TERMINAL DEHYDRATION

Sir,—Intravenous infusions are often continued until death in seriously ill patients because it is thought that electrolyte imbalance and dehydration may cause distress. However, the infusion may cause discomfort and distress to the patient, act as a barrier to relatives, and divert the attending medical and nursing personnel from the care of the patient to that of the electrolyte and fluid balance.

During the first four months of 1984, in the course of a study of hyperalcaemia, blood was taken from 200 patients with advanced cancer, within the first three days of admission to St Christopher's Hospice. Although it was not the intention to subject patients to venepuncture near to death, 22 patients did die within a short time of the blood test—12 within 24 hours and 10 between 24 and 48 hours. Of these 22 patients, dying without intravenous infusions or nasogastric tubes, 12 had essentially normal results. The urea was only mildly raised, the mean being 9.6 mmol/l (range 3.9–14.4, normal 2.5–6.5) but the other electrolytes were all within, or just outside, the normal range. Two patients had a raised bilirubin, but again the other electrolytes were normal. 10 patients, dying within 48 hours of the blood test, had abnormal results. 5 were uremic (mean urea 24.7 mmol/l, range 21.1–34.5) and 5 were hyperalcaemic and uremic (mean corrected calcium 3.36 mmol/l, range 2.84–4.05; mean urea 23.3 mmol/l, range 12.5–58.0).

Thus in these seriously ill patients, who died peacefully without distress, the electrolyte balance was essentially normal, without the use of intravenous fluids but using medical means to control their symptoms.1

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DAVID OLIVER


CO-TRIMOXAZOLE TOXICITY IN CHILDREN

Sir,—In December, 1981, Asmar et al1 published results of a study which suggested that trimethoprim-sulfamethoxazole (co-trimoxazole, TMP/SMZ) might lower the white blood cell count in children shortly after the drug is started. On the other hand, Feldman in 1983 reported that though neutropenia did occur in children treated with antibiotics, there was no material difference in the frequency of this event between children randomly assigned to amoxycillin or TMP/SMZ.2 To evaluate the possible adverse effects of TMP/SMZ on the bone marrow, as well as other systems, we have done a follow-up study of a large number of children under the age of 10 years who received the drug as outpatients at the Group Health Cooperative of Puget Sound (GHC).3

From the health cooperative's automated pharmacy files, 3,4 we identified all children below age 10 years who had filled one or more prescriptions for oral TMP/SMZ between January, 1979, and December, 1981. There were 4828 such children. Over the three-year study period, about 30% of all the health cooperative's children aged 0–4 used TMP/SMZ at some time. Among children aged 5–9, about 7% used the drug. We did two separate studies. We reviewed all hospital admissions among the 4828 recipients, following the use of the drug, to identify anyone admitted for blood disorder or leukemia. Among the 4828 recipients of TMP/SMZ in the period January, 1979, to December, 1981, none was subsequently admitted to hospital for any blood disorder or leukemia. We also reviewed by hand the outpatient records of a subset of 2622 unselected children who were recorded on the pharmacy file as having filled at least one prescription for TMP/SMZ. In all but 103 (4%), notification of the use of the drug was present in the clinical record. 64% of patients received only one prescription; 19% received two prescriptions; 17% received three or more prescriptions. The drug was routinely prescribed in recommended dosages according to the approved package insert in the United States. For each child the medical record was reviewed from the first day of receiving the drug until 7 days after the drug was stopped. All adverse reactions attributed to the drug clinically were noted. In addition, we noted the indication for the drug, all other untoward clinical events noted, all hospital admissions during the period, and all recorded white blood cell counts.

Among the 2622 recipients of TMP/SMZ, there were 66 (2.5%) in whom an adverse event was attributed to the drug. Of these events, 46 (70%) were rashes and 15 (23%) were episodes of vomiting and/or diarrhea. The remaining reactions were 1 each of the following: dizziness, headache, swollen lips, blue lips and hands, and constipation. Among the 46 rashes, 3 were described as erythema multiforme (1 specifically was described as Stevens-Johnson syndrome) and 4 were accompanied by other symptoms—joint aches and fever (1), flushing and conjunctivitis (1), fever and vomiting (1), and tightness in chest with difficulty breathing (1). In no case was the child admitted to hospital because of the adverse reaction and in all cases there was rapid recovery after the drug was stopped. There were no reports of lowered white blood cell counts, nor of any other type of blood disorder.

There were also 66 untoward events that were not attributed clinically to TMP/SMZ. In 59 instances, the event was rash which was attributed to other causes. There were 2 instances of arthralgia, 2 of vomiting, 1 of diarrhea, 1 of toe pain, and 1 of rash with vomiting and swollen hands and face.

Among the 2622 recipients of TMP/SMZ, there were 55 with white blood cell counts recorded after the drug was started. All but 3 of these counts were greater than 5000/mm³ (2600, 3400, and 4700). Our follow-up study of 2622 children using TMP/SMZ did not reveal any serious adverse reactions that could be reasonably attributed to the drug. In particular, there were no reported blood disorders, nor any hospital admissions secondary to drug toxicity.

Despite some limitations, the study provides considerable reassurance that serious adverse reactions to TMP/SMZ in children are uncommon.


CIRCULATING PITUITARY AUTOANTIBODIES AGAINST CELLS SECRETING LUTEINISING AND FOLLICLE STIMULATING HORMONES IN CHILDREN WITH CRYPTORCHIDISM

Sir,—Circulating pituitary autoantibodies have been described in some cases of anterior pituitary insufficiency, including patients with gonadotropin deficiencies.1,2 Such autoantibodies are found in less than 1% of control sera.3 The frequency of hypogonadotropic hypogonadism and infertility in males with a history of cryptorchidism in infancy prompted us to look for autoantibodies against pituitary cell components in children with maldevelopment of the testis. Of 52 sera from children with cryptorchidism aged 2½ to 16 years studied by an indirect immunofluorescent test (IFT) on 5 μm sections of fresh frozen human and guinea pig pituitaries, 25 (48%) were positive. In most cases (19), the pattern obtained was a positive cytoplasmic staining of only a few cells in the entire section (type I) or single cell. In the other 6 cases more cells were stained (type II or multi-cell). The autoantibodies were IgG or IgG and IgA. Titres varied between 4 and 32. The best results were obtained on guinea pig pituitary sections.

Identification of the reactive cell type by four-layer double fluorochrome immunofluorescent test showed that LH and FSH secreting cells only were involved in cases with the type II pattern while the type I pattern was associated with prolactin (4 cases) and/or corticotropin (2 cases) secreting cells as well.

Autoantibodies were more frequent in cases of bilateral cryptorchidism (8/12) than in unilateral cases (15/37). Autoantibodies are not directed against the hormones themselves, as shown by

absorption experiments, and there was no relation with previous hormonal treatment.

Several disorders are associated with circulating autoantibodies. These autoantibodies often react with cells or tissues from healthy donors, but, except in a few cases, the antigen determinant has not been characterized. The significance of our finding remains to be worked out. The cause of undescended testis is still unclear in cases where mechanical factors are absent, but there may be a disturbance of the hypothalamic-pituitary testicular axis with an early deficiency of LH secretion. Testicular descent usually happens in the last week in utero, so if autoantibodies play a role in maldevelopment they would have to act on the fetus. Preliminary results suggest that this may be so. We have detected such antibodies in 5 out of 12 mothers of cryptorchid children tested during the first week after delivery. The same antibodies of IgG class were detected in the newborn babies. Longitudinal and collaborative studies are in progress.

Polyendocrine disease apart, true autoimmunity against the pituitary gland has been mainly described in relation to pregnancy.\(^2\) and profound qualitative and quantitative changes in hormone levels occur during pregnancy. Whether autoimmunity against pituitary is associated with pregnancy because of the release of pituitary antigens as pituitary size and vascularity increase remains a matter of speculation.

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PRENATAL TREATMENT OF ALLOMUNE THROMBOCYTOPENIA

Sir,—The frequency of neonatal alloimmune thrombocytopenia (NAIIT) has been estimated at about 1 per 5000 births.\(^1\) The PL-A-1 platelet-specific antigen has been involved in the vast majority of the reported cases.\(^2\) A PL-A-1 negative mother acquires immunity to the PL-A-1 antigen of her fetus, even though in 20% of typical cases PL-A-1 antibody cannot be demonstrated serologically.\(^3\) Risk factors are PL-A-1 negativity, and HLA B8, DR3 positivity in mothers,\(^4\) and PL-A-1 positivity in fathers. NAIT is a serious condition, and central nervous system bleeding is responsible for a high rate of morbidity and mortality. Most of these complications have been associated with delivery and other perinatal stresses and have justified caesarean section in at-risk pregnancies.\(^5\) However, intracranial haemorrhage has also been observed during fetal life\(^6\) and no laboratory tests have been available to predict whether the infant will be affected or not.

In 1982 a woman now aged 24 was delivered of her first daughter, who had NAIT with severe intracranial haemorrhage and neurological sequelae. The mother was PL-A-1 negative and HLA DR3 positive; the father was PL-A-1 positive as was the child. Anti-PL-A-1 antibody was found in a blood sample taken 8 days after delivery. This woman was sent to us in the 32nd week of her second pregnancy for the prenatal testing of the PL-A-1 platelet phenotype of her fetus. 5 ml of the fetal blood were obtained by direct puncture of the umbilical cord with a needle guided by ultrasound,\(^7\) the only procedure available for fetal blood sampling during the third trimester of pregnancy.

The fetal platelet count was very low on a Coulter counter S plus II, and this was confirmed by microscopy and blood smear. The platelet count (15×10\(^3\)/μl) was well below our reference range (253±36 SD; n=22), at this period of gestation and was too low to permit identification of PL-A phenotype.

By the 37th week the pregnancy was proceeding normally and there was no ultrasound evidence of fetal paresis. Anti-PL-A-1 antibody was present in the mother's serum. With the approval of the local ethic committee we suggested to the patient that in-uterus transfusion of platelets a few hours before delivery be attempted.

The maturity of the fetal lungs was confirmed by the leucine sphenonymelin ratio in amniotic fluid. 20 ml of washed maternal platelets containing 250×10\(^3\)/μl platelets was prepared. 2 h later 10 ml fetal blood was withdrawn from the umbilical vein. Thrombocytopaenia was confirmed and 10–5 ml of the platelet preparation was injected slowly into the umbilical vein.

6 h later the mother was delivered by caesarean section of a 2700 g healthy baby (Appgar 10). The platelet count in cord blood was 95×10\(^3\)/μl. A further 8.5 ml of platelet concentrate was injected 15 min after birth via the umbilical cord. No other platelet transfusion was necessary. Subsequent platelet counts are summarised in the figure. Clinical and ultrasound examinations of the baby were normal 8 days after birth. The baby's PL-A phenotype was subsequently shown to be PL-A-1 positive.

We have done 400 fetal blood samplings by direct puncture of the umbilical cord under ultrasound without any complications. The procedure can be repeated several times during pregnancy and permits fetal therapy via the intravenous route. This case suggests that intravenous platelet transfusion just in time to a child with NAIT can be used to avoid haemorrhage in the neonatal period. The effects of platelet transfusion are short-lived but repeated intravenous injections to the fetus may prevent or delay prenatal haemorrhages in cases of severe fetal thrombocytopenia.

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ENDORPHINS AND PAIN CONTROL

Sir,—Dr Willer and his colleagues (Aug 4, p 295) report that plasma β-endorphin concentration is poorly related to pain control