POEMs
PATIENT ORIENTED EVIDENCE THAT MATTERS
Practice Recommendations from Key Studies

Breastfeeding reduces pain in neonates

Carbajal R, Veerapen S, Couderc S, Jugie M, Ville Y. Analgesic effect of breast feeding in term neonates: randomized controlled trial. BMJ 2003; 325:13–15.

Beth Potter, MD, and Kirsten Rindfleisch, MD,
Department of Family Practice, University of Wisconsin–Madison. E-mail: bepotter@wisc.edu.

PRACTICE RECOMMENDATIONS

Breastfeeding is a safe and effective analgesic for healthy neonates undergoing painful minor procedures. This may be another reason to encourage mothers to breastfeed their infants when possible.

Increasing evidence suggests long-term deleterious effects associated with the experience of pain in the neonatal period. A remaining question is: should we encourage mothers to breastfeed when infants are receiving their vaccinations?

BACKGROUND

Healthy neonates routinely undergo painful minor procedures. Evidence suggests that infants do feel pain, and painful experiences may lead to subsequent increased pain sensitivity. Due to concerns regarding the potential adverse effects of pharmacological interventions in newborns, effective alternatives for pain control have been sought.

Previous studies have demonstrated analgesic benefit with the oral administration of sugar solutions, nonnutritive sucking, and skin-to-skin contact. Further studies have suggested that breastfeeding may have similar value in pain control, but no study has sought to directly compare these approaches.

POPULATION STUDIED

The researchers observed 180 term, breastfed infants ranging in age from 1 to 5 days. All infants included in the study were healthy, with 5-minute Apgar scores ≥7 out of 10. Infants who were unstable or who had received a sedative, major analgesic, or naloxone in the previous 24 to 48 hours were excluded from the study.

STUDY DESIGN AND VALIDITY

Infants and their mothers were taken to a quiet room for venipuncture. They were randomly assigned to 1 of 4 groups. In the first group, infants were breastfed for 2 minutes prior to and during venipuncture. In the second group, infants were held in their mothers' arms without breastfeeding prior to and during the procedure. In the third group, infants were laid on a table and given 1 mL of sterile water orally through a syringe over the course of 15 seconds. In the fourth group, infants were laid on a table and given 30% sucrose solution orally followed by a pacifier.

The infants' heart rate and oxygen saturation were monitored. All infants and their monitoring equipment were videotaped from the beginning to the end of venipuncture. Two independent, specially trained observers evaluated these tapes. The observers were blinded to the purpose and

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What is a POEM?

Each month, the POEMs (Patient-Oriented Evidence that Matters) editorial team reviews 105 research journals in many specialties, and selects and evaluates studies that investigate important primary care problems, measure meaningful outcomes, and have the potential to change the way medicine is practiced. Each POEM offers a Practice Recommendation and summarizes the study's objective, patient population, study design and validity, and results. The collected POEMs are available online at www.jfponline.com.

Pain scores in infants being breastfed were lower than those who were held but not breastfed

hypothesis of the study. There was a high degree of agreement between the 2 observers in the outcomes measured.

Overall, this study was well designed. Allocation of participants to treatment groups was effectively concealed. The observers were blinded to the purpose and hypothesis of the study. However, they clearly did observe a difference in the treatment groups. Pre-existing perceptions of the benefits of breastfeeding could have affected the observers ratings of the infants' responses.

OUTCOMES MEASURED

The observers rated the infants' expression of pain. The Douleur Aiguë Nouveau-né (DAN) scale evaluates facial expressions, limb movements, and vocalizations in infants to generate a score from 0 (no pain) to 10 (maximum pain). A second pain scale, the Premature Infant Pain Profile (PIPP), measures age, behavioral state, heart rate, oxygen saturation, and facial expression to generate a score from 0 (no pain) to 18 (maximum pain) in term infants.

RESULTS

The median pain scores were lowest with breastfed infants (DAN=1 and PIPP=4.5). The next-lowest median scores were in infants receiving sucrose and pacifier (DAN=3 and PIPP=4). Infants held in their mothers' arms and those given sterile water had similar median pain scores (DAN=10 and PIPP=13, and DAN=10 and PIPP=12, respectively).

Pain scores in breastfed infants were significantly lower ($P<.0001$) as measured by both scales than in those who were held without breastfeeding and those who received sterile water. There was a nonsignificant trend towards lower pain scores in breastfed infants when compared with those receiving sucrose and a pacifier.

Zinc nasal gel effective for the common cold

Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. Q J Med 2003; 96:35–43.

Gloria Rizkallah, PharmD, and Terry Seaton, PharmD, *Mercy Family Medicine, St. Louis, Mo. E-mail: tseaton@stlcop.edu.*

PRACTICE RECOMMENDATIONS

Zinc nasal gel (Zicam) reduced the duration of the common cold by 41 hours, was well tolerated, and was relatively inexpensive.

More studies, in a broader population, comparing zinc nasal gel with other cold remedies (such as decongestants, antihistamines, antitussives, and antipyretics/analgesics) are needed before recommending it as first-line therapy.

BACKGROUND

Although the common cold is self-limiting, adults develop colds approximately 2 to 4 times per year. Zinc may decrease the length and severity of cold symptoms by several possible mechanisms. Studies using other zinc dosage forms, including lozenges, have demonstrated mixed results.

Although a zinc nasal spray (delivering a total daily dose of 0.044 mg) appears to be ineffective, a previous study employing zinc nasal gel (total daily dose of 2.1 mg) shortened the duration of common cold symptoms if started within 24 hours of onset of symptoms.[1,2]

POPULATION STUDIED

This study enrolled 49 women and 29 men with mean age of 26 years (range=21–40 years); 2 additional subjects in the control group were lost to follow-up. Study groups were similar at baseline. Subjects had common cold symptoms (2 major and 1 minor or 1 major and 3 minor symptoms) for more than 24 hours and less than 48 hours.

Major symptoms were defined as nasal drainage and sore throat; minor symptoms were nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, muscle aches, or fever (defined as temperature >98.6°F).

The investigator excluded patients with a known immune system disorder, diabetes, deviated septum, or a history of recurrent sinusitis, bronchitis, or otitis. Smokers, pregnant women, and subjects taking decongestants, antihistamines, antibiotics, aspirin, other zinc products, or prescription medications for asthma or allergic rhinitis were also excluded.

STUDY DESIGN AND VALIDITY

This was a randomized, double-blind trial of a nasal gel containing zinc gluconate administered via a pump, or an identical placebo. One investigator recruited all patients, and allocation was concealed from the enroller. Patients applied 2 sprays 4 times daily (total daily elemental zinc dose, 2.1 mg) until symptoms resolved or for 10 days, whichever came first. Patients were asked to refrain from using other cold remedies, but they could take acetaminophen for fever control if desired.

Patients scored their cold symptoms on a scale from 0=none to 3=severe. Coordinators assessed patient-reported compliance, symptom scores, and adverse events daily via telephone.

Although the definition of fever was low, the diagnostic criteria were appropriate. The use of a validated symptom-scoring tool also strengthened the internal validity. The investigator used intention-to-treat analysis. However, the researcher excluded patients with diabetes and smokers from the study, 2 groups frequently seen in primary care.

OUTCOMES MEASURED

The primary outcome was time to cold resolution, defined as number of symptomatic days from onset until resolution. Secondary outcomes included self-reported total daily symptom scores and incidence of adverse events. Although not an explicit outcome, the investigator collected and reported viral cultures to identify the viral isolates.

RESULTS

Zinc gel reduced the median time to cold resolution more than placebo (4.3 vs 6 days; P=.002) and decreased the median time to resolution of nasal congestion, nasal drainage, and sore throat. Active drug improved total symptom scores but data were not reported. Adverse events did not differ between the 2 groups; nasal stinging or burning were common (12.5% zinc vs 5% placebo). Subjects were unable to correctly guess which treatment they were receiving after 1 day.

REFERENCES

1. Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *Am J Med* 2001; 111:103–108.
2. Hirt M, Nobel S, Barron E. Zinc nasal gel for the treatment of common cold symptoms: A double-blind, placebo-controlled trial. *Ear Nose Throat J* 2000; 79:778–782.

Use of sputum eosinophil count decreases asthma exacerbations

Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. Lancet 2002; 360:1715–1721.

Heather Bittner Fagan, MD, and Marc Harwood, MD, *Thomas Jefferson University Family Practice, Philadelphia, Pa. E-mail: heather.bittner@mail.tju.edu.*

PRACTICE RECOMMENDATIONS

The use of regular sputum eosinophil counts to initiate and follow treatment in patients with asthma produced a small decrease in the number of hospitalizations and asthma exacerbations in compliant, moderate-to-severe asthmatics.

The definition of asthma exacerbation used in this study (a 30% decrease in morning peak expiratory flow on 2 consecutive days or initiation of oral corticosteroids) may not be clinically relevant.

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BACKGROUND

Asthma exacerbations are preceded by airway hyperresponsiveness; proinflammatory cells, including eosinophils, are implicated as the cause. Sputum eosinophilia develops weeks before an asthma exacerbation, and reduction of sputum eosinophilia often parallels the reduction of asthma symptoms. Therefore, regular testing for sputum eosinophils could allow physicians to predict and prevent severe asthma exacerbations.

POPULATION STUDIED

Patients, aged 18 to 75 years, were recruited from 1 of 3 specialist clinics. Subjects had moderate to severe asthma. The study excluded current smokers, former smokers with >15 pack-year tobacco history, patients with inadequately controlled gastroesophageal reflux disease or rhinitis, patients with a severe asthma exacerbation within 4 weeks of entry, and patients considered to be poorly compliant.

STUDY DESIGN AND VALIDITY

Patients were randomized to receive treatment based on the British Thoracic Society (BTS) guidelines or treatment based on eosinophil counts. Patients in the BTS management group were managed during exacerbations according to guidelines similar to the National Institute of Health's stepwise approach to asthma management. The sputum management group was managed according to a preset treatment algorithm; in this group, treatment with steroids or bronchodilators was initiated based on changes in eosinophil count rather than when symptoms appeared.

Patients were seen 9 times over a 12-month period. At these visits, symptoms were reviewed, some pulmonary function testing was performed, and sputum eosinophil counts were obtained for patients in both groups. When the patient could not produce sputum, exhaled nitrous oxide was used as a surrogate marker for sputum eosinophilia. Exhaled nitrous oxide rises in periods of increased asthma activity and falls with steroid treatment of asthma.

Regardless of symptoms, investigators initiated treatment based on eosinophil counts. Patients in the sputum management group were prescribed additional corticosteroids if their sputum eosinophil counts were greater than 3%. Patients were informed of treatment recommendations 3 to 5 days after these clinical evaluations.

A 30% decline in peak expiratory flow rate, which was the definition used in this study, may not be clinically apparent to the patient and may not result in changes in therapy. Patient use of acute care and emergency care services would also be of practical interest but were not evaluated in this study.

OUTCOMES MEASURED

The primary outcome measured was severe asthma exacerbations, defined by the authors as a minimum 30% decrease morning peak expiratory flow on 2 consecutive days, or symptoms requiring treatment with oral steroids. Other outcomes included quality of life (measured using an asthma quality-of-life questionnaire), the use of B_2 agonist rescue medications, symptoms (measured using a visual analog scale), and postbronchodilator pulmonary function. In addition, the researchers also evaluated the number of rescue courses of steroids, amount of steroids per patient day, and number of hospitalizations required for each patient.

RESULTS

The sputum management group had fewer severe exacerbations compared with the BTS group (35 vs 109, respectively; P=.01) and fewer hospitalizations (1 vs 6, P=.047). These data translate into a number needed to treat for benefit of 7 (95% confidence interval [CI], 3–100). Based on this confidence interval—the result of a small sample size—one more hospitalization in either group could have strongly affected the number needed to treat for benefit.

Sputum eosinophilia and exhaled nitrous oxide were lower in the sputum treatment group: 63% (95% CI, 24–100) and 48% (95% CI, 12–85), respectively. The 2 groups did not differ in symptom or quality-of-life scores, need for rescue medicines, and pulmonary function following use of a bronchodilator.

The sputum management group had fewer rescue courses of oral steroids than the BTS group (24 vs 73, respectively; P=.008), although the mean dose of inhaled corticosteroids and oral prednisolone per patient day over the year of the study did not differ between groups. Yearly cost per patient was similar between the groups ($2768 for the sputum management group and $3082 in the BTS group).

Ultrasonography helpful in diagnosing developmental hip dysplasia

Elbourne D, Dezateux C, Arthur R, et al. Ultrasonography in the diagnosis and management of developmental hip dysplasia (UK Hip Trial): clinical and economic results of a multicentre randomised controlled trial. Lancet 2002; 360:2009–2017.

Jennifer Bowe, MD, and Erik J. Lindbloom, MD, MSPH, *Department of Family and Community Medicine, University of Missouri–Columbia. E-mail: lindbloome@health.missouri.edu.*

PRACTICE RECOMMENDATIONS

Ultrasonography for diagnosis and management of possible hip instability may lead to less splinting and surgery in the first 2 years of life, with no significant difference in radiographic abnormalities. Cost-effectiveness, long-term hip mobility, and consistency of ultrasound interpretation is not proven.

BACKGROUND

Developmental dysplasia of the hips is a condition that can impair normal growth and development of the hip, leading to abnormalities of gait and early degenerative changes of the joint. The Ortolani-Barlow test has been the mainstay for screening for hip instability, but the use of ultrasonography has increased over the last 20 years. Splinting and surgery have potential risks and costs, and ultrasound may assist in focusing such treatments on those who truly need either intervention.

POPULATION STUDIED

The researchers studied 629 infants aged <43 days, recruited from 33 centers in the United Kingdom and Ireland, that had been diagnosed with neonatal hip instability. They excluded infants who had already undergone ultrasonography of their hips, those where immediate splinting of the hip was a certainty, and those with a hip click without signs of instability. Infants with clinically normal hips who had recognized risk factors for subsequent dislocation were also excluded.

STUDY DESIGN AND VALIDITY

This randomized controlled trial allocated (in a concealed manner) 314 infants to diagnosis and management with ultrasonography and 315 to clinical examination alone. Infants randomized to ultrasonography received static and dynamic ultrasounds of the hip at age 2 weeks. The hip was splinted if it appeared significantly unstable or displaced initially, or if minor abnormalities persisted up to age 8 weeks. In the no-ultrasound group, the infant underwent splinting if clinical suspicion was high enough initially or if a specialist found the hip to be unstable up to age 8 weeks.

Each child underwent formal examination at 12 to 14 months and had a plain anteroposterior radiograph of the hips and pelvis. Children with abnormal hips continued to have radiography follow-up until the hips were considered normal or until age 2 years. Resource use and costs were also compared between groups.

This was not a study of initial screening with ultrasound, since all of the infants were already diagnosed clinically with hip instability. Over half

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Ultrasound led to a reduction in unnecessary splinting in children with hip dysplasia

of them were already being seen by an orthopedic surgeon or physiotherapist. Radiologists were blinded to study groups. There were adequate data for 82% of the ultrasound group and 88% of the no-ultrasound group for the intention-to-treat analysis.

This study was relatively small, powered to detect a greater than twofold difference in radiologic abnormalities. In addition, radiographic appearance at age 2 years may or may not be a reasonable surrogate for long-term outcomes such as growth, development, and function of the adult hip. The results, particularly regarding cost, may not apply in the United States.

OUTCOMES MEASURED

The primary outcome was the appearance of abnormalities on hip radiographs at age 2 years. Secondary outcomes measured were the amount of required hip treatment (specifically surgery and splinting), as well as level of mobility, resource use, and cost.

RESULTS

Twenty-one children had abnormal or borderline radiographs by age 2 years in both groups. The 10 children with abnormal radiographs (4 of whom were in the ultrasound group) all started treatment before age 8 weeks. Overall, fewer children from the ultrasound group received treatment of any kind (relative risk=0.79; 95% confidence interval, 0.67–0.95), and this difference was almost entirely due to less splinting in the ultrasound group (37% vs. 48%).

The need for surgical treatment was similar in the 2 groups. Five children were not walking by age 2, 4 of whom were in the no-ultrasound group. Mean total costs trended lower for the ultrasound group (not statistically significant), mainly due to fewer hospital days.

Low-dose tricyclics effective for depression

Furukawa TA, McGuire H, Barbui C. Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. BMJ 2002; 325:991–995.

R. Eugene Bailey, MD, and Kenneth M. Johnson, III, MD, *Center for Evidence-Based Practice, Department of Family Medicine, SUNY Upstate Medical University, Syracuse, NY. E-mail: baileye@upstate.edu.*

PRACTICE RECOMMENDATIONS

Minimum effective dosage and ranges for antidepressants have not been established. While studies suggest that lower-dose tricyclic antidepressants (TCAs) may be as effective as higher-dose TCAs, dose comparison studies with other antidepressants have not been conducted.

Low-dose TCAs may not be as effective as standard doses, but they do have fewer treatment dropouts due to side effects, and thus patients may have better long-term compliance. Regular monitoring of patient rate of reduction in severity of depression should be used to help determine optimal individual dosing.

BACKGROUND

Despite widespread marketing of selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants, TCAs are prescribed as often as SSRIs (albeit not all of these prescriptions are for major depressive disorder). Yet evidence regarding the efficacy of TCAs is limited.

Although many guidelines recommend TCAs in higher doses (100 mg/day to 125 mg/day), the effectiveness of lower doses of TCAs is not clear.

POPULATION STUDIED

The authors performed a comprehensive search of the Cochrane Collaboration's *Depression, Anxiety and Neurosis Controlled Trials Registry* (a compilation of studies in MEDLINE, Embase, CINAHL, PsychINFO, PSYINDEX, and LILACS). They also searched major psychiatric and medical journals, ultimately identifying 2418 studies. After

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excluding trials that didn't meet their criteria, they had 39 double-blind, randomized-controlled trials for inclusion. Six of 39 trials compared low-dose TCAs with standard doses of TCAs (551 participants), and 35 of 39 trials compared low-dose TCAs with placebo (2013 participants).

TCAs studied included amitriptyline, imipramine, clomipramine, doxepin, dothiepin, trimipramine, and lofepramine. Ten studies focused on use of TCAs in primary care and 12 studies in psychiatric settings. Five studies examined patients aged >65 years, and 6 dealt with depression and comorbidities (migraine or rheumatoid arthritis).

STUDY DESIGN AND VALIDITY

Two authors determined independently whether studies met inclusion criteria, and then graded the eligible studies for quality. The studies included were not consistent for population (primary care vs psychiatric, comorbidities, and definition of depression), medication and duration of treatment (4 to 52 weeks), and outcomes measured. Significant heterogeneity existed only for the response rates at 4 to 6 weeks in the TCA vs placebo groups. When the smallest 5 studies reporting the differences were excluded, the results were no longer heterogeneous.

The authors assessed individual study quality using the *Cochrane Collaboration Handbook,* focusing on allocation concealment and double-blinding. The authors used "per protocol" analysis, examining only data where patients stayed on the medication—dropouts were handled either by analyzing them by the primary study (last observation carried forward) or by worst-case scenario, intention-to-treat analysis.

OUTCOMES MEASURED

Outcomes included response rates at 4 weeks, 6 to 8 weeks, and 3 to 12 months.

RESULTS

Low-dose TCAs (75–100 mg/day) were more likely than placebo to bring about a response at 4 weeks (relative risk (RR)=1.65; 95% confidence interval [CI]=1.36–2.00, number needed to treat [NNT] [benefit]=6), 6 to 8 weeks (RR=1.47; 95% CI=1.12–1.94, NNT [benefit]=5), and 3 to 12 months (RR=2.14; 95% CI=1.41–3.26, NNT [benefit]=3).

Standard-dose TCAs were not significantly more effective at achieving response than low-dose TCAs at 4 weeks or at 6 to 8 weeks. In elderly people, TCAs were more likely to produce a result at 4 to 6 weeks but were also more likely to cause at least one side effect. Results were similar in primary care and psychiatric settings.

Overall, dropout rates were similar (24%) for placebo, low-dose, and standard-dose TCAs. Compared with placebo, low-dose TCAs caused more dropouts due to side effects; compared with standard-dose TCA, low-dose TCAs caused fewer dropouts due to side effects.

What is a reasonable interval for retinopathy screening in patients with diabetes?

Younis N, Broadbent DM, Vora JP, Harding SP. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. Lancet 2003; 361:195–200.

Seth Miller, MD, and Erik J. Lindbloom, MD, MSPH, *Department of Family and Community Medicine, University of Missouri–Columbia. E-mail: lindbloome@health.missouri.edu.*

PRACTICE RECOMMENDATIONS

Assuming that a given patient is reliable for follow-up and that a clinical system is in place to handle a more individualized screening protocol, the investigators suggest the following approach: 3-year intervals for patients with no retinopathy and no risk factors (risk factors being diabetes for longer than 20 years or use of

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insulin); annual screening for patients with no retinopathy and 1 or both risk factors or for patients with background retinopathy; and 4-month intervals for patients with mild preproliferative retinopathy.

These intervals provide at least a 95% probability of remaining free of sight-threatening diabetic retinopathy between screenings.

BACKGROUND

Diabetes mellitus is the leading cause of blindness among adults in the US. The onset of diabetic retinopathy is often asymptomatic, and treatments for reducing visual loss are most effective in the earlier stages. The most widely accepted guidelines for intervals between screening exams are based on opinion rather than direct evidence.

POPULATION STUDIED

The Liverpool Diabetic Eye Study screening program identified 9890 patients from general practices in western England with diabetes mellitus type 2. Of these patients, 7615 underwent baseline ophthalmologic screening, which identified 7265 individuals who did not have sight-threatening diabetic retinopathy. The study reports on the 4770 patients without sight-threatening retinopathy who received at least 1 follow-up examination.

STUDY DESIGN AND VALIDITY

In this prospective cohort study, patients underwent visual acuity testing and retinal photography. Retinal images were graded using a standardized algorithm based on the Early Treatment Diabetic Retinopathy Study protocol. Graded images were divided into 4 groups: no retinopathy, background retinopathy, mild preproliferative retinopathy, and sight-threatening retinopathy (defined as moderate preproliferative retinopathy or worse, or clinically significant maculopathy).

Patients with no retinopathy or background retinopathy received annual examinations, while those with mild preproliferative retinopathy were screened every 6 months. Patients with sight-threatening retinopathy were referred to retinal disease specialists.

Given that this is an English cohort, generalizability to the US is a concern. Continuity and cost of care can be quite different between the 2 countries, and the potential for patients being lost to follow-up may be greater in the US. Even in this study, less than half of the patients with diabetes had adequate follow-up to be included. Those lost to follow-up may have been more prone to develop sight-threatening diabetic retinopathy.

In addition, this study did not address the other potential benefits of annual eye screening, such as the diagnosis of cataracts and glaucoma. Ophthalmologists may also further emphasize to the patient the importance of glycemic and blood pressure control, and these aspects of diabetes management were not assessed in this trial.

OUTCOMES MEASURED

The investigators report the presence, incidence, and severity of retinopathy at baseline screening and at follow-up examinations.

RESULTS

One year after baseline, 5.3% (95% confidence interval [CI], 4.6%–6.0%) of patients with normal initial retinal examinations developed at least some degree of retinopathy. The incidence of sight-threatening retinopathy in patients with no retinopathy at baseline was 0.3% (95% CI, 0.1%–0.5%) in the first year, and the yearly incidence steadily increased to reach a cumulative incidence of sight-threatening retinopathy at 5 years of 3.9% (95% CI, 2.8%–5.0%).

The rate of progression to sight-threatening retinopathy in 1 year was 5.0% (95% CI, 3.5–6.5%) for those with background retinopathy at baseline, and 15% (95% CI, 10.2%–19.8%) for mild preproliferative

retinopathy at baseline. Patients with diabetes for less than 10 years had a 3-year incidence of sight-threatening retinopathy of 0.7%, compared with 13.5% in patients who had had diabetes for longer than 20 years. Patients using insulin showed a much higher incidence as well, probably reflecting an increased length of time with the disease.

The mean screening intervals for a 95% probability of remaining free of sight-threatening retinopathy were calculated for each baseline status: 5.4 years (95% CI, 4.7–6.3) for no retinopathy at baseline, 1.0 year (95% CI, 0.7–1.3) for background retinopathy, and 0.3 years (95% CI, 0.2–0.5) for mild preproliferative retinopathy.

Nebulized 3% saline effective for viral bronchiolitis

Sarrell EM, Tal G, Witzling M, et al. Nebulized 3% hypertonic saline solution treatment in ambulatory children with viral bronchiolitis decreases symptoms. Chest 2002; 122:2015–2020.

Andrea D. Tribastone, MD, *University of Virginia, Stoney Creek Family Practice, Nellysford, Va. E-mail: adg5a@hscmail.mcc.virginia.edu.*

PRACTICE RECOMMENDATIONS

This small, poorly described study suggests that nebulized 3% hypertonic saline improves outcomes for nonhospitalized infants with bronchiolitis more than the use of normal saline.

While this study has significant flaws, the intervention appears safe. It would be reasonable to use nebulized 3% saline while waiting for larger, better studies.

BACKGROUND

Viral bronchiolitis is a common cause of illness in children aged <24 months. Studies have found no benefit in treatment with steroids or ribavirin. A Cochrane review of bronchodilators for the treatment of bronchiolitis showed only modest short-term improvement in clinical scores, which must be weighed against side effects. Hypertonic saline solution, by absorbing water from the submucosa, can theoretically reverse some of the bronchiolar edema.

Hypertonic saline, by absorbing water from the submucosa, can theoretically reverse edema

POPULATION STUDIED

The authors studied 70 infants under the age of 24 months who presented to an ambulatory pediatric clinic with a clinical presentation of mild-to-moderate bronchiolitis. Infants were excluded if they had any cardiac or chronic respiratory illness, previous wheezing episode, oxygen saturation <96% on room air, or need for hospitalization.

STUDY DESIGN AND VALIDITY

In this double-blinded, randomized study, infants were assigned to either a control or treatment group. The control group received inhalations of 0.5 mL (5 mg) terbutaline in 2 mL of 0.9% saline solution as a wet nebulized aerosol, while the treatment group received inhalations of the same dose of terbutaline in 2 mL of 3% saline solution. Infants in both groups were given 3 treatments per day (every 8 hours) for 5 days.

An investigator examined each infant upon entry into the study, and then every morning at treatment time and 30 minutes after the beginning of each inhalation. Clinical severity scores were recorded for each infant on the first day of the study (baseline) and each subsequent day, using 4 variables (respiratory rate, wheezing, retraction, and general condition), each rated on a scale of 0 (normal) to 3 (severe).

The details of this small study were not well

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It would be reasonable to use nebulized 3% saline while waiting for larger, better studies

described, though similar results were found in a subsequent study of hospitalized infants with bronchiolitis.[1] Specific inclusion criteria were not reported.

The method of randomization and concealment of allocation were also not discussed. Contact with the authors produced no answers to these questions, only an attachment of the subsequent study.

The analysis of data was not by intention-to-treat (5 infants who were hospitalized were excluded, 3 in the control group and 2 in the treatment group), though the authors did state that analysis of intention-to-treat was not significantly different from that which was reported. The follow-up was 100% at the 5-day completion of the study.

OUTCOMES MEASURED

The examiners compared the change in a 12-point clinical severity score over a 5-day course of treatment. The rate of hospitalization in each group was also measured.

RESULTS

The clinical severity of each group was similar at the beginning of the study (6.4 for the control group and 6.6 for the treatment group). After day 1, the clinical severity score before inhalation therapy was significantly better ($P<.005$) in the treatment group than the control group (day 2, 3.9 vs 5.2; day 3, 2.1 vs 4.8; day 4, 1.1 vs 3.8; day 5, 0.9 vs 2.9).

There was no significant difference in rate of hospitalization between the control and treatment groups (8.6% vs 5.7%).

REFERENCE

1. Mandelberg A, Tal G, Witzling M, et al. Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. *Chest* 2003; 123:481–487.

Optimal digoxin range for men is 0.5 to 0.8 ng/mL

Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz, HM. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003; 289:871–878.

Jeffrey Rosenberg, MD, and Carol Federiuk, MD, PhD, *Department of Family Medicine, Thomas Jefferson University, Philadelphia, Pa. E-mail: drjsrosenberg@yahoo.com.*

PRACTICE RECOMMENDATIONS

The optimal serum drug concentration for digoxin among men in sinus rhythm with stable heart failure is 0.5 to 0.8 ng/mL. This range is associated with decreased risk of hospitalization and mortality compared with placebo. Higher levels are associated with either no reduction, or an increased risk of hospitalization and mortality compared with placebo.

BACKGROUND

The Digitalis Investigation Group (DIG) trial of patients with heart failure found no effect on mortality from digoxin therapy at serum concentrations of 0.5 to 2.0 ng/mL, but did find that hospitalization due to worsening heart failure was modestly reduced. The original investigators did not evaluate the relative efficacy of different concentrations.

Other studies have demonstrated an association between serum drug concentrations <1.0 ng/mL and improved left ventricular function, but have not shown beneficial effects on neurohormonal function, hemodynamic profiles, or exercise tolerance. The authors of this study obtained a public use copy of the DIG data to evaluate the association of various serum concentrations on risk of mortality and hospitalization among men with heart failure and left ventricular dysfunction.

POPULATION STUDIED

This reanalysis of data from the DIG trial included 5281 men with stable heart failure

recruited from 229 cardiology and 73 primary care sites in the United States and Canada from 1991 to 1995. All participants were in sinus rhythm, had stable and clinically confirmed heart failure, and had a left ventricular ejection fraction of less than 45% as determined by radionuclide, contrast angiography, or 2-dimensional echocardiography.

Important exclusion criteria included age <21 years, recent myocardial infarction or interventional cardiac procedures, unstable angina, and significant renal dysfunction (serum creatinine >3 mg/dL).

Study participants were all men, with mean age of 63 years; 13% of the subjects were of African descent. The majority of the patients were New York Heart Association Class II or III and had >4 signs or symptoms of heart failure. Other medications known to benefit heart failure, such as angiotensin-converting enzyme inhibitors and diuretics, were continued. Patients using digoxin at the time of enrollment could be allocated to drug or placebo.

STUDY DESIGN AND VALIDITY

This study is a post-analysis of data collected from the DIG study. The DIG study was a double-blind, placebo-controlled study of digoxin in the treatment of heart failure. Digoxin dosing was based on a published algorithm; serum digoxin levels were drawn 1 month after randomization. The present study is a subgroup analysis of men based on serum drug concentrations at 1 month of 0.5–0.8 ng/mL, 0.9–1.1 ng/mL, or ≥1.2 ng/mL. These ranges have been used in previous studies of digoxin in the treatment of heart failure.

The study was sufficiently well done to draw conclusions about use of digoxin in treatment of heart failure. Patients and data investigators were blinded with respect to treatment, and cause of death was determined without knowledge of assigned treatment group. Digoxin levels were reported from the 1 month visit only. No subsequent levels were documented.

Lower doses of digoxin favorably affected mortality compared with placebo

Generalizability to the general population is limited, as only men with heart failure in sinus rhythm and a left ventricular ejection fraction <45% were evaluated. Concealment of allocation occurred, but method of randomization and intention-to-treat analysis were not reported.

OUTCOMES MEASURED

The primary outcome measure is all-cause mortality at follow-up (mean 37 months, range 24–48 months). Secondary endpoints include death due to cardiovascular causes, death due to worsening congestive heart failure, and hospitalization for worsening heart failure.

RESULTS

There was no overall difference in all-cause mortality for patients assigned to placebo as compared with those treated with digoxin (36.2% placebo vs. 36.6% digoxin, *P* not significant). When separated by serum concentration, however, lower doses of digoxin affected mortality. Patients with serum concentration of 0.5 to 0.8 ng/mL had a 6.3% lower rate (29.9% vs. 36.2%; 95% confidence interval [CI], 2.1%–10.5%; number needed to treat [NNT]= 15) of all-cause mortality and 5.9% lower rate (61.9% vs. 67.8%; 95% CI, 1.5%–10.2%; NNT=17) of hospitalizations compared with placebo.

Secondary endpoints, including cardiovascular mortality and mortality due to worsening heart failure, also showed benefit with lower serum drug concentrations. Serum concentrations of 0.9–1.1 ng/mL have similar rates of primary and secondary endpoints as placebo. Patients with serum concentrations of ≥1.2 ng/mL had higher all-cause and cardiovascular mortality compared with patients assigned to placebo.

Transdermal progesterone ineffective for menopausal symptoms

Wren BG, Champion SM, Willetts K, Manga RZ, Eden JA. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. Menopause 2003; 10:13–18.

Deborah Sturpe, PharmD, BCPS, *Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore. E-mail: dsturpe@rx.umaryland.edu.*

PRACTICE RECOMMENDATIONS

Transdermal progesterone cream, at the dose used in this study, did not improve menopausal symptoms compared with placebo. The study, however, might not have been large enough to detect a difference if one really exists.

In light of recent safety concerns over the use of other types of hormone replacement therapy, treatment of menopausal symptoms with transdermal progesterone should not be used unless better information supporting its benefit becomes available.

BACKGROUND

Natural progesterone is touted as treatment for the vasomotor, mood, and sexual disturbances associated with menopause. No well-designed clinical trials have assessed this claim. This study evaluates the effectiveness of transdermal progesterone cream in the treatment of menopausal symptoms.

POPULATION STUDIED

Investigators recruited 80 study participants from the Sydney Menopause Centre at the Royal Hospital for Women in Australia. Postmenopausal women aged 45 to 70 years were eligible if they suffered at least 1 hot flush daily and had not used drugs or herbs for hot flushes within 8 weeks of study enrollment. The average age of study participants was 54 years, and median time since menopause was 3.2 years.

Women were not enrolled if they had a history of major illness, cancer, vaginal bleeding, thrombosis, or uterine fibroids. Eight women dropped out of the study due to bleeding (n=2), return of hot flushes (n=3), inability to attend appointments (n=1), and noncompliance (n=2). Investigators did not indicate whether dropouts were from the progesterone or placebo group. The study subjects may not be reflective of the average postmenopausal population encountered in family medicine, since participants were recruited from a specialized tertiary referral center.

STUDY DESIGN AND VALIDITY

In this randomized, blinded study, participants used progesterone cream 32 mg or matching placebo daily for 12 weeks. The progesterone cream used in the study was Pro-Feme, a commercially available product manufactured by Lawley Pharmaceuticals. Participants applied 4 cm (equivalent to 32 mg) once daily to the skin, the manufacturer's recommended dose for treating menopausal women.

There are several limitations to this study. The allocation of the patient to the treatment or control group may not have been concealed from the researcher enrolling patients into the study, and women could have been selectively enrolled. The authors did not provide power analysis for the study, and there may not have been enough participants to detect differences between treatment and placebo, if one existed. Not all women completed every portion of the quality-of-life questionnaires at baseline, and the number completing was inconsistent between study group and symptom area. There was a considerable amount of dropped data between baseline and 12 weeks. This loss of data may have led to underestimation of potential benefit of progesterone.

OUTCOMES MEASURED

Investigators evaluated menopausal symptoms monthly using the Greene Climacteric Scale and, at the end of the study, the Menopause Specific Quality of Life Questionnaire (MENQOL). The

Greene Climacteric Scale assesses 5 symptom areas (vasomotor, somatic, anxiety, depression, and sex response), and the MENQOL assesses 4 types of symptoms (vasomotor, physical, psychosocial, and sex-related). Higher scores indicate more severe symptoms on both instruments. The study also measured serum progesterone, lipid levels, and indices of bone metabolism.

RESULTS

Severity scores for menopausal symptoms appeared similar between groups at baseline, but statistical analysis was not reported. Investigators did not find a significant decrease in menopausal symptoms between progesterone and placebo based on the Greene Climacteric Scale or MENQOL. No differences were found in serum lipid levels or markers of bone metabolism. Serum progesterone significantly increased in the treatment group compared with placebo, but this increase did not induce a biological response in the endometrium.

What is the best NSAID regimen for arthritis patients with bleeding ulcer?

Chan FK, Hung LC, Suen BY, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. N Engl J Med 2002; 347:2104–2110.

Eric A. Jackson, PharmD, *University of Connecticut School of Medicine and Saint Francis Hospital and Medical Center, Hartford. E-mail: ejackson2@stfranciscare.org.*

PRACTICE RECOMMENDATIONS

Among arthritis patients with a recent history of bleeding ulcer, celecoxib was just as likely as diclofenac plus omeprazole to cause recurrent bleeding. The effectiveness of these two regimens in preventing recurrent bleeding compared with a general nonsteroidal anti-inflammatory drug (NSAID) used alone cannot be determined from this study. Unfortunately, adverse renal effects were common with both regimens.

BACKGROUND

Patients who take NSAIDs for arthritis are at high risk for bleeding ulcers because of their age, functional disability, and the long-term nature of NSAID use. Patients with a history of ulcer bleeding who use NSAIDs are at the highest risk of ulcer complications. Previous studies have shown that adding a proton pump inhibitor (PPI) or misoprostol to a traditional NSAID reduces ulcer recurrence.

This study compared the effectiveness of a selective cyclooxygenase-2 inhibitor, celecoxib, with a regimen of diclofenac plus omeprazole in reducing recurrent bleeding in arthritis patients with a recent bleeding ulcer.

POPULATION STUDIED

The researchers enrolled 290 arthritis patients who presented with a bleeding ulcer to an endoscopy center in Hong Kong, China. The average age of these Chinese patients was 68 years, 63% were male, and most (58%) had gastric ulcers. After randomization, treatment groups were relatively well matched for characteristics that would affect the outcome of interest.

Only those patients with healed ulcers who required continued use of NSAIDs were included. Patients were excluded if they were taking anticoagulants or corticosteroids, or had a history of gastric or duodenal surgery, erosive esophagitis, gastric-outlet obstruction, renal failure (serum creatinine >2.2 mg/dL), terminal illness, or cancer.

STUDY DESIGN AND VALIDITY

This was a prospective, double-blind trial in which patients with healed ulcers were randomized to receive either celecoxib 200 mg twice daily plus placebo once daily (n=144) or extended-release diclofenac 75 mg twice daily plus omeprazole

CONTINUED

20 mg once daily (n=143) for 6 months. Double-blinding was maintained by repackaging all medications and placebo in identical capsules.

After randomization, patients were contacted by telephone at month 1 and returned for endoscopy, laboratory monitoring (serum hemoglobin and biochemical values), and safety and efficacy evaluation every 2 months until the end of the study. Patients were allowed to take antacids, acetaminophen and other non-NSAID analgesics, disease-modifying anti-rheumatic drugs, and low-dose aspirin, but were not allowed to take other NSAIDs or other anti-ulcer medications.

The appropriate study design and an intention-to-treat analysis were used in this drug safety trial. Neither the patients nor those assessing ulcer bleeding clinically or endoscopically were aware of treatment status. Concealed allocation to treatment groups was assured by having an independent staff member assign treatment according to code numbers in sealed envelopes.

All the subjects in the study were Chinese; the generalizability of these results to a broader population is unknown. Conclusions drawn from the results are limited because the investigators did not include patients just getting an NSAID or provide expected recurrent bleeding rates in such patients.

OUTCOMES MEASURED

The primary outcome was recurrent ulcer bleeding within 6 months. Prespecified criteria for bleeding ulcer included clinical or laboratory evidence confirmed by endoscopy. Secondary outcomes included treatment efficacy (based on patients' global assessment of disease activity and arthritis pain), recurrent ulcer bleeding in those patients not taking low-dose aspirin, and other adverse events.

RESULTS

Three of the 290 patients originally enrolled in the study withdrew consent before taking any medication, leaving 287 patients in the intention-to-treat analysis. At the end of the study period, the probability of recurrent ulcer bleeding was similar between groups, about 5%. Patients' assessments of arthritis activity and pain did not differ between the groups at any visit. Recurrence rates were similar in patients taking low-dose aspirin, which is reassuring because other research has shown that low-dose aspirin negates any benefit of celecoxib.

Adverse events (gastrointestinal, renal, and cardiovascular) leading to discontinuation of treatment were similar in the 2 treatment groups. Adverse renal events (new hypertension, peripheral edema, or renal failure) were common: 24.3% for celecoxib and 30.8% for diclofenac and omeprazole. The risk for renal failure (rise in serum creatinine to >2.2 mg/dL) was 5.6% and 6.3%, respectively.