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A Comparative Study between Vaginal and Rectal Routs of Bromocriptine Administration

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SUMMARY : To assess the efficacy and possible potential side effects of alternate routes of treatment, 2.5mg bromocriptine was administered vaginally or rectally to five normoprolactinemic and four idiopathic hyperprolactinemic women.

Serum bromocriptine and prolactin (PRL) levels were measured hourly for the first 12 hours, then every 2 hours for the following 12 hours. The mean peak bromocriptine levels were 641.0 ± 200.1 pg/ml and 386.5 ± 134.8 pg/ml in the normoprolactinemic and hyperprolactinemic groups, respectively. Maximum PRL reduction rate was 67.7 ± 3.4% at 11.3 ± 1.1 hours and 44.8 ± 0.7% at 21.5 ± 1.5 hours after vaginal administration in the normoprolactinemic and hyperprolactinemic groups, respectively.

In contrast, in the rectal treatment group the mean peak values of serum bromocriptine were 364 pg/ml and 314.5 ± 3.9 pg/ml in the normoprolactinemic and hyperprolactinemic groups, respectively. Maximum PRL reduction rate was 38.1% at 8 hours and 21.0 ± 10.4% at 17.0 ± 3.5 hours in the normoprolactinemic and hyperprolactinemic gryoups, respectively. In conclusion, we suggest that the vaginal route of administration is as effective and has fewer side effects than by the oral route. Furthermore, the rectal route is an alternate method of treatment for patients who cannot be administered bromocriptine by vaginal route.

INTRODUCTION

Oral bromocriptine is one method of treatment that has been proven effective in the treatment of hyperprolactinemic and normoprolactinemic women. However, the gastrointestinal side effects associated with oral administration of bromocriptine remain a problem. Recently, it has been suggested that vaginal administration of bromocriptine may reduce the side effects associated with oral administration (1, 2). In this study, a single 2.5mg tablet of bromocriptine was administered by either the vaginal or rectal route, and bromocriptine, and prolactin (PRL) concentrations in blood were measured to assess the efficacy and tolerance of these alternate routes.

MATERIALS AND METHODS

The study group consisted of five normoprolactinemic and four idiopathic hyperprolactinemic female subjects. In the normoprolactinemic group, four subjects were administered 2.5mg bromocriptine vaginally during the follicular phase (7-10th day of the menstrual cycle) and the remaining one subject was administered 2.5mg bromocriptine rectally. In the hyperprolactinemic group, two subjects were

administered 2.5mg bromocriptine vaginally and two subjects were administered 2.5mg bromocriptine rectally. Blood samples were obtained prior to treatment, then every hour for the first 12 hours and every 2 hours for the following 12 hours after bromocriptine administration. Bromocriptine and PRL concentrations in blood were measured by radioimmunoassay. All symptoms and side effects following bromocriptine administration were also recorded.

RESULTS

Table 1 shows blood levels of bromocriptine following vaginal administration of bromocriptine. Bromocriptine in blood was initially detectable at 3.8 ± 0.6 hours and 3.0 ± 0.7 hours after vaginal administration in the normoprolactinemic and hyperprolactinemic groups, respectively. Mean peak bromocriptine level was reached at 10.3 + 1.7 hours and 14.5 ± 1.8 hours after vaginal administration and the values were 641.0 ± 200.1 pg/ml and 386.5 ± 134.8 pg/ml in the normoprolactinemic and the hyperprolactinemia groups, respectively. The hyperprolactinemic group required a greater length of time to reach peak level than the normoprolactinemic group. Bromocriptine concentrations in blood at 24 hours after vaginal administration were 187.0 ± 63.0 pg/ml and 75.5 ± 6.3 pg/ml in the normoprolactinemic and gyperprolactinemic groups, respectively. The normoprolactinemic group demonstrated a higher blood concentration of bromocriptine than the hyperprolactinemic group at peak level and at 24 hours after vaginal administration.

Table 2 presents blood levels of bromocriptine following rectal administration of bromocriptine. Bromocriptine in blood was initially detectable at 1 hour and 5.5 ± 3.2 hours after rectal administration in the normoprolactinemic and hyperprolactinemic groups, respectively. The mean peak bromocriptine level was reached at 7 hours and 10.0 ± 5.7 hours and the values were 364 pg/ml and 314.5 ± 3.9 pg/ml in the normoprolactinemic and hyperprolactinemic groups, respectively. Blood concentration of bromocriptine at 24 hours after rectal administration was 37 pg/ml and 192 pg/ml in the normoprolactinemic and hyperprolactinemic groups, respectively, but bromocriptine was not detectable in one hyperprolactinemic subject.

Table 3 presents blood PRL levels following vaginal administration of bromocriptine. Mean basal levels of serum PRL in the normoprolactinemic and hyperprolactinemic groups were 16.7 ± 2.2 ng/ml and 56.2 ± 2.9 ng/ml,

Table 1. Serum bromocriptine pharmacokinetics after vaginal administration of 2.5mg bromocriptine (Mean±SE)

	Normoprolactinemia (n=4)	Hyperprolactinemia (n=2)
Initial detection (h)	3.8±0.6 (3~6)	3.0±0.7 (2~4)
Time to peak (h)	10.3±1.7 (4~16)	14.5±1.8 (18~24)
Mean Peak Value (pg/ml)	641.0±200.1 (131~1255)	386.5±134.8 (117~656)
Mean level at 24h (pg/ml)	187.0±63.0 (13~335)	75.5±6.3 (63~88)

( ) : range

Table 2. Serum bromocriptine pharmacokinetics after rectal administration of 2.5mg bromocriptine (Mean±SE)

	Normoprolactinemia (n=1)	Hyperprolactinemia (n=2)
Initial detection (h)	1	5.5±3.2 (1~10)
Time to peak (h)	7	10.0±5.7 (2~18)
Peak Value (pg/ml)	364	314.5±3.9 (309~320)
Level at 24h (pg/ml)	37	192 (N.D.~192)

N.D. not detectable

Table 3. Serum prolactin levels following vaginal administration of 2.5mg bromocriptine (Mean±SE)

	Normoprolactinemia (n=4)	Hyperprolactinemia (n=2)
Mean baseline (ng/ml)	16.7±2.2 (11.1~21.1)	56.2±2.9 (52.1~60.3)
Maximun decline (h)	11.3±1.1 (8~14)	21.0±1.5 (18~24)
Reduction rate at maximun decline (%)	67.7±3.4 (56.9~73.9)	44.8±0.7 (43.4~46.1)
Reduction rate at 24h (%)	27.3±6.0 (12.6~45.2)	44.6±0.7 (43.3~45.9)

( ) : range

Table 4. Serum prolactin levels following rectal administration of 2.5mg bromocriptine (Mean±SE)

	Normoprolactinemia (n=1)	Hyperprolactinemia (n=2)
Baseline (ng/ml)	13.9	42.9±3.6 (37.8~48.0)
Maximum decline (h)	8	17.0±3.5 (12~22)
Reduction rate at maximun decline (%)	38.1	21.0±10.4 (6.3~35.6)
Reduction rate at 24h (%)	10*	32.9, 14.8*

* : increase

respectively. Maximum PRL reduction rate was 67.7 ± 3.4% at 11.3 ± 1.1 hours and 44.8 7% at 21.0 ± 1.5 hours in the normoprolactinemic and hyperprolactinemic groups, respectively. The hyperprolactinemic group required a greater length of time to reach maximum PRL reduction rate than the normoprolactinemic group ($p<0.05$). The inhibitory effect of bromocriptine on PRL was remarkable in normoprolactinemic subjects ($p<0.05$). But PRL reduction rate at 24 hours in the hyperprolactinemic group was higher than in the normoprolactinemic group. Therefore, bromocriptine appears to have a greater inhibiting effect on PRL in hyperprolactinemic women.

Table 4 presents blood PRL levels following the rectal administration of bromocriptine. Basal level of blood PRL in the normoprolactinemic and hyperprolactinemic groups was 13.9 ng/ml and 42.9 ± 3.6 ng/ml, respectively. Maximum PRL reduction rate was 38.1% at 8 hours and 21.0 ± 10.4% at 17.0 ± 3.5 hours in the normoprolactinemic and hyperprolactinemic groups, respectively. The hyperprolactinemic group required a greater length of time to reach maximum PRL reduction rete than the normoprolactinemic group in both methods of administration. The inhibitory effect of bromocriptine on PRL in the normoprolactinemic group was greater than in the hyperprolactinemic group. At 24 hours, only one hyperprolactinemic subject showed PRL suppression. On the contrary, the remaining hyperprolactinemic subjects and the normoprolactinemic subjects showed an increased reduction rate of 14.8% and 10%, respectively.

The following side effects were reported by subjects in this study. Only transient general fatigue, nasal disturbances or headaches were experienced by subjects in the normoprolactinemic group. Amongst subjects in the hyperprolactinemic group,three subjects who had previous oral treatment and had subsequently suffered vomiting upon the first treatment day, reported no side effects after vaginal (2 subjects) or rectal (1 subject) treatments.

DISCUSSION

Because of gastric absorption, oral administration of bromocriptine is frequently accompanied by gastrointestinal side effects such as nausea and vomiting because of which treatment is discontinued. Vaginal or rectal

administration rarely produces such side effects since the drug does not pass through the gastrointestinal tract. In this study, bromocriptine was adminstered by vaginal or rectal route and no gastrointestinal side effects were observed. Patients who had previously suffered from side effects by oral administration, had no side effects, supporting the view that vaginal or rectal routes of administration are superior methods of administration. However, further investigations are needed to determine the absorption and efficacy of bromocriptine. The mean peak value of blood concentration of bromocriptine was more than 300 pg/ml in both vaginal and rectal routes of administration. From a viewpoint of the PRL reduction rate, a single dose of bromocriptine appears to be effective for treatment of hyperprolactinemic patients. Administration by the vaginal route resulted in a higher blood concentration of bromocriptine and a greater PRL reduction rate than by the rectal route. Furthermore, by analysis of PRL kinetics at 24 hours after administration, it was found that PRL was suppressed. in all subjects who received bromocriptine by vaginal administration.

Conversely, rectal administration of bromocriptine increased PRL in two of three subjects, implying that the period of PRL inhibition is longer when bromocriptine was administered vaginally than rectally. Although it is not known what contributes to this observed difference, difference in absorption route may be one reason. When a drug is administered by vaginal route, it avoids the "first pass" through the liver. In comparison, by the rectal route the drug passes through the liver, thus lowering serum bromocriptine concentrations and diminishing its efficacy. Additionally, it is difficult for patients to administer bromocriptine rectally themselves. Therefore, vaginal administration is a better method than rectal administration. However, there was a large difference (117 pg/ml-1255 pg/ml) observed in serum bromocriptine cocentrations amongst subjects who received vaginal administration. In all cases of vaginal administration, loss of bromocriptine from the vagina was not observed, therefore individual variation may exist in the absorption from the vaginal mucosa. For poor absorption cases, a greater PRL reduction can be seen if a larger dose of bromocriptine is administered, because linear regression analysis of serum bromocriptine and PRL values yield a highly significant negative correlation (2). Comparing the PRL reduction rates between the normoprolactinemic and hyperprolactinemic groups, the former has a greater reduction rate than the latter in both routes of administration independent of serum bromocriptine concentrations. This may be explained by the difference in basal prolactin level. Kletzky *et al.* (1) reported that two of fifteen hyperprolactinemic patients adminstered with 2.5 mg vaginal bromocriptine demonstrated an extremely poor PRL inhibition response in spite of the same bromocriptine dose that was administered to all fifteen patients. The results remained the same even when the dose was increased to 5.0mg vaginal bromocriptine.

CONCLUSIONS

Serum bromocriptine and PRL concentrations and associated side effects of both vaginal and rectal administration of bromocriptine were studied. It is concluded that vaginal route of bromocriptine administration is useful in patients who can not be administered by oral route. In patients who can not be administered by vaginal route, rectal route is an alternate method which is inferior to the method of vaginal administration as judged by ease of insertion techinique and effeicacy.

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