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ORIGINAL ARTICLE

Effect of multiple honey doses on non-specific acute cough in children. An open randomised study and literature review

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Abstract
Background: Honey is recommended for non-specific acute paediatric cough by the Australian guidelines. Current available randomised clinical trials evaluated the effects of a single evening dose of honey, but multiple doses outcomes have never been studied.
Objectives: To evaluate the effects of wildflower honey, given for three subsequent evenings, on non-specific acute paediatric cough, compared to dextromethorphan (DM) and levodropropizine (LDP), which are the most prescribed over-the-counter (OTC) antitussives in Italy.
Methods: 134 children suffering from non-specific acute cough were randomised to receive for three subsequent evenings a mixture of milk (90 ml) and wildflower honey (10 ml) or a dose of DM or LDP adjusted for the specific age. The effectiveness was evaluated by a cough questionnaire answered by parents. Primary end-point efficacy was therapeutic success. The latter was defined as a decrease in cough questionnaire score greater than 50% after treatment compared with baseline values.
Results: Three children were excluded from the study, as their parents did not complete the questionnaire. Therapeutic success was achieved by 80% in the honey and milk group and 87% in OTC medication group ($p = 0.25$).
Conclusions: Milk and honey mixture seems to be at least as effective as DM or LDP in non-specific acute cough in children. These results are in line with previous studies, which reported the health effects of honey on paediatric cough, even if placebo effect cannot be totally excluded.

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Introduction

For many years antitussives for paediatric usage have been under critical observations. In 1997 the American Academy of Pediatrics (AAP) remarked that the use of cough sedatives, including dextromethorphan (DM) and codeine, was not sustained by sufficient effectiveness proof.[1] More recently, Smith et al.[2] ended a Cochrane Library systematic review (SR) and reported that: ''There is no good evidence for or against the effectiveness of over-the-counter (OTC) medicines in acute cough''. Moreover, Kelly et al.[3] pointed out that codeine products could cause fatal events. In the end, Australian cough guidelines[4] strongly recommended both to avoid antitussive therapy with narcotics and to minimise the use of medications other than demulcents such as honey (if no contraindications to its use exist). However, honey prescription still raises some doubts. Oduwole et al.,[5] in a SR published in the Cochrane Library, wrote that: ''We included two RCTs of high risk of bias involving 265 children ... Honey may be better than no treatment and diphenhydramine in the symptomatic relief of cough but not better than dextromethorphan''. The authors ended their SR stating that: ''There is no strong evidence for or against the use of honey''. Oduwole et al.[5] concluded their research in December 2011, so they could only include two RCTs, which were those of Paul et al.[6] and Shadkam et al.[7] Later on, Cohen et al.[8] published a study which showed the health effects of three different types of honey versus placebo which was silan data extract. All three studies available[6–8] had only evaluated the effect of a single evening dose of honey. The Israeli authors wrote [8]: ''Another limitation is the fact that the effect of only a single dose was evaluated. If the intervention period would have been longer and more than 1 dose given, the results would have been more reliable and more valuable''. The goal of our study was to evaluate the effectiveness of honey on nonspecific acute paediatric cough given for three consecutive evenings. We compared honey and milk mixture with DM and levodropropizine (LDP), among the most prescribed antitussives in Italy.

Methods

From January 1st 2013 to 31st March 2013, subjects aged between 1 and 14 years were recruited from ambulatories of 18 primary care paediatricians. Eligible patients were those complaining of cough, attributable to an upper airway infection, which lasted $\leq$7 days, with or without fever. Patients were excluded if: (a) they suffered from asthma, pneumonia, streptococcal tonsillitis, sinusitis, bronchitis, allergic rhinitis; (b) previous therapy until the week before the recruitment, were analgesic medications for cough over the counter (OTC, including natural, herbal and homoeopathic products), oral antihistamines, cortisone given in all forms, non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen but not paracetamol, or honey; (c) informed consent refused by parents. Parents were instructed to complete an Italian version of Paul et al.'s[6] questionnaire, given by primary care paediatricians. This was a 5-item questionnaire regarding gravity, frequency and bothersome nature of cough (Table 1). Answers were graded on a 7-point Likert scale with a score from 0 to 6. Children with a basal score $\geq$12 were enrolled.

Table 1 Paul et al. questionnaire[6] used in our study.

1. How frequent was your child's coughing last night?
2. How severe was your child's cough last night?
3. How bothersome was last night's cough to your child?
4. How much did last night's cough affect your child's ability to sleep?
5. How much did last night's cough affect your (parent's) ability to sleep?

Scoring: 0 = not at all, 1 = not much, 2 = a little, 3 = somewhat, 4 = a lot, 5 = very much, 6 = extremely.

In our experience, some primary care paediatricians prescribed DM, while others preferred LDP and they were all reluctant to change their habits. For this reason, we created two randomising lists: the first one (Milk & Honey Study – Dextromethorphan, M&HS-DM) included children randomised to receive DM (DM group) or honey and milk (M&H-DM group); the second one (Milk & Honey Study – Levodropropizine, M&HS-LDP) enrolled children randomised to receive honey and milk (M&H-LDP group) or LDP (LDP group). Each primary care paediatrician chose his/her favourite list and received an ensemble of 10 randomised choices. DM (Lisomucil antitussive syrup, Sanofi-Aventis, Milan) was administered at doses of 7.5 mg/dose for children aged 2–5 years, 15 mg/dose for children aged between 5 and 11, and 30 mg/dose for children between 12 and 14 years of age. LDP (Levotuss drops, Dompé, Milan) was given at the dose of 1 drop/kg until a maximum of 20 drops. Both DM and LDP contained some excipients such as sucrose and fruit aromas. Children assigned to the honey group received 90 ml of warm pasteurised cow's milk mixed with 10 ml of wildflower honey (milk and honey, M&H). All treatments were administered 30 minutes before bedtime during three consecutive evenings. If body temperature was $\geq$38.5 °C, children were allowed to take, in addition to the randomised treatment, paracetamol. Extra doses of honey were prohibited.

In our study there was no placebo group, neither blindness for parents, children and primary care paediatricians. However, raw data were examined blindly by one author (SMS) and by a statistician. These two did not take part in children enrolment, neither in the follow-up. During the three days of treatment, patients' parents answered the Italian version of Paul et al.'s questionnaire.[6] Treatment adherence was evaluated looking at the residual volume of DM and LDP containers after their use. In case of honey and milk prescription, parents recorded the residual volume of the mixture after each administration. We considered adherence to treatment patients who had taken at least 80% of the expected dose basing on each evening administration. A percentage of non-adherence to the treatment by patients of at least 20% was tolerated. In the event of treatment interruption the time at which it occurred was registered as was the cause and an eventual substitutive choice.

Statistical analysis

Statistical analyses were computed by the SPSS package for Windows (version 15.0.1, SPSS, Chicago, IL, USA). The