

Commentary: A Herbal Treatment for Type 2 Diabetes – The Dangers of Adulterated and Falsified Products

David W Holt* and Atholl Johnston

Analytical Services International, St George's, University of London, London S17 0RE, UK

*Correspondence should be addressed to Prof. David W Holt, david.holt@bioanalytics.co.uk

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In 2018, our group published a letter in *The Lancet* detailing a case in which a patient had taken a herbal preparation to treat her diabetes [1]. In essence, our laboratory was approached by the treating physician after the patient, a 58 year old lady of south Asian origin with a 30 year history of type 2 diabetes said that, during the previous two years, she had replaced some of her prescribed anti-diabetic medication with a herbal remedy purchased in India. The manufacturer of the herbal treatment claimed that it was a cure, rather than a treatment, for diabetes. The patient had stopped taking the herbal preparation as she had experienced recurrent hypoglycaemia whilst taking it.

The patient supplied some of the herbal preparation and our laboratory was asked to analyse the contents for any identifiable active pharmaceutical ingredients (API). What we received for analysis were rather crudely formed, irregular, ball-shaped tablets. They varied in weight (191 - 309mg) and colour – pink, green and brown. When the tablets were crushed, they formed a chalky mass; there was no evidence of any plant material. The crushed material was extracted into methanol and the extracts were analysed using liquid chromatography with time-of-flight mass-spectrometry. Extracts from the brown tablets contained no identifiable API but extracts from the other two colours (pink and green) contained two oral hypoglycaemic agents, glibenclamide and metformin, in varying amounts (1.0 - 2.3 mg and 89 - 153 mg, respectively).

Patients turn to alternative therapies for a variety of reasons. In the case of herbal treatments, the perception is often that the constituents are of natural, rather than manufactured, origin and that they will be free from adverse effects. Patients may also come from a cultural

background in which it is common to mix more than one approach to the treatment of an illness. In our case, the patient noted that some of her Indian acquaintances were taking the same preparation to treat their diabetes. We will try to summarise the implications of our findings for clinicians treating diabetes, and to assess whether the treatment of other diseases is affected by adulterated or falsified medicines.

The overriding finding in our case was that the patient ingested varying amounts of pharmacologically active compounds, of unknown provenance, in a preparation she thought to be of herbal origin. As a consequence, her diabetic control was compromised and she may have been exposed to toxic material in the crudely formed tablets. When patients present with unexpected responses to prescribed drugs, or complain of adverse events not normally associated with their known therapy, clinicians need to rule-out the possibility that alternative therapies have been used. If they have, analysis of the formulations taken by the patient may help to explain any unexpected symptoms or signs.

The practice of substituting or combining allopathic medicines for the treatment of diabetes with herbal remedies is not uncommon amongst some patients. A recent study of diabetic patients from India and Pakistan, who were living in the Scottish city of Edinburgh, found that patients substituted allopathic medicines for herbal remedies to treat their diabetes, without informing their physician [2]. In semi-structured interviews with 21 patients, it emerged that the main reason for using the herbal remedies was to avoid adverse effects attributed to prescription medicines. There was no attempt to analyse

any of the herbal remedies used, so it is not possible to say whether they were adulterated with conventional anti-diabetic medications.

Similarly, a study of 200 patients with type 2 diabetes in Thailand revealed that over 60% had used herbal remedies or dietary supplements to treat their diabetes and that 28% were current users at the time of the study [3]. The principal reason for using these compounds was recommendation from friends or family members. Most patients were unaware of the possibility of interactions between their prescribed medication and herbal remedies or dietary supplements, and most had not reported the use of these nonprescribed medications to their physician.

A study by Ching et al., who investigated antidiabetic herbal products available in Hong Kong, demonstrated that pharmaceutical drugs had been added to the herbs [4]. The authors, at a Toxicology Reference Laboratory, studied proprietary Chinese herbal preparations taken by diabetic patients referred for suspected adverse effects, or a clinical suspicion of adulteration after ingesting these preparations. Of 25 patients with diabetes, 14 had also been prescribed conventional drugs to control their diabetes. On analysis of the herbal preparations, eight undeclared antidiabetic pharmaceutical agents were detected. In 22 of 29 products analysed glibenclamide was found; other drugs included phenformin, metformin and rosiglitazone. Non-antidiabetic drugs were found in five of the products analysed, including hydrochlorothiazide, cimetidine, prednisolone and tadalafil. A high proportion of preparations contained more than one undeclared pharmaceutical agent. Adverse events were noted in 63% of the patients referred, mostly hypoglycaemia.

As our case shows, ingestion of adulterated antidiabetic medication purporting to be of herbal or natural origin is not confined to Far East communities. So serious is this problem that the FDA has issued online guidance to consumers on the prevalence of illegal compounds marketed to treat diabetes, many sold as cures for the disease [5]. The FDA noted that all the “natural” compounds that they had analysed contained undeclared active ingredients found in prescription drugs for the treatment of diabetes.

In a second study, Ching et al. [6] also highlighted that the problem of adulteration of proprietary Chinese herbal medicines and health products with undeclared drugs extended to other therapeutic areas. The study examined 404 cases referred to their Toxicology Reference Laboratory in which the products ingested had been found to contain undeclared adulterants. A total of 487 adulterated products was analysed and 1234 adulterants were detected; one product contained a staggering 17

adulterants. The adulterants included both approved and banned pharmaceutical drugs, drug analogues and animal thyroid tissue. The indications for use included pain reduction, diuretics, weight loss, erectile dysfunction and diabetes. Antidiabetic drugs comprised 10% of the adulterants, but the most common class of drug used to adulterate the products was non-steroidal anti-inflammatories. Over 60% of patients had an adverse reaction that could be attributed to adulterants found in the product they had taken. Two cases resulted in fatalities, both involving products sold to achieve weight reduction. Of 14 severe adverse effects, three were caused by products sold for the treatment of diabetes. One patient suffered hypoglycaemia and loss of consciousness after taking a product for the treatment of erectile dysfunction laced with sildenafil, tadalafil and glibenclamide.

From these data, it is clear that manufacturers of products sold as herbal or “natural” remedies will happily adulterate them with undeclared API. Mostly the drugs used give a clinical effect that is in-line with the indication for which the product is sold. However, adulteration is not confined to prescription drugs, as shown in a recent study by Hoban et al. [7]. In this study the authors examined psychotropic herbal medicines available in Australia for the presence of undeclared ingredients. Of 59 herbal products analysed, 29 had one or more substance not listed amongst the ingredients. Whilst the authors did not find any prescription medicines in these products, they did find heavy metals in 12% and undeclared caffeine in 10% of the products. On DNA analysis of the products, a disturbing finding was that 11 contained animal DNA from one or more of the species mice, goats, dogs, cattle or pigs, an observation suggesting poor quality control of manufacture or storage.

Herbal remedies are not the only problem when considering variable clinical response or toxicity due to therapy. Our case should be seen in the context of the wider clinical issues caused by substandard and falsified manufacture of pharmaceutical preparations. Attention has focused on these problems for over a decade, exacerbated by the practice of subcontracting the manufacture of API and, in some cases, the finished pharmaceutical product to countries outside the highly regulated drug sector. This has made the enforcement of Good Manufacturing Practice more difficult than when drug manufacture was confined to within national borders. This shift in manufacturing practice has given rise to some tragic clinical consequences, for instance severe adverse effects resulting from the substandard manufacture of heparin [8]. In addition, falsified drug manufacture, without any regulatory control, has become a major issue because of the ready availability of these products by on-line drug purchases. A recent publication has noted the incursion

of falsified medicines into both the European Union and North America and suggested the need to promote awareness amongst health professionals of the dangers of falsified medicines [9]. Many of the falsified products contain doses of API below the stated dose or no API at all, a particularly abhorrent case being the import into the USA of the anti-cancer medicine bevacizumab, which was found to contain no API [10].

We have already highlighted the clinical issues related to substandard manufacture of medicines, including substandard manufacture of the API, poor reproducibility of the dose, the use of inappropriate and substandard excipients, and failure to remove impurities from the final preparation [11]. Of course, these are issues that have also been noted in the papers quoted above on the use of herbal preparations.

The presence of undeclared API in products marketed as entirely of herbal origin is of clinical importance. Their presence is either of deliberate intent or the result of poor manufacturing practices. In addition to the possibility of erratic treatment effects, patients may be exposed to either toxic or infectious contaminants, again, as a result of substandard manufacture.

So, the watchword for prescribers is always to enquire of their patients exactly what they are taking to treat their diabetes or, indeed, other clinical indications. Questions should not be confined to what a patient might consider to be a drug, but should include herbs, dietary supplements and so-called holistic remedies. Otherwise the cause of poor or variable clinical response, or toxicity, may be missed, leading to suboptimal treatment and unwanted effects.

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