Correspondence

Effect of bucolome in preterm infants

Sir,
Segni *et al.* (Archives, 1977, 52, 549) reported the prevention of hyperbilirubinaemia in premature infants by bucolome. The effect of bucolome on hyperbilirubinaemia in Gilbert's syndrome was well established by observation of about 30 cases of the syndrome (Yamamoto *et al.*, 1974). However, as for the mechanism of the effect, we found that bucolome showed no induction of liver microsomal enzymes (Adachi and Yamamoto, 1976) but did show a strong tendency to dissociate bilirubin from serum albumin (Yamamoto and Adachi, 1974). This dissociation was shown *in vivo* in Gunn rats, and *in vitro* using human albumin and red cells.

We believe, therefore, that although bucolome is useful in cases of Gilbert's syndrome, it should not be further tried in premature infants.

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Dr. Romagnoli and co-workers comment:

We are indebted to Drs Yamamoto and Adachi for their preciseness about the different mechanism of action of bucolome compared with phenobarbital in animals

(Yamamoto *et al.*, 1974; Adachi and Yamamoto, 1976). However, our results suggest that the mechanism of serum bilirubin reduction induced by bucolome in man is different from the one reported by Yamamoto and by Semba in Gunn rats (Yamamoto and Adachi, 1974; Semba *et al.*, 1975). In fact bucolome administration to Gunn rats reduces serum bilirubin rapidly, while our results show that bucolome does not reduce serum bilirubin significantly in newborn infants during the hours after oral administration; its effect is delayed for about 48 hours. Moreover, serum bilirubin continues to fall after discontinuation of treatment. Our results agree with those of Baba (1972/73) in term newborns, and are not consistent with the hypothesis that the mechanism of action of bucolome in man is the displacement of bilirubin from the plasma compartment to the cellular one, as shown in Gunn rats.

We have studied the effect of bucolome on albumin-bilirubin binding capacity in a group of 20 healthy newborn infants with nonhaemolytic jaundice in the first 5 days of life. The evaluation of albumin-bilirubin binding capacity was done by gel filtration technique (Kernlute test, Ameis-Yissum, Jerusalem, Israel) before and after oral administration of a single dose of 15 mg/kg bucolome corresponding to the dosage of 30 mg/kg per day that we used in our previous study. The results of the study are given in the Table.

Our experience does not absolutely exclude a reduction of albumin-bilirubin binding capacity caused by bucolome; nevertheless it shows that, if there is such a

Table

Case no.	Sex	Weight (g)	Gestational age (w)	Total serum bilirubin (mg/100 ml)		Serum albumin (g/l)	Kernlute test	
				Before bucolome	6-8 h after bucolome		Before bucolome	6-8 h after bucolome
1	F	3300	40	10.2	11.4	38.7	Neg*	Neg
2	F	2930	39	12.8	11.4	36.6	"	"
3	F	2920	38	13.3	13.5	35.1	"	"
4	F	2500	36	16.3	14.5	35.3	"	"
5	M	2400	35	14.8	15.2	34.2	"	"
6	F	3680	38	12.8	13.5	33.0	"	"
7	M	3400	38	18.9	16.8	34.1	"	"
8	F	3100	40	13.5	14.0	31.2	"	"
9	F	3450	39	16.3	14.2	32.1	"	"
10	M	3560	39	17.2	18.9	35.1	"	"
11	F	4070	40	15.4	17.1	35.9	"	"
12	M	3180	40	15.5	15.6	36.4	"	"
13	F	3900	39	14.1	12.4	38.0	"	"
14	F	2460	37	10.4	10.3	34.2	"	"
15	M	3260	40	17.2	15.9	33.7	"	"
16	F	3100	39	10.9	12.1	37.0	"	"
17	F	3100	38	14.8	13.9	36.0	"	"
18	M	3480	40	12.8	11.9	33.1	"	"
19	M	2110	36	2.5	4.9	32.0	"	"
20	F	2130	32	9.2	10.2	33.0	"	"

*Albumin-bilirubin binding capacity > 5 mg/100 ml.

Conversion: Traditional units to SI—Bilirubin: 1mg/100 ml $\approx$ 17.1 μ mol/l.

reduction, it is not clinically significant in our experimental conditions because the albumin-bilirubin binding capacity always remained greater than 5 mg/100 ml in any case. Further, the babies included in our study are being followed-up; and we have not so far seen any significant neurological damage in infants treated with bucolome.

In conclusion we think that the mechanism of action of bucolome is not clear and needs further investigation *in vivo*. Meanwhile we consider that bucolome should not be used therapeutically in newborn infants with high levels of serum bilirubin because of the possibility of reduction in albumin-bilirubin binding capacity and because its effect is slow. On the contrary, in the prophylaxis of hyperbilirubinaemia bucolome should be used only when there is careful control of the albumin-bilirubin binding capacity during treatment.

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Protracted diarrhoea in infancy

Sir,

We read with great interest the article by Larcher *et al.* (*Archives*, 1977, **52**, 597) and would like to comment on several points. The authors included patients diagnosed as having secondary disaccharide intolerance in category 1, those with a specific diagnosis. Secondary disaccharide intolerance, as its name implies, is secondary to an insult which causes small intestinal mucosal damage with secondary disaccharidase deficiency. We think that this entity should be included in category 2 where no cause for the diarrhoea could be established.

In the past year we have treated 14 infants with a diagnosis of protracted diarrhoea in infancy. The diagnosis was made according to the criteria of Avery *et al.* (1968) with modification regarding the age of the patient. All had variable disaccharidase deficiencies, documented by specific enzyme assays done on jejunal biopsy material. We believe that if more patients in

category 2 had had jejunal biopsies and disaccharidase activity determination, the number with secondary disaccharidase deficiencies (made apparent with appropriate tolerance tests) would be far greater than was found by Larcher *et al.*

The small intestinal biopsy is an important tool in diagnosis as well as in determining modes of treatment; namely, parenteral hyperalimentation versus some modification of an elemental diet (Branski, 1978).

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Dr Larcher and co-workers comment:

We welcome the letter of Drs Branski, Hatch, and Leblenthal. In the main they comment on two important issues. We agree, of course, that clinical intolerance to disaccharides may be a primary or secondary phenomenon, and that it can be related to a variety of pathophysiological events. We assumed that this would be evident to readers when categorising our patients.

Clinical intolerance to disaccharides is *not* synonymous with the *in vitro* activity of the substrate-specific enzyme activity assayed in intestinal biopsies obtained from the proximal small gut. Hydrolysis of ingested oligosaccharides is an extremely efficient physiological process, and clinical intolerance of ingested oligosaccharides will only occur when there is extensive reduction in the brush border membrane activity of disaccharidases. In clinical practice the important issue is whether ingested sugars provoke gastrointestinal symptoms, *not* what the activity of a particular enzyme is in an *in vitro* laboratory assay system. Our category 2 patients did not clinically respond to elimination of disaccharides from their diets. This does not necessarily imply that they were not intolerant to disaccharides, but does indicate that other pathophysiological factors were operating in the genesis of the protracted diarrhoea.

We also agree that small intestinal biopsy can be a very useful procedure in the diagnosis and management of protracted diarrhoea in infancy. It should be stressed, however, that a biopsy is not mandatory to the diagnosis and management of very sick infants with protracted diarrhoea, and that an empirical approach based on currently available knowledge is sometimes unavoidable. The procedure is not without risk in severely malnourished infants such as those reported in our publication. Unfortunately a detailed diagnostic work-up is not always