Hypovolemic shock due to severe gastrointestinal bleeding in a child taking an herbal syrup

Paola Angela Moro(a), Valerio Flacco(b), Federica Cassetti(a), Valentina Clementi(a), Maria Laura Colombo(a), Giulia Maria Chiesa(a), Francesca Menniti-Ippolito(a), Roberto Raschetti(b) and Carmela Santuccio(b)

(a) Centro Antiveleni, Ospedale Niguarda Ca’ Granda, Milan, Italy
(b) Dipartimento Pediatrico, “Ospedale Civile”, Lanciano (Chieti), Italy
(c) Dipartimento di Scienza e Tecnologia del Farmaco, Facoltà di Farmacia, Università di Torino, Turin, Italy
(d) Dipartimento di Scienze Farmacologiche, Università degli Studi di Milano, Milan, Italy
(e) Centro Nazionale di Epidemiologia, Istituto Superiore di Sanità, Rome, Italy
(f) Unità di Farmacovigilanza, Agenzia Italiana del Farmaco, Rome, Italy

INTRODUCTION

Widespread opinion that natural remedies are completely harmless lead parents to use them instead of conventional drugs to treat their children diseases [1-4]. Nevertheless, safe and confident use of herbal supplements is an issue gaining more and more attention as they can lead to mild-to-severe adverse reactions [4, 5].

Moreover, physicians and paediatricians do not usually undergo adequate training for prescribing Complementary and Alternative Medicines (CAM) remedies, evaluating their clinical effects and assisting families in using them wisely [4, 6].

The case we report shows the potential harm of herbal supplements if incorrectly used in paediatric patients.

CASE REPORT

A 4-years-old boy weighting 17 kg was admitted to the hospital for sudden gastrointestinal bleeding leading to hypovolemic shock. The day before the child...
had evacuated dark stool and had some episodes of hematemesis during the night. At the admission he was drowsy, pale, hypotensive (BP = 60/40 mmHg) and anemic (Hb = 6.4 g/dL). Blood test showed RBC (red blood cells) 2.4 x 10^6/L, MCH (mean cell hemoglobin) 26.4 pg/cell, MCHC (mean corpuscular hemoglobin concentration) 33.7 g/dL, Plt (platelets) 280 000 x 10^9/L, WBC (white blood cells) 9.3 x 10^9/L with normal formula. The patient was admitted to the paediatric intensive care unit (ICU), where emergency treatment was provided and stabilization achieved.

Esophagogastroduodenoscopy (EGDS) showed hiatus hernia, erosions and ulcerations of the lower esophagus (possibly related to a gastroesophageal reflux) and a small duodenal erosion; about 150 ml of coagulated blood were removed from the stomach. Since the boy had not previously shown any symptoms of gastroesophageal reflux, the disease had never been investigated.

Two days before the child had shown fever and a mild cold likely due to a viral respiratory infection, not accompanied by any gastrointestinal manifestation.

On the first day of illness a single rectal dose of acetaminophen, 250 mg, was administered; the next day he was treated with 15 ml (5 ml for three times) of an herbal syrup and he started bleeding on the night. The syrup, containing ribwort plantain (*Plantago lanceolata* L.), liquorice (*Glycyrrhiza glabra* L.), willow (*Salix* spp.), black elder (*Sambucus nigra* L.), meadowsweet (*Filipendula ulmaria* (L.) Maxim.), and propolis, was prescribed by his paediatrician and never taken before.

No other drugs had been administered in the previous twenty days, but thirty days before he was treated for five days with 285 mg/day of niflumic acid with no other drugs had been administered in the previous twenty days, but thirty days before he was treated for five days with 285 mg/day of niflumic acid with no other drugs. The herbal product was discontinued and the patient recovered.

The case was evaluated according to the Naranjo causality algorithm scale [7].

The probability determination score was 7, which means that the reaction was probably caused by the syrup.

**DISCUSSION**

The product label reported the name but no the percentage content of the ingredients; technical data sheet was achieved but titration of active extract was not available.

MEDLINE, EMBASE and MICROMEDEX searches were performed to find articles related to gastrointestinal bleeding associated to *Plantago lanceolata*, *Glycyrrhiza glabra*, *Salix* spp., *Sambucus nigra*, *Filipendula ulmaria*, propolis, salicylates, niflumic acid and acetaminophen internal use.

No reports of gastric damage related to use of *Plantago lanceolata*, *Sambucus nigra*, and propolis were found.

Some studies showed a possible anti-inflammatory and anti-ulcer action of *Glycyrrhiza glabra* and its internal use.
extracts [9, 10]; on the other hand, licorice root is thought to contain coumarins or coumarin derivatives that demonstrated antiplatelet activity in vitro [11]. Therefore, it may theoretically increase the risk of bleeding especially if taken with antiplatelet drug [12]. Nevertheless, it is really difficult to ascertain pharmacological interactions between licorice and salicylates or other components of the herbal remedy, while it is unlikely any interaction with acetaminophen due to the short half-life of this drug [13] and the time elapsed (20 hours) between the suppository administration and the consumption of the syrup.

Surprisingly, one case of gastrointestinal bleeding related to *Filipendula ulmaria* and *Salix* spp. (Fam. Salicaceae) are known to contain various salicylates. In particular, Meadowsweet contains a minimum of 0.1% v/w of steam-volatile substances (dried drug), among which gaultherin (glycoside of methyl salicylate); *Salix* contains not less than 1.5% of salicylic derivatives, mainly as salicin (an alcoholic beta-glucoside) [15-18].

*In vitro*, it is possible to obtain the hydrolysis of salicin by alkaline saponification according to the *European Pharmacopoeia* 6th ed. or by means of enzymatic reaction, according to Association of Agricultural Chemists (AOAC) International [19]. The result of the hydrolysis is the loss of the glucose moiety and the discharge of the alcoholic genin saligenin (phenolic alcohol called also salicyl alcohol).

*In vivo* pharmacological studies in rats indicate that salicin acts as a prodrug which is transformed into its active metabolite, salicylic acid, via saligenin formation [20, 21]. Both gaultherin and salicin are supposed to have less gastric ulcerogenic effect compared to aspirin [22, 23].
Nevertheless, the strong colourimetric response to the addition of ferric chloride revealed the presence of free salicylates in the syrup. The qualitative analysis confirmed the presence of methyl salicylic and salicylic acid derived by hydrolysis of natural occurring glycoside compounds (Figure 2).

This spontaneous hydrolysis reaction shows up that pharmacological activity of multiple ingredients natural preparations may be unpredictable and should be assessed by testing the final product.

Methyl salicylic and salicylic acid are not intended for oral consumption because of their irritative action on the mucosa and for their high salicylate potency (which is almost 1.4 times the potency of acetyl salicylic acid) [24].

Salicylates are strong analgesic and antipyretic derivatives of salicylic acid often prescribed or used as self-medication to relieve fever and mild pain, especially headache and arthromyalgia; although these compounds are OTC drugs, they can be used in children only under medical prescription.

Salicylates have often been implicated in the development of gastrointestinal damages [2, 13, 25]. Their gastrointestinal toxicity can be ascribed to two distinct mechanisms:

a) indirect action: salicylates act mainly by inhibiting the enzyme prostaglandin endoperoxide synthase (or cyclooxygenase or COX), which exists in two isoforms (COX1, constitutive, and COX2, induced during inflammation) and converts arachidonic acid to several prostanoids. The specific inhibition of both COX1 and COX2 results in attenuation of pain, fever and other symptoms of inflammation (mediated by the prostaglandins produced by COX2), and in weakening of several defensive mechanisms in the tissues that express COX1 (including the gastrointestinal tract) [13];

b) direct action: most salicylates, when ingested, increase by topic contact the gastric mucosa permeability to hydrogen ions, mainly by reducing its hydrophobicity; this leads to an inflammatory response that enhances the epithelial damage [13, 26-29].

According to the literature, upper gastrointestinal complications associated with several NSAIDs in children can be expected; in particular, several cases of gastrointestinal bleeding, both in adults and children, related to the administration of salicylates are reported [2, 25, 26].

On the other hand, only mild effects but no serious events (hemorrhage, hypovolemic shock) connected to the use of niflumic acid are described [30] and there is a general agreement about the safety of therapeutic doses of acetaminophen compared to aspirin and other NSAIDs [31, 32] unless it is taken at high doses together with other analgesic/antipyretic agents [33, 34].

In the present case, the child took about 15 ml of the herbal syrup, containing 0.4 mg/ml of salicylates, corresponding to a total dose of 6 mg (0.35 mg/kg), an amount far from being a toxic dose.

It is not clear whether the reaction observed resulted from the exacerbation of an existing pathology or was the first manifestation of a disease just developed, but several factors suggest that the symptoms were probably caused by the herbal remedy.

The child was previously healthy, and had already taken both acetaminophen and niflumic acid in the past without any side effects; moreover, the time elapsed between the last administration of niflumic acid and the accident makes the correlation unlikely, while there is a close temporal association between the consumption of the syrup and the onset of the symptoms. Naranjo score confirmed this hypothesis.

Besides causing gastrointestinal injuries, salicylates have been reported to cause allergic reactions (in some cases even anaphylaxis) in sensitive subjects [35, 36].

Furthermore, they are suspected to act as co-factors in the development of Reye's syndrome (acute non inflammatory encephalopathy accompanied by selective hepatic abnormalities and metabolic decompensation) in children affected by viral infections [1, 37, 38]; for this reason, starting from 1986 several alerts were issued against the use of salicylates-containing medications in children and teenagers affected by or recovering from chicken pox or flu, and mandatory warning labels were instituted in many countries [1, 37-40].

Apart from medical and pharmacological considerations, it seems important to highlight some other aspects of this event.

The syrup involved in our case was marketed as “food”, therefore, according to the European law (89/395/CEE, 2000/13/CE), it should have been free from any therapeutic activity; for this reason its label reported all the constituents but not their active principles (salicylates were not mentioned) and it did not undergo the notification procedure that is mandatory for supplements. Nevertheless, its name (“FreddoBaby” in Italian; literally translated “ColdBaby” into English) suggested that the syrup could be useful in the treatment of cold states in children and it could be bought without medical prescription.

On the other hand, the remedy was prescribed by a paediatrician, unaware of pharmacological properties of herbal ingredients and of possible presence of salicylates.

This explains why our patient was treated with this remedy despite the known risks connected with the use of salicylates in children with febrile illnesses.

The spreading use of natural remedies is strongly related to the common opinion, frequently diffused through the mass media, that they are suitable for subjects in any age group and health condition because they always are beneficial and harmless [41].

Our report shows that this misconception can lead both common people and health practitioners to use carelessly such remedies without regard to any possible adverse effects.
CONCLUSIONS

Herbs contain several constituents that may exert a pharmacological activity, in the same way as conventional medicines do. Therefore they can not be claimed as absolutely safe and free from adverse effects. Products containing salicylates can be highly hazardous if used by children or aspirin-sensitive subjects. Natural remedies should be used under the supervision of adequately trained practitioners and administered cautiously to paediatric patients, unless reliable evidence of their safety is provided. Spontaneous reporting can contribute to improve knowledge about potential adverse reactions to medicinal plants and increase awareness among health personnel and public about their benefit–harm assessment.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Received on 23 March 2011.
Accepted on 4 July 2011.

References


