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Does treatment with Echinacea purpurea effectively shorten the course of upper respiratory tract infections in children?

Report by

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You are a paediatric specialist registrar on a Sunday late shift in the accident and emergency department. A 4 year old boy presents with a two day history of fever (maximum temperature 38.8°C) and clinical signs of an upper respiratory tract infection (URTI). At home, his mother gave regular paracetamol to treat his fever and extracts from ivy to alleviate the cough. She asks you about Echinacea purpurea therapy for her son's illness.

Structured clinical question

In children with upper respiratory tract infection [patient], is treatment with Echinacea purpurea [intervention] effective for alleviating symptoms and shortening the course of URTI [outcome]?

Search strategy and outcome

Cochrane Database of Systematic Reviews: 1 relevant hit.

Pubmed: "Echinacea" AND ("respiratory infection" OR "cold"). Limits: "Randomized controlled trial" or "clinical trial". 15 hits, 7 relevant. "Echinacea" AND ("respiratory infection" OR "cold") AND ("children" OR "infants"). Limits: "Randomized controlled trial" or "clinical trial". 2 hits, 1 relevant. Embase: "Echinacea" AND "respiratory" AND "infection" AND "trial". No further relevant hits. "Echinacea" AND "respiratory" AND "infection" AND "children" AND "trial". No further relevant hits.

See table 2.

Commentary

In recent years, alternative medicines have gained much popularity. According to a recent survey, more than one third of the US population consumes herbal medicines regularly.¹¹ Reasons for the surge of herbal remedies include the widely assumed good tolerance of "natural" products and a supposed lack of side effects, a belief often paired with scepticism towards the efficacy of "conventional" medicine. Particularly in paediatric medicine, it seems in vogue to treat common childhood ailments using herbal medicines. Among the most commonly used remedies are Echinacea preparations, constituting approx. 10% of the total US market in herbal medicine, with annual sales worth over US\$300 million.¹¹ Complaints about an URTI account for about 40% of visits to paediatricians during winter months, and herbal

substances are increasingly being prescribed by medical practitioners despite a lack of convincing proof of their effectiveness or safety.¹² In particular, Echinaceas attributed immune modulating effects may not only be beneficial: Echinacea possibly reduces the effectiveness of corticosteroids, commonly used by asthmatics and for treating viral induced wheeze, and can cause hypersensitivity reactions in susceptible individuals.^{13 14}

Treatment of the common cold in children with Echinacea has only been investigated in one randomised, double blind, placebo controlled trial: Taylor *et al* examined the efficacy and safety of Echinacea purpurea in children with URTI. The authors studied a large cohort by using a stringent methodology, but the results failed to show an influence on duration of illness or severity of symptoms.¹ To further elucidate our clinical question, we extended our search to treatment trials in the adult population. A Cochrane review about Echinacea treatment, published in 1999, found no definite treatment effect and criticises methodological inconsistencies among the studies available.¹⁰ We reviewed six recent randomised controlled trials of adults receiving Echinacea treatment for symptoms of URTI (table 2). Neither the study populations, nor the preparations of Echinacea investigated in the trials were standardised, a fact that complicates the comparability of the results. The results are inconsistent; trials with a larger number of individuals failed to show a significant effect of Echinacea treatment, whereas smaller trials did document positive effects. Treatment with Echinacea purpurea was perceived as beneficial by a number of individuals, possibly due to the placebo effect.

Currently, there is a lack of evidence on the efficacy of Echinacea purpurea, especially in paediatric patients. Under the present circumstances, the use of Echinacea as a treatment for URTI cannot be suggested as being effective. In particular, Echinacea should be not be taken by patients with chronic immune mediated disease on treatment with corticosteroids and those with allergy to ragweed and related allergens.^{13 14}

CLINICAL BOTTOM LINE

- There is currently no evidence for the efficacy of Echinacea purpurea in the treatment of children with upper respiratory tract infections. (Grade A)
- Echinacea should be avoided by patients who receive corticosteroids and by those with allergy to ragweed and related allergens. (Grade B)

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Table 2 Echinacea in upper respiratory tract infections

Citation	Study group	Study type	Echinacea dose and preparation	Outcome	Key results	Comments	Level of evidence
Taylor <i>et al</i> (2003) ¹	524 children randomised (age 2–11 years), 200 with 337 URTIs included in analysis received arial EP extract versus 207 with 370 URTIs receiving placebo	Randomised, double blind, placebo controlled trial	EP juice from dried pressed herbs. Children 2–5 years received 2×3.75 ml; 6–11 years received 2×5 ml until symptoms resolved (max. 10 days)	Duration of URTI: Severity of URTI (score): Adverse effects (no.):	Echinacea v placebo 9 v 9 days (p=0.89) 33 v 33 (p=0.69) 152 v 146 (p=0.14)	No effect of treatment of URTI with EP in shortening duration or decreasing severity despite multiple subanalysis	1b 95% CI: 8–10 days for durations Large sample size The only paediatric trial
Goel <i>et al</i> (2004) ²	282 adults (age 18–65 years) randomised, 128 with cold, 59 receiving EP extract, 69 placebo	Randomised, double blind, placebo controlled trial	Extract from EP plants with 0.25 mg/ml alkamides + 2.5 mg/ml cichoric acid + 25 mg/ml polysaccharides, combined in 40% ethanol. 10×4 ml day 1; 4×4 ml days 2–7	Total daily symptom score: Duration of 50% reduction of maximum symptom score (days)	Signif. decrease in symptom score by Echinacea (p<0.05) 4/5.5 (EP v placebo) (statistical significance not mentioned)	Only relief/decrease of symptoms examined, no statistical power on duration of URTI	1b 95% CI for total daily symptom score: 13.6–19.0 for EP 17.5–22.5 for placebo Large sample size
Yale <i>et al</i> (2004) ³	128 adults (age 18–62 years), presenting with acute sneezing or nasal discharge (common cold). 63 receiving arial EP extract, 65 placebo	Randomised, double blind, placebo controlled trial	Aerial EP extract in 100 mg capsules. 3×1 capsule until symptoms resolved (max. 14 days)	Duration of cold: Total symptom score:	No signif. difference (p=0.73) No signif. difference (p=0.29–0.90)	No effect of EP treatment on duration or total symptoms.	1b CI not mentioned Modest sample size
Barrett <i>et al</i> (2002) ⁴	148 adults (students, mean age 21 years), presenting with 2 of 15 listed cold symptoms. 73 receiving capsules of EP herb and root and EA root, 75 placebo	Randomised, double blind, placebo controlled trial	Echinacea capsules containing EP herb (62 mg), EP root (62 mg) and EA root (123 mg). 6×4 capsules day 1; 3×4 capsules until symptoms resolved (max. 10 days)	Duration of cold: Symptom severity: Adverse effects (no.):	Echinacea v placebo 6.27 v 5.75 days (95% CI –1.09 to 0.22 days) No signif. difference 13 v 7 (no signif. difference)	No effect of a specific Echinacea mixture preparation on duration and severity of cold symptoms. Probanders were healthy college students.	1b 95% CI: –1.09 to 0.22 days for EP group Adjusted hazard ratio 1.24 (CI 0.8 to 1.78) Modest sample size
Schulten <i>et al</i> (2001) ⁵	80 adults (mean age 37.3/38.8 years), presenting first signs of common cold. 41 receiving EP juice, 39 placebo	Randomised, double blind, placebo controlled trial	EP juice (pressed from fresh flowering purple cornflower). 2×5 ml for 10 days	Duration of illness (days): Area under the curve of symptoms: Patients' subjective assessment (shorter duration of cold) (%):	Echinacea v placebo 6 v 9 (p=0.0112) 36.18 v 51.63 (p=0.008) 61.0 v 28.2 (p=0.007)	Positive effect of EP, probanders were company workers	1b CI not mentioned Small sample size Drug company sponsored
Lindenmuth <i>et al</i> (2000) ⁶	95 adults (age 24–62 years), presenting early symptoms of cold. 48 receiving EP tea preparation, 47 placebo tea	Randomised, double blind, placebo controlled trial	Tea bags of leaves, flowers and stems of EP and EA plus dry extract of EP roots (6:1). In combination 1.275 mg of dried herb + root per tea bag. 5–6 tea bags day 1, every following day one tea bag less	Subjective relief of symptoms (score): Duration of symptoms (days): Duration of subjective change of symptoms (days):	Echinacea v placebo 4.125 v 2.787 (p<0.001) 4.333 v 2.34 (p<0.001) 3.854 v 2.297 (p<0.001)	Echinacea tea preparation has only positive effect in relief of symptoms.	1b CI not mentioned. Small sample size Authors' interpretation of the results controversial
Brinkenborn <i>et al</i> (1999) ⁷	559 adults recruited, 246 treated (mean age 40–42 years). 55 receiving EP extract, 64 EP concentrate, 63 EP special extract, 64 placebo	Randomised, double blind, placebo controlled trial	Echinacea tablets: EP extract (6.78 mg; 95% herb, 5% roots); EP concentrate (48.27 mg; 95% herb, 5% roots); EP extract (29.6 mg; 100% roots). 3×2 tablets until symptoms resolved (max. 7 days)	Reduction of complaint index (based on symptoms by doctors' records): Reduction of complaint index by patients' diaries: Adverse effects:	Signif. reduction of index by EP extract (p=0.02) and concentrate (p=0.003) v placebo Signif. reduction of index by EP extract (p=0.032) and concentrate (p=0.01) v placebo More AE in the EP special extract (not signif.)	EP concentrate only slightly more effective than EP extract despite 7-fold higher dosage. No effect by EP roots-based preparation Effects on duration of cold not examined	1b CI not mentioned Small subgroup samples

EP, Echinacea purpurea; EA, Echinacea angustifolia, CI, confidence interval.

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In juvenile idiopathic arthritis, is folate supplementation effective against methotrexate toxicity at the expense of methotrexate's efficacy?

Report by

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A 7 year old girl with sero-negative polyarticular juvenile idiopathic arthritis (JIA) has recently commenced weekly methotrexate (MTX). Within six months she develops painful aphthous ulcerations, alopecia, and generalised gastrointestinal upset. Her hepatic transaminases (AST/ALT) are now raised. Her parents are obviously distressed and have read on the internet about the role of folate supplementation in counteracting the adverse side effects of MTX. They have also read however, that this beneficial effect may be at the expense of the efficacy of MTX. They ask you, the prescribing physician, if this additional medication is warranted, and if so in what form?

Structured clinical question

In children with juvenile idiopathic arthritis [patient], does folate supplementation [intervention] counteract the adverse side effects and/or effect the efficacy of methotrexate [outcome]?

Search strategy and outcome

Secondary source: Cochrane Library, nil relevant.

Primary source: Medline via Pubmed: search terms "methotrexate" or "methotrexate efficacy" or "methotrexate toxicity", or "methotrexate side effects" and "juvenile arthritis" and "folinic acid supplementation" or "folate supplementation". Limits: all child: 0–18 years.

Search result: nine papers identified, three papers relevant. See table 3.

Search date: June 2005.

Commentary

Methotrexate, a dihydrofolate reductase (DHR) inhibitor, is now the leading disease modifying antirheumatic drug

(DMARD) used in the management of juvenile idiopathic arthritis. In a double blind, randomised controlled multicentre study, MTX was found to be efficacious in 63% (n = 127) of patients with resistant JIA, and it is now the standard first line agent in those with polyarticular disease.¹ Adverse reactions are generally mild and transient and it is generally well tolerated, much more so than in the adult population in whom approximately 30% will discontinue the drug one year after therapy is initiated.² Estimates for common toxicities range from 5% to 21%, with nausea (21%), vomiting (11%), mouth sores (10%), loss of appetite (7.5%), cited most commonly and hair loss (5%), malaise (5%), elevated liver function tests (5%), and leucopenia (5%) less commonly.³ Toxicity has been suggested to be a result of an induced state of folate depletion.⁴ The addition of folate has therefore been suggested to counteract the signs of toxicity, either as folic acid or the reduced form folinic acid which is able to function in biosynthetic pathways independent of DHR. Meta-analysis of seven trials assessing the benefits of folic and folate supplementation in rheumatoid arthritis (RA), clearly show a reduction in gastrointestinal and mucosal side effects.⁵ A randomised controlled study directly comparing folic acid to folinic acid in RA, showed no beneficial difference between the two forms of supplementation.⁶ Nevertheless, there is no consensus practise for folate supplementation in RA. The concern is that folate supplementation may have a detrimental effect on the therapeutic benefit of MTX. Folinic acid has been associated with a reduction in the effectiveness of MTX, thought to possibly be explained by competition between folinic acid and MTX for binding to cellular transport molecules.^{7–8} The same concerns exist for the paediatric population and where compliance is often an issue, any additional medication can be a great burden to the patient and family involved.

With the exception of a small case series (three patients) examining weekly folinic acid, neither folic acid or folinic acid have shown any reduction in the benefit of methotrexate administration in JIA.⁹ This effect however may have been as a result of a dosage effect. The folinic acid was administered at an equivalent dose to the methotrexate which is the dose required to reverse haematological toxicity.

In terms of reducing MTX toxicity, there may be evidence for weekly folinic acid at 25–50% of the MTX dose in diminishing hepatic and gastrointestinal related toxicities.¹⁰ The mean number of episodes per patient-year of hepatotoxicity and gastrointestinal toxicity decreased significantly after the start of folinic acid supplementation. Folinic acid was also reported to have a favourable response in the small case series above.⁹ As there was no reports of any MTX toxicity (hepatotoxicity measured only) in the study examining folic acid versus placebo, it is difficult to make any conclusion whether folic acid has any effect, beneficial or not.¹¹

The evidence for weekly folinic acid for diminishing MTX related toxicities is weak (grade 4) and limited. All three studies only address hepatic and gastrointestinal toxicity and no reference is made to other common toxicities such as mucositis. Despite the widespread and variable practise of prescribing folate supplementation to prevent or counteract MTX toxicity in JIA, to date there have been no trials comparing the efficacy of folic acid and folinic acid directly. No conclusions can be made regarding the effect of folate supplementation on methotrexate's efficacy in JIA.

The effectiveness, form, and dosage of folate supplementation for treating or preventing MTX related toxicities, and whether it has any effect detrimental or not on methotrexate's efficacy, needs therefore to be urgently determined in a prospective, randomised, double blinded, placebo controlled trial.