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A randomized double-blind trial of glypressin in the management of acute epistaxis*

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SUMMARY

This is the first randomised double-blind trial of glypressin in the treatment of acute epistaxis, where no localized bleeding point was found and where the patient would normally be treated with a form of nasal packing. It shows a statistically significant benefit with the intravenous drug compared to placebo. In addition, the dose of glypressin used to achieve control appears to be free of major side effects. Acute epistaxis is a common problem, nasal packing is unpleasant and not without side effects, and therefore an alternative form of treatment would have clear advantages. The mechanism of action of glypressin is discussed along with the implications of the results for the future role of glypressin in the treatment of acute epistaxis.

Key words: glypressin, epistaxis, nasal packing

INTRODUCTION

The conventional treatment of acute epistaxis requiring admission to hospital depends on nasal packing in some form with the occasional, severe case requiring operative intervention such as carotid ligation as discussed by Shaheen (1970) or selective vessel embolization as described by Strutz and Schumacher (1990). Adequate packing is an unpleasant procedure for the patient and may be difficult to achieve in the presence of unfavourable anatomy, such as a deviated nasal septum. In addition, total nasal obstruction leads to a dry mouth and reflex pulmonary changes as described by Widdicombe (1986). Thus, methods of treatment not involving packing would have clear advantages.

Vasopressin has been used for nearly 30 years as an agent to control bleeding from oesophageal varices. It is thought to act by constriction of the splanchnic arteriolar bed, causing an increase in resistance to inflow of blood to the gut and, consequently, a reduction in portal venous pressure (Shaldon et al., 1961). Several studies have confirmed the effectiveness of vasopressin in the management of bleeding oesophageal varices (Soderlund et al., 1990; Freeman et al., 1982). However, side effects, especially cardiovascular ones, limit application to other sites such as the nose and have led to alternatives being sought.

One such alternative is glypressin (triglycyl-lysine-vasopressin). Glypressin has been shown to have fewer side effects and longer duration of action in acute oesophageal haemorrhage (Freeman et al., 1989; Walker et al., 1986; Soderlund, 1987). In addition, it requires only intermittent intravenous bolus injections, as opposed to continuous infusion for vasopressin. When injected intravenously the glycyl-residues of the molecule are cleaved off by enzymatic action to generate the active substance, lysine-vasopressin (Forsling et al., 1980). Glypressin can therefore be regarded as a circulating depot-releasing lysine-vasopressin at a constant rate. After an intravenous dose of 7.5 µg/kg of glypressin, sufficiently high concentrations of the biologically active lysine-vasopressin can be maintained for 2 h as has been shown by Forsling et al. (1980).

This study was designed to examine the applicability of glypressin as an alternative to nasal packing in the management of severe acute epistaxis.

MATERIAL AND METHODS

Subjects

All patients presenting to the ENT Department of St. Mary's Hospital with acute epistaxis warranting admission to hospital were considered for inclusion in the trial.

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Exclusion criteria were: (1) pregnancy; (2) any history of rheumatic fever, ischaemic heart disease, and left ventricular failure; (3) diastolic blood pressure over 120 mm Hg; (4) patients with well-localized and easily-accessible bleeding points. In the event of failure to control bleeding within 30 min, the patient was treated with anterior nasal packing in the conventional manner. Written informed consent was obtained from all patients and the trial was approved by the Paddington and North Kensington (now Parkside) Ethics Committee.

Methods

The patients were given an intravenous bolus dose of 1 mg glypressin in 5 ml diluent or an equivalent volume of placebo in a randomized and double-blind fashion. Blood was taken immediately prior to this for serum sodium estimation. Pulse, blood pressure and side effects were noted every 30 min for 4 h. At the end of this time a further blood sample was taken for serum sodium estimation. The patients were admitted to hospital and any subsequent rebleeding or side effects noted. The in-patient stay was managed along conventional lines. Any deviations from the protocol were noted. A successful treatment was deemed to have occurred if bleeding ceased within 30 min of injection of glypressin or placebo.

Treatment success was measured using Fisher's exact test. Changes in serum sodium concentration, pulse and blood pressure and maximum values of pulse and blood pressure were compared using the paired t-test.

RESULTS

During the two-year study period, 190 patients presented with acute epistaxis severe enough to merit admission to hospital. Of these, 23 patients (12%) conformed to inclusion criteria and of these, 20 (mean age 58; range 31-82) consented to participate in the trial. Eleven patients received glypressin (Table 1 and Figure 1). Control was achieved in eight cases, although bleeding recurred in two of these, 60 min after initial control. The mean time to control the epistaxis in these patients was 11.5 ± 6.4 min (range 5-25 min). Placebo was given to nine patients, control being achieved, after 10 min, in one case. Glypressin was significantly better at achieving control than placebo (p=0.0183). There was no difference in the pulse, blood pressure and serum sodium between the test and control groups (Table 2). However, subjective side effects were only reported in the test group. Abdominal colic was the most common (8 out of 11), tenesmus and flushing occurred in 3 out of 11 of the test group. The tenesmus was severe in one patient, all the other side effects were mild.

DISCUSSION

The mechanism of action of glypressin in the control of epistaxis is believed to be via selective vasoconstriction, resulting in reduction of nasal blood flow arising from the branches of the external carotid artery and shunting of this

Table 1. Table of age, sex, control of epistaxis, and side effects in glypressin and control groups. Y: control; F: failure (see text for definitions). Time to control is: time taken to achieve control in min. P: packed after 30 min. Side effects: T: Tenesmus; C: Colic; F: Flushing.

	Patient number	age	sex	control	time to control	side effects
Glypressin	1	74	F	y	10	T, C
	2	63	M	y	5	T, F
	3	49	M	N	p	T, C
	4	31	F	y	5	F
	5	40	M	y	15	C
	6	73	M	y	10	C
	7	82	F	y	12	C
	8	49	M	N	p	C
	9	64	M	y	25	C, F
	10	57	M	N	p	
	11	42	M	y	10	C
Placebo	1	50	M	N	p	
	2	70	F	N	p	
	3	72	F	N	p	
	4	55	M	y	10	
	5	67	M	N	p	
	6	55	M	N	p	
	7	49	M	N	p	
	8	37	F	N	p	
	9	81	M	N	p	

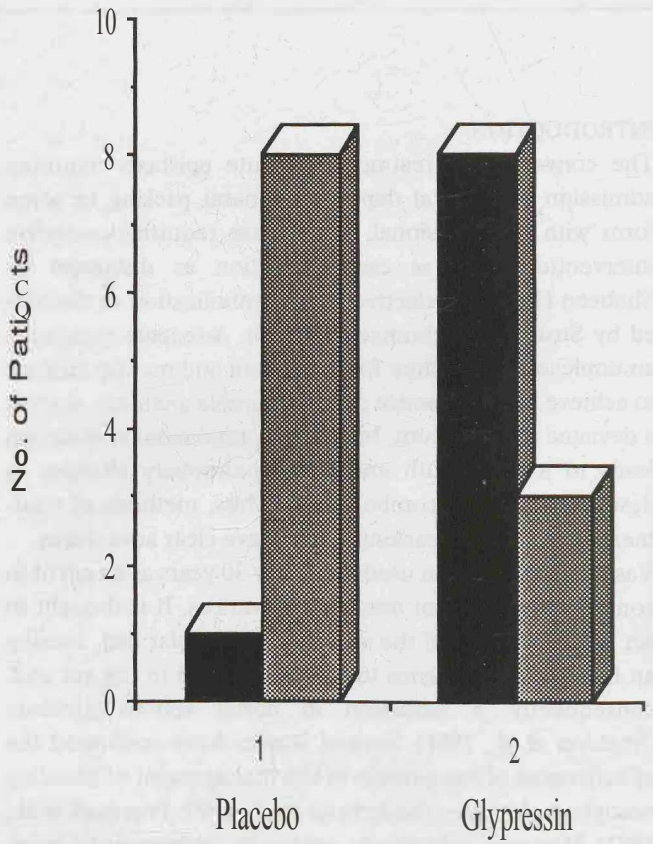

Figure 1. Histogram showing numbers controlled with placebo and glypressin. Solid box is control achieved, shaded box is anterior nasal pack required.

Table 2. Table of mean sodium, pulse, and blood pressure for patients receiving glypressin and placebo, from time of administration (in hours).

	time from injection	serum sodium	pulse	systolic BP (mmHg)	mean BP (mmHg)	diastolic BP (mmHg)
Glypressin	0	138±-3				
	0.5		88±16	145±38	115	84±18
	1		88±11	147±32	117	87±14
	1.5		85±10	147±30	119	90±9
	2		85±9	155±33	123	90±8
	'2.5		84±8	150±29	119	88±15
	3		81±9	168±33	129	89±14
	3.5		80±9	156±33	125	93±15
	4	137±4	81±11	172±34	135	97±12
Placebo	0	138				
	0.5		86	148	119	90
	1		85	166	125	84
	1.5		84	156	120	84
	2		83	159	122	85
	2.5		82	154	124	94
	3		82	166	131	95
	3.5		81	176	143	110
	4	138	81	169	133	97

flow to the internal carotid artery. The effects of glypressin on human nasal mucosa! blood flow have been studied by Bentle et al. (1986) using mxe wash-out. This showed a dose-dependent reduction of nasal blood flow resulting from both intravenous and intranasal glypressin, which is interpreted as being a result of the activating effect of glypressin on the smooth muscles in the walls of the resistance vessels, mainly small arteries and arterioles as shown by Altura (1973). Glypressin also reduces nasal airway resistance, as measured by anterior rhinomanometry. This indirectly implies that it may have an effect on the capacitance vessels.

Vasopressin infusion is known to have a rapid beneficial effect on haemorrhage from the external carotid artery. Angiographic and haemodynamic studies in dogs by Bentle and Flisberg (1979) have shown that vasopressin shunts blood from the external to the internal carotid artery. It is not yet established if the same shunt exists in man. If this were to occur in man, it may worsen nasal bleeding dependent on the anterior ethmoid artery, a branch of the internal carotid artery, rather than ease it. This effect may have contributed to our failures and may limit its future use to epistaxis arising from branches of the external carotid artery.

The reported side effects of glypressin are mainly gastrointestinal, cardiovascular and endocrine. Abdominal colic, loose and frequent stools are due to increased peristalsis. Serious ischaemic sequelae affecting the bowel have been reported but are extremely rare (Stotnick and Teigland, 1951; Brearley et al., 1985; Schmitt et al., 1987). The cardiac effects include bradycardia, arrhythmias, reduced coronary blood flow and a drop in cardiac output. Peripheral vasoconstriction can lead to arterial hypertension and transient blanching, followed by rebound cutaneous flushing. The anti-diuretic effects are not seen unless the use is prolonged and over 2 days. Glypressin is contra-indicated in pregnancy due to its effect on smooth muscles. Mild gastrointestinal side effects were common in our study, but there was no difference in the pulse, blood pressure, serum sodium levels or any other serious side effects. We used a single dose of 1 mg, whereas in its established use in acute oesophageal bleeding a dose of 2 mg is used and repeated every 4-6 h until bleeding is stopped, up to a maximum of 72 h. Cardiovascular complications have been reported in association with the latter regimen. It appears likely that a single 1-mg dose of glypressin is free of cardiovascular problems. This needs further evaluation.

The dose-response curves for the reduction of nasal mucosa! blood flow are similar for both the intranasal and intravenous routes. However, topical application using glypressin in 3% carboxymethyl cellulose gel required fifty times the dose of the intravenous route for the same effect as shown by Bende et al. (1986). A recent study by Bende and Pipkorn (1990) evaluated a different gel preparation, 3% hydroxyethyl cellulose (Natrosol), and showed it to be ten times more efficacious in reducing the nasal blood flow compared to the 3% carboxymethyl cellulose gel. Therefore, using this new vasoconstrictor gel as a carrier, topical application of glypressin requires a five-fold greater dose compared with the intravenous route, to achieve the same reduction in nasal blood flow. However, when tested in epistaxis, Bentle and Pipkorn (1990) found no significant benefit using the topical preparation compared with placebo. This suggests that reduction in superficial nasal mucosal blood flow is not the only important factor in stopping epistaxis. Significant benefit in controlling epistaxis using the intravenous preparation, as shown by our study, would support a theory that most benefit in controlling epistaxis is achieved by the action of intravenous glypressin on the deeper-situated resistance and capacitance vessels.

It is concluded that there is a place for intravenous glypressin in the management of acute epistaxis in a selected group of patients. A larger-scale, probably multicentric trial would seem indicated.

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