An Early Look at the Therapeutic Uses of Some New Vasopressin Analogs in Gastroenterology¹

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Natural vasopressins have been used, with varying success, in attempts to stop bleeding from esophageal varices for over two decades. Reasons for lack of success include (a) failure to induce a sufficiently prolonged and constant vasoconstrictor effect at the bleeding site, (b) dangerous side-effects, and (c) release of plasminogen activator induced by the peptides which can lyse any clot as it forms.

In the last decade analogs of vasopressin have been developed with a prolonged action, using two separate principles of chemical modification: (1) hormonogens, and (2) blockage of sites of inactivating enzymatic cleavage (in particular “carba” analogs without a disulfide bridge). These two categories of analog are compared here: the carba analogs have the advantages of high potency (higher than the parent hormone) with prolongation, but are also very active on the plasminogen activator release system. The hormonogens combine prolongation with low potency, but have lost not only a releasing action on plasminogen activator, but also, by virtue of altered release kinetics, have effectively lost cardiovascular toxicity.

Mechanisms of analog action and receptor interaction are presented, along with initial clinical experiences.

Over 20 years ago an aqueous mixture of vasopressins (VP) was first used intravenously in an attempt to stem the flow from bleeding esophageal varices [1]. This application of one of the many actions of VP, i.e., contraction of smooth muscle associated with the bleeding site, followed recognition that the gut is highly sensitive to VP [2]. Quantitative studies in the rat, using ⁸⁶Rb [3] to measure both cardiac output and regional organ flows [4] showed that the highest sensitivity of both vascular and non-vascular smooth muscle was in the gut and in the estrogenized uterus [4,5]. Decreases in blood flow and increases in motility and tone occurred even at subpressor doses, leaving the kidney and liver relatively unaffected until much larger doses had been given. Other work demonstrated that both large [6] and small [7] veins in the abdominal cavity were constricted. More recently, it has been shown that the shutdown of blood flow to the pancreas is the basis of “ADH inhibition of secretin-induced exocrine pancreatic secretion” [8].

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The spectrum of biological actions of VP is one of the widest of any known substance, from claims of memory consolidation and known hormone releasing actions in the CNS to contractile and permeability effects in all peripheral organs [2,4]. At about the same time that VP was first being used in cases of bleeding into the gut lumen, it was also recognized as the most potent known "releaser" of plasminogen activator [9]—hardly an activity to be desired in a bleeding state.

Because of the complexities of combinations of biologically advantageous and disadvantageous actions, along with limitations imposed by the short biochemical and response half-lives of the parent hormones, efforts have been directed over the past decade to "reshuffle" their advantages and to prolong their actions by synthetic alteration of the natural cyclic nonapeptide. The present communication deals with some of the details of these efforts in terms of both mechanism of action and apparent clinical effects.

THE LONG-ACTING VP ANALOGS—TWO APPROACHES

Two principles of prolonging the action of oligopeptide hormones have so far been used: (a) retardation of the degradative action of enzymes which inactivate the hormones, or (b) utilization of these and/or similar enzymes in order to cleave inactive synthetic prohormones or hormonogens, thereby releasing the active hormone at a slow rate. We can illustrate this in the case of VP by indicating preferential sites of primary cleavage in the sequence formula of the molecule, which causes immediate inactivation:

\[
\begin{array}{cccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 \\
\text{NH}_2\text{-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-} & \text{Lys} & \text{Gly-NH}_2 \\
\text{S} & \text{Arg} & \text{S} \\
\end{array}
\]

(LVP)

(AVP)

In order of probable quantitative significance, the inactivating cleavage sites are: (a) 1-2 C-N (aminopeptidase), (b) 8-9 C-N ("carboxamidopeptidase"), (c) 1-6 S-S (disulfide reductase), (d) 7-8 C-N ("post-Proline cleaving enzyme"), (e) 6-7 C-N ("pressinoicase"). Of these five sites, the first three would account for the vast majority of inactivated peptide since the first is present intracellularly in all tissues and the others are in liver and kidney, each of which has a very large blood flow [4]. The fifth site has so far been localized to the median eminence region of the midbrain [10] so that, while not quantitatively significant, it could still be functionally important if part of the VP molecule were acting in the midbrain in different areas than those associated with the parent hormone. Change in the biological spectrum of activity—in contrast to prolongation of action—generally involves the side-chains rather than the backbone of a bioactive peptide.

The classical first approach to prolonging activity is prevention of aminopeptidase action by desamination of the N-terminus [11]:

\[
\begin{array}{cccccccccc}
\text{CH}_2\text{-CH}_2\text{-CO-Tyr-Phe-Gln-Asn-Cys-Pro-} & \text{Lys} & \text{Gly-NH}_2 \\
\text{S} & \text{Arg} & \text{S} \\
\end{array}
\]

(dLVP)

(dAVP)

Blockage of enzymes operative at sites (b) and (c) can be achieved, for instance, by replacement of L-Arg by D-Arg, and this is so drastic a steric alteration that the
desired smooth muscle actions of VP are almost completely eliminated in, for instance [8-D-Arg]-VP:

\[
\text{NH}_2\text{-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH}_2 \quad \text{(DAVP)}
\]

Thus, if we combine both of the above in 1-desamino-[8-D-Arg]-VP (desmopressin, dDAVP) the resultant molecule has practically no pressor or other smooth muscle contractile activity, but has very enhanced and prolonged antidiuretic action and release effects on plasminogen activator (PA) and factor VIII (F-VIII) [27]:

\[
\text{CH}_2\text{-CH}_2\text{-CO-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH}_2 \quad \text{(dDAVP)}
\]

These properties have made dDAVP the drug of choice in the management of diabetes insipidus [28] and also of use in treating actual or potential bleeding episodes in hemophilic patients and those with von Willebrand's disease [27].

Finally, site (c) can be stabilized by supplanting the S-S bridge by a thioether (SCH\(_2\) or CH\(_2\)S) or an ethylene (CH\(_2\)CH\(_2\)) bridge (referred to here as monocarba and dicarba, respectively) [12]. A schematic representation of a monocarba analog of VP is shown below:

\[
\text{CH}_2\text{-CO-Tyr-Phe-Gln-Asn-NH-CH-CO-Pro-Arg-Gly-NH}_2 \quad \text{(dCAVP)}
\]

where \(Y = \text{CH}_2\text{S or SCH}_2\) (if \(Y = \text{CH}_2\text{CH}_2\), the molecule is dicarba [dCCAVP]).

Except for the case of antidiuresis, where dCCAVP has both high potency and prolonged action, dicarba analogs have prolonged VP-like actions but low potency [12,13] so that large doses would be required in therapeutic applications. The monocarba VP analogs (either at sequence position 1 or 6) however have not only a prolonged action, but their potency is higher than that of the parent hormone [14]. Physical chemical parameters related to conformation in solution do not reveal any alteration by monocarba substitution of the active stereochemical form of the parent molecule [13].

The second principle for obtaining prolonged action is illustrated by the formula:

\[
\text{X-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH}_2
\]

where \(X = \text{N-terminal peptide chain extensions, the most useful of which is Gly-Gly-Gly} [15]\). Such hormonogens, including N\(^2\)-glycyl-glycyl-glycyl-[8-lysine]-vasopressin (Glypressin = tGLVP) provide an inefficient approach to prolonging activity because during the time interval required for aminopeptidase "activation" by cleavage of the added N-terminal glycines, other enzymes inactivate by cleavage of the C-terminal tripeptide (and for this reason it is 8-Lys and not 8-Arg, since in the latter case inactivation would be even more rapid and efficient [4]). At most only 10% of an injected dose is "activated" to release the effective nonapeptide, LVP. The remainder
consists of inactive fragments [16]. On the other hand, what is released is a natural hormone or fragments thereof and the rate-limiting N-terminal cleavage-activation so alters distribution kinetics that cardiotoxic levels of LVP are not released into the circulation even at bolus i.v. doses of tGLVP 1,000 times greater than ordinary therapeutic ones. Thus, the safety factor seems to favor the hormonogen approach.

Experimental data to prove LVP release, and study its kinetics, was obtained in cats [16] which allowed serial sampling of sufficient blood for parallel estimations of both plasma antidiuretic activity (rat assay) and "LVP" concentrations by RIA. The inverted commas about LVP refer to the fact that the Ab for LVP is sensitive to the C-terminal tripeptide, so that it cannot distinguish between tGLVP and LVP or even some fragment thereof. The time courses of both parameters suggested that tGLVP per se disappears from the circulation as rapidly (3-min half-life) as most other oligopeptide hormones, with a subsequent slow rise in both activities to peak at about 20 min. This was followed by a slow disappearance curve which was hard to quantitate. When release kinetics are estimated by biological action on the target organ, response durations vary greatly depending upon the organ and, in the case of the uterus, very much also on the stage of the estrus cycle. Thus, in man durations vary from 120 min on gut motility and facial blanching to over 8 h in the just pre-menstrual uterus after a single bolus dose of about 5 mcg/kg. Since it seems highly unlikely that injected peptide would still be circulating 8 h after injection of a hormonogen, the suggestion has been made both for dDAVP and tGLVP that some sequestration may occur in a "receptor compartment" which protects the peptide from inactivating enzymes [12,14].

VP AND VP-ANALOG ACTIVITIES OF RELEVANCE TO GASTROENTEROLOGY

Ever since crude posterior pituitary extracts were available, it has been known that they induce gut hyperperistalsis involving colic and/or diarrhea. While this is invariably labelled as an "undesirable side-effect" of any VP preparation it may well be clinically useful and desirable for patients bleeding into the gut lumen, particularly those with cirrhosis. Acceleration of the passage of blood shortens transit time and diminishes the nitrogenous substrate that induces hepatic coma.

Of greater importance, however, is the action of VP and its analogs on gut blood flow. Figure 1 compares LVP and tGLVP in rat experiments [4]. The natural hormones have the same short actions in reducing gut blood flow as they do in eliciting general pressor and antidiuretic responses, while the hormonogen produces much more prolonged blood flow effects. Equipotent doses demonstrate that the monocarba VP analogs are 10 to 100 times more potent than the hormonogen in reducing blood flow. Similar results have been obtained with both the rat and the human uterus, particularly when the latter is just pre-menstrual [4,17,18] and this has been the basis of a successful pilot trial of the efficacy of tGLVP in the control of menorrhagia and metrorrhagia [19]. Thus, if potentially toxic vascular actions on the coronary circulation can be substantially decreased (as in the case of tGLVP) all of the remaining vasopressin-like hemodynamic response pattern is useful in any bleeding state. If these vascular effects are combined with hyperperistalsis without impairment of blood clotting, we have a constellation of changes optimal for the patient with GI bleeding. Table 1 documents that both in healthy volunteers and in patients with advanced liver cirrhosis, tGLVP administration does not result in PA release, whereas LVP has a marked, if short-lived, effect.
PLATE 1. The action of tGLVP (4 mg i.v.) in a patient with heavy bleeding from esophageal varices. Photographs at the same site in the lower esophagus with a fiberoptic endoscope before (left) and 20 min after (right) the first tGLVP injection (cf. [26]).
VASOPRESSINS IN GASTROENTEROLOGY

**FIG. 1.** Hemodynamic responses in anesthetized rats to injection (at time 0 on the abscissa) of 10 ng LVP/100 g body wt (dashed lines) vs. 100 ng tGLVP/100 g body wt (solid lines). The LVP dose was just pressor, the larger tGLVP dose not at all (BP = blood pressure in mm Hg). Ut = total uterine blood flow and GIT = total gut blood flow (measured by *Rb distribution) in % of pre-injection levels. CO = cardiac output in ml/min/200 g body wt. The prolonged responses in visceral blood flows shown after tGLVP are identical with those observed after 10 ng/100 g doses of dCAVP.

**TABLE 1**

| Substance (Dose, Total) | -15 | 0   | +15 | +45 | +75 min |
|------------------------|-----|-----|-----|-----|---------|
| **LVP—10 µg**          |     |     |     |     |         |
| Controls (n = 5)        | 9.1 | 9.0 | 27.5*| 17.3*| 13.3    |
| ±1.2                   | ±0.9| ±1.9| ±1.8| ±1.4|         |
| Patients (n = 7)        | 28.6| 22.5| 60.7*| 36.0| 24.6    |
| ±14.2                  | ±11.2| ±15.2| ±11.4| ±9.8|         |
| **tGLVP—0.75 mg**      |     |     |     |     |         |
| Controls (n = 5)        | 8.3 | 8.2 | 8.8 | 10.7 | 11.6    |
| ±1.0                   | ±0.7| ±0.7| ±1.1| ±0.6|         |
| Patients (n = 7)        | 24.1| 19.2| 24.6| 24.9 | 24.6    |
| ±10.1                  | ±8.7| ±12.2| ±8.2| ±9.9|         |
| **tGLVP—2.0 mg**       |     |     |     |     |         |
| Patients (n = 3)        | 52.9| 48.7| 53.4| 51.7 | 51.4    |
| ±10.1                  | ±8.9| ±10.2| ±10.3| ±10.1|         |

PA levels in venous blood 15 min before (-15) peptide infusion, at the start of infusion (0) at the end (+15 min) and at 30 and 60 min after the end of the infusion (+45, +75 min, resp.). Proposit: 5 healthy normal volunteers vs. 7 patients with advanced liver cirrhosis, documented esophageal varices and abnormal liver function tests. Substances compared: LVP vs. tGLVP. Note that both controls and cirrhotics responded to LVP with a short-lived rise in PA (Euglobulin Lysis Time units) while neither group responded to any dose of tGLVP (Cash JD, Prowse C, personal communication). Mean values ± SEM presented. * = value significantly higher than the -15 baseline level.
If the principal mechanism of action of a hormonogen is merely to release LVP slowly, what then are the advantages over slow, controlled administration of LVP i.v. or i.a.? Intra-arterial infusion from a pump should theoretically have less of a PA release action than i.v. infusion [9] but it is difficult and time-consuming to place the catheter so that the perfused area includes the probable bleeding site and the catheter can be left in place only a limited time, which may not be long enough to ensure closure of a variceal wall defect. Intravenous drip infusion is hard to control and carries with it the danger of overdosage and toxicity. Intravenous pump infusion of low LVP doses could well compete with tGLVP, but only in those centers in which sufficient personnel could always be devoted to careful monitoring of all variceal bleeders on an intensive care unit, and those personnel all had the requisite training and sufficient reliable pumps were at hand. Since, however, conditions prevailing in some university hospital centers with a low patient load do not prevail for most patients who arrive bleeding at hospitals for treatment, it would seem at least to the present authors that building in prolonged action and engineering out—on a kinetic basis—the more dangerous and lethal of the side-effects on a molecular basis gives tGLVP definite advantages over LVP. This is particularly so if we consider administering one of the two peptides at home or outside of a hospital environment. Finally, it is not yet clear whether the only difference between tGLVP and LVP is the kinetics of distribution of the nonapeptide. So far, even low rates of LVP infusion have been followed by rises in PA plasma levels, while even large doses of bolus injection of tGLVP have not. This cannot yet be explained, but the difference to the bleeding patient should be of importance to treatment.

THE CLINICAL USE OF VP-ANALOGS IN GASTROENTEROLOGY

Glypressin has been tested in four gastroenterological situations to date:

**Bleeding Esophageal Varices**

Hemorrhage from varices remains a very serious problem which neither intravenous nor intra-arterial administration of natural VP has been demonstrated to solve [20]. The mortality of a large second or third bleed in a decompensated cirrhotic patient remains between 60 and 80% in various reports [21,22]. Careful use of VP or correct placement of a Blakemore-Sengstaken tube improves results, but both procedures require great skill and experience for successful use, and these latter parameters are not available at all clinical establishments—which often results in long and dangerous transport of actively bleeding patients to specialized centers. When one looks at the walls of the submucosal varix, particularly near the site of a hemorrhage, there appears to be little smooth muscle to respond to any VP stimulus by contraction. In fact, the suggestion has been made on the basis of X-ray and balloon studies of experimental cirrhosis in dogs and also in patients [23] that the VP effect is actually on the smooth muscle of the lower one-third of the esophageal wall. Theoretically, constriction of esophageal smooth muscle may shut off blood flow in the penetrating vessels connecting the para-esophageal coronary vein with the submucosal varices (Fig. 2). If this mechanism is valid, it is clear that any pharmacological effect, to be useful, must be continuous for a sufficiently long period to allow the defect in the wall to seal, close off, and organize, and this long-acting activity must not involve an increase in plasma PA levels. A further mechanism of VP action in variceal bleeding is the documented [7] prolonged and significant decrease in portal venous pressure induced particularly by tGLVP, which would be reflected into the coronary vein. Since VP and tGLVP are both venoconstrictors in the abdominal
cavity, the decrease in portal venous pressure must result from a decreased arterial inflow into the bed drained by the portal vein (unless, in addition, the portal vein reacts differently to VP peptides than the other small and large veins in the visceral bed).

In a recently published preliminary series of heavy variceal bleeders, tGLVP therapy with a mean treatment duration of 5 days was associated with a 13% mortality, compared with 67% in the control group which received either no peptide drug or only intravenous Pitressin. The only other therapeutic measures used (Blakemore-Sengstaken intubation, blood replacement, frequent bacotracin enemas) were applied to both the treated (tGLVP) and control groups [7]. The acute effects of tGLVP have been observed directly by fiberoptic esophagoscope and sequential color photographs in such patients and one case is so documented in Plate 1 (courtesy of Dr. A. Thiede, Christian-Albrechts-Universitaet, Kiel, FRG).

Clearly, in variceal bleeders as in peptic ulcer bleeders, more extensive clinical data are needed. We still do not know even in the small series already treated whether tGLVP changed the ultimate prognosis of these patients.

Bleeding Peptic Ulcers, Both Gastric and Duodenal (24)

In the first published series of patients to receive tGLVP, 9 of the 11 gut bleeders had peptic ulceration with acute onset of heavy bleeding starting from an otherwise compensated and "normal" baseline state. Most of the cases had X-ray proven diagnoses before the bleeding episode in question, and many had bled once previously but had not been subjected to gastric resection. The therapeutic approach was adapted to the trial—in order to try to evaluate the effect of tGLVP, the patients were treated only with blood replacement at a rate which allowed them to reach a balanced state (with respect to Hb and Hct levels) during 1–3 days of close observation in hospital with no other medication. These balanced states were established at quite low levels (e.g., about 8–9 g% of Hb (Fig. 3)) with an unchanged rate of transfusion which was then equated to the rate of blood loss from a hypovolemic patient. At this
point tGLVP was administered at a dosage of 50 mcg/kg/day in divided doses every 6–8 h i.v., and blood replacement was either stopped or slowed—it was in no case continued at the same or a greater rate than before onset of drug therapy. No other drugs were used. In all patients in this small group, the onset of tGLVP therapy was associated with a rising curve of Hb, Hct, and rbc levels, as well as of arterial BP. Stool benzidine tests showed that bleeding had stopped within 2 days after the onset of tGLVP and all of the patients were discharged in good condition within one week. Under ordinary conditions, continuous heavy bleeding over 3–4 days would have been taken as indication for surgical intervention.

In addition to this therapeutic action, later experience has shown that tGLVP may be useful in rapid prognosis. It seems that the action of tGLVP is useful in treating blood loss from small vessels in shallow ulcers. If the gastro-duodenal artery has been eroded, no vasoconstrictor drug can stop the flow and a lack of response to tGLVP (given in as high a dosage as 3–4 mg q 6–8 h) has been considered as indication for prompt surgical intervention [26].

FIG. 3. Responses (BP in mm Hg, thin line, Hb levels in gm %, heavy lines) of six patients with heavy bleeding from a proven shallow peptic ulcer, treated with tGLVP (GP) at the dosage levels given (GP − 50 = 50 µg/kg/day in 3–4 divided doses, GP − 100 = 100 µg/kg/day in 3–4 divided doses) over the period indicated by the arrows. Days = hospital days. Numbers above abscissa = no. of blood units (= 500 ml) transfused that given day. Large no. in each square is pt. no. See text and [24].
**Profuse Mucosal Bleeding from Gastritis**

Several cases of profuse GI bleeding from endoscopically verified, diffuse hemorrhagic gastritis have occurred in patients with no previous symptoms of peptic ulcer, but who were on high doses of aspirin, butazolidine, etc., for arthritic conditions. Their response to tGLVP appeared to be both marked and rapid. Bleeding stopped within 20 min as monitored by direct intragastric observation [24,26].

**Control of Profuse Bleeding During Upper Abdominal Surgery Related to Liver Cirrhosis**

While this application might eventually prove to be generally useful in abdominal surgery or trauma because of the prolonged arteriolar and venoconstrictor action of the drug, the action is most marked in portocaval and splenorenal shunt surgery. The presence of a profuse bed of collateral veins around the liver combined with portal venous hypertension often results in very profuse small vessel bleeding during the surgery which is hard to control. One mg i.v. doses of tGLVP have been reported to result in lessening or stopping of this bleeding within 5 min and these findings could be correlated with a decrease in portal venous pressure measured by direct venipuncture [7]. There was no evidence that this method of hemostasis was associated with any bledding “rebound.”

There is no experience as yet with the action of VP-analogs in bleeding from the lower bowel. The blood flow effects of the analogs on the gut in rats was measured in the entire gut at once and no differentiation was made between different parts. Since there is a clear clinical response to upper GI bleeding, we know that the pharmacological action involves the upper gut—only further experimental and clinical observation will determine whether the actions are equally valid on the lower bowel as well.

The only human experience with any carba modification of VP (1-desamino-6-monocarba-AVP) has involved healthy, non-pregnant women volunteers. In these studies of uterine blood flow and intraluminal pressure tGLVP was shown to be one-tenth as potent as dCAVP in reducing endometrial and myometrial blood flow and increasing luminal pressure. tGLVP is an approved drug in some parts of Europe for the treatment of menorrhagia and metrorrhagia.

In conclusion, it would appear that structure-activity studies and synthetic alterations have been successful in reshuffling the broad spectrum of VP activities. For clinical application the problems have been: (1) to suppress some actions and leave others either untouched or augmented, and (2) to prolong the duration of action after single doses in a controlled manner. Of the two basic approaches presented—hormonogen and monocarba VP analogs—each has some advantages and some faults. In the present state of the art, monocarba analogs have the advantages of enhanced potency and prolonged action, whereas hormonogens combine prolongation of the most desirable actions of VP, suppression of undesirable actions on clotting and the myocardium with a high safety factor.

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