Acta Paediatrica Hungarica, 25 (3), pp. 271—274 (1984)

Neonatal intensive care does not cause chromosome damage

K Méhes[1], L Pelz[3], G Kosztolányi[2], Katalin Bajnóczky[1], Veronika Meggyessy, Marlies Uhlemann[3]

Departments of Paediatrics, County Hospital, Győr[1]; University Medical School, Pécs[2], Hungary; and Department of Paediatrics, Wilhelm Pieck University, Rostock[3], GDR

In three neonatal units a total of 30 gravely ill newborn infants requiring intensive care were investigated cytogenetically. The results were compared with those obtained in 28 matched control neonates. No significant difference in the frequency of chromosome breaks, gaps, satellite associations, and sister chromatid exchange was found between the two groups of neonates.

Several studies have shown that certain drugs and procedures used in neonatal intensive care may have mutagenic effects under experimental conditions. Thus, for instance, chromosome damage has been observed after exposure to oxygen [9, 19] after phototherapy for neonatal hyperbilirubinaemia [16, 18], after the administration of antibiotics [2] and analeptics such asc affeine [4, 8, 12]. A possible genotoxicity of trimethoprim-sulfamethoxazole [17] and of glucocorticoids, widely used for antenatal prevention of IRDS, has been demonstrated [1], and even the mutagenicity-enhancing effect of glucose has recently been discussed [14].

Since all these observations were based on animal experiments or cell culture studies, we have attempted to clarify the *in vivo* effect of various combinations of the agents in question. Therefore we performed cytogenetic examinations in intensively treated gravely ill neonates in three referral intensive care units.

Material and Methods

In each of the neonatal units of Győr and Pécs (Hungary) and of Rostock (GDR) 10 seriously ill neonates were examined. The control groups were composed of newborn infants of similar gestational age, birth weight and sex, who required no intensive care. The survey of the material is demonstrated in Table I.

From both the intensively treated and control babies lymphocyte cultures were set up on the 4th or 5th day of life. Traditional Giemsa-stained, trypsin G-banded [6], and sister chromatid exchange (SCE) [15] preparations were analysed, and at least 30 mitoses were evaluated for structural aberrations and satellite associations (SA) according to the criteria of Hansson [10]. The frequency of SCE was determined from at least 15 mitoses. In two cases of the Győr control group the preparations were not sufficient to fulfil these requirements, therefore these infants were excluded from the study.

Although a certain variation in the therapy of seriously ill neonates should be considered, all the 30 intensively treated babies may be characterized by receiving for at least 12 hours some type of mechanical ventilation with an oxygen concentration of 40% or more, various antibiotics, glucose

TABLE I

Survey of the material

Neonatal intensive care unit	Neonates receiving intensive treatment			Control neonates		
	n	Birth weight		n	Birth weight, g	
		Mean	Range		Mean	Range
Győr	10	1760	1400–2350	8	1950	1500–2300
Pécs	10	2210	1470–3150	10	2240	1550–3000
Rostock	10	1850	1050–2400	10	2350	1850–4260

TABLE II

Cytogenetic findings in the intensively treated and control neonates

Features examined	Neonatal unit	No. of cells examined per neonate	Intensively treated neonates mean±SD	Controls mean±SD	P
Satellite associations: associated chromosome per cell	Győr Rostock	30–50	1.46 ±0.29	1.50 ±0.26	N.S.
Structural aberrations: Gap per mitosis	Győr	30–50	0.010±0.002	0.016±0.002	N.S.
	Rostock	100	0.014±0.002	0.011±0.001	N.S.
Chromatid and chromosome break per cell	Győr	30–50	0.006±0.001	0.004±0.001	N.S.
	Rostock	100	0.005±0.001	0.004±0.001	N.S.
Dicentrics and rearrangements	Győr	30–50	0.000	0.002	N.S.
	Rostock	100	0.000	0.000	...
Sister chromatid exchange per mitosis	Győr	15–50	11.06±0.68	10.74±0.63	N.S.
	Pécs	18–30	6.62±0.44	6.56±0.39	N.S.

infusion and phototherapy. Each of these infants had undergone one or more X-ray examinations by the time of setting up the lymphocyte cultures. In addition, furosemide and theophylline were often administered in Pécs, D-penicillamine, barbiturates, caffeine and antenatal maternal steroid medication were usually given in Győr. A part of the Rostock babies received tocopherol, calcium gluconate and human albumin.

The control neonates essentially differed from the intensively treated ones in surviving without oxygen supplementation, and in being neither septic nor seriously icteric. A single chest radiography was done in a few of them, and these infants also received glucose infusion and some antibiotics, and naturally were fed with breast milk much earlier than the intensively treated infants.

The two groups did not differ in nursing, environmental temperature, and in possible exposure to viral or microbial agents such as Mycoplasma, which was not controlled systematically in this study.

RESULTS

Results are summarized in Table II.

As shown by the figures, there was no significant difference between the findings in the intensively treated

and those of the control neonates. The values refer to cells with 46 chromosomes in each case. The occasionally seen hypodiploid mitoses were regarded as artefacts, their number was similar in the two groups of infants.

The figures reflect inter-laboratory variations; the satellite association frequency was higher in Győr than in Rostock, more SCEs occurred in Győr than in Pécs, but when the values were plotted against the own controls, no significant difference was found in any comparison.

Discussion

The optimum method for cytogenetic mutagenicity testing has often been discussed, and especially the achromatic lesions or chromatid gaps have been considered unsuitable for analytical work. According to recent studies, however, gaps are sensitive indicators of exposure to genotoxins and should be scored in the class of structural aberrations [3]. The same idea has been expressed by Evans [5] who said that even in the era of sophisticated methods the incidence of chromosome aberrations ascertained from studies on peripheral blood lymphocytes is a reliable indicator of exposure to mutagens. When stressing the importance of the SCE technique, Gebhart [7] suggested that it should be regarded as a valuable additional method for mutagenicity testing, but it is not suitable to replace the classical methods of analysis of structural chromosome damage. In view of the methodological recommendations, the procedures performed in our study seem to be appropriate to judge the possible acute mutagenicity of neonatal intensive care.

The majority of the infants studied was premature and in part of the cases small-for-gestational age. In accordance with earlier investigations [11, 13], the data reported here provide no evidence of any correlation of neonatal chromosome damage with low birth weight per se, whether associated with intrauterine growth retardation or with shorter gestation. Hatcher and Hook [11] found an increased frequency of chromosome aberrations in postnatal lymphocyte cultures of small-for-gestational age newborns, which they interpreted as a reflection of diagnostic and therapeutic procedures (e.g. irradiation, drugs, diet). In contrast to this observation, our results suggest that the complex therapy and diagnostics of severely ill neonates do not result in alteration of SA-frequency, in chromosome breakage and SCE frequency. This is all the more convincing, since besides common principles, a certain variation in selection of the patients, in their therapy, and in the cytogenetic methods could not be ruled out. In spite of that, no increase of chromosome aberrations and SCE in the intensively treated newborns was observed in any of the three neonatal units. This is favourable chiefly from the point of view of oxygen administration, which has

otherwise several undesirable side-effects.

The present results provided evidence that in contrast to findings obtained from *in vitro* and animal studies, the same drugs and procedures used in neonatal intensive care do not damage the chromosomes. This is probably due to the fact that the doses are significantly lower and the application much more tolerable in infants than in tissue cultures and animal experiments. Therefore, from a merely practical point of view, we think that chromosome examinations and follow-up of intensively treated neonates are not advocated. As compared to the many potential complications, the cytogenetic hazards seem to be negligible.

Acknowledgement

This work was supported in part by the Hungarian Ministry of Health, grant 09/7—19/113 M.

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Received June 28, 1983

K Méhes MD
P.O. Box 92
H-9002 Győr, Hungary