Corticosteroid adulteration in proprietary Chinese medicines: a recurring problem

YK Chong, CK Ching, SW Ng, Tony WL Mak *

A B S T R A C T

Objectives: To investigate adulteration of proprietary Chinese medicines with corticosteroids in Hong Kong.

Design: Case series with cross-sectional analysis.

Setting: A tertiary clinical toxicology laboratory in Hong Kong.

Patients: All patients using proprietary Chinese medicines adulterated with corticosteroids and referred to the authors' centre from 1 January 2008 to 31 December 2012.

Main outcome measures: Patients' demographic data, clinical presentation, medical history, drug history, laboratory investigations, and analytical findings of the proprietary Chinese medicines were analysed.

Results: The records of 61 patients who consumed corticosteroid-adulterated proprietary Chinese medicines were reviewed. The most common corticosteroid implicated was dexamethasone. Co-adulterants such as non-steroidal anti-inflammatory drugs and histamine H_1-receptor antagonists were detected in the proprietary Chinese medicine specimens. Among the patients, seven (11.5%) required intensive care, two (3.3%) died within 30 days of presentation, and 38 (62.3%) had one or more complications that were potentially attributable to exogenous corticosteroids. Of 22 (36.1%) patients who had provocative adrenal function testing performed, 17 (77.3% of those tested) had adrenal insufficiency.

Conclusion: The present case series is the largest series of patients taking proprietary Chinese medicines adulterated with corticosteroids. Patients taking these illicit products are at risk of severe adverse effects, including potentially fatal complications. Adrenal insufficiency was very common in this series of patients. Assessment of adrenal function in these patients, however, has been inadequate and routine rather than discretionary testing of adrenal function is indicated in this group of patients. The continuing emergence of proprietary Chinese medicines adulterated with western medication indicates a persistent threat to public health.

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YK Chong, MB, BS
CK Ching, FRCPA, FHKAM (Pathology)
SW Ng, MPhil
TWL Mak *, FRCPath, FHKAM (Pathology)

Hospital Authority Toxicology Reference Laboratory, Princess Margaret Hospital, Laichikok, Hong Kong

* Corresponding author: makwl@ha.org.hk

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New knowledge added by this study

- Adulteration of proprietary Chinese medicines (pCMs) with corticosteroids is a significant yet under-recognised phenomenon. Co-adulteration with non-steroidal anti-inflammatory drugs and histamine H_1-receptor antagonists is often seen.
- Adrenal insufficiency is a common complication in patients who have consumed pCMs adulterated with corticosteroids.

Implications for clinical practice or policy

- Adrenal function testing is essential for patients suspected to have taken corticosteroid-adulterated pCMs.
- Public health education on the danger of taking pCMs of dubious sources and implementation of effective regulatory measures are important to address the problem of corticosteroid-adulterated pCMs.

Introduction

Proprietary Chinese medicines (pCMs) are products claimed to be made of Chinese medicines and formulated in a finished dosage form. As with traditional Chinese medicine, pCMs are generally regarded by the public as benign and non-toxic, as compared with western medications.

Undeclared corticosteroids, among other adulterants, have been reported to be added to pCMs, Ayurvedic medicine, and homeopathic medicine.[1-5] There are multiple incentives for adding corticosteroids: they have powerful analgesic and anti-inflammatory actions, making these proprietary products effective against various allergic,

摻雜皮質類固醇的中成藥：一個經常出現的問題

張耀君、程楚君、吳秀華、麥永禮

目的：探討香港中成藥摻雜皮質類固醇的情況。

設計：病例系列的橫斷面分析。

安排：香港一所臨床毒理學化驗室。

患者：2008年1月1日至2012年12月31日期間因服用摻雜皮質類固醇的中成藥被轉介至上述化驗室的病人。

主要結果測量：病人的人口學統計數據、臨床表現、病史、用藥史、實驗室檢查結果，以及中成藥的分析結果。

結果：本研究共分析61名服用摻雜皮質類固醇中成藥病人的醫療紀錄，其中最常見的皮質類固醇為地塞米松。這些中成藥亦含有其他西藥成分，如非類固醇抗炎藥和組織胺H_1受體拮抗劑。有7人（11.5%）須入住深切治療部，2人（3.3%）在病發30天內死亡，38人（62.3%）因外源性糖皮質類固醇而出現最少一項併發症。22人（36.1%）接受激發性腎上腺皮質功能測試，當中17人（即受驗者的77.3%）有腎上腺皮質功能不全。

結論：這是有關摻雜皮質類固醇中成藥研究中最大型的病例系列。病人服用這些非法藥品會出現嚴重的副作用、甚至可以引起致命的併發症。本研究顯示腎上腺皮質功能不全在這類病人中很普遍，惟對這些病人的腎上腺皮質功能評估仍有改善空間，而我們應為這些病人測試腎上腺皮質功能。中成藥被摻雜西藥成分的個案持續出現，會對公眾健康構成威脅。

autoimmune, dermatological, and musculoskeletal pain disorders.

From 2008 to 2012, the Hospital Authority Toxicology Reference Laboratory, the only tertiary referral centre for clinical toxicological analysis in Hong Kong, confirmed 61 cases of corticosteroid-adulterated pCMs. We report these cases to highlight the severity and danger of using such adulterated medications.

Methods

From 1 January 2008 to 31 December 2012, all cases referred to the Hospital Authority Toxicology Reference Laboratory that involved the use of pCMs, which were subsequently found to contain corticosteroids, were retrospectively reviewed.

Clinical data were obtained by reviewing the laboratory database as well as the patients' electronic and, where necessary, paper health records. Demographic data, clinical presentation, medical history, drug history, laboratory investigations, radiological investigations, and analytical findings of the pCMs were reviewed. For the evaluation of adrenocortical function, due to the heterogeneity of patient population and the nature of the retrospective case series for the present study, both low-dose short synacthen test (LDSST) and short synacthen test (SST) have been used for the diagnosis of adrenal insufficiency. We adopted a cutoff of 550 nmol/L, which has been traditionally used for SST, and previously validated in the local population for LDSST.[6]

The presumed causal relationship between the clinical features or complications or both of the patients and the adulterants was evaluated based on the temporal sequence, the known adverse effects of the detected drugs, and the presence of underlying diseases.

The presence of corticosteroids was analysed qualitatively by liquid chromatography–tandem mass spectrometry (LC-MS/MS) with a linear ion trap instrument. The presence of other co-adulterants was analysed qualitatively by high-performance liquid chromatography with diode-array detection. Confirmations by LC-MS/MS or gas chromatography–mass spectrometry were performed as required.

This study was approved by the Hong Kong Hospital Authority Kowloon West Cluster Research Ethics Committee (approval number KW/EX-13-121). The Committee exempted the study group from obtaining patient consent because the presented data were anonymised, and the risk of identification was low.

Results

A total of 61 patients involving the use of 61 corticosteroid-adulterated pCMs were referred to the Hospital Authority Toxicology Reference Laboratory in Hong Kong. There were 30 men and 31 women, with an age range of 1 to 91 years (median, 65 years). Seven (11.5%) patients were younger than 18 years. The usage duration ranged from 3 days to 10 years, with a median of 4 months.

Most (n=47, 77.0%) patients obtained the corticosteroid-adulterated pCMs over-the-counter and 13 (21.3%) obtained the steroid-adulterated pCMs from Chinese medicine practitioners. The source for one case remained unknown. Among the 47 patients who obtained their pCMs over-the-counter, 38 (80.9%) obtained the pCMs in the Mainland China, seven (14.9%) obtained the pCMs in Hong Kong, and the remaining two patients (each accounting for 2.1%) obtained the pCMs from Taiwan and Malaysia. For patients who obtained their pCMs from Chinese medicine practitioners (n=13), the practitioners were located in Hong Kong in nine (69.2%), Mainland China in two (15.4%), and Macau in two (15.4%) cases.

The three most common indications for the use of pCMs were musculoskeletal pain (n=36; 59.0%), skin disorders such as eczema and psoriasis (n=13; 21.3%), and airway problems such as asthma, bronchiectasis, and chronic obstructive airway disease (n=8; 13.1%). The indications for all seven

(11.5%) paediatric patients were for skin disorders.

Dexamethasone, present in 29 (47.5%) pCMs, and prednisone, present in 21 (34.4%) pCMs, were the most common corticosteroid adulterants among the pCMs submitted for analysis. Details of the corticosteroid adulteration are listed in Table 1.

Other than steroids, co-adulterants were also detected in 53 (86.9%) pCMs. The most common co-adulterants were non-steroidal anti-inflammatory drugs (NSAIDs; present in 33 [54.1%] pCMs) and histamine H_1-receptor antagonists (present in 20 [32.8%] pCMs). The co-adulterants are listed in Table 2.

Overall, 38 (62.3%) patients had one or more complications that were either attributable or potentially attributable to the use of exogenous corticosteroids: 18 (29.5%) were documented to have clinical Cushing's syndrome; eight (13.1%) had endoscopic-proven gastritis or peptic ulcer disease, of whom six (9.8%) were proven to be *Helicobacter pylori*–negative; five (8.2%) had sepsis at presentation; three (4.9%) had hepatitis B exacerbation; and two (3.3%) had tuberculosis. Other clinical presentations included hepatitis C reactivation, transient diabetes that resolved after discontinuation of corticosteroids, and cataract occurring in a paediatric patient. Overall, 22 (36.1%) patients had adrenal function testing performed, and among them 17 (77.3%) had biochemically confirmed adrenal insufficiency.

For the subgroup in whom Cushing's syndrome was not identified (n=43; 70.5%), LDSST/SST were performed in 11 (25.6%), and among those, seven (63.6%) had biochemically confirmed adrenal insufficiency.

Seven (11.5%) patients in this series required intensive care, and two (3.3%) died within 1 month of initial presentation. Among the patients who had consumed pCMs adulterated with corticosteroids and required intensive care unit admission, the clinical presentations of two patients may have been related to the use of corticosteroids, which are described below.

Case 1

The patient was a 67-year-old man who had a history of psoriasis, diabetes, hypertension, and chronic renal impairment. He presented in 2012 with fever, decreased urine output, and gastrointestinal upset. He reported a 2-month history of using a pCM for psoriasis, and his skin condition dramatically improved. He was in shock on admission, with acute renal failure and respiratory distress. He was admitted to the intensive care unit where he stayed for 7 days. He required inotropic support and mechanical ventilation. Computed tomography revealed a large lung abscess and blood culture showed *Pseudomonas* species. During his hospitalisation, SST was performed, and the results

TABLE 1. Corticosteroids used to adulterate the proprietary Chinese medicines (pCMs) taken by patients in this study (n=61)

Corticosteroids (and its conjugates)	No. (%) of pCMs
Dexamethasone	25 (41.0)
Prednisone	20 (32.8)
Betamethasone	5 (8.2)
Prednisolone	4 (6.6)
Clobetasol, fluocinonide	2 (3.3)
Dexamethasone, prednisolone	2 (3.3)
Dexamethasone, prednisone	1 (1.6)
Dexamethasone, triamcinolone, fluocinonide	1 (1.6)
Triamcinolone	1 (1.6)

TABLE 2. Co-adulterants in the proprietary Chinese medicines taken by patients in this study (n=61)

Indication (No. of pCMs)	Drug class (No. of cases)
Pain (36)	NSAIDs (26)
	Paracetamol (4)
	H_2 antagonists (4)
	Diuretics (7)
	H_1 antagonists (6)
	Benzodiazepines (1)
	Methylxanthines (1)
Dermatological conditions (13)	H_1 antagonists (5)
	Antifungals (4)
	Antibiotics (2)
	NSAIDs (6)
	Diuretics (1)
	Paracetamol (1)
Respiratory conditions (8)	H_1 antagonists (7)
	β_2-agonists (5)
	Antibiotics (3)
	Methylxanthines (1)
	Benzodiazepines (4)
	Opioids (3)
Others (4)	H_1 antagonists (2)
	NSAIDs (1)
	Diuretics (1)
	Oral antidiabetic drugs (1)
	Paracetamol (1)
	PDE5 inhibitors (1)

Abbreviations: β_2-agonists = beta-2 adrenergic agonists; H_1 antagonists = histamine H_1-receptor antagonists; H_2 antagonists = histamine H_2-receptor antagonists; NSAIDs = non-steroidal anti-inflammatory drugs; pCMs = proprietary Chinese medicines; PDE5 inhibitors = phosphodiesterase type 5 inhibitors

were adequate (cortisol level of 944 nmol/L at 30 minutes after synacthen injection).

In the pCM submitted for analysis, prednisone acetate was detected, among other herbal markers. His condition improved with drainage of the abscess and prolonged intravenous antibiotics, including cefoperazone and sulbactam (1 g and later 2 g every 12 hours intravenously [IV] for 39 days) as well as imipenem and cilastatin (500 mg every 8 hours IV for 51 days). He was discharged after a long rehabilitation programme, 3 months after the initial admission.

Case 2

The patient was a 61-year-old man. He presented in 2009 with a history of asthma, and was a chronic smoker. He initially presented with low back pain after slipping and falling. He, however, was noted to have bilateral apical opacities on chest radiograph, and was found to have smear-positive, open pulmonary tuberculosis.

He was put on piperacillin (4 g every 6 hours IV), augmentin (1.2 g every 8 hours IV), clarithromycin (500 mg twice a day orally), isoniazid (300 mg daily orally), rifampicin (450 mg daily orally), and ethambutol (700 mg daily orally) initially while he was intubated, ventilated, and admitted to intensive care unit for respiratory failure. During his initial improvement in the intensive care unit, he reported the use of a kind of herbal powder, which he took to alleviate his airway condition. In the herbal powder, opium alkaloids (morphine, codeine), oxytetracycline, diazepam, clenbuterol, and prednisone were detected, among other herbal markers.

His condition later deteriorated and he went into respiratory failure and required intubation. Subsequently, he died of ventilator-associated *Escherichia coli* pneumonia. In this patient, adrenal function testing with LDSST/SST was not performed.

TABLE 3. Complications attributable to exogenous corticosteroids in the proprietary Chinese medicines (pCMs) taken by patients in this study (n=61)

Classification	Complications	No. (%) of pCMs
Attributable	Cushing's syndrome	18 (29.5)
	Adrenal insufficiency	17 (27.9)
	Cataract occurring in paediatric patient	1 (1.6)
Potentially attributable	Sepsis	5 (8.2)
	Reactivation of tuberculosis	2 (3.3)
	Helicobacter pylori–negative gastritis	6 (9.8)
	Exacerbation of underlying hepatitis B	3 (4.9)
	Exacerbation of underlying hepatitis C	1 (1.6)
	Transient diabetes	1 (1.6)

Discussion

Corticosteroids are notorious for causing side-effects such as Cushing's syndrome, adrenal insufficiency, cataracts, peptic ulcer disease, osteoporosis, and decreased immune response, particularly when used for a protracted period of time in high doses. The latest Endocrine Society guidelines on the diagnosis of Cushing's syndrome has also stressed obtaining a thorough history to exclude excessive exogenous glucocorticoid exposure leading to iatrogenic Cushing's syndrome.[7] The continuing emergence of corticosteroid-adulterated pCMs indicates that iatrogenic Cushing's syndrome is a persistent problem with public health implications.

The incentive behind adulteration of pCMs is easily understandable. Most of the pCMs involved suggest that they are useful for the treatment of pain, skin problems, or respiratory ailments. Steroids, notwithstanding their many adverse effects, are effective therapy for pain, inflammatory disorders, allergic skin problems, and respiratory disorders such as asthma and chronic obstructive airway disease.

Although the side-effects of corticosteroids have been extensively described over the past century, many of these effects are multifactorial in their pathophysiology, and the effect of corticosteroids is difficult to quantitate in isolation. For example, Cushing's syndrome and adrenal insufficiency as adverse drug reactions associated with the use of corticosteroid-adulterated pCMs are less likely to be disputed, for example *H pylori*–negative peptic ulcer disease can be due to stress, alcoholism, use of NSAIDs, and other concomitant illnesses.

Despite the presence of confounding factors, the adverse effects of corticosteroid use are suspected in many of the patients who use corticosteroid-containing pCMs: for example, the deep-seated infection in patient 1 and open tuberculosis in patient 2 could well be a result of immunosuppression due to the use of corticosteroids. For the paediatric patient with cataract on presentation, given that the patient had no other clinical features to suggest a metabolic or exogenous cause for the cataract, it is more likely that the presence of the cataract was due to the use of corticosteroids. The authors considered all cases of Cushing's syndrome, adrenal insufficiency, and cataract occurring in paediatric patients to be attributable to the use of exogenous steroids. The prevalence of these conditions in this case series and other conditions that are potentially attributable to the use of exogenous corticosteroids are listed in Table 3.

The presence of co-adulterants in steroid-adulterated pCMs appears to be the rule rather than the exception. It cannot be overstressed that co-adulterants present in pCMs are equally dangerous, even when compared with corticosteroids, for

example, the presence of multiple NSAIDs together with steroids puts patients at high risk for complications (such as acute kidney injury and peptic ulcer disease), and opiates (such as codeine and morphine) present in pCMs indicated for respiratory conditions puts patients, who most likely have asthma or chronic obstructive airway disease, at high risk for respiratory depression and carbon dioxide narcosis. While effective at ameliorating symptoms, these drugs delay the clinical presentation and hence the opportunity to treat the disease at an early stage.

Many therapeutically irrelevant medications were also found in the pCMs. Examples include histamine H_1-receptor antagonists found in adulterated pCMs that are intended to treat bone pain, and the presence of tadalafil (a drug used to treat erectile dysfunction) found in an adulterated pCM that is supposed to treat diabetes.

It is difficult to comprehend the reason behind the addition of such co-adulterants, although contamination due to poor pharmaceutical manufacturing practice is likely a contributing factor, if not the sole reason.

For the diagnosis of exogenous corticosteroid intake, maintaining a high index of suspicion is of utmost importance. The classical feature of Cushing's syndrome was present in less than 30% of patients in this series. This indicates that a large proportion of cases would likely be missed if biochemical testing was only performed following demonstration of classical features of exogenous steroid intake. This experience indicates that it is often worthwhile testing patients who improve dramatically with the use of pCMs from dubious sources, especially when the treatment claims to be effective for treating pain, airway diseases, and childhood eczema. In these cases, a detailed drug history, and laboratory analysis of suspicious pCMs can help to confirm the diagnosis.

The management of these patients starts with termination of exposure to the adulterated pCMs, and treatment of the complications that have already occurred. It is prudent to provide corticosteroid replacement therapy pending dynamic function test for adrenal function. For patients with underlying inflammatory or autoimmune disorders such as gouty arthritis, psoriasis, and eczema, abrupt discontinuation of corticosteroid medications may trigger an exacerbation of disease. In these groups of patients, slow, gradual tapering should be considered.

A worrying observation in the present series is the occurrence of adrenal insufficiency, as well as the lack of investigations thereof. Patients who were exposed to pCMs adulterated with corticosteroids were clearly at risk of adrenal insufficiency due to suppression of adrenocorticotropic hormone secretion and the resultant adrenocortical atrophy.

In this series, LDSST/SST was only performed in 36.1% of the patients, and in those patients in whom the tests were performed, 77.3% were inadequate. It is clear that, among the patients who were not tested, some were likely to have undiagnosed adrenal insufficiency. As undiagnosed adrenal insufficiency carries a high risk of morbidity and mortality, the authors believe that LDSST should be performed on all patients who have significant exposure to pCMs adulterated with corticosteroids, even if they have no signs of Cushing's syndrome.

While spot cortisol obtained in the morning is diagnostic if it is <100 nmol/L or >420 nmol/L as verified locally by Choi et al,[6] we recommend LDSST as the test for adrenal function; LDSST (1 μg) is preferred over the standard (250 μg) SST because studies indicate that LDSST may be more sensitive in detecting partial adrenal insufficiency.[8,9] The authors further recommend that a sensitive cutoff of 550 nmol/L at 30 minutes be used for the purpose of diagnosing adrenal insufficiency in this group of patients. Our recommendation for use of provocative adrenal testing and a sensitive cutoff level is based on the high probability of adrenal insufficiency in this group of patients.

Prevention is always better than cure, and this is especially true for public health issues. While analytical and clinical toxicologists are well aware of the situation, it is important to bring this matter to the other stakeholders in society, namely, policy-makers, frontline clinicians, and the general public, with communication tailored to the recipients.

For the general public, a simple rule can be taught: if it sounds too good to be true, it probably is; and this is especially so for pCMs that claim to treat certain conditions in which western-drug adulteration is common, for example, weight reduction and diabetes, as previously reported by our unit,[10,11] and pain, respiratory conditions, and skin problems, as reported in the present study. It is prudent to consider brands and retailers that are trustworthy and, in case of doubt, patients should seek opinion from their primary care doctors.

For frontline clinicians, we wish to bring to their attention that this adulteration issue is common, recurring, and worthy of consideration, and that patients who have a history of using such corticosteroid-adulterated pCMs should have their adrenal function tested. It is also important that iatrogenic Cushing's syndrome subsequent to the use of corticosteroids that are from a source of adulteration be reported to the relevant authorities. It is the opinion of the authors that liberal, but careful, reporting would contribute to better understanding of this problem, further the prosecution of those behind steroid-adulteration of pCMs, and help to ameliorate this public health problem.

As for legislation and policies, consideration of fraudulent prescription contrary to the expectation of patients, who would expect traditional Chinese medicine rather than the inappropriate use of corticosteroids seen in many of these cases, by the legislators, judiciary, and relevant councils and constituents, rather than focusing on the possession and unlawful sale of the relevant compounds, would be a great deterrent to these illicit practices.

Conclusion

The present case series is the largest series of patients using pCMs adulterated with corticosteroids. The continuing emergence of pCMs adulterated with western medications indicates a persistent threat to public health. It is thus important that the risk be communicated not only to the medical profession, but also to the public, and effective regulatory measures to combat these illicit pCMs should be in place.

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