

- 24 Spencer K. The measurement of hCG subunits in screening for Down's syndrome. In: Grudzinskas JG, Chard T, Chapman M, Cuckle HS, eds. Cambridge: Cambridge University Press, 1993 (in press).
- 25 Laundon C, Spencer K, Macri JN, Buchanan P. Turner syndrome detection by MSAFP/Free Beta (hCG) screening. *J Med Genet* 1993;30:340-1.
- 26 Spencer K, Mallard AS, Coombes EJ, Macri JN. Prenatal screening for trisomy 18 with free β human chorionic gonadotrophin. *BMJ* 1993 (in press).
- 27 Haddow JE, Palomaki GE, Knight GJ, Williams J, Pulkkinen A, Canick JA, et al. Prenatal screening for Down's syndrome with use of maternal serum markers. *N Engl J Med* 1992;327:588-93.
- 28 Cheng EY, Luthy DA, Zebelman AM, Williams MA, Lieppman RE, Hickok DE. A prospective evaluation of a second trimester screening test for fetal Down syndrome using maternal serum alpha fetoprotein, hCG and unconjugated estriol. *Obstet Gynecol* 1993;81:72-7.
- 29 Phillips OP, Elias S, Shulman LP, Andersen RN, Morgan CD, Simpson JL. Maternal serum screening for fetal Down syndrome in women less than 35 years of age using alpha fetoprotein, hCG and unconjugated estriol: a prospective 2 year study. *Obstet Gynecol* 1992;80:353-8.
- 30 Cuckle HS, Lilford R. Antenatal screening for Down's syndrome. *BMJ* 1992;305:1017.
- 31 Wald N, Hackshaw A. Antenatal screening for Down's syndrome. *BMJ* 1993;306:1198-9.
- 32 Cuckle H, Lilford R. Antenatal screening for Down's syndrome. *BMJ* 1993;306:1199.
- 33 Spencer K, Macri JN, Coombes EJ, Milford Ward A. Antenatal screening for Down's syndrome. *BMJ* 1993;306:1616.
- 34 Parsons L, Richards J, Garlick R. Screening for Down's syndrome. *BMJ* 1992;305:1228.

(Accepted 13 July 1993)

Chronic constipation in long stay elderly patients: a comparison of lactulose and a senna-fibre combination

A P Passmore, K Wilson-Davies, C Stoker, M E Scott

Abstract

Objectives—To compare the efficacy and cost effectiveness of a senna-fibre combination and lactulose in treating constipation in long stay elderly patients.

Design—Randomised, double blind, cross over study.

Setting—Four hospitals in Northern Ireland, one hospital in England, and two nursing homes in England.

Subjects—77 elderly patients with a history of chronic constipation in long term hospital or nursing home care.

Intervention—A senna-fibre combination (10 ml daily) or lactulose (15 ml twice daily) with matching placebo for two 14 day periods, with 3-5 days before and between treatments.

Main outcome measures—Stool frequency, stool consistency, and ease of evacuation; deviation from recommended dose; daily dose and cost per stool; adverse effects.

Results—Mean daily bowel frequency was greater with the senna-fibre combination (0.8, 95% confidence interval 0.7 to 0.9) than lactulose (0.6, 0.5 to 0.7; $t=3.51$ $p \leq 0.001$). Scores for stool consistency and ease of evacuation were significantly higher for the senna-fibre combination than for lactulose. The recommended dose was exceeded more frequently with lactulose than the senna-fibre combination ($\chi^2=8.38$, $p \leq 0.01$). As an index of the standard daily dose, the dose per stool was 1.52 for lactulose and 0.97 for the senna-fibre combination, at a cost per stool of 39.7p for lactulose and 10.3p for senna-fibre. Adverse effects were no different for the two treatments.

Conclusions—Both treatments were effective and well tolerated for chronic constipation in long stay elderly patients. The senna-fibre combination was significantly more effective than lactulose at a lower cost.

Introduction

Constipation may affect up to 20% of people aged over 65 years.¹ In the elderly person constipation develops in association with poor mobility and is common in long term hospital or nursing home care. Prolonged laxative treatment is often necessary to avoid serious morbidity. Laxative use has been reported in 75% of long stay hospital patients and 32% of nursing home patients.²

Treatment of constipation involves bulking agents initially, followed if necessary by stimulant or osmotic

laxatives.³ The chosen laxative should be efficacious, safe, without excess unwanted effects, and relatively inexpensive but cost effective. There are no good comparative clinical studies of the commonly used laxatives.³ Our study compared lactulose, a relatively expensive synthetic disaccharide,⁴ with a granular senna-fibre combination (ispaghula 54.2%, senna 12.4%; Manevac, Galen UK), both of which are more effective than placebo in treating constipation.^{5,6} The object was to compare the relative efficacy and cost effectiveness of the senna-fibre combination and lactulose at recommended doses in long stay elderly patients with chronic constipation.

Methods

PATIENTS

This multicentre study was conducted in long stay elderly patients in hospital or nursing home care (five hospitals and two nursing homes). Subjects had a history of chronic constipation (fewer than three bowel movements a week) or a need for regular laxatives. Exclusion criteria were important bowel pathology, diabetes mellitus, severe renal impairment, anti-diarrhoeal therapy, and faecal incontinence. The protocol was approved by local ethics committees, and written informed consent was obtained from patients or relatives.

STUDY DESIGN

According to a randomised, double-blind, cross over design, patients received active senna-fibre combination 10 ml daily with lactulose placebo 15 ml twice daily, or active lactulose 15 ml twice daily with senna-fibre placebo 10 ml daily for two 14 day periods, according to a computer generated randomisation code. Doses could be increased or decreased according to response. The maximum daily dose for active or placebo senna-fibre was 20 ml (10 ml twice daily) and for lactulose or lactulose placebo 60 ml. Dosage alterations and weight of medication before and after each period were recorded. Before entry into the first phase, and between treatments, subjects had a three to five day period free of laxatives. For ethical reasons the maximum period without a bowel movement was three days.

The number of stools and their consistency and ease of evacuation, together with any other symptoms or adverse effects (scoring system, see box), were noted daily. From the weight of medication administered the number of doses per patient and the daily dose for each treatment were estimated. Total cost and cost per stool for each treatment were calculated.

Department of Geriatric Medicine, Queen's University of Belfast, Belfast BT9 7BL
A P Passmore, senior registrar

Drug Utilization Research Unit, Department of Therapeutics and Pharmacology, Queen's University of Belfast
K Wilson-Davies, statistician

Department of Pharmacy, Waveney Hospital, Ballymena BT43 6HH
C Stoker, senior pharmacist
M E Scott, assistant director, pharmacy services

Correspondence to:
Dr A P Passmore,
Department of Geriatric Medicine, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL.

BMJ 1993;307:769-71

Scoring system for stool consistency, ease of evacuation, and other symptoms or effects noted

Stool consistency	Other symptoms or effects:
0 No bowel movement	0 No other symptoms
1 Hard, pellet-like	1 Tummy cramps
2 Hard and solid	2 Urge to pass stools quickly
3 Comfortable and solid	3 Wind or flatulence
4 Soft and solid	4 Nausea
5 Loose	5 Bloating or full feeling
Ease of evacuation	6 Headache
0 No movement	7 Anorexia
1 Difficult or painful	8 Other
2 Some difficulty	
3 Easy or comfortable	
4 Difficult to control	
5 No controls	

STATISTICAL ANALYSIS

To compare the efficacy, we tested the null hypothesis that there was no statistical difference between the two preparations. A difference of 0.2 in stool frequency per day was set as being important. The power of the test was set at 80% and the significance level of 5% chosen. From the results of a pilot study the standard difference was calculated, and the Altman nomogram method⁷ gave a sample size of 85 in order to avoid a type II statistical error in accepting the null hypothesis.

Frequency of stools per day, stool consistency, and ease of evacuation were compared with a cross over analysis.⁸ Data were analysed for carryover effects. To test for a treatment effect, the means for each variable were calculated for each treatment and compared. The data were analysed for period effect to test whether patients tended to obtain better relief in either period regardless of treatment. The *t* test for difference of two means was used, and statistical significance was accepted at the 5% level.

Adverse effects and the frequency with which the standard daily dose was exceeded for each treatment were compared using χ^2 analysis.

Results

Initially 85 patients were included. Data suitable for analysis were available in 77 patients (57 women; mean age 82.9 years), with the following exclusions: three patients were withdrawn after the first treatment period; three patients had unacceptable compliance; one patient had deteriorating health; and one patient had incomplete data. There was no evidence of carryover effect.

For evacuation frequency there was a significant treatment effect but no period effect ($t=1.2005$, $df=75$, $p>0.2$); the senna-fibre combination resulted in a higher frequency than lactulose ($p<0.001$, table I). Stool consistency scores (box) were significantly higher with the senna-fibre combination than with lactulose ($p<0.005$, table I). There was no period effect ($t=0.1588$, $df=75$, $p>0.8$). For ease of evacuation the senna-fibre combination gave a significantly higher mean score than lactulose ($p=0.02$, table I). There was no period effect ($t=0.8856$, $df=75$, $p>0.3$).

Twenty one patients had adverse effects with lactulose and 24 with the combination (table II). There was no difference between treatments when adverse effects were analysed, individually or overall.

The standard daily dose was exceeded significantly more often with lactulose ($\chi^2=8.38$, $p>0.01$). In terms of recommended daily dosages this equates with a dose per stool of 1.52 for lactulose and 0.97 for senna-fibre

combination, at a cost per stool for lactulose of 39.7p and for the senna-fibre combination of 10.3p. The total cost of treatment for 77 patients for two weeks was £283.93 for lactulose and £92.31 for the senna-fibre combination.

Discussion

The primary aim of this study was to compare the efficacy, acceptability, and cost effectiveness of the senna-fibre combination and lactulose. The senna-fibre combination proved significantly more effective. The recommended dose was exceeded significantly more often for lactulose, which resulted in reduced cost effectiveness compared with the senna-fibre combination.

The prevalence of chronic constipation has been reported as 40% or above in long stay elderly patients.⁶ Associated high rates of laxative use^{2,10} can result in considerable cost of treatment.¹¹ While there are problems with long term use of laxatives, considerable morbidity is associated with chronic constipation in frail elderly people. Management of constipation consists of establishing the diagnosis and correcting any underlying cause. Patients should be treated with a bulking agent followed by a stimulant or osmotic laxative.^{3,4,12}

Comparative studies have shown no difference between lactulose and ispaghula¹ or between lactulose and irritant laxatives,¹³ and psyllium with senna has been shown to be better than psyllium alone.¹⁴ Pico-sulphate and senna were equally effective in long stay geriatric patients.¹⁵ The treatments in the present study are well established, but the senna-fibre combination proved significantly better on all variables studied. Frequency and consistency of stools are the most commonly used measures in studies of this kind.¹⁵ The dose of medication required for satisfactory effect has also been used as an index of efficiency.¹

Both bran and lactulose act in part through an increase in faecal mass, with resultant bowel distension and increased intraluminal pressure, which ultimately works a mass reflex in the colon. For this response to occur the contractile power of the bowel must be intact. This may not be the case in atonic constipation, which is often encountered in elderly patients. The additional properties of senna¹⁶ may explain the superior efficacy of the senna-fibre preparation in the present study.

Despite the increased efficacy of the senna-fibre

TABLE I—Effect of senna-fibre combination and lactulose on bowel frequency, stool consistency, and ease of evacuation. Results are shown as mean (95% confidence interval)

	Senna-fibre combination	Lactulose	<i>t</i>	df	p Value
Daily frequency	0.8 (0.7 to 0.9)	0.6 (0.5 to 0.7)	3.51	75	0.001
Consistency	3.4 (3.2 to 3.6)	3.1 (2.9 to 3.3)	3.03	75	0.005
Ease	3.1 (2.9 to 3.3)	2.9 (2.7 to 3.1)	2.37	75	0.02

TABLE II—Incidence of adverse effects with senna-fibre combination and lactulose

	Senna-fibre combination		Lactulose		p Value
	No of patients	No of episodes	No of patients	No of episodes	
Cramps	7	3.1	7	2.7	NS
Urgency	13	2.5	7	2.9	NS
Wind or flatulence	10	2.3	8	3.3	NS
Nausea	2	1.5	0	0	NS
Bloated	3	1.3	3	1.3	NS
Headache	0	0	1	2.0	NS
Anorexia	1	1	4	1.3	NS
Total	24	3.6	21	3.6	NS

NS=Not significant.

Clinical implications

- Chronic constipation is common in elderly people in long stay hospital and nursing home care and regular laxative treatment is often required
- There are few comparative clinical studies of commonly used laxatives
- In this study a senna-fibre combination was more effective than lactulose in long stay elderly patients with constipation
- Both treatments were well tolerated
- The superior efficacy of the senna-fibre combination, without increase in side effects, resulted in considerable cost benefit compared with lactulose.

combination the incidence of adverse effects was no different, both compounds being well tolerated.

The issue of cost effectiveness was addressed in this study. A higher daily dose was needed for an effect with lactulose. There were significant cost savings with the senna-fibre combination over the study period. Extrapolation of these data to the large numbers of long stay elderly people in nursing homes and hospitals who require regular laxatives could result in considerable cost savings. These results would seem to concur with statements on the relative expense and efficacy of lactulose.^{3 4 12}

In conclusion, both the senna-fibre combination and lactulose were effective, well tolerated treatments for chronic constipation in long stay elderly patients. Under the study conditions the senna-fibre combination was more effective than lactulose and was a less expensive regimen, a significant advantage in times of clinical and financial audit.

Study participants were Dr A Mehrzad, Mr J Milligan, and

Ms G Johnston of Bishop Auckland General Hospital, Co Durham; Drs P Dalton and N Plant of The Surgery, Kingsmillford, Dudley, West Midlands; Drs P G Flanagan, A Sarkar, and A Moore and Ms M Hetherington of Waveney Hospital, Ballymena, and Masserene Hospital, Antrim, Co Antrim; Dr T R O Beringer of Royal Victoria Hospital, Belfast; Drs J G McConnell and I C Taylor of Ulster Hospital, Dundonald, Northern Ireland.

We thank the medical, nursing, and pharmacy staff in the participating units for their assistance with this study and Galen Limited and Madaus AG for their contribution towards the study.

- 1 Rouse M, Mahapatra M, Atkinson SM, Prescott P. An open randomised, parallel group study of lactulose versus ispaghula in the treatment of chronic constipation in adults. *Br J Clin Practice* 1991;45:28-30.
- 2 Primrose WR, Capewell RE, Simpson GR, Smith RG. Prescribing patterns observed in registered nursing homes and long stay geriatric wards. *Age Ageing* 1987;16:25-8.
- 3 Laxatives: replacing danthron. *Drug and Therapeutics Bulletin* 1988;26:53-6.
- 4 Bateman DN, Smith JM. A policy for laxatives. *BMJ* 1988;297:1420-1.
- 5 Fintelmann V, Haase W. Chronic habitual constipation: double blind trial of a laxative of known efficacy. *Arztliche Praxis* 1977;29:25-6.
- 6 Sanders JF. Lactulose syrup assessed in a double blind study of elderly constipated patients. *J Am Ger Soc* 1978;26:236-9.
- 7 Altman DG. *Practical Statistics for Medical Research*. London: Chapman Hall, 1991:457.
- 8 Hills M, Armitage P. The two period crossover clinical trial. *Br J Clin Pharmacol* 1979;8:7-20.
- 9 Godding EW. Laxatives and the special role of senna. *Pharmacology* 1988;36(suppl 1):230-6.
- 10 Andersson M. Drugs prescribed for elderly patients in nursing homes or under medical home care. *Compr Gerontol* 1989;3(suppl):8-15.
- 11 Upton DR, Taylor JK, Holmes GKT, Poston JW. Effects of withdrawal of co-danthramer on use of laxatives in a district general hospital. *BMJ* 1988;297:1446-7.
- 12 Tedesco FJ, Dipiro JT. Laxative use in constipation. *Am J Gastroenterol* 1985;80:303-9.
- 13 Connolly P, Hughes IW, Ryan G. Comparison of 'dupalac' and 'irritant' laxatives during and after treatment of chronic constipation: a preliminary study. *Curr Med Res Opin* 1975;2:620-5.
- 14 Marlett JA, Li BUK, Patron CJ, Bass P. Comparative laxation of psyllium with and without senna in an ambulatory constipated population. *Am J Gastroenterol* 1987;82:333-7.
- 15 MacLennan WJ, Poder AFWM. A comparison of sodium picosulphate (Laxoberal) with standardised senna (Senokot) in geriatric patients. *Curr Med Res Opin* 1975;2:641-7.
- 16 DeWitte P, Lemli L. The metabolism of anthranoid laxatives. *Hepato-gastroenterology* 1990;37:601-5.

(Accepted 23 July 1993)

Problems in assessing contents of metered dose inhalers

D J Williams, A C Williams, D G Kruczek

Heathcot Practice, York House Medical Centre, Woking, GU22 7XL
D J Williams, general practitioner
A C Williams, psychologist

St Peter's Hospital, Chertsey, KT16 0PZ
D G Kruczek, anaesthetics registrar

Correspondence to:
Dr Williams.

BMJ 1993;307:771-2

Treatment of asthma with β agonists delivered via metered dose aerosol inhalers has been associated with excess mortality from asthma.¹ The canisters of these inhalers are opaque, and patients cannot see how much medication remains in a canister. This means that such patients may tend to run out of medication, which could be related to the excess mortality from asthma. We investigated whether asthmatic patients were able to reliably assess the amount of medication remaining in a metered dose inhaler and whether they ever ran out of medication.

Subjects, methods, and results

From details of repeat prescriptions we identified all asthmatic patients attending a general practice who were aged 13-22 and used a metered dose inhaler. We notified the patients to come to the surgery with the inhalers they were currently using and any held in reserve. We asked the patients about their use of inhalers and assessed the inhalers by weight.² When an inhaler's canister floats (at its floating weight) it has delivered its licensed number of doses.² Although

expellant may be obtained from an inhaler beyond its licensed number of doses (36 extra puffs on average for a Ventolin inhaler), there are no published data on the drug content of each puff. As 48 hours is generally required to get a repeat prescription from a general practice, a canister's red weight is when it contains enough expellant for 48 hours' use. β Agonists in metered dose inhalers are usually prescribed at two puffs four times daily. The red weight is thus the empty weight (when no further expellant can be obtained) plus the weight of eight doses. We emptied four canisters of each of the metered dose inhalers available (allowing 30 seconds between each expelled dose), measured the appropriate weights, and calculated average weights.

The table shows the answers given by the 51 patients who were interviewed. Only three patients assessed their inhalers by flotation, and when given a nearly empty inhaler none of the patients asked to float the canister before saying that they would continue to use it. Altogether 37 patients sought a replacement when their last inhaler was almost or completely empty, and 36 subjects occasionally or frequently ran out of inhalant (33 of whom had consequently become wheezy or very wheezy). Of the 81 inhalers in current use that were assessed, 21 were at their floating weight and 12 were at their red weight. For five patients both their inhaler for prophylaxis and their inhaler for symptomatic relief were at their floating weights, and for three patients both inhalers were at their red weights. Nineteen patients had no inhaler in reserve.