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Research Article

Cabergoline versus Quinagolide for the Management of Macroprolactinoma and Erectile Dysfunction: A Randomized, Open-Label Study

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Abstract

Background: Pituitary prolactinomas are recognized cause of male sexual dysfunction and infertility. Dopamine agonists have been used with variable success rates in the management of prolactinomas. In this study we compared between cabergoline (CAB) and quinagolide (QIN), two selective dopamine agonists, in male patients with erectile dysfunction (ED) and macroprolactinomas.

Methods: Thirty-nine male patients with macroprolactinomas, ED, and variable rates of infertility were recruited in the study. Twenty-one patients received CAB 0.5-1mg twice/week and 18 patients received QIN75-150µg once daily for 6 months. Tumor size, assessed by magnetic resonance imaging, and serumprolactin (PRL), gonadotrophic hormones (FSH, LH), and testosterone (TS) as well as erectile function and sperm characteristics were evaluated at study entry and after 3 and 6 months of treatments.

Results: Both CAB and QIN achieved significant success in tumor shrinkage, decrease serum PRL, improve erectile functions core, elevation of serum TS, and improvement of sperm characteristics after 3 months with greater results after 6 months of treatment; however, CAB treatment was comparably more effective in promoting most of these improvements and was well tolerated than QIN.

Conclusion: In conclusion, Both CAB and QIN showed significant success in the treatment of macro prolactinomas associated with ED in 39 male Egyptian patients. Large multicenter studies with longer duration would be more useful to consider limitations of data and their context in comparison with those of similar studies.

Keywords: Cabergoline; Quinagolide; Prolactinoma; Erectile dysfunction

Introduction

The prolactin (PRL) secreting adenomas (prolactinomas) are the most identified type of hormone secreting pituitary neoplasms that account for approximately 30 to 40% of all clinically identified pituitary neoplasms [1]. They are classified radiologically according to the maximum tumor diameter into microadenoma (<1cm) or macroadenoma (>1cm) [2]. Hyper secretion of PRL by lactotroph cells of the anterior pituitary results in hyperprolactinemia (HPRL) which, inseveralinstances, can drastically affect male sexual function and cause in fertility as high levels of PRL can inhibit hypothalamo-hypophyseal gonadotropic axis and consequently testosterone (TS) production and male sexual function [3]. According to a large study published in 2007 and involved 2,146 male patients, Corona and co-workers have found that mild HPRL was found in 69 (3.3%) while severe HPRL was found in 32(1.5%) of patients with sexual dysfunction [4].

Pharmacological therapy with dopamine agonists represents the first line treatment option for prolactinomaas PRL-secreting lactotrophsare undertonic inhibition of dopamine produced by tubero-infundibular neurons and acting upon dopamine D2 receptors in the anterior lobe of the pituitary gland [5]. This the rapyhas shown significant success in reduction of PRL levels, restoration of the gonadal function and decrease of the tumor size in large proportion of patients [6]. Pharmacological researches have also focused on the role of dopamine and dopamine receptors in the central regulation of sexual behavior and allied sexual response in males [7]. Dopamine-mediated improvement of sexual behavior was first observed when administration of L-dopa to male patients with Parkinson's disease promoted increased libido and sexual potency [8]. Following that, dopamine agonists have been used successfully for medical treatment of male erectile problems [9]. They have been also reported to potentiate erectile function in experimental models [10].

The available data on the therapeutic role of dopamine agonists in male patients with sexual dysfunction associated with macroprolactinomas indicate that there is adequate evidence to continue with further studies indifferent demographic groups to augment clinical evidence for the therapeutic function of these drugs in such conditions. In this study we aimed at comparing the therapeutic potential of two selective dopamine agonists, namely cabergoline (CAB) and quinagolide (QIN), in male Egyptian patients with macroprolactinomas associated with erectile dysfunction (ED).

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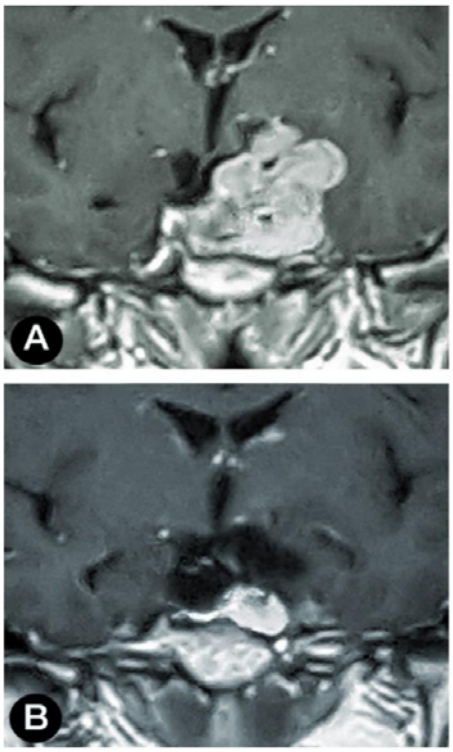

Figure 1: (A) MRI coronal view before treatment showing macroprolactinoma compressing the left temporal lobe and invading the left cavernous sinus. (B) Significant tumor shrinkage after 6 months of treatment with CAB (up to 1mg twice/week).

Were as one that pharmacological differences between the two drugs, their adverse effects, and ethnic variations in the response to these drugs [11] may impart differences regarding their efficacy and patient tolerability in a sample of Egyptian patients.

Patients and Methods

Subjects and ethics

Thirty-nine out of 423 (9.2%) male patients with sexual dysfunction aged between 28 and 44 years, and living in as table marital partnership, attending Mansoura University Faculty of Medicine outpatient clinics between August 2015 and July 2017, were sequentially recruited in the study. Initial PRL measurement and Magnetic Resonance Imaging (MRI) of the hypothalamic-pituitary region were available for all subjects. Inclusion criteria included patients with ED associated with macroprolactinomade fined as those with serum PRL levels ≥200ng/ml [12] and pituitary tumor ≥1cm india meteronpituitary MRI. Exclusion criteria included psychological disorders, organic ED, thyroidoradrenal abnormalities, the current use of dopamine agonists, antidepressants, antipsychotics, oranykindofanti-ED medication. The study was conducted after complete informed consents were obtained from the patients and was approved by the Institutional Research Board of Mansoura University Faculty of Medicine. The study was not funded from any public or commercial agency and was conducted independently of any institutional influence.

Study design

Patients were sequentially assigned in two groups with continuous reduction of covariate imbalances. Twenty-one patients received CAB orally (Dostinex TM, Pfizer, NY, USA) at a starting dose of 0.25mg twice weekly and 18 patients received QI Norally (Norprolac TM, NovartisPharma, Basel, Switzerland) at a starting dose of 37.5µg once daily, then the doses of the drugs were increased to 0.5mg twice weekly and 75µg once daily respectively from the second week. In some patients with inadequate laboratory and radiological response after 3 months, the doses were increased to 1mg twice weekly for CAB and 150µg once daily for QIN. Patients were subjected to physical, laboratory and imaging examinations is for study entry then followed up monthly with laboratory investigations, and after 3 and 6 months of treatment with pituitary MRI. The International Index of Erectile Function (IIEF5) question naire was done for all patients at baseline, 3 and 6months [13]. The presence of drug side effects was assessed with a non-structured question naire after 3 and6 months of therapy and the severity of each side effect was grade dasmild (required no intervention), moderate (required treatment with other medication) and severe (required stopping of the drug). Neither of the patients was blinded to the drug he receives.

Hormonal assay

For serum hormone analysis, venous blood samples were obtained for all patients from the antecubital region between 08:00 and 09:00 AM after 12h over night fast. Serum PRL, follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone (TS) were assayed using commercially available ELISA kits according to manufacturer instructions.

Semen analysis

Semen processing and analysis was done according to the 2010 World Health Organization guidelines [14]. Normal ranges of sperm characteristics are as follows: volume ≥2ml; sperm concentration >15x106 spermatozoon/ml; total motility >40% or progressive motility >32% within 60min after ejaculation; and morphologically normal forms >4%.

IIEF-5 score for evaluation of ED

This verity of ED was evaluated using the IIEF-5 questionnaire. The IIEF-5 is a validated score that is frequently used in clinical research studies [13]. It employs five precise questions that evaluate erectile function from the full version of the IIEF questionnaire (questions 2, 4, 5, 7, and 15). The maximum score for the IIEF-5 is 25 with a cut-off of less than 22 for ED. Severity rankings for ED according to the IIEF-5 score are as follows–severe (5–7); moderate (8–11); mild to moderate (12–16); mild (17–21); and noED (22–25).

Pituitary imaging

Tumor size and extension outside the sellar space was assessed by MRI. Coronal and sagittal thin sections were obtained at T1 and T2 weighted spin echo targeted to there gi on of the pituitary gland. The maximal tumor diameter in the transverse, antero-posterior and cranio-caudal planes was measured before and after gadolinium injection. Based on the criticism that tumors are rarely of spherical shape and thus the calculation of tumor volume according to the ellipsoid formula could lead to misinforming results, we evaluated tumor reduction in accordance with previous studies [15-16] as decrease of the maximal tumor diameter compared to base line measurement. A tumor size reduction of >80% was chosen as a major

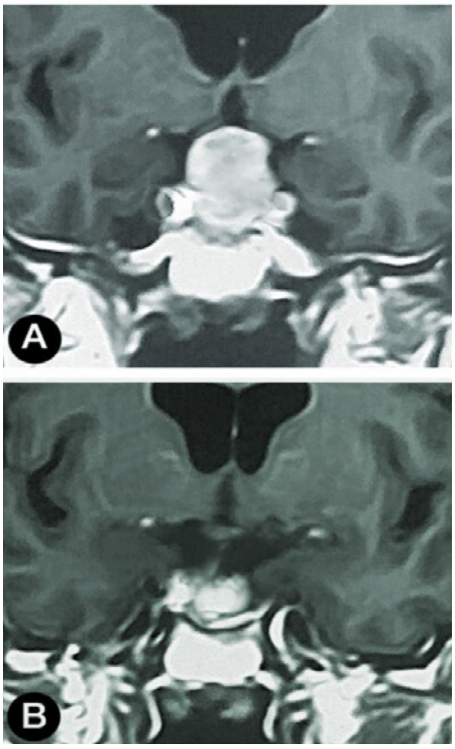

Figure 2: (A) MRI pituitary before treatment showing macroprolactinoma with para – and supra-sellar extension compressing the optic chiasm. (B) MRI of the same pituitary region with significant tumor reduction after 6 months of treatment with QIN (up to 150µg once daily).

end point [17].

Visual perimetry

The evaluation of visual field defects and visual acuity was performed in all patients before study entry by automated perimetry. The ophthalmological examination was repeated after 3 and 6 months of treatment in all patients with visual disturbance.

Data analysis

All statistical calculations were done using SPSSv22.0 (SPSS Inc., Chicago, USA). Data were represented as mean ± SD or frequency (number-percent). Statistical analyses were performed as appropriate by using the Student's *t*-test for parametric data and Pearson's chi-square "χ2" or Fischer's sex act tests to compare qualitative data. The Pears on product was used to analyse correlations between variables. P-values of 0.05 or less were considered significant.

Results

Baseline characteristics

Table1 summarizes the demographic, endocrine and radiological findings at time of study entry. All 39 patients were symptomatic of ED as their principal complaint at time of study entry. Visual disturbance and head ache were found in 7 (18%) and 12 (30%) patients respectively, while primary infertility, secondary infertility, and gynecomastia were found in 4 (10%), 9 (23%), and 5 (13%) patients respectively. There was no significant difference in the mean age between CAB and QIN treated groups. Likewise, the mean ± S Dof serum PRL, FSH, LH, TS, semen characteristics, and maximal tumor diameter showed no significant differences between the two groups. Approximately 46% (18 patients) demonstrated tumors with para–and supra-sellar extension. The PRL levels were found positively correlated with the maximal tumor diameter in both CAB and QIN groups (r=0.869 and r=0.9 respectively). The TS levels were below the normal reference range in 25 patients (64%) and were found positively correlated with the IIEF-5 score (r=0.567 and r=0.519 respectively) and negatively correlated with PRL levels (r=−0.782 and r=−0.730 respectively) and the maximal tumor diameter (r=−0.684 and r=−0.609 respectively) in both groups.

Table 1: Collective baseline characteristics of 39 male patients with sexual dysfunction and macroprolactinoma before the study entry.

	CAB group	QIN group
No. of patients	21	18
Age (years)	34.9 ± 4.1	35.3 ± 4.5
No. of patients with erectile dysfunction	21 (100%)	18 (100%)
No. of patients with visual field defects	4 (19.0%)	3 (16.7%)
No. of patients with headache	8 (38.1%)	4 (22.2%)
No. of patients with gynecomastia	3 (14.3%)	2 (11.1%)
No. of patients with primary infertility	2 (9.5%)	2 (11.1%)
No. of patients with secondary infertility	5 (23.8%)	4 (22.2%)
Pituitary maximal diameter (mm)	22.8 ± 9.4	24.5 ± 10.1
IIEF-5 score	12.4 ± 3.5	13.9 ± 4.3
Serum PRL (ng/ml)	742.8 ± 357.2	823.2 ± 378.1
Serum FSH (mIU/ml)	3.74 ± 0.94	3.96 ± 1.28
Serum LH (mIU/ml)	3.31 ± 1.12	2.94 ± 1.05
Serum testosterone (ng/ml)	2.57 ± 0.93	2.81 ± 1.23
Semen volume	2.2 ± 0.71	2.1 ± 0.76
Sperm count (10^6/ml)	14.8 ± 9.4	15.4 ± 10.8
Sperm total motility (%)	27.3 ± 13.5	25.2 ± 13.8
Forward progression (%)	15.6 ± 8.8	13.7 ± 7.6
Normal morphology (%)	12.8 ± 6.4	14.0 ± 6.2

Data are presented as mean ± SD or numbers-percent. Reference ranges of the laboratory values according to the age are as follows: PRL, <15 ng/ml; FSH and LH, 1.3–10mIU/ml; testosterone, 2.4–9 ng/ml. For semen analysis, reference values were mentioned in the patients and methods section.

Hormonal response to treatment

The mean baseline hormonal levels were similar in the CAB and QIN groups (Table1). All patients showed significant fall in serum PRL after one month of CAB and QIN treatment. Three months after CAB treatment (0.5mg twice weekly), serum PRL normalized in 13 out of 21 patients (62%). The dose was then increased to 1mg twice weekly for the remaining patients who still have relatively high hormonal levels where serum PRL was normalized in another 6 patients after 6 months (90%). The remaining 2 patients still had mildly elevated PRL levels. Likewise, serum PRL was normalized in 8 out of 18 patients (44%) after 3 months of QIN therapy (75µg/day). The dose was then increased to 150µg/day for the remaining patients where normalization of PRL was seen in another 4 patients after 6 months (66.7%; P=0.034). Five of the residual 6 patients still had mildly elevated PRL levels while one patient kept relatively high level (198ng/ml compared to 587ng/ml at study entry). Serum TS was

Table 2: Serum hormone levels at study entry and after 3 and 6 months of CAB (*n*=21) and QIN (*n*=18) treatments.

	Baseline		3 months		6 months	
	CAB	QIN	CAB	QIN	CAB	QIN
PRL (ng/ml)	742.8 ± 357.2	823.2 ± 378.1	39.3 ± 18.4‡	65.6 ± 24.7‡a	18.7 ± 10.4‡	34.9 ± 15.3‡a
FSH (mIU/ml)	3.74 ± 0.94	3.96 ± 1.28	5.77 ± 1.14	4.26 ± 1.03	5.85 ± 1.22	5.16 ± 1.34
LH (mIU/ml)	3.31 ± 1.12	2.94 ± 1.05	4.82 ± 1.34	4.24 ± 1.29	5.71 ± 1.42	4.91 ± 1.60
TS (ng/ml)	2.57 ± 0.93	2.81 ± 1.23	4.25 ± 1.26‡	3.55 ± 0.88†	5.37 ± 1.34‡	4.91 ± 1.18‡

Data are presented as mean ± SD.
Significance levels †*P*<0.05 and ‡*P*<0.001 *vs.* corresponding baseline value; [a]*P*<0.001, CAB *vs.* QIN treatment (*t*-test).

Table 3: Greater than 80% reduction of the maximal tumor diameter after 3 and 6 months of CAB (*n*=21) and QIN (*n*=18) treatment.

	Baseline		Number of patients (%) ≥80% shrinkage	
	Number of patients (%)	Maximal tumor diameter (mm; mean±SD)	3 months	6 months
CAB	21 (100)	22.8 ± 9.4	6 (28.6)	16 (76.2)†
QIN	18 (100)	24.5 ± 10.1	4 (22.2)	8 (44.4)

Data are presented as number of patients and their percentage to total number.
Significance levels †*P*<0.05 CAB *vs.* QIN after 6 months (χ2 test).

Table 4: IIEF-5 score at study entry and after 3 and 6 months of CAB (*n*=21) and QIN (*n*=18) treatment.

IIEF-5 score	Number of patients (%)					
	Baseline		3 months		6 months	
	CAB	QIN	CAB	QIN	CAB	QIN
22-25 (No ED)	0 (0)	0 (0)	10 (47.6)‡	8 (38.1)†	14 (66.7)‡	9 (50)†
17-21 (Mild ED)	10 (47.6)	11 (61.1)	7 (33.3)	7 (38.9)	5 (23.8)	7 (38.9)
12-16 (Mild-mod ED)	6 (28.6)	4 (22.2)	3 (14.3)	2 (11.1)	1 (4.8)†	2 (11.1)
8-11 (Moderate ED)	3 (14.3)	2 (11.1)	1 (4.8)	1 (5.6)	1 (4.8)	0 (0)
5-7 (Severe ED)	2 (9.5)	1 (5.6)	0 (0)	0 (0)	0 (0)	0 (0)

Data are presented as number of patients and their percentage to total number.
Significance levels †*P*<0.05 and ‡*P*<0.001 *vs.* corresponding baseline value (χ2 test).

almost normalized in 15 (71.4%) and 10 (55.6%) patients respectively after 6months of CAB and QIN treatments, while FSH and LH moved within normal ranges without significant changes for all patients (Table 2). The decrease in serum PRL was positively correlated with the reduction of tumor size while serum TS showed negative correlations with PRL levels at all time points.

Tumor size

As shown in Table 3, after 3 months of treatment with CAB, there was reduction of the maximal tumor diameter of more than 80% in 6 out of 21 patients (28.6%) as documented by MRI reports. After 6 months of treatment, there was reduction greater than 80% in 16 patients (76.2%) of whom, the tumor mass completely disappeared in 5 patients (Figure 1 demonstrates an example), while the residual 5 patients had reduction of less than 80% of the maximal tumor diameter. Significant improvement in visual field occurred in all patients with visual disturbance. Likewise, after 3 months of QIN treatment, there was reduction of the maximal tumor diameter greater than 80% in 4 out of 18 patients (22.2%). After 6months of treatment, there was reduction greater than 80% in 8 patients (44.4%, P=0.043; Figure 2 demonstrates an example) while the residual 10 patients had reduction of less than 80% of the base line measurements. Significant improvement in the visual field was obtained in all patients with visual disturbance after 6 months. The mean tumor shrinkage percentile of CAB group was significantly higher than that of QIN after 6 months (77.6±20.4 vs. 63.8±21.0%, P=0.047, *t*-test).

Erectile function and sperm characteristics

At the time of study entry, all patients had variable degrees of ED as evaluated by the IIEF-5 score (Table 1). After 3 months of CAB and QIN treatment there was significant improvement of the IIEF-5 scores with 10 out of 21 and 8 out of 18 patients respectively had scores>21. The improvement of sexual function coincided with the fall of serum PRL and elevation of TS. After 6 months of treatment the number of patients with scores higher than 21 increased to 14 (67%) and 10 (50% respectively while the remaining patients still have some degree of ED but with relatively higher scores compared to their baseline values (Table 4). Modest improvement of sperm characteristics such as sperm count, total motility, and forward progression was also observed in 9 patients (43%) on CAB versus 6 patients (33%) on QIN treatments after 6 months of treatment (data not shown).

Drug side effects

During the whole 6 months duration of the study, no side effects were reported in 15 out of 21 patients on CAB and 7 out of 18 patients on QIN. Mild to moderate side effects were reported in 6 (28.6%) patients on CAB and in 11 (61.1%) patients on QIN treatments (P=0.044), while there was no severe side effects reported in any patient, and no patient dropped out of the study. Only one patient with QIN required reducing the dose of the drug (from 150 to 112.5μg/day) because of nausea that has not been well-controlled with ondansetron. The numbers of patient sex perienced nausea/vomiting,

Table 5: Reported adverse effects in CAB (*n*=21) and QIN (*n*=18) groups.

	Number of patients (%)		
	CAB	QIN	*P*-value
Nausea/vomiting	6 (28.6)	11 (61.1)	0.041† (χ2)
Fatigue	4 (19)	10 (55.6)	0.024†(FE)
Dizziness	4 (19)	9 (50)	0.087 (FE)
Headache	2 (9.5)	5 (27.8)	0.2 (FE)
Abdominal pain	2 (9.5)	3 (16.7)	0.6 (FE)

Data are presented as number of patients and their percentage to total number. Significance level †*P*<0.05 (χ2 or Fisher exact test (FE).

fatigue, and dizziness were more significant in QIN compared to CAB groups (P<0.05) z. Other adverse effects included headache and upper abdominal pain (Table 5).

Discussion

In the present study we evaluated the efficacy of two selective dopamine agonists in macroprolactinomas associated with ED and occasional infertility in 39 male Egyptian patients. Although the efficacy of dopamine agonists in the management of pituitary prolactinomas has been documented in substantial body of literature, but we have two rationales underlying the design of this study–first, we wanted to evaluate dopamine agonists in different ethnic group of patients who might show variation in drug response based on the irracial or demographic characteristics in such manner parallel to that reported by some studies of the demographic variation in the incidence of pituitary adenomas [18]; second, we wanted to compare between the effectiveness of two selective dopamine agonists with considerably contrasting pharmacologic and cost-effective properties, and consequently with financial impact on Egyptian patients [19]. From the financial point of view, the cost of one week treatment – as of 2017 prices – with CAB is 91 Egyptian Pounds (L.E.) which is considerably more expensive than QIN which costs 27.3 L.E. per week. Additional charges may also arise from the cost of treatment of drug side effects. These issues are of worth considerations for tailoring drug medication to our patients to get better response and to minimize adverse effects. The dose of QIN was thus chosen based on the only available drug concentration in the Egyptian market which is 75μg tablets. We did not include microprolactinomas in this study as we aimed at studying the efficacy of drug treatment in those tumors with considerable large mass especially those with extension into the cavernous sinus where surgical intervention warrant considerable risk. Previous imaging studies have shown that PRL secreting adenomas are most frequently associated with cavernous sinus extension [20]. As soon as these tumors gain access to the sinus, there would be jacking up of serum PRL levels, and once in the sinus, these tumors become difficult to be completely resected [21-22]. Accordingly, comparing the efficacy of dopamine agonists in these cases would be of great value.

The relationship between HPRL and erectile function has been for long time a matter of debate albeit some studies have suggested the existing of this relation [23-24]. In our patients, there was positive correlation, at all time points, between serum PRL and tumor size from one side, and negative correlation between PRL and both of serum TS and IIEF -5 score of ED on the other side supporting the intimate pathogenic link between HPRL and ED. Previously, DeRosaandco-workers also reported strong correlation between HPRL and male sexual dysfunction and reduction of nocturnal erections in 51 patients [24]. Following treatment with CAB, nocturnal penile erection was normalized in 60% of patients who got normalized PRL levels and in 8% of patients who did not. Later studies conducted on larger samples have shown that high serum PRL levels with associated decrease in TS, more than isolated elevation of serum PRL alone, is consistently associated with ED. In other words, HPRL could be associated with ED when it causes suppression of TS [23].

Pituitary PRL plays important role in the regulation of spermatogenesis, and normal PRL levels in blood are essential to maintain normal testicular function. In men, HPRL is often under estimated by the majority of patients, but in general, the most frequent symptoms are the decrease in libido and/or ED [2]. It has been documented that HPRL can interrupt the hypothalamic production of gonadotrophin-releasing hormone, inhibiting their lease of LH and FSH, as well as impairing testicular steroid genesis. As a consequence hyperprolactinemic men have reduced sexual potency, altered seminal quality, and in fertility [25]. In our study there were 13 patients out of 39 suffering from either primary or secondary infertility, of whom semen parameters and sperm characteristics were below the reference ranges.

Our data clearly demonstrate that both of CAB and QIN achieved comparable success in tumor reduction and lowering of serum PRL in male patients with macroprolactinomas; this was associated with improvement of erectile function, elevation of serum TS, and improvement of sperm characteristics, atleast partially, after 6 months of treatment; however, CAB treatment observed to be generally more effective in promoting tumor shrinkage and reducing PRL than QIN. Likewise, CAB treatment exhibited better improve men to erectile function and normalization of TS levels after both 3 and 6 months; however, differences between the two drugs regarding the improvement of sperm characteristics were not remarkable.

As with previous reports [26-27], the most frequent side effects of both CAB and QIN were nausea/vomiting, fatigue, dizziness, headache, and abdominal pain which are far less than reported with bromocriptine in other studies [28]. Nausea and fatigue were the most frequent adverse effects and were especially significant with QIN compared to CAB treatments; however, nausea/vomiting were mild and were well-controlled in all patients by anti-emetics (other than dopamine blockers). In general, the percentages of patients developed adverse effects were comparably higher in QIN than CAB groups, while CAB was better tolerated by all patients. Other adverse effects reported in previous studies [27,29] such as hypotension, constipation or somnolence did not happen in our study and no patient dropped out of the study.

A major limitation of this study is the relatively small sample size which may touch its power; however, one reason for this was because of the strict exclusion criteria upon which we carefully selected narrow sector of male patients having macroprolactinomas associated with ED. Another limitation is that we did not monitor the effects of reducing the drug doses after tumor shrinkage and endocrinal control have been achieved. However, attention is required when long-term therapy with CAB has been conducted due to it sexceptionally long half-life, since PRL level scan, in some instances, take months or even

years to rebound again [30]. Accordingly, continuous long standing monitoring of PRL (several years) is necessary before we can make a solid conclusion on tumor size and hormonal stabilization after drug withdrawal [31].

Conclusion

In conclusion, both CAB and QIN exerted comparable success in the management of macroprolactinomas associated with ED in 39 male Egyptian patients; however, CAB was partially well tolerated and more effective in reducing tumor size and improving sexual function and endocrinal disturbance. Despite the limitations of this study, we think this little piece of research might provide useful information on the medical treatment of ED in a sample of Egyptian patients with macroprolactinomas. Larger multicenter studies with longer duration would be indeed more useful to.

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