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Dicyclomine hydrochloride in infantile colic

Dicyclomine hydrochloride is often used to treat infantile colic in Sweden, although in the United Kingdom it is now regarded as being contraindicated in infants aged six months and under. Results from three previous studies suggested its effectiveness.¹⁻³ In these studies, however, the placebo did not taste like dicyclomine (in the most recent study, for instance, cherry syrup was used as the placebo³), and thus whether these studies were blind is not clear, as parents often taste their children's drugs. One aim of the present study was to investigate the effects of dicyclomine compared with a placebo with identical smell, taste, colour, and texture. Another goal was to identify factors, such as age and rhythm and amount of crying, that would predict whether treatment would be successful.

Method and results

Thirty infants with colic were included in the study. Crying was diagnosed as infantile colic if it lasted for more than three hours a day and occurred for more than three days a week. The average age of the infants was 4.5 weeks. The infants were given the placebo and dicyclomine for one week each, with the order counterbalanced. The parents were interviewed before and after treatment to obtain background data and evaluate therapeutic efficiency. In addition, parents kept 24 hour records about their infants' crying, irritability, and sleeping. The placebo was designed to have the same taste, smell, colour, and texture as the active solution. The infants were given 5 mg dicyclomine four times a day.

Twenty parents rated dicyclomine as better, seven rated placebo as better ($p < 0.05$), and three thought both treatments equally effective. Twenty five infants were reported to have improved when receiving dicyclomine and 17 when receiving placebo ($p < 0.05$). The table shows that the effects were less evident when the 24 hour records were analysed.

Eight infants cried at least one third less during treatment with dicyclomine; they did not differ with regard to sex, age, or amount and rhythm of crying from the rest of the infants.

Four infants taking dicyclomine and one taking placebo were reported as drowsy during the first few days after treatment.

Infants' behaviour according to 24 hour records. Figures are means (SD)

	Before treatment	During placebo treatment	During dicyclomine treatment
Time spent crying (h)	4.9 (3.7)	4.3 (3.9)	3.3 (3.0)
Time spent sleeping (h)	13.7 (3.0)	13.3 (3.6)	13.8 (3.7)
No of feeds	6.6 (2.7)	6.0 (1.9)	6.1 (1.8)
No of stools	1.6 (1.5)	2.1 (1.6)	1.7 (1.6)

Comment

Our findings showed a significant improvement during treatment with dicyclomine. The babies were, however, not symptom free. The crying decreased from 4.9 (SD 3.7) hours to 3.3 (3.0) hours after treatment with dicyclomine, and to 4.3 (3.9) hours after treatment with placebo. Data from a comparable group of infants without colic showed an average of 1.2 (1.0) hours of crying daily (unpublished observations). Unfortunately, the current study did not suggest a way of identifying which infants would benefit substantially from the drug.

Seventeen of the infants were reported to have improved during treatment with placebo. We achieved similar effects with a placebo

in a recent study of dimethicone in infantile colic.⁴ Clearly, it is difficult for parents to evaluate pharmacological effects, and physicians' clinical impressions of improvement are easily obscured by the placebo effect.

The mode of action of dicyclomine in infantile colic is unknown. One suggestion is that its anticholinergic effect reduces spasms of the intestines. Another possibility is that it acts on the central nervous system. If this is true, side effects such as drowsiness might be better understood.⁵

Dicyclomine reduces, but does not abolish, the crying for some "colicky" babies. The decision to prescribe dicyclomine to these otherwise healthy babies should be carefully considered. It is our impression that the reduction of symptoms is often limited and that psychological support may in many instances offer similar relief.

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Diabetes mellitus and early mortality from stroke

Diabetes mellitus is a risk factor for both an excess incidence of and mortality from stroke.¹ Hyperglycaemia is a fairly common and poor prognostic feature in non-diabetic patients with stroke.² Such hyperglycaemia may represent premorbid undiagnosed diabetes or a stress response. We undertook a study to determine the prevalence of undiagnosed diabetes in patients with stroke, to evaluate the relation between hyperglycaemia on admission and premorbid undiagnosed diabetes, and to determine the clinical course of stroke in these patients.

Methods and results

The study population consisted of all patients ($n = 100$) admitted to this hospital with stroke between June 1984 and January 1985. Stroke was defined as sudden onset of neurological deficit within three days before admission and lasting at least 24 hours. Patients with subarachnoid haemorrhage were excluded. The severity of stroke was graded using a stroke score. Venous blood was taken to measure random plasma glucose and glycosylated haemoglobin (HbA_{1c}) concentrations. Cumulative mortality was determined one week, one month, and three months after admission. The concentration of HbA_{1c} , free of labile adducts, was determined using an isoelectric focusing technique within one week after collection of the blood samples. Patients were defined as having clearly normal HbA_{1c} ($< 6.9\%$, group 1), borderline abnormal HbA_{1c} ($6.9-7.8\%$, group 2), or clearly abnormal HbA_{1c} concentrations ($> 7.8\%$, group 3).³

Statistical analysis was by non-parametric methods of comparison (Mann-Whitney U test) and correlation (Spearman's rank correlation R_s), Student's t test, and χ^2 test with Yates's correction where appropriate.

Group 1 comprised 71 patients, group 2 comprised 15 patients, and group 3 comprised six patients. Eight patients had been previously diagnosed as diabetics (group 4). Plasma glucose concentrations were obtained for 80 of the 94 patients not known to be diabetic. There was a highly significant correlation between plasma glucose and HbA_{1c} concentrations in these patients ($R_s = 0.51$, $p < 0.0001$). Four of the five patients not known to be

diabetic whose plasma glucose concentrations were ≥ 11 mmol/l (198 mg/100 ml) were in group 3.

Mortality and clinical findings did not differ significantly between groups 1 and 2 ($p > 0.5$) or groups 3 and 4. Accordingly, groups 1 and 2 and groups 3 and 4 were combined for analysis. The diabetics (groups 3 and 4) showed significantly greater mortality at one week ($\chi^2 = 11.2$, $p < 0.001$) than the non-diabetic patients. All the deaths in the diabetic group occurred within a week of stroke, whereas deaths continued to occur throughout the follow up period in groups 1 and 2 (table).

Admission characteristics and mortality of combined groups

	Non-diabetics (groups 1 and 2) (n = 86)	Diabetics (groups 3 and 4) (n = 14)	Significance
Mean (SD) age (years)	75 (10)	70 (13)	NS
No (%) of men	39 (45)	6 (43)	NS
No (%) of smokers	34 (40)	4 (28)	NS
No (%) being treated for hypertension	35 (41)	5 (36)	NS
No (%) with past ischaemic heart disease/stroke/transient ischaemic attack	34 (40)	8 (57)	NS
Mean (SD) blood pressure on admission (mm Hg):			
Systolic	160 (31)	170 (51)	NS
Diastolic	92 (17)	92 (18)	NS
Mean (SD) packed cell volume	0.43 (0.06)	0.41 (0.04)	NS
No (%) with atrial fibrillation on admission	21 (24)	3 (22)	NS
No (%) with stupor/coma on admission	24 (28)	6 (43)	NS
Median stroke score	15	18	NS
No (%) of deaths:			
At 1 week	14 (16)	9 (64)	$p < 0.001$
At 1 month	27 (31)	9 (64)	$p < 0.05$
At 3 months	33 (38)	9 (64)	NS

Comment

The only previous study of HbA_{1c} concentrations in patients with stroke indicated that 42% of such patients had abnormal concentrations.⁴ The colorimetric assay method used, however, would have been affected by labile adducts, and we suspect that these results were artefacts. By contrast, a clearly abnormal concentration of stable HbA_{1c} determined by isoelectric focusing in patients surviving myocardial infarction appears to be specific for overt diabetes mellitus (with fasting hyperglycaemia) at follow up.³ Accordingly, we consider the prevalence of undiagnosed diabetes mellitus in our patients with acute stroke to have been at least 6%. Diabetes, known and previously unknown, although present in only 14% of the patients, accounted for 39% of the total mortality at one week, giving an early mortality four times greater than that in the patients without diabetes. All deaths of known diabetics and patients in group 3 occurred within the first week, implying that these patients are more prone to extensive infarction or cerebral oedema, or both.⁵

The highly significant relation between plasma glucose and HbA_{1c} concentrations suggests that premorbid abnormal glucose tolerance is a major determinant of the hyperglycaemic response to stroke. Previous observations of poor outcome from stroke in patients with "stress hyperglycaemia" may reflect the clinical course of stroke in diabetics.

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Rheumatoid factors and amyloidosis in rheumatoid arthritis

The precise mechanism of the formation and deposition of amyloid in rheumatic diseases is not known. Important factors appear to be high circulating concentrations of the lipoprotein associated precursor protein serum amyloid A together with altered enzymatic degradation of the precursor and tissue amyloid A protein.¹ Probably there are other factors, however, since only a few patients with these characteristics make amyloid. We have found that in adult rheumatoid arthritis seronegativity—that is, very low values of circulating IgM, IgG, and IgA rheumatoid factors—is strongly associated with the complication.

Subjects, methods, and results

Group 1 consisted of 46 patients (32 women, 14 men; mean age 54.4 years, range 32-84) with definite or classical rheumatoid arthritis complicated by reactive amyloidosis proved by histological examination of renal or rectal biopsy specimens, or both. The mean duration of the rheumatoid arthritis was 16.5 years (range 4-30 years). Patients with the HLA-B27 associated arthropathies ankylosing spondylitis, reactive arthritis, and psoriatic arthritis and those with juvenile onset rheumatoid arthritis were carefully excluded. Group 2 consisted of 47 patients (33 women, 14 men; mean age 53.5 years, range 30-73) with definite or classical rheumatoid arthritis with no clinical signs of secondary amyloidosis. The mean duration of their disease was 15.2 years (range 4-31 years). Patients in the two groups were matched for age, sex, and duration of rheumatoid arthritis. Fifty five healthy blood donors (43 men, 12 women; mean age 37 years, range 21-72) served as controls.

IgM, IgG, and IgA type rheumatoid factors were measured by enzyme immunoassay using swine IgG and specific alkaline phosphatase labelled swine antibodies to human IgG, IgA, or IgM (Orion Diagnostica, Finland). Rheumatoid factor activities were expressed as a change in absorbance at 406 nm over 30 minutes. A value greater than the mean plus two standard deviations recorded in the healthy controls was taken as raised. Statistical evaluation was by χ^2 test and Wilcoxon's ranking test for unpaired data.

IgM, IgG, and IgA type rheumatoid factors in patients with rheumatoid arthritis with or without amyloid

	No of subjects	No (%) with raised values of rheumatoid factors of type:		
		IgM	IgG	IgA
Healthy controls	55	1 (1.8)	1 (1.8)	2 (3.6)
Rheumatoid arthritis	47	38 (80.9)	35 (74.5)	41 (87.2)
Rheumatoid arthritis and amyloid	46	10 (21.7)*	14 (30.4)*	17 (37.0)*

*Compared with rheumatoid arthritis alone: $p < 0.001$.

Patients with rheumatoid arthritis complicated by amyloid had significantly lower values of IgM, IgG, and IgA rheumatoid factors than those without amyloid (table). In neither group did inflammatory activity, as reflected by C reactive protein concentrations, significantly influence the rheumatoid factor value.

Comment

Amyloid was much more common in our subset of patients who had very low values of circulating IgM, IgG, and IgA rheumatoid factors. This confirms the clinical impression based on conventional differential (sheep cell) agglutination tests (which measure only IgM rheumatoid factor) showing that many patients with rheumatoid arthritis complicated by amyloid are seronegative. In this study the subgroup of patients with rheumatoid arthritis not complicated by amyloid were matched with the others for age, sex, and duration of rheumatoid arthritis, so these factors are not likely to have influenced the results. The patient groups were not matched directly for the use of drugs, but review of the clinical records showed that the patients had received the same types of medication, including steroids and gold salts. Since uraemia may be immunosuppressive² it might be inferred that seronegativity in the amyloid group may have resulted from the amyloid state. Many of the patients with amyloid were not uraemic, however, and, based on Waaler-Rose tests, they had been seronegative at an early stage of the disease. Moreover, patients who are clearly seropositive generally remain so, and seronegative patients usually continue to be seronegative regardless of clinical course. We