The Impact of Digestive and Colon Drugs on the Human Hormones Profile

Emad F. Eskander · Ahmed A. Abd-Rabou ·
Hanaa H. Ahmed

Received: 25 November 2012 / Accepted: 23 February 2013 / Published online: 26 March 2013
© Association of Clinical Biochemists of India 2013

Abstract Hormones play an important role in the digestive system. The main hormones that control digestion are gastrin, secretin, and cholecystokinin. Herein, the current study is concerned with assessing the effect of spasmocanulase and librax drugs on the human hormones profile. Blood samples were withdrawn from adult patients to measure serum FSH, E2, LH, prolactin, progesterone, DHEAS, testosterone, TSH, T₃, T₄, fasting insulin, and cortisol. All hormone concentrations were determined quantitatively using ELISA procedure. Intriguingly, the present study showed putative changes including thyroid and sex hormonal profiles. Eventually, we concluded that the prospective study could be important in drug dose optimization and providing new medical guidelines to avoid side effects that could harm patients.

Keywords Spasmocanulase · Librax ·
Human hormones profile

Introduction

Peptic ulcer disease is the most common ulcer of an area of the gastrointestinal tract or duodenal mucosa down to the sub-mucosa that is usually acidic and thus extremely painful. As many as 70–90 % of such ulcers are associated with *Helicobacter pylori*, a spiral-shaped bacterium that lives in the acidic environment of the stomach and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin. Other important causes of gastric ulceration are gastric adenocarcinoma and lymphoma, and these must be excluded by biopsy and follow-up [1]. Moreover, one of the most common peptic ulcer complications is gastrointestinal bleeding [2, 3].

Gastritis, an inflammation of the gastric mucosa, is diagnosed and classified histologically because endoscopic appearances such as redness are often misleading [4]. However, magnification endoscopy can increase diagnostic accuracy [5]. Gastritis is seldom, if ever, symptomatic, but can have important clinical sequelae in a minority of patients. These sequelae vary depending on the type of gastritis, but include duodenal and gastric ulceration, gastric adenocarcinoma and primary gastric lymphoma [6, 7].

Irritable bowel syndrome (IBS) or spastic colon is a symptom-based diagnosis characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits. As a functional bowel disorder, IBS has no known organic cause. Diarrhea or constipation may predominate, or they may alternate (classified as IBS-D, IBS-C or IBS-A, respectively). Historically a diagnosis of exclusion in the absence of alarm features such as age of onset greater than 50 years, weight loss, gross hematochezia, systemic signs of infection or colitis, or family history of inflammatory bowel disease, a diagnosis of IBS can now be made on the basis of symptoms alone [8, 9]. Although there is no cure for IBS,

---

E. F. Eskander (✉) · A. A. Abd-Rabou (✉) · H. H. Ahmed
Hormones Department, Medical Research Division,
National Research Centre, Cairo 12622, Egypt
e-mail: gysi_pharma@yahoo.com

A. A. Abd-Rabou
e-mail: ahmedchemia87@yahoo.com

H. H. Ahmed
e-mail: hanaaomr@yahoo.com

A. A. Abd-Rabou
Center for Aging and Associated Diseases, Helmy Institute for
Medical Sciences, Zewail City of Science and Technology,
Sheikh Zayed District, 6th of October City, Giza, Egypt

there are treatments that attempt to relieve symptoms, including dietary adjustments, medication and psychological interventions. Patient education and good doctor-patient relationship are also important [10].

Librax is a drug consisting of chlordiazepoxide 5 mg and clidinium bromide 2.5 mg and used to treat peptic ulcers, spastic colon, and gastritis. It helps to relieve stomach spasms, abdominal cramps, and anxiety related to gastric disorders [11, 12]. Chlordiazepoxide is the first benzodiazepine to be synthesised [13]. Chlordiazepoxide has a medium to long half-life but its active metabolite has a very long half-life. The drug has amnestic, anxiolytic, hypnotic and skeletal muscle relaxant activities [14].

The thyrotropin-releasing hormone receptor (TRHR) is a G protein-coupled receptor which binds the tripeptide thyrotropin releasing hormone. The TRHR is found in the brain and by binding to thyrotropin-releasing hormone (TRH), it acts through phospholipase C transduction mechanisms to increase intracellular inositol trisphosphate [15, 16]. Chlordiazepoxide acts as a competitive antagonist at the level of the TRHR [17].

Spasmo Canulase, a gastrointestinal drug, is consisting of methixene hydrochloride 1 mg, dimethylpolysiloxane 40 mg, glutamic acid hydrochloride 100 mg, sodium dehydrochloride 20 mg, pepsin 120 FIP U, amylase 2,100 FIP U, lipase 1,200 FIP U, protease 80 FIP U, cellulose 600 U. It was suggested that spasmo canulase is beneficial in improving symptoms of IBS [11]. The authors suggested that glutamine is absorbed by the pars tuberalis (PT) cells through the amino acid transporter A2 (ATA2) and then, glutamate produced locally from glutamine by glutaminase induces thyroid-stimulating hormone (TSH β) expression via the KA2, which is an ionotropic glutamic acid receptor (iGluR), in an autocrine and/or paracrine manner in the PT [18].

The current study is concerned with assessing the effect of the precursors of spasmo canulase and librax drugs on human hormone profiles including; (1) sex hormones profile; follicle-stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH), prolactin, progesterone, dehydroepiandrosterone (DHEAS), and testosterone, (2) Thyroid hormones profile; TSH, triiodothyronine (T3), and thyroxine (T4), (3) fasting insulin, and cortisol.

Materials and Methods

Subjects

The present study was conducted on eighty-four adult volunteers between ages 16 and 60 years. Subjects were divided into two major groups; forty-two patients group with digestive and colon problems and forty-two healthy

controls. Age and weight were noticed and determined during the duration of the study. Controls and patients groups had the same age and weight. The protocol and informed consent were approved by the Ethics Committee of National Research Centre. Patients received spasmo canulase or librax treatments for a period of 30–45 days were enrolled in the prospective study.

Regarding to the Scientific Office of Novartis company, spasmo canulase is consisting of methixene hydrochloride 1 mg, dimethylpolysiloxane 40 mg, glutamic acid hydrochloride 100 mg, sodium dihydrochloride 20 mg, pepsin 120 FIP U, amylase 2,100 FIP U, lipase 1,200 FIP U, protease 80 FIP U and cellulose 600 U. On the other hand, librax is a drug consisting of chlordiazepoxide 5 mg and clidinium bromide 2.5 mg.

Methods

Blood samples were collected from males and females to measure serum FSH, E2, LH, prolactin, progesterone, DHEAS, testosterone, TSH, T3, T4, fasting insulin, and cortisol. Blood samples were collected from patients. All hormone concentrations were measured quantitatively using ELISA Kits provided by DRG International, Inc., USA, Diagnostic Systems Laboratories, Inc., and Adaltis Italia SPA Company, Italy.

Statistical Analysis

Data were statistically described in terms of range, mean, standard deviations ($\pm$ SD), and frequencies (number of cases) when appropriate. Comparison of variables between the study groups was performed using analysis of variance (ANOVA) test. A probability value (*P* value) less than 0.05 has been considered statistically significant. Statistical calculations were done using statistical computer program: SPSS (Statistical Package for the Social Science; SPSS Inc., version 17.0, USA).

Results

Follow up data obtained from all patient volunteers treated with spasmo canulase or librax drugs and healthy control individuals. Table 1 illustrates the hormonal data obtained from the adult patients received spasmo canulase or librax drugs, for period extended from 30 to 45 days.

Intriguingly, male patients received either spasmo canulase or librax drugs have high significant increase ($P < 0.01$) in serum FSH, E2, LH, and prolactin were showed non-significant difference as in serum progesterone, TSH, and T₃ the same as the control group. Moreover, T₄ and fasting insulin levels have non-significant difference

Table 1 Hormones profile of patients against healthy controls

Hormones Mean $\pm$ SD	Controls (<i>n</i> = 42)				Patients (<i>n</i> = 42)											
	Male (<i>n</i> = 20)		Female (<i>n</i> = 22)		Male (<i>n</i> = 20)						Female (<i>n</i> = 22)					
					D1			D2			D1			D2		
	M	SD	M	SD	M	SD	P	M	SD	P	M	SD	P	M	SD	P
FSH (mIU/ml)	5.1	0.1	9.0	0.1	9.0	1.1	S*	7.0	0.1	S*	17.0	0.1	S*	4.0	1.1	S*
E2 (pg/ml)	12.3	0.6	33.2	0.2	28.0	0.7	S*	27.0	1.9	S*	62.0	0.3	S*	45.0	1.2	S*
LH (mIU/ml)	1.5	0.8	4.5	1.5	1.8	0.3	S	3.1	1.2	S*	2.9	0.3	S*	6.7	1.3	S*
Prolactin (ng/ml)	5.7	0.3	12.0	0.3	6.0	0.2	S	7.2	1.2	S*	11.0	0.2	S*	9.1	0.3	S*
Progesterone (ng/ml)	0.2	0.4	0.7	0.2	0.11	1.5	NS	0.16	1.3	NS	1.3	0.4	S*	1.1	0.9	S
TSH (μ IU/ml)	0.4	0.1	0.4	0.2	0.8	2.1	NS	0.26	3.1	NS	2.3	0.7	S*	3.1	0.5	S*
T3 (ng/ml)	1.4	1.1	1.4	0.3	1.1	0.3	NS	1.5	1.1	NS	2.9	0.1	S*	3.7	0.2	S*
T4 (ng/dl)	0.5	0.2	0.8	0.3	0.6	1.6	NS	1.6	2.1	S	1.1	0.2	S*	1.9	0.2	S*
DHEAS (μ g/dl)	156.0	1.4	198	1.7	168.0	2.1	S*	127.0	1.2	S*	221	1.1	S*	236	0.1	S*
Fasting insulin (mIU/ml)	16.0	1.1	16.4	0.5	16.0	0.1	NS	19.0	1.2	S*	21	1.2	S*	27.0	0.3	S*
Testosterone (ng/dl)	1.0	0.1	0.8	0.1	9.0	0.3	S*	8.0	1.4	S*	5.9	1.2	S*	4.4	1.1	S*
Cortisol at a.m. (mg/dl)	27.4	0.1	27.4	0.2	2.11	1.1	S*	1.9	2.1	S*	19	1.3	S*	22.7	0.1	S*
Cortisol at p.m. (mg/dl)	1.4	0.2	8.4	1.1	1.0	0.2	S*	1.2	0.3	S*	6.3	1.2	S*	6.7	1.9	S*

All data were represented in term of mean (M) and standard deviation (SD)

N represents samples size, *D1* drug 1 represents Spasmo canulase, *D2* drug 2 represents librax, *P* P value, *S** represents high significant difference ($P < 0.001$), *S* represents significant difference ($P < 0.05$), *NS* represents non-significant difference ($P > 0.05$)

when comparing male patients received spasmo canulase drug with healthy controls. While, Female patients received either spasmo canulase or librax drugs have significant increase ($P < 0.01$) in serum E2, progesterone, DHEAS, testosterone, TSH, T_3 , T_4 , and fasting insulin compared to the control group.

Additionally, male patients treated with spasmo canulase drug have significant increase ($P < 0.01$) in serum DHEAS and significant decrease in serum testosterone, and cortisol in comparison to the control group. While, males treated with librax drug have significant increase ($P < 0.01$) in serum (T_4) and significant decrease in serum DHEAS, fasting insulin, testosterone, and cortisol in comparison to the control group.

On the other side, female patients treated with spasmo canulase drug have significant increase ($P < 0.01$) in serum FSH and decrease in serum LH, and prolactin in comparison to the control group. Eventually, females treated with librax drug have significant increase ($P < 0.01$) in serum LH and decrease in serum FSH, and prolactin compared to the control group.

Discussion

The current study was designed to evaluate the effect of spasmo canulase and librax drugs on different hormone profiles among patients suffering from digestive and colon

disturbances and the goal of this study is to answer and understand inquiries about increase blood flow to the brain and antioxidant properties, increase cognitive function, including learning, recall and memory, and to reduce the pain associated with claudication, a leg clotting condition and can reduce anxiety symptoms when taken regularly. Furthermore, providing new medical guidelines to alter the drug dose according to the effect of the drug on the different human hormones and it is extremely important to avoid a lot of burden and negative side effects that could harm patient health.

Intriguingly, studying female patients treated with either spasmo canulase or librax drugs have revealed statistically significant increase in thyroid hormones including; T_3 , T_4 , and TSH, as compared to the control group which may lead to severe dysfunction in thyroid system and imbalance within the homeostasis of body functions accompanied with burden negative side effects. Conversely, male patients treated with either spasmo canulase or librax drugs have non-significant difference in serum T_3 and TSH in addition to T_4 among males who treated with spasmo canulase drug as compared to the control group. The present study results agreed with the previous study which indicated that glutamine, an effective precursor of spasmo canulase drug, is taken up by the PT cells through the ATA2 and that glutamate locally converted from glutamine by glutaminase enzyme induces TSH β expression via the KA2, which is an iGluR, in an autocrine and/or paracrine

manner in the PT [18], therefore this suggestion supports the significant increase of the thyroid hormones among patients treated with spasmo canulase drug.

The current result is in contradiction with a previous study indicated that chlordiazepoxide, an active precursor of librax drug, acts as a competitive antagonist at the level of the TRHR [17], therefore, thyroid hormones depending on this suggestion must be significantly decreased. Moreover, some scientists studied the effects of the administration of chlordiazepoxide on the TRH binding to TRHRs in membranes. They showed that regional differences in the response of TRHR to chlordiazepoxide administration, suggesting that reduced affinity of TRH receptors may be related to some of the neurobiological actions of chlordiazepoxide and/or its metabolites [19]. Hinkle and Shanshala [20] suggested that chlordiazepoxide did not appear to internalize TRHR, because TRH-binding sites became available rapidly and at the same rate after they had been saturated with chlordiazepoxide. Potentiation of the behavioral effects of sedative-hypnotic and anxiolytic drugs by TRH suggests that TRH may play an important role in modulating the behavioral effects of these compounds and that combination of neuro active peptides with certain psychotherapeutic agents may be of some therapeutic value [21]. Also, previous data indicate that some differences between the brain and pituitary TRH receptor complex show that the inhibition produced by chlordiazepoxide is not mediated via a classical benzodiazepine receptor and the effect of chlordiazepoxide may be of pharmacological relevance [22].

In the present study, males and females treated with either spasmo canulase or librax drugs have high significant increase in serum sex hormones including; FSH, E2, LH, prolactin, progesterone, DHEAS, and testosterone as compared to the control group. Moreover, males treated with spasmo canulase drug have significant increase in serum DHEAS and significant decrease in serum testosterone as compared to the control group. Moreover, male patients treated with librax drug have significant decrease in serum DHEAS and testosterone as compared to the control group. Moreover, female patients received spasmo canulase drug have significant increase in serum FSH and decrease in serum LH and prolactin as compared to the control group. Finally, females treated with librax drug have significant increase in serum LH and decrease in serum FSH and prolactin as compared to the control group.

The present results have been supported by Kamat et al. [23] hypothesis indicated that glutamic acid stimulates luteinizing hormone-releasing hormone (LHRH) release via release of nitric oxide (NO) from NOergic neurons in the arcuate median eminence region. To determine if glutamic acid releases LHRH via direct stimulation of NOergic neurons, or via stimulation of noradrenergic terminals,

accurate median eminence of explants from male rats were incubated with various compounds, and the LHRH release into the medium was measured. The inhibitory neurotransmitter, glutamic acid, is involved in regulation of sexually dimorphic patterns of behavior and gonadotropin secretion in the adult. Therefore, authors quantified levels of mRNA for glutamic acid decarboxylase (GAD), the rate-limiting enzyme in glutamic acid synthesis. Also, they examined the role of gonadal steroids in regulating GAD by removing testes of males and administering testosterone to females at birth. Exposure to testosterone was correlated with increased GAD mRNA in the dorsomedial nucleus. A sex difference in GAD mRNA was also observed in the medial preoptic area, but the influence of testosterone was inconclusive. They hypothesized that steroid-induced changes in glutamic acid neurotransmission during this critical period are important mediators of sexual differentiation in brain [24].

These alterations within male and female sex hormones profile may lead to malfunction within the physiological performance of both males and females in addition to negative psychological effects, therefore the determination of drug dose must be dependent on its effect on human hormones profile.

In conclusion, spasmo canulase and librax drugs alter the human sex and thyroid hormones profile among patients suffering from digestive and colon disturbances. Additionally, the present study may be useful in drug dose optimization depending on the effect of the drug on each human hormone and providing new medical guidelines for drug companies and to avoid negative side effects that could harm the patient.

References

1. Majumdar D, Bebb J, Atherton J. *Helicobacter pylori* infection and peptic ulcers. *Medicine*. 2010;39:3.
2. Snowden FM. Emerging and reemerging diseases: a historical perspective. *Immunol Rev*. 2008;225(1):9–26.
3. Brown LM. *Helicobacter pylori*: epidemiology and routes of transmission. *Epidemiol Rev*. 2000;22(2):283–97.
4. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis: the updated Sydney system. *Am J Surg Pathol*. 1996;20:1161e81.
5. Anagnostopoulos GK, Yao K, Kaye P, Fogden E, Fortun P, Shonde A, et al. High resolution magnification endoscopy can reliably identify normal gastric mucosa, *Helicobacter pylori*-associated gastritis, and gastric atrophy. *Endoscopy*. 2006;39:202e7.
6. Atherton JC. The pathogenesis of *Helicobacter pylori*-induced gastroduodenal disease. *Annu Rev Pathol Mech Dis*. 2006;1: 63e96.
7. Gillen D, El-Omar EM, Wirz AA, Ardill JES, McColl KEL. The acid response to gastrin distinguishes duodenal ulcer patients from *Helicobacter pylori*-infected healthy subjects. *Gastroenterology*. 1998;114:50e7.

8. Malagelada JR. A symptom-based approach to making a positive diagnosis of irritable bowel syndrome with constipation. *Int J Clin Pract.* 2006;60(1):57–63.
9. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. *Am J Gastroenterol.* 2002;97(11):2812–9.
10. Mayer EA. Clinical practice. Irritable bowel syndrome. *N Engl J Med.* 2008;358(16):1692–9.
11. Mohamed AE, Ghandour ZM, Al-Karawi MA. Spasmo canulase in irritable bowel syndrome. *Saudi Med J.* 2002;23(9):1074–7.
12. Head HB, Hammond JB. Antisecretory effects of librax in patients with duodenal ulcer. *Am J Dig Dis.* 1968;13(6):540–50.
13. Ban TA. The role of serendipity in drug discovery. *Dialogues Clin Neurosci.* 2006;8(3):335–44.
14. Liljequist R, Palva E, Linnoila M. Effects on learning and memory of 2-week treatments with chlordiazepoxide lactam, N-desmethyldiazepam, oxazepam and methyloxazepam, alone or in combination with alcohol. *Int Pharmacopsychiatry.* 1979;14(4):190–8.
15. Yamada M, Monden T, Konaka S, Mori M. Assignment of human thyrotropin-releasing hormone (TRH) receptor gene to chromosome 8. *Somat Cell Mol Genet.* 1993;19(6):577–80.
16. Gershengorn MC. Thyrotropin-releasing hormone receptor: cloning and regulation of its expression. *Recent Prog Horm Res.* 1993;48:341–63.
17. Drummond AH. Chlordiazepoxide is a competitive thyrotropin-releasing hormone receptor antagonist in GH3 pituitary tumour cells. *Biochem Biophys Res Commun.* 1985;127(1):63–70.
18. Aizawa S, Sakai T, Sakata I. Glutamine and glutamic acid enhance thyroid-stimulating hormone β subunit mRNA expression in the rat pars tuberalis. *J Endocrinol.* 2012;212(3):383–94.
19. Shimoda K, Mason GA, Walker CH, Garbutt JC, Prange AJ Jr. Administration of chlordiazepoxide affects $[3H][3-MeHis2]$ thyrotropin-releasing hormone binding in rat brain. *Peptides.* 1991;12(1):199–202.
20. Hinkle PM, Shanshala ED 2nd. Pituitary thyrotropin-releasing hormone (TRH) receptors: effects of TRH, drugs mimicking TRH action, and chlordiazepoxide. *Mol Endocrinol.* 1989;3(9):1337–44.
21. Witkin JM, Sickie J, Barrett JE. Potentiation of the behavioral effects of pentobarbital, chlordiazepoxide and ethanol by thyrotropin-releasing hormone. *Peptides.* 1984;5(4):809–13.
22. Simasko S, Horita A. Chlordiazepoxide displaces thyrotropin-releasing hormone (TRH) binding. *Eur J Pharmacol.* 1984;98(3–4):419–23.
23. Kamat A, Yu W, Rettori V, McCann S. Glutamic acid induces luteinizing hormone releasing hormone release via alpha receptors. *Brain Res Bull.* 1995;37(3):233–5.
24. Davis AM, Grattan DR, Selmánoff Michael, McCarthy MM. Sex differences in glutamic acid decarboxylase mRNA in neonatal rat brain: implications for sexual differentiation. *Horm Behav.* 1996;30(4):538–52.