International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

International Journal of Pharmacology 6 (5): 691-695, 2010
ISSN 1811-7775

A Systematic Review on the Efficacy of Herbal Medicines in the Management of Human Drug-induced Hyperprolactinemia; Potential Sources for the Development of Novel Drugs

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Abstract: Several drugs may increase blood prolactin concentration. Dopamine receptor antagonists are one of the most common causes of hyperprolactinemia. To reduce happening of hyperprolactinemia, some medicinal plants have been traditionally used. This review focuses on the efficacy of effective herbal medicines in the management of human drug-induced hyperprolactinemia. PubMed, Scopus, Web of science, Cochrane library database were searched for any relevant studies that investigated the effect of herbal medicines on drug induced hyperprolactinemia up to May 2010. The inclusion criteria were clinical trials studied efficacy of herbal medicines in drug-induced hyperprolactinemia. Among different compounds, four herbal supplements including Shakuyaku-kanzo-to (TJ-68), Peony-Glycyrrhiza Decoction (PGD), Zhuangyang capsule, Tongdatang serial recipe (TDT) were found clinically effective and safe in management of drug-induced hyperprolactinemia. Although, the quality of included clinical trials was low not allowing us to conduct a meta-analysis but positive results on efficacy (TJ-68), (PGD), Zhuangyang capsule and (TDT) cannot be ignored. Interestingly compounds with prolactin-suppressive effects have a number of diterpenes mainly clerodadienols that seem almost identical for their efficacy. Further studies to isolate and characterize constituents of the effective herbs are needed to reach novel therapeutic and more effective agents.

Key words: Hyperprolactinemia, prolactinoma, galactorrhea, herbal medicine, antipsychotics, neuroleptic, schizophrenia, systematic review, new drugs

INTRODUCTION

Any process interfering with dopamine synthesis, its transport to the pituitary gland, or its action at the level of lactotroph dopamine receptors can cause hyperprolactinemia (Mancini *et al*., 2008). Hyperprolactinemia is mostly seen in women, but also observed in men and even in adolescence and childhood (Patel and Bamigboye, 2007). Hyperprolactinemia is a common endocrinological disorder that is caused by many physiological or pathological conditions (Torre and Falorni, 2007). Women with oligomenorrhea, amenorrhea, or galactorrhea and men with symptoms of hypogonadism or impotence or infertility should be checked for blood prolactin to determine pharmacologic or extrapituitary causes of hyperprolactinemia and neuroradiologic evaluation of the hypothalamic-pituitary region (Casanueva *et al*., 2006).

Several drugs may cause a significant increase in blood prolactin concentration (Torre and Falorni, 2007) which dopamine D2 receptor antagonists are the main. These include antipsychotic drugs such as risperidone, phenothiazines, haloperidol (David *et al*., 2000), butyrophenones (Rivera *et al*., 1976), metoclopramide (McCallum *et al*., 1976) and domperidone (Sowers *et al*., 1982). These drugs can be categorized for their potency to the pituitary dopamine receptors that is in correlation with their prolactin release, as follows: sulpiride>risperidone>haloperidol> olanzapine>clozapine (David *et al*., 2000; Markianos *et al*., 2001). The high prevalence of psychotic disorders (Perala *et al*., 2007) and the need for long-term therapy makes antipsychotic adverse effects, such as hyperprolactinemia, a major problem. In patients taking neuroleptic medications, drug-induced hyperprolactinemia should be confirmed with temporary drug withdrawal or

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pituitary Magnetic Resonance Imaging (MRI). Dopamine agonist drugs like bromocriptine, cabergoline, pergolide and quinagolide are usually the first choice for controlling of hyperprolactinemia but they have gastrointestinal, cardiovascular and neurological adverse effects (Vance *et al*., 1984; Gillam *et al*., 2006). Of course, for treatment of drug-induced hyperprolactinemia, combined use of dopamine antagonists and dopamine agonists is not advised because of increased risk of side effects (Perovich *et al*., 1989; Tollin, 2000).

To best of present knowledge, there is no review on the use of herbal medicines in the management of drug-induced hyperprolactinemia. Thus, in the present study, we systematically reviewed all existing data on the efficacy of herbal medicines in the management of drug-induced hyperprolactinemia in human.

MATERIALS AND METHODS

PubMed, Scopus, Web of science, Cochrane library database were searched for any relevant studies that investigated the effect of herbal medicines on hyperprolactinemia up to May 2010. The search terms were: prolactin, hyperprolactinemia, prolactinoma, galactorrhea and herb, herbal medicine, plant, traditional medicine and antipsychotics, neuroleptic, schizophrenia and human.

The quality of trials was assessed by Jadad score for characterizing studies according to appropriate randomization, blinding and description of study withdrawals or dropouts (Moher *et al*., 1995). The description of this score is as follows:

- Whether randomized (Yes = 1 point, No = 0)
- Whether randomization was described appropriately (Yes = 1 point, No = 0)
- Double-blind (Yes = 1 point, No = 0)
- Was the double-blinding described appropriately (Yes = 1 point, No = 0)
- Whether withdrawals and dropouts were described (Yes = 1 point, No = 0).

The quality score ranges from 0 to 5 points; a low-quality report score is = 2 and a high-quality report score is at least 3.

Three reviewers evaluated studies by reading the title and abstract of the search results to eliminate duplicates, reviews, case studies and letters. The inclusion criteria were clinical trials studied efficacy of herbal medicines in drug-induced hyperprolactinemia.

RESULTS AND DISCUSSION

After searching databases, 48 results were found which only 6 of them were appropriate for inclusion. Four were written in English and 2 in Chinese languages. Full text of 3 English articles and abstract of the 2 Chinese articles were studied. Data were extracted and shown in the Table 1. Four herbal supplements including Shakuyaku-kanzo-to (TJ-68), Peony-Glycyrrhiza Decoction (PGD), Zhuangyang capsule, Tongdatang serial recipe (TDT) were found clinically effective and safe in management of drug-induced hyperprolactinemia.

All of the studies showed a significant decrease in blood prolactin level. In the first trial, the prolactin levels decreased by more than 50% with Shakuyaku-kanzo-to (TJ-68) treatment among 5 patients. Plasma prolactin level at 8 weeks was not significantly different with the baseline. Three of 10 patients, who had complained of reduced sexual desire, experienced subjective improvement (Yamada *et al*., 1997). In the second trial, decreased plasma prolactin level was observed in nine patients treated with TJ-68 and in four, the plasma prolactin decreased more than 50%. Subjective improvement of reduced sexual desire was observed in three patients at 4 weeks (Yamada *et al.,* 1996).Yamada has reported a case with risperidone-induced amenorrhea and demonstrated TJ-68 to be effective in correcting neuroleptic-induced amenorrhea and hyperprolactinemia (Yamada *et al.,* 1999). The exact mechanism of TJ-68 is unknown although it may have a direct inhibitory effect on prolactin release from pituitary (Yamada *et al*., 1996, 1997). It also decreased estradiol in rats and this reduction might decrease prolactin levels.In the third trial, both Peony-Glycyrrhiza Decoction (PGD) and bromocriptine treatment had a similar percentage of amplitude of the decrease in blood prolactin. Nevertheless, unlike bromocriptine therapy, the herbal remedy did not cause worsening of psychotic symptoms, either transiently or individually. Conversely, a significant greater proportion of patients (nearly 56%) showed improvements on adverse effects related to hyperprolactinemia during PGD treatment (Yuan *et al*., 2008). The PGD with multiple contents including albifloran, paenoiflorin, benzoylpaeoiflorin, liquiritin and glycyrrhetinic acid had putative mechanisms and multiple actions deserves needed to be further investigated.

In the fourth trial, after 8 weeks of treatment with either Zhuangyang capsule (n = 39) or placebo capsule (n = 37) supplemented to risperidone, the serum level of prolactin decreased significantly, while in the control

Table 1: Human studies considering herbal medicines for treatment of drug-induced hyperprolactinemia

Study No.	Researchers	Target	Herbs (scientific name)	Study	Dose/ Duration	Main outcome	Other relevant effects and complications	Jadad score
1	Yamada *et al.* (1997)	10 Schizophrenic male inpatient on neuroleptic drugs	Shakuyaku-kanzo-to (TJ-68) (paeoniae radix+glycyrrhizae radix)	Open label trial (without control)	Case: 7.5 g 4 weeks	Decreased PRL 5.8 ng mL^{-1}	No change of potassium, improvement of sexual desire	0
2	Yamada *et al.* (1996)	11 Schizophrenic male inpatient on neuroleptic drugs	Shakuyaku-kanzo-to (TJ-68) (paeoniae radix+glycyrrhizae radix)	Open label trial (without control)	Case: 7.5 g 4 weeks	Decreased PRL 6.9 ng mL^{-1}	No exacerbation of psychosis, no significant change of potassium, improvement of sexual desire	0
3	Yuan *et al.* (2008)	20 Schizophrenic women under risperidone diagnosed with hyperprolactinemia (serum PRL levels >50 μg L^{-1}), experiencing oligomenorrhea or amenorrhea	Peouy-Glycyrrhiza Decoction (PGD)	Randomized, crossover	Case: PGD (45 g day 1) followed by BMT (5 mg day 1) or BMT followed by PGD at the same doses/ 4 weeks each, with an interval of 4 week washout period	Both treatments decreased PRL	Significant improvements in adverse effects associated with hyperprolactinemia with PGD treatment more than BMT treatment (56 vs. 17%,)	0
4	Chen *et al.* (2008)	76 Schizophrenic patients; 39 cases 37 controls	Zhuangyang capsule	RCT	Case: Zhuangyang capsule+ risperidone Control: placebo capsule+ risperidone/ 8 weeks	Decreased PRL in cases increased PRL in controls		≥1
5	Ding *et al.* (2008)	100 female schizophrenic patients with antipsychotic drug-induced GAS. 50 cases 50 controls	Tongdatang serial recipe (TDT)	RCT	4 and 8 weeks	Decreased PRL: in case group total effective rate was 93.9%, in control group, the total effective rate was 21.3%		≥1

BMT: Bromocriptine; PRL: Prolactin; RCT: Randomized control trial; GAS: Galactorrhea-amenorrhea syndrome

group, the prolactin markedly increased. There was a significant difference (decreased 26.51 ng mL^{-1} vs increased 15.56 ng mL^{-1}) in improvement of serum prolactin in trial group compared with that of control group. This effect of Zhuangyang capsule was not different between male and female groups (Chen *et al.*, 2008).

In the fifth trial, serum prolactin reduced in the group treated with Tongdatang serial recipe (TDT) significantly more than that of control group (Ding *et al.*, 2008). From 49 patients of the treatment group, 31 patients got cure (63.3%).

The first two studies did not have control group and were done only in men. Instead, the third and the fifth ones were done in women, based on the fact that the incidence of events associated with hyperprolactinemia is much higher and more severe in women (Yuan *et al.*, 2008).

There are some other herbal medicines which are useful in treatment of hyperprolactinemia, such as *Vitexagnus castus* (Wuttke *et al.*, 2003) but they are not studied on antipsychotic-induced hyperprolactinemia. The search for chemical identity of the dopaminergic compounds resulted in isolation of a number of diterpenes of which some clerodadienols were most important for the prolactin-suppressive effects. They were almost identical in their prolactin-suppressive properties than dopamine itself.

CONCLUSIONS

Although, the quality of included clinical trials was low that is a limitation of this review not allowing us to conduct a meta-analysis but positive results on efficacy and safety of Shakuyaku-kanzo-to (TJ-68), Peony-Glycyrrhiza Decoction (PGD), Zhuangyang capsule and Tongdatang serial recipe (TDT) cannot be ignored. As herbal medicines produce definite therapeutic effects with few side effects, in the recent years, many traditionally-used remedies have found evidenced-based

places in novel medicine in various diseases like diabetes (Rahimi *et al*., 2010, 2005; Hasani-Ranjbar *et al*., 2008, 2010), obesity (Hasani-Ranjbar *et al*., 2009a), oxidant- and age-related diseases (Hasani-Ranjbar *et al*., 2009b), colitis (Rahimi *et al*., 2009), pancreatitis (Mohseni-Salehi-Monfared *et al*., 2009a), islet transplantation (Mohseni-Salehi-Monfared *et al*., 2009b), bone health and osteoporosis (Salari *et al*., 2008) and multi-organ benefits (Momtaz and Abdollahi, 2010) making the present report worthy. Further studies on isolation and characterization of their constituents would open a new approach for novel therapeutic and more effective agents.

ACKNOWLEDGMENT

This study is the outcome of an in-house study and has not been supported financially.

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