index was 23.1 $kg \cdot m^{-2}$. The following leading diagnoses were made after bronchoscopy and pathological examination of the obtained specimens: 16 × bronchial carcinoma, 4 × bronchitis, 2 × interstitial fibrosis, 2 × pneumonia, and in 3 cases there was no pathological finding.

Premedication and monitoring

Premedication was performed in 14 patients with midazolam (usually 0.1 $mg \cdot kg^{-1}$; Roche) and in 13 with diazepam (usually 0.2 $mg \cdot kg^{-1}$; Roche) given intravenously 5 min before endoscopy. 15 mg hydrocodon-HCl (Knoll) were administered subcutaneously and 0.5 mg

atropine sulphate (Braun) were given intravenously. The larynx, trachea and bronchi were anaesthetized with 1% lidocaine (Astra) *via* the bronchoscope (type BF 1 T10 Olympus). The major portion of the applied lidocaine was immediately suctioned after instillation. Usually the transnasal route, being anaesthetized with 2% lidocaine gel (Farco Pharma), was preferred for intubation of the instrument.

The examination was performed with the patients lying in the supine position. All patients breathed 10 $l\ O_2 \cdot min^{-1}$ by face mask during the whole procedure.

The blood gases were continuously monitored by a combined transcutaneous Po_2- and Pco_2-electrode ($tcPo_2$ and $tcPco_2$, TCM-UNIT, Radiometer). The sensor was fixed at the subclavian region and heated to 44°C. Comparisons with blood gases measured in an arterialized blood sample from the hyperaemic ear lobe were performed at the start and at the end of the transcutaneous measurement. Arterial blood pressure was monitored with an automatic blood pressure device (Dinamap, Critikon) at two minute intervals. Control measurements of extreme high or low values were performed by stethoscope and cuff method. Heart rate and rhythm were continuously monitored by ECG-scope.

Glypressin application

In cases when unusual bleeding occurred already with mucosal brushing, glypressin was given to prevent further bleeding expected to follow biopsy; in other cases glypressin was given when intensive bleeding followed biopsy necessitating suction almost continuously for at least 5 min in order to keep optimal view.

Every two minutes for 6 min after glypressin application a venous blood sample was drawn from a separate line to measure the actual glypressin plasma level. The glypressin levels were determined by using the cross-reaction (RIA) of glypressin with a vasopressin-antibody [9]. Thus the initial glypressin levels before glypressin application represent the endogenous vasopressin level, being always part of the measured total glypressin level.

A randomization according to year of birth of the patient was performed between endobronchial and intravenous application of glypressin. Sixteen patients received a 1 mg glypressin bolus (5 ml) by the endobronchial route near the site of bleeding (usually no wedging position) *via* the endoscope; 11 by the intravenous one. To clear the instrumentation channel of the bronchoscope 5 ml air injections immediately followed the glypressin application. The small amount of instillated glypressin was not sucked back. After the bleeding stopped, saline lavage (usually 5–10 ml) was performed to remove endobronchial blood and fibrin rests to again achieve optimal view.

Statistical analysis

Data are expressed as mean±SEM. Concerning the patients' characteristics of age, body mass index, initial heart rate, initial blood pressure, and initial transcutaneously measured blood gases, unpaired two-tailed t-tests were performed between the endobronchial and the intravenous group. The distribution of non-numerical data, as of sex and smoking habits was checked by chi-squared analysis. A statistical description of the measured data was performed by analysis of variance between the initial value and the sixth-minute value within the same group of glypressin application and between both groups. The whole analysis was performed by using the BMDP computer package [10]. Values of $p<0.05$ were considered to be significant.

Results

Patients' characteristics

There were no differences in age, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, transcutaneous Po_2, and transcutaneous Pco_2 between the groups receiving endobronchial or intravenous glypressin (tables 1 and 2).

Table 1. – Patients' characteristics according to "endobronchial" and "intravenous" application of 1 mg glypressin (mean±SEM)

	endobronchial (n=16)	intravenous (n=11)
males	12	9
females	4	2
smoker	13	8
non-smoker	3	3
age (yrs)	58±3.4	62±3.2
body mass index ($kg \cdot m^2$)	23.1±1.1	23.2±1.1
carcinoma	7	9

The analysis of possible relationships between the measured data and those patients' characteristics seemed not meaningful, because of extreme imbalance within the subgroups concerning sex, smoking habits, and diagnosis (*e.g.* endobronchial subgroup: 12 males, 4 females; intravenous subgroup: 9 males, 2 females, endobronchial subgroup: 13 smokers, 3 nonsmokers; intravenous subgroup: 8 smokers, 3 nonsmokers). On the other hand a chi-squared test revealed no differences between the distribution of sex and smoking habits between groups.

Haemodynamics and blood gases after glypressin

The initial vasopressin levels between the groups did not differ. The further course of glypressin's plasma level up to the sixth-minute value differed significantly ($p<0.001$, table 3). Because of technical difficulties in blood sampling (lack of good arm veins) only 15 glypressin plasma levels could be determined after endobronchial application and only 8 after intravenous application.

Table 2. – Time course of transcutaneous Po_2 ($tcPo_2$, mmHg), transcutaneous Pco_2 ($tcPco_2$ mmHg), heart rate (HR, min^{-1}), systolic blood pressure (P_{syst}, mmHg), and diastolic blood pressure (P_{diast}, mmHg) following 1 mg glypressin (GLYP) given endobronchially (eb) or intravenously (*i.v.*). The time course of P_{diast} differs significantly ($p<0.05$) between the groups; P_{diast} itself increased significantly ($p<0.05$) in the intravenous group up to the sixth minute. (BR: bronchoscopy; mean±SEM)

		before GLYP	2 min GLYP	4 min GLYP	6 min GLYP	end of BR	8 min later
$tcPo_2$	eb	137±10	134±9	129±8	126±8	132±9	-
	i.v.	161±16	164±14	167±14	164±15	161±19	-
$tcPco_2$	eb	47±2	47±2	47±1	47±1	47±2	-
	i.v.	44±3	44±2	45±2	45±2	46±2	-
HR	eb	99±5	103±4	102±5	103±4	101±3	97±4
	i.v.	84±6	84±5	84±4	87±5	81±5	75±4
P_{syst}	eb	128±6	132±7	127±7	129±8	125±7	116±6
	i.v.	137±7	148±5	151±6	150±7	144±9	135±6
P_{diast}	eb	80±5	80±5	82±6	80±6	77±4	74±4
	i.v.	75±5	85±4	88±4	89±6	79±4	75±4

Table 3. – Plasma level ($pg \cdot ml^{-1}$) of endobronchially and intravenously applied glypressin (GLYP, 1 mg) measured by using the cross-reaction of glypressin with a vasopressin antibody. The difference between both groups and the plasma level increase within each group are significant ($p<0.001$), (mean±SEM)

	endobronchial GLYP (n=15)	intravenous GLYP (n=8)
before GLYP	5±1	7±2
2 min GLYP	57±8	14294±464
4 min GLYP	89±11	11305±305
6 min GLYP	111±13	9804±323

The initial vasopressin level and the further time course of plasma level did not depend on the kind of premedication (diazepam or midazolam) and initial heart rate.

No significant influence on $tcPo_2$, $tcPco_2$, heart rate, rhythm and systolic blood pressure occurred during the six minute period and immediately after the end of the bronchoscopy (table 2). The mean diastolic pressure increased from 75±5 mmHg to 89±6 mmHg (sixth minute) following intravenous application of glypressin but did not change after endobronchial glypressin application (80±5 mmHg to 80±6 mmHg). However, after the end of bronchoscopy - as already before applying glypressin - there were no differences between both groups. Because of difficulties with the measuring equipment complete data were obtained in only 15 out of 16 patients receiving glypressin endobronchially.

The clinically most striking response following either kind of glypressin application was bronchial mucosa and skin pallor. The bronchial mucosa pallor occurred about one minute after endobronchial glypressin application It appeared somewhat earlier after topical than after systemic application. Mucosa pallor seemed to precede skin pallor.

Discussion

The present study describes a new therapeutic scheme to manage pulmonary bleeding. Severe bleeding during diagnostic fibreoptic bronchoscopy was chosen as model for pulmonary haemorrhage.

Resorption of glypressin from the bronchial mucosa could be demonstrated (table 3), yet the achieved levels were lower than after intravenous application. Two minutes after glypressin application the plasma level after intravenous administration was 251 fold higher than after endobronchial application. There was also a different time course in the plasma levels. A continuous increase occurred after endobronchial drug application whereas after intravenous application the highest value was already recorded two minutes after application. Obviously absorption, resorption and diffusion will be responsible for this phenomenon. As the clinically observed mucosal pallor occurred earlier after endobronchial than after intravenous drug application, topical effects of the drug's metabolite lysine-vasopressin must be postulated. A recent report mentioning superior effects of vasopressin-aerosol therapy compared with intravenous drug administration in cutting down bronchial arterial blood flow supports our results [11].

The observations of FORSLING *et al.* [12] are analogous to the present results. When glypressin was given by intranasal instillation, only a small proportion of the administered dose was detected in the plasma. Although the intranasal dose was approximately ten times the intravenous dose, the peak plasma glypressin

concentration was only about 8% of that occurring with intravenous glypressin. So it is not surprising that significant changes in blood pressure or heart rate occurred only after the intravenous application. The bradycardia observed by FORSLING *et al.* [12] may be due to baroreceptor response following the increase in diastolic blood pressure. The increase in diastolic blood pressure, statistically significant but clinically not threatening, became also obvious in our patients (table 2), yet there was no slowing of heart rate. Whether this lack of heart rate slowing may be attributed to the atropine premedication cannot be clarified.

Because of the low plasma levels of glypressin after topical application, side effects cannot be expected after endobronchial glypressin application even if the applied dose is increased. With other drugs, such as catecholamines which are sometimes endobronchially instilled to treat pulmonary bleeding, extreme haemodynamic side effects occur with increasing doses.

The obvious pallor of mucosa and skin after glypressin application should be accompanied by changes in microcirculation and thus in transcutaneously measured Po_2 [13]. As hyperaemia was induced by warming the skin, changes in microcirculation were counteracted. Probably only measurements at 37°C would be able to demonstrate the expected decrease in microcirculation. On the other hand monitoring of the patients' blood gases would have been less sensitive at 37°C compared with 44°C.

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Effets comparés de la glypressine endo-bronchique ou intraveneuse sur les gaz du sang et l'hémodynamique au cours d'une bronchoscopie à visées diagnostiques. H-W.M. Breuer, S. Charchut, H. Worth, H. J. Trampisch, K. Glänzer.

RÉSUMÉ: Pour étudier les effets comparés de la glypressine administrée soit par voie intraveineuse soit par voie endo-bronchique, sur l'hémodynamique et sur les gaz du sang mesurés par voie transcutanée, 27 sujets ont fait l'objet d'une étude au cours d'une broncho-fibroscopie diagnostique. Les gaz du sang mesurés par voie transcutanée, ainsi que l'hémodynamique, ont été analysés après que 1 mg de glypressine ait été administré pour prévenir ou arrêter le saignement pulmonaire. Une augmentation significative du taux plasmatique de glypressine a été observée avec les deux voies d'administration. Le taux plasmatique de glypressine est 251 fois plus élevé après dosage intraveineux qu'après administration endo-bronchique. Aucune modification significative n'a été observée en ce qui concerne la pression sanguine, le pouls ou les gaz du sang, après une application endo-bronchique du médicament. Toutefois, après application intraveineuse de la glypressine, on a noté une augmentation significative de la pression sanguine diastolique. La pâleur de la muqueuse bronchique apparaît plus tôt après application topique qu'après administration systémique de la glypressine. En ce qui concerne l'effet hémostatique, on n'a pas vu de différence évidente selon les deux voies d'application.

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