- 3 Greco AV, Bianco A, Altomonte L, D'Acquarica L, Ghirlanda G. Effect of somatostatin on lower esophageal sphincter (LES) pressure and serum gastrin in normal and achalasic subjects. *Horm Metab Res* 1982;14:26-8.
- 4 Kleber G, Sauerbruch T, Fisher G, Paumgartner G. Somatostatin does not reduce oesophageal variceal pressure in liver cirrhotics. *Gut* 1988;29:153-6.
- 5 Bornman PC, Krige JEJ, Terblanche J. Management of oesophageal varices. *Lancet* 1994;343:1079-84.
- 6 Williams SGJ, Westaby D. Management of variceal haemorrhage. *BMJ* 1994;308:1213-7.
- 7 Shulkes A, Wilson JS. Somatostatin in gastroenterology: for unresectable hormone secreting neuroendocrine tumours, secretory diarrhoeas, and bleeding varices [editorial]. *BMJ* 1994;308:1381-2.
- 8 Valenzuela JE, Schubert T, Fogel MR, Strong RM, Levine J, Mills PR, et al. A multicenter, randomized, double-blind trial of somatostatin in the management of acute hemorrhage from esophageal varices. *Hepatology* 1989;10:958-61.
- 9 Burroughs AK, McCormick PA, Hughes MD, Sprengers D, D'Heygere F, McIntyre N. Randomized, double-blind, placebo-controlled trial of somatostatin for variceal bleeding. Emergency control and prevention of early rebleeding. *Gastroenterology* 1990;99:1388-95.
- 10 Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27:335-71.
- 11 Shadish WR, Haddock CK. Combining estimates of effect size. In: Cooper H, Hedges LV, eds. *The handbook of research synthesis*. New York: Russell Sage Foundation, 1994:261-81.
- 12 Sheppard M, Shapiro B, Pimstone B, Kronheim S, Berelowitz M, Gregory M. Metabolic clearance and plasma half-disappearance time of exogenous somatostatin in man. *J Clin Endocrinol Metab* 1979;48:50.

(Accepted 4 April 1995)

The analgesic effect of sucrose in full term infants: a randomised controlled trial

Nora Haouari, Christopher Wood, Gillian Griffiths, Malcolm Levene

Abstract

Objective—To evaluate the effects of different sucrose concentrations on measures of neonatal pain.

Design—Randomised, double blind, placebo controlled trial of sterile water (control) or one of three solutions of sucrose—namely, 12.5%, 25%, and 50% wt/vol.

Setting—Postnatal ward.

Patients—60 healthy infants of gestational age 37–42 weeks and postnatal age 1–6 days randomised to receive 2 ml of one of the four solutions on to the tongue two minutes before heel prick sampling for serum bilirubin concentrations.

Main outcome measure—Duration of crying over the first three minutes after heel prick.

Results—There was a significant reduction in overall crying time and heart rate after three minutes in the babies given 50% sucrose as compared with controls. This was maximal one minute after heel prick in the 50% sucrose group and became statistically significant in the 25% sucrose group at two minutes. There was a significant trend for a reduction in crying time with increasing concentrations of sucrose over the first three minutes.

Conclusion—Concentrated sucrose solution seems to reduce crying and the autonomic effects of a painful procedure in healthy normal babies. Sucrose may be a useful and safe analgesic for minor procedures in neonates.

Introduction

The ability of neonates to perceive and react to pain has been much debated in recent years. We know that most of the anatomical pathways and neurotransmitter function necessary for pain perception are fully or nearly fully developed in the neonatal period.^{1,2} Yet many people are still reluctant to believe that pain felt by neonates may be as severe as that felt by older children or adults.

All neonates born in developed countries are subjected to painful procedures. Heel pricks for Guthrie tests are near universal and intramuscular vitamin K injections and routine circumcision are still common in some countries. Blood samples for serum bilirubin and blood sugar estimations are taken when clinically indicated, and if a neonate is sick frequent blood sampling, venepuncture, and more severe procedures which cause tissue injury are common. We estimate that in our hospital every baby has at least one heel prick procedure, 15% of babies have two to five blood

samples taken or intramuscular injections, and 2% have five or more such procedures.

We assessed the use of sucrose to reduce pain in neonates subjected to routine blood sampling by heel prick.

Patients and methods

Healthy full term infants who required heel prick sampling for serum bilirubin estimations were recruited from the postnatal wards of this hospital over six months. Babies with Apgar scores of less than 7 at one minute or who had received naloxone were excluded. All heel prick samples were drawn by a single, experienced nurse (GG) using a sterile lance. The babies responses were observed by NH and CW.

Infants were taken to a warm, quiet nursery for blood sampling and were fully clothed apart from the foot used for sampling. Before skin preparation a pulse oximeter was applied to the baby's hand to measure changes in oxygen saturation and heart rate during the study. Parents could be present if they wished but did not speak to or touch the baby during the procedure. We calculated that to achieve 80% power to show a 50% reduction in crying time ($P=0.05$) 15 babies would be required in each group.

Babies were allocated at random to receive one of four solutions on to the tongue: sterile water (control) or 12.5%, 25%, or 50% sucrose (wt/vol). Randomisation was by means of pre-prepared solutions in coded bottles. Investigators were blind to the nature of the solutions throughout. Stratification was not used. The test solution (2 ml) was given by syringe into the baby's mouth over less than one minute. The heel was then exposed, cleaned with a sterile swab, and held gently. Two minutes after the test solution the heel was lanced and gently squeezed.

The baby's behavioural state³ was recorded immediately before lancing. Four facial expressions reported to occur during an acute painful stimulus⁴ were also recorded on a 0–4 scale. Crying during sampling and during the three minutes after sampling (recovery phase) was recorded on audio tape and later analysed blindly for the duration of crying. Crying time was defined as the number of seconds that the baby cried within the first three minutes and the duration of the first cry was the duration of continuous crying before a quiet interval of five seconds.

The study was approved by the hospital ethics committee and all parents gave informed consent. Analysis of non-parametric data was by the Mann-Whitney U test (Minitab) or a trend test.⁵ Changes in

University Division of Paediatrics and Child Health, D Floor, Clarendon Wing, Leeds General Infirmary, Leeds LS2 9NS

Nora Haouari, visiting clinical fellow
Christopher Wood, lecturer
Gillian Griffiths, research nurse
Malcolm Levene, professor of paediatrics

Correspondence to: Professor Levene.

BMJ 1995;310:1498–500

heart rate were expressed as a percentage of resting heart rate. Parametric statistical analysis was by Student's *t* test.

Results

Sixty babies were studied. There were no withdrawals after randomisation. Details of the babies in each group are shown in table I. There were no significant differences between the groups in sex, gestational age, birth weight, postnatal age, mode of delivery, behavioural state at rest, or time since last feed.

Figure 1 shows the duration of crying in the first three minutes after heel prick in each treatment group. The median crying time and median duration of first cry are shown in table II. There was a significant reduction in both the total crying time and the duration of first cry in the 50% sucrose group as compared with the controls ($P=0.02$). Over the range of sucrose doses studied there was a significant trend towards a reduction in crying time with greater concentrations of sucrose ($P=0.007$). There was a similar trend in the reduction of the duration of first cry with increasing concentrations of sucrose ($P=0.004$).

The median time crying in each one minute epoch after heel prick is shown in figure 2 and table II. There was a significant reduction in crying time at the end of the first minute in the 50% sucrose group as compared with the controls ($P<0.02$), and in the second minute the duration of cry was significantly less in the 25% ($P=0.02$) and 50% ($P=0.003$) sucrose groups. By the

FIG 1—Total time crying in first three minutes after heel prick in 60 babies given sterile water (controls) or 12.5%, 25%, or 50% sucrose. Points are individual values. Horizontal lines are median values. Shaded areas are interquartile ranges. (Test for trend across groups: $P=0.007$)

TABLE I—Details of neonates studied

Sucrose concentration (%)	No	Median gestational age (weeks) (range)	Median birth weight (kg) (range)	Boys/girls	Vaginal/caesarean delivery	Median postnatal age (days) (range)	Median arousal state score (0-5) (range)	Median time from last feed (min) (range)	Breast/formula feed
0 (Control)	15	38 (37-41)	3.22 (2.87-4.46)	6/9	9/6	3 (2-5)	2 (0-3)	120 (30-240)	11/4
12.5	15	39 (38-41)	3.35 (2.54-4.11)	7/8	14/1	3 (2-6)	2 (0-4)	120 (20-240)	11/4
25.0	15	38 (37-40)	3.14 (2.56-3.85)	9/6	8/7	4 (2-6)	2 (0-3)	120 (30-285)	11/4
50.0	15	39 (37-42)	3.22 (2.54-3.85)	7/8	13/2	3 (1-6)	1 (0-4)	120 (30-240)	11/4

FIG 2—Time crying during each one minute epoch after heel prick in infants given sterile water (controls) or 12.5%, 25%, or 50% oral sucrose. Points are median values for each group

end of the third minute crying was reduced in all four groups, with no significant differences between them.

There were no significant differences in oxygen saturation values before, during, or after sampling. Changes in heart rate are shown in table II. There was a significant difference in heart rate three minutes after lancing ($P=0.02$) in the controls as compared with the 50% sucrose group. There were no differences between babies given less concentrated solutions of sucrose. There were no significant differences in facial responses between the four groups.

Discussion

Using a lancet to draw blood is a common procedure and is recognised to cause pain in patients able to report it. We have shown that there is a dose-response effect of increasing concentrations of sucrose, resulting in a reduction in crying time in healthy full term infants. This effect is evident by the end of the first minute after heel prick and with a 50% sucrose solution seems to be maximal by the end of the second minute. Sucrose not only reduces the duration of crying but also reduces tachycardia induced by a painful procedure.

A fairly high proportion of infants in this study were born by caesarean section (27%). These babies spent longer in hospital with their convalescing mothers and were therefore more likely still to be in hospital when jaundice was noted. The proportions of babies born by caesarean section were not significantly different among the groups and we think it unlikely that anaesthetic agents given to the mothers would have affected their babies responses to painful stimuli.

Sucrose increases pain latency in animals after a standard noxious procedure. Blass *et al* found that in 10 day old rats intraoral infusions of 3.5%, 7.5%, and 11.5% sucrose all increased latency before each animal

TABLE II—Crying time and change in heart rate after heel prick

Sucrose concentration (%)	No	Total time (in seconds crying) over three minutes (median) (interquartile range)	Time (in seconds) crying in each minute (median) (interquartile range)			Duration (in seconds) of first cry (median) (interquartile range)	% Change in heart rate after heel prick (t=0) (mean) (SE)		
			First minute	Second minute	Third minute		t=1 min	t=3 min	t=5 min
0 (Control)	15	135 (100-155)	60 (50-60)	60 (40-60)	29 (0-40)	95 (57-136)	+11.4 (3.0)	+17.5 (6.0)	+1.8 (5.3)
12.5	15	106 (45-150)	53 (40-60)	40 (0-60)	4 (0-53)	50 (30-150)	+17.8 (9.4)	+6.6 (3.4)	+0.5 (4.0)
25.0	15	81 (12-150)	55 (12-60)	18 (0-55)	0 (0-30)	65 (5-144)	+21.3 (3.8)	+14.5 (3.1)	-1.1 (5.0)
50.0	15	45 (14-88)	35 (14-60)	0 (0-25)	0 (0-40)	20 (5-80)	+14.0 (6.5)	+0.1 (3.3)	-5.9 (3.4)

Key messages

- Every newborn baby in Britain is subjected to several painful procedures
- Little is done to minimise the discomfort of these procedures
- Placing 2 ml of a 25% or 50% sucrose solution on the tongue before heel prick significantly reduces crying time
- There is a dose-response effect in the reduction of crying with increasing concentrations of sucrose
- Sucrose on the tongue may be a useful and safe form of analgesia in newborn infants

lifted its paw off a hotplate.⁶ This effect was completely reversed by naltrexone. Blass and Hoffmeyer subsequently showed that 2 ml of 12% intraoral sucrose significantly reduced the duration of cry in newborn babies subjected to heel prick or circumcision.⁷ Our group repeated that study with 7.5% sucrose and found no difference in the duration of crying.⁸ However, we remained intrigued by the reports of Blass *et al* and undertook this study with different sucrose concentrations. We conclude that in our first study we used a sucrose solution too weak to induce a measurable analgesic effect.

Non-sucrose sweet substances such as saccharin also seem to increase pain latency in animals.⁹ Other substances such as milk and in particular milk fat seem to have a similar effect through the endogenous opiate pathways.¹⁰ We do not know whether simply cuddling an infant after heel prick is as effective in reducing crying as 50% sucrose. We are undertaking further clinical studies to evaluate the effect of sucrose and other substances in pain prevention in immature babies and older children.

This study was supported by the Special Trustees of the Leeds General Infirmary.

- 1 Fitzgerald M, McIntosh N. Pain and analgesia in the newborn. *Arch Dis Child* 1989;64:441-3.
- 2 Anand KJS, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med* 1987;317:1321-9.
- 3 Prechtl HFR. The behavioural states of the newborn infant (a review). *Brain Res* 1974;76:185-212.
- 4 Rushforth JA, Levene MI. Behavioural response to pain in healthy neonates. *Arch Dis Child* 1994;70:F174-6.
- 5 Cusick J. A Wilcoxon-type test for trend. *Stat Med* 1985;4:87-90.
- 6 Blass E, Fitzgerald E, Kehoe P. Interactions between sucrose, pain and isolation distress. *Pharmacol Biochem Behav* 1987;26:483-9.
- 7 Blass EM, Hoffmeyer LB. Sucrose as an analgesic for newborn infants. *Pediatrics* 1991;87:215-8.
- 8 Rushforth JA, Levene MI. Effect of sucrose on crying in response to heel stab. *Arch Dis Child* 1993;69:388-9.
- 9 Lieblich I, Cohen E, Ganchrow JR, Blass EM, Bergmann F. Morphine tolerance in genetically selected rats induced by chronically elevated saccharin intake. *Science* 1983;97:871-3.
- 10 Blass EM, Shide DJ, Weller A. Stress-reducing effects of ingesting milk, sugars and fats. *Ann N Y Acad Sci* 1989;575:292-305.

(Accepted 11 April 1995)

Occurrence of different cancers in patients with Parkinson's disease

Henrik Møller, Lene Mellemkjær,
Joseph K McLaughlin, Jørgen H Olsen

International Agency for
Research on Cancer,
F-69372 Lyons, France
Henrik Møller,
epidemiologist

Danish Cancer Society,
Division for Cancer
Epidemiology,
Copenhagen, Denmark
Lene Mellemkjær,
epidemiologist
Jørgen H Olsen,
epidemiologist

National Cancer Institute,
Epidemiology and
Biostatistics Program,
Bethesda, Maryland, USA
Joseph K McLaughlin,
epidemiologist

Correspondence to:
Dr Møller.

BMJ 1995;310:1500-1

Parkinson's disease is a chronic, progressive neurological disorder with well defined clinical and pathological features. Smokers are less likely to develop Parkinson's disease.¹ The disease is associated with a reduced risk of cancer overall,² but the risk of malignant melanoma may be increased.³ The objective of this study was to assess the occurrence of cancer in a large cohort of patients with Parkinson's disease.

Patients, methods, and results

The study was based on three computerised registers in Denmark. From the Danish hospital discharge register we extracted all records of admissions of patients with a primary diagnosis of Parkinson's disease during 1977-89 and identified a cohort of 7046 people with the disease (3470 men and 3576 women). Information on cancer incidence and death among cohort members from their first recorded admission for Parkinson's disease till the end of 1990 was obtained from the Danish cancer registry and from the Danish register of deaths. The expected numbers of cases of cancer were calculated from the person years at risk among cohort members and the incidences of cancer in the Danish population, with due account being taken of age and calendar period. Relative risks were calculated as the ratios of the observed to the expected numbers of cases of cancer and are presented with their 95% confidence intervals. The average duration of follow up was 4.6 years.

The overall incidence of cancer was lower than expected (table; relative risk 0.88). Relative risks were significantly reduced for lung cancer (0.29) and bladder cancer (0.42). Significantly increased relative risks were seen for skin melanoma (1.96) and for malignancies of unknown origin (1.76). Brain tumours occurred more frequently than expected (relative risk 1.61). The excess was, however, confined to the first three years after Parkinson's disease had been diag-

Relative risks of cancer in 7046 people with a primary diagnosis of Parkinson's disease in Denmark, 1977-89

Cancer	Observed No	Expected No	Relative risk (95% confidence interval)
All cancers	554	629.42	0.88 (0.8 to 1.0)
Mouth and pharynx	6	10.94	0.55 (0.2 to 1.2)
Oesophagus	7	5.76	1.22 (0.5 to 2.5)
Stomach	24	26.35	0.91 (0.6 to 1.4)
Colon	59	61.78	0.96 (0.7 to 1.2)
Rectum	32	32.76	0.98 (0.7 to 1.4)
Liver:			
Primary	6	6.80	0.88 (0.3 to 1.9)
Unspecified	5	5.60	0.89 (0.3 to 2.1)
Gall bladder	5	7.84	0.64 (0.2 to 1.5)
Pancreas	19	22.02	0.86 (0.5 to 1.3)
Lung	23	80.32	0.29 (0.2 to 0.4)*
Breast	60	49.88	1.20 (0.9 to 1.5)
Cervix uteri	6	6.96	0.86 (0.3 to 1.9)
Corpus uteri	11	12.40	0.89 (0.4 to 1.6)
Ovary	9	11.63	0.77 (0.4 to 1.5)
Prostate	40	50.68	0.79 (0.6 to 1.1)
Kidney	13	17.65	0.74 (0.4 to 1.3)
Urinary bladder	17	40.95	0.42 (0.2 to 0.7)*
Melanoma of skin	16	8.17	1.96 (1.1 to 3.2)*
Other skin cancer	104	83.92	1.24 (1.0 to 1.5)
Brain	15	9.33	1.61 (0.9 to 2.7)
Non-Hodgkin's lymphoma	9	11.91	0.76 (0.3 to 1.4)
Multiple myeloma	4	7.12	0.56 (0.2 to 1.4)
Leukaemia	13	15.82	0.82 (0.4 to 1.4)
Other specified sites	19	24.68	0.77 (0.5 to 1.2)
Metastases and unspecified	32	18.15	1.76 (1.2 to 2.5)*
Cancers associated with tobacco smoking†	91	184.60	0.49 (0.4 to 0.6)*
All other specified cancers	431	426.67	1.01 (0.9 to 1.1)

*95% Confidence interval excludes 1.0.

†Includes cancers of mouth and pharynx, oesophagus, pancreas, lung, cervix, kidney, and bladder.