Serum Levels of Follicle-Stimulating Hormone and Luteinizing Hormone After Subcutaneous Administration of Human Menopausal Gonadotropin During Pituitary Suppression

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ABSTRACT: Objective—The present study investigated the pharmacokinetics of a single subcutaneous dose of human menopausal gonadotropin (hMG) on serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations. Subjects and Methods—Six healthy female volunteers, aged 20-40 years, with regular menstrual cycles and normal endocrine profiles, who were not receiving any hormonal medication, were treated with the gonadotropin-releasing-hormone agonist buserelin to suppress endogenous gonadotropin release. One volunteer dropped out during treatment. When the serum estradiol concentration had fallen to below 500 pmol/L, an injection of 150 IU hMG (Humegon®) was given subcutaneously. Immediately before injection and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15, 20, 24, 48 and 96 hours after, blood samples were drawn for determination of FSH and LH concentrations. Results—The baseline FSH level was 2.8 IU/L, and peak concentration (6.8 IU/L) was reached 12 hours after hMG injection (median values). Exogenous LH could not be measured because of the presence of endogenous gonadotropin release. Discussion—The pattern of serum FSH concentrations after a single injection of hMG was found to resemble that seen after intramuscular hMG administration, although the peak FSH value was reached somewhat later. Int J Fertil 40(6):307-310, 1995

KEY WORDS: human menopausal gonadotropins (hMG), subcutaneous administration, pharmacokinetics, FSH, LH, ovarian stimulation, recombinant hMG

INTRODUCTION

Gonadotropin preparations, such as human menopausal gonadotropin (hMG), are usually administered via the intramuscular (i.m.) route. The recent development of gonadotropin preparations of high purity, especially recombinant human follicle-stimulating hormone (FSH), makes possible subcutaneous (s.c.) administration. Compared with i.m. administration, s.c. injections are less painful, and self-administration by the patient is more feasible.

The most appropriate dosage interval for s.c. administration is not known, since information is sparse regarding the pharmacokinetics of exogenous FSH and luteinizing hormone (LH) after s.c. gonadotropin injection. We therefore decided to study the effect of a single s.c. hMG injection on...
serum FSH and LH concentrations in female volunteers. Since the presence of high levels of endogenous FSH and LH complicates interpretation of the results, pituitary function was suppressed by administering the gonadotropin-releasing-hormone (GnRH) agonist buserelin.

MATERIALS AND METHODS

Six female volunteers participated in the study. The inclusion criteria were as follows: age 20–40 years, a regular menstrual cycle (between 24 and 35 days), a normal endocrine serum profile in the early follicular phase of the cycle (FSH concentration below 8 IU/L, LH/FSH ratio less than 3, testosterone concentration below 2.5 nmol/L, prolactin concentration below 58 and 148 nmol/L) and no intake of hormonal medication, including oral contraceptives, for at least 3 months prior to the study. The median age of the five volunteers who completed the study was 29 years (range 29–38 years) and the median body mass index was 20.4 kg/m² (18.4–27.3 kg/m²).

All the women were treated with the GnRH-agonist buserelin [Suprefact® nasal spray, Hoechst A.G., Frankfurt, Germany] at a dose of 300 µg three times a day, from day 21 of the previous menstrual cycle onwards. On day 10 of the buserelin treatment, the serum 17β-estradiol concentration was determined and then measured every three or four days until it was below 500 pmol/L. One volunteer dropped out during the buserelin treatment because of sinusitis and nasal bleeding. As soon as the estradiol concentration was found to be below 500 pmol/L, a single subcutaneous injection of 150 IU Humegon® (NV Organon, Oss, The Netherlands) was given the next day at 8 a.m. and the buserelin treatment was continued. Two ampules of Humegon were diluted in 0.5 mL solvent and injected subcutaneously in the abdomen using a syringe injector (Monoject®, Sherwood Medical, St. Louis, USA). Each ampule contains 75 IU FSH and 75 IU LH activity, as determined by in vivo bioassays. Due to inherent inaccuracy of bioassays, results of determinations are within 80–125% of stated activity. One batch of Humegon was used for the study.

Blood samples were collected, either by venipuncture or via an intravenous cannula, immediately before injection and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15, 20, 24, 48 and 96 hours after. Buserelin administration was stopped after the last blood samples were taken. The samples were centrifuged within three hours after collection and serum was frozen at -20°C until assayed.

The serum estradiol concentration on the tenth
day of buserelin treatment was determined by a
time-resolved fluoroimmunoassay (Delfia®, Wallac
Oy, Turku, Finland). The limit of 500 pmol/L was
chosen because of the low sensitivity of the assay in
the range from 150 to 500 pmol/L. The estradiol
concentration immediately before the hMG injec­
tion was measured retrospectively by a more sensi­
tive radioimmunoassay [1]. FSH and LH
concentrations were determined in all serum sam­
ples by immunoradiometric assays [IRMAs], as pre­
viously described [2].

Statistical analysis was performed using the
Wilcoxon signed-rank test.

RESULTS

The median estradiol concentration immediately
before the hMG injection, as measured by radioim­
munnoassay, was 88 pmol/L (range <75–390 pmol/L).
The median values of the FSH and LH concentra­
tions and the 10th and 90th percentiles, before and
after Humegon® injection, are shown in Figures 1
and 2, respectively. The median FSH concentration
before injection was 2.8 (10th percentile [p10] 1.4
IU/L; 90th percentile [p90] 4.9 IU/L). Median FSH
concentrations started to increase within the first
half-hour after injection and reached a maximum
value of 6.8 IU/L after 12 hours (p10 10 hours; p90
12 hours), the increase being statistically significant (P < .05). Serum LH concentra­
tions remained at a low level throughout the
study. A small increase in median LH concentra­
tions was seen in the first two hours after the
Humegon injection, but there was great interindi­
vidual variation and the increase was not statisti­
cally significant.

The subcutaneous injections were well tolerated.
Two patients experienced transient pain at the injec­
tion site, starting 7 and 10 hours after injection,
respectively, and lasting for a few hours. In one of
these two patients the injection site showed redness
without swelling (diameter of red area 1 to 2 cm).
The symptoms were not severe in either case.

DISCUSSION

Subcutaneous administration of 150 IU hMG leads
to an increase in serum FSH concentrations, reach­ing
a peak approximately 12 hours after injection
and gradually decreasing thereafter. In a previous
study of similar design, the effect of a single i.m. or
i.v. injection of 150 IU hMG on serum FSH and LH
levels was described [3]. The increase in serum FSH
levels after i.m. injection of hMG showed a substanc­
tially similar pattern to that following s.c. injection,
although the peak concentration seemed to occur
somewhat earlier (8 hours after i.m. injection as
against 12 hours after s.c. injection).

In a study by Le Cotonnec et al [4], serum FSH
concentrations were determined in male subjects
after single i.m. and s.c. injections of 150 IU highly
purified urinary FSH (Metrodin HPR®). These investi­
gators found similar patterns of FSH concentra­
tions after s.c. and i.m. administration, with maximum
concentrations occurring 13 and 18 hours after i.m.
and s.c. injection, respectively. In a study by Saal et
al [5], pharmacokinetic parameters were described
after single s.c. and i.m. injections of human chorio­
nic gonadotropin (hCG) in male subjects. Serum
hCG concentrations reached a peak value 6 and 16
hours after i.m. and s.c. injection, respectively, the
half-lives being 31 ± 3 and 38 ± 3 hours. The authors
concluded that diffusion of hCG into the circulation
was slower after s.c. administration. These investi­
gations differed from ours as regards the groups stud­
died (male instead of female subjects) and the
preparations administered (highly purified FSH and
hCG instead of hMG). Nevertheless, serum concen­
trations showed a slightly slower and more pro­
longed increase after s.c. administration than after
i.m. administration in all studies.

Serum LH concentrations were insufficiently sup­
pressed to enable measurement of exogenous LH.
There was great interindividual variation in the
serum LH profiles and no clear pattern could be
seen.

In the present study, a single s.c. hMG injection
was well tolerated by all subjects. Repeated s.c.
injections with hMG might induce local skin reac­
tions, such as swelling, redness or induration, since
the urine-derived hMG preparations are of low puri­
ty and contain a large number of non-gonadotropin
proteins [6]. However, a recombinant human FSH
preparation of very high purity has been developed
recently [7]. In contrast to hMG, recombinant
human FSH should be very suitable for daily s.c.
administration.

Since the FSH profile after s.c. injection showed
that serum concentrations remained adequate over a
period of 24 hours, subcutaneous gonadotropin
injections can presumably be given once daily. This assumption is supported by the findings of Howles et al [8], who treated in vitro fertilization patients with a highly purified urinary FSH preparation which was administered once daily subcutaneously. This treatment schedule was found to be effective in stimulating multiple follicular development. The injections were also well tolerated. A pharmacokinetic study now needs to be carried out to measure serum FSH concentrations after repeated s.c. gonadotropin injections.

It may be concluded from the results of the present study that once-daily subcutaneous administration of gonadotropins induces adequate serum concentrations of FSH and LH.

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