The Adjuvant Effect of Oxytocin on (inRH Analogue Buserelin

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The mucosa of the nasal cavity has relatively high premeability for peptides. Because of the digestive peptidase activity of the gut, the nasal pathway is currently the route of choice for non- parenteral administration of many peptides including gonadotropin releasing hormone analogues (GnRH-a) [1]. Nevertheless, the transmucosal route of administration may have some problems. Variations exist from patient to patient in the absorption of GnRH-a and is also related to the molecular size and hydrophitic/tipophilic characteristics of the individual analogue[2]. Thus, we are confronted with the problem of failure to maintain estradiol suppression despite careful use in few patients receiving intranasal buserelin in our clinic.

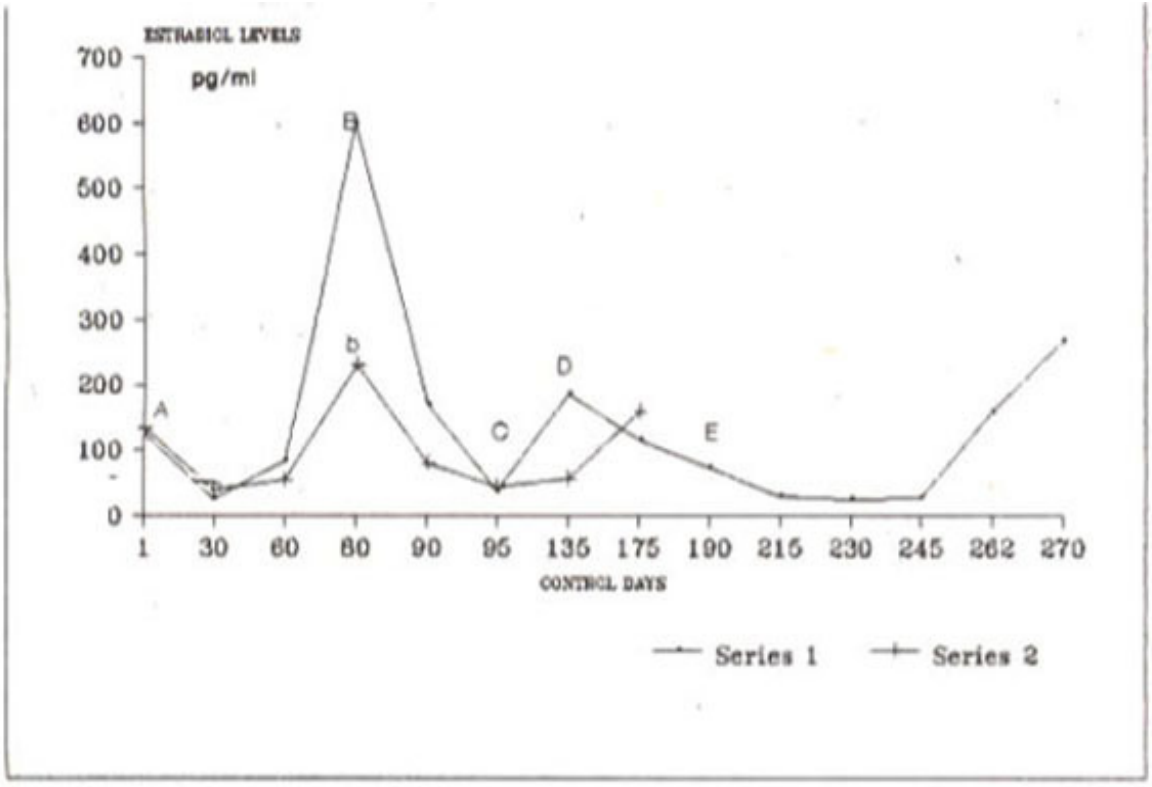
The low permeability ofpeptidepenneationandmaded mucosal peptidase activity within the nasal mucosa complemented the use of suitable absorption adjuvants[3]. With this regard special interest has been focussed on inhibitors of peptidase activity which am located in the mucus itself or on/within the mucosal cells[4]. Based on a hypothesis that oxytocinand GnRH-a are degradedthrough the same enzymes in the nasal mucosa and in the hypothalamus[3,5], we evaluated the use of oxytocin in combination with buserelin both intranasally in two patients who were found to respond poorly to use of intranasal buserelin alone.

Case Reports

Case 1

Threnty-seven year old primaiy infertile patient was diagnosed as endometriesis by laparoscopy and was given buserelin therapy 1000 ug/day in four divided doses {300+200+200+300} (Suprefact intranasal spray, Hoechst, 100 ug/puff). During monthly controls for the evaluation of her hormonal parameters (FSH, LH, E2), sufficient suppression was not observed and estradiol levels were 84 pg/mI on the 60th and 600 pg/mi on the 80th day (up regulation). Therefore, the patient was examined and found to have a normal nasal mucosa. We decided to test whether oxytocin could be useful in this pailicular case and combined oxytocin diluted in saline with buserelin (Synpitan amp. 5 lU/ml Deva, Tuikey). The final dilution of the solution was 0.33 IU=3.8 pg/sniff and no other preservatives or other chemicals were added to the solution. Oxytocin was given intranasally 5 minutes before eveiy application of buserelin. Five days after the addition of Oxytocin she had menstruation and estradiol levels dropped to 169 pg/mi on the 10th and 38 pg/mi on the 16th day.

In order to determine the effective Oxytocin dose dilution was further reduced to 0.25 IU=2.8 ug/sniff. When this dose was given, estradiol level increased to 187 pg/nil on the 40th day. Oxytocin was discontinued and buserelin dose was increased to 1200 pg/day. When it was noticed that E2 level was 116 pg/mi 1 month later, Oxytocin was added again at the dose of 0.33 IU q.i.d. and E2 levels were measured as follows:



A •1000µg/day Buserelin
B,b •1000µg + 0.33IU qid oxytocin
C •1000µg + 0.28IU qid oxy
D •1200µg/day
E •1200µg/day + 0.33IU/qid oxy

Figure. Estradiol levels in two patients using buserelin with/without oxytocin.

Case II

Twenty-four years old primaiy infertile patient diagnosed as endometriosis onlaparoscopy and was administered buserelin therapy 1000 ug/day in four divided doses. During monthly controls for the evaluation of her hormonal parameters (FSH, LH, E2), sufficient suppression was not observed and estradiol levels were 230. pg/nil on the 80th day. On examination the patient had a normal nasal mucosa. Oxytocin (0.33 IU=3.8 ug/sniff) was givenintranasally 5 minutes before eveiy application of buserelin. Five days after the addition of Oxytocin she had menstruationand estradiol levels dropped to 80 pg/mI on the 10th and 46 pg/nil on the 15th day. Estradiol level were 280 pg/mI on the 95th day (When buserelin dose was increased to 1200 ug/day, sufficient suppression was observed and this dose was continued).

Discussion

Oxytocin which consists of 9 aminoacids is synthetized in supraoptic and paraventricular nuclei and secreted via posterior pituitaiy pathway. Oxytocin looks like GnRH-a decapeptide. Oxytocin and its transport peptide Neurophysin I (estrogen stimulated neurophysin) levels are elevated in the plasma, after the ingestion of estrogen[6,7]. Robinson[8] found a close correlation among midcycle surge of LH, the midcycle elevation of estrogen and a midcycle increase in neurophysin I. The peak levels of both neurophysin I and oxytocin are found at the time of LH surge[9]. Oxytocin can influence gonadotropin secretion[5]. The rise in neurophysin I begins 10 hours after the rise in estrogen, precede that of the LH

surge and the elevation of neurophysin lasts longer than the L.H surge[5,9]. The half-life of GnRH is 2-4 minutes and that of oxytocin 5-17 minutes[5]. Because GnRH and oxytocin are competing substrates for hypothalamic degradation enzymes, it has been hypothesized that oxytocin in the portal blood at the midcycle may inhibit the metabolism of GnRh, thus increasing the availability amount of GnRH[5]. Both in vitro and vivo studies show that oxytocin also plays a physiological role in the regulation of the life span of the corpus luteurn. After intraluteal injection of oxytocin, Bennegard B, showed an inter-relation between oxytocin and endogenous PGF2a production determining the fall in serum progesterone value coincided with the rise in PGF2a-metabo-lite[10] . The patients menstruation and fall in estradiol level soon after the addition of oxytocin may be related to oxytocin's luteolytic effect on coipus luteum. Using absorption adjuvants of different types, (i.e., sodium taurodihydrofusidate (STDHF) and bacitracin) marked increases in nasal absorption and therefore, significant nasal adjuvant activity were found, as demonstrated by an increase in the biological response after nasal administration of the peptides[3]. In two patients reported here and according to our clinical experience some patients though respond to GnRH-a initially as shown by the drop in E2 levels, lose their responsiveness to the drug during the course of the treatment. Although we cannot derive definite conclusions, an increase in the activation of degradation enzymes of the drug might play a role in this phenomenon in these particular patients.

In these two patients, we observed that oxytocin had an additive role on buserelin but this was transient. Thà additive effect of oxytocin onbuserelin may be either in the hypothala mus as a result of competitive enzyme inhibition[5]or enzyme-substrate inhibition on the local peptidase activity in the nasal mucosa may exist[3].

GnRH agonists are marketede with different routes of administration. Parenteral (Sc. or im.) injection although providing abetter compliance is more expensive compared to intranasal preparation and in certain groups of patients in whom parenteral injection is contraindicated (bleeding disor¬ders) nasal route may still be preferable. Therefore, it is concluded that in patients receiving intranasal buserelin if estradiol suppression cannot be main¬tained, combining the drug with intranasal oxytocin may be valuable, although this effect is transient.

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